National assessment of chemicals associated with coal seam gas extraction in Australia

Technical report number 12

Human health hazards of chemicals associated with coal seam gas extraction in Australia: Appendix A – Hazard assessment sheets

This report was prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS)

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Department of Health
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2	Literature review: Human health implications	NICNAS
3	Literature review: Environmental risks posed by chemicals used coal seam gas operations	Department of the Environment and Energy
4	Literature review: Hydraulic fracture growth and well integrity	CSIRO
5	Literature review: Geogenic contaminants associated with coal seam gas operations	CSIRO
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Abbreviations and units of measure

Units	Description
°C	Degrees Celsius
cm^2	Square centimetre
cm^3	Cubic centimetre
m^3	Cubic metre
dL	Decilitre
g	Gram
h	Hour
kg	Kilogram
kPa	Kilopascal
L	Litre
µm	Micrometre
µmol	Micromole
µL	Microlitre
µg	Microgram
mg	Milligrams
mL	Millilitre
mm	Millimetre
mM	Millimolar
mmol	Millimole
ng	Nanogram
ppm	Parts per million
%	Per cent

1 Introduction

This Report: *Human health hazards of chemicals associated with coal seam gas extraction in Australia: Appendix A – Hazard assessment sheets*

This appendix describes part of the fourth stage of the *Assessment* – the risk assessment and characterisation stage. An investigation undertaken in the initial stages of the *Assessment* identified a total of 113 chemicals used in drilling and hydraulic fracturing for coal seam gas extraction in Australia during the period 2010 to 2012. Chemicals were then screened to identify chemical of low conern. The remaining chemicals were then assessed to determine their hazards and risks. The findings of these investigations are documented in the preceding reports entitled:

- Identification of chemicals associated with coal seam gas extraction in Australia (NICNAS 2017a)
- Chemicals of low concern for human health based on an initial assessment of hazards (NICNAS 2017b)
- Human health risks associated with surface handling of chemicals used in coal seam gas extraction (NICNAS 2017c)

This Appendix to the Human Health Hazard Assessment report[1] contains individual human health hazard assessments for a total of 69 drilling and hydraulic fracturing chemicals. It has been prepared as a set of stand-alone chapters presenting chemical (or groups of chemicals) assessment information.

In addition to information on chemical identity and human health hazards, the assessment for each chemical, or groups of chemicals, describes regulatory controls (in Australia and overseas), and a health hazard characterisation based on information available at the time of assessment. NICNAS has subsequently forwarded recommendations from these hazard assessments to risk management agencies for adoption, so the current regulatory status of individual chemicals may now reflect adoption of recommendations by these agencies.

The health hazards were characterised by analysing the toxicokinetics (the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals), acute toxicity, irritation and corrosivity, repeat dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity, and other health effects.

Details on the methodology used for human health hazard characterisation are available in the human health hazard assessment report (NICNAS 2017d).

[1] NICNAS 2017d, *Human health hazards of chemicals associated with coal seam gas extraction in Australia*, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia project, Commonwealth of Australia, Canberra.

A1 Boric acid, Sodium borate, Sodium tetraborate

CAS No.	CAS Name
10043-35-3	Boric acid (H_3BO_3)
12008-41-2	Boron sodium oxide ($B_8Na_2O_{13}$)
1303-96-4	Borax ($Na_2(B_4O_7).10H_2O$)

This assessment is conducted as a group assessment of three substances – boric acid (H_3BO_3), boron sodium oxide ($B_8Na_2O_{13}$) (also referred to as boric acid disodium salt) and borax ($Na_2(B_4O_7).10H_2O$). To more easily distinguish various forms of borates in this report, boric acid disodium salt will be referred to from here on by the synonym disodium octaborate anhydrate.

1.1 Justification for group assessment

The toxicity of inorganic borates is driven predominantly by boron. Boric acid is a weak acid with a pKa of 9.2 and exists, along with borate salts, in aqueous solutions at physiological pH primarily as the undissociated acid (H_3BO_3) (Woods 1994). In general, the chemical and toxicological properties of boric acid and the sodium salts boric acid disodium salt (also known as disodium octaborate anhydrate) and disodium tetraborate decahydrate (borax) are expected to be similar on a mol boron/L equivalent basis when dissolved in water or biological fluids at the same pH and low concentration (WHO 1998). Due to these expected similarities, data gaps for individual borates in Table A1.1 can be filled by inference based on information available for other borate species that differ in their degree of hydration (i.e. the number of water molecules bound to the chemical in its crystal structure).

Table A1.1 Matrix of available toxicity endpoint data

Toxicity endpoints	Boric acid	Boric acid disodium salt (Disodium octaborate anhydrate)	Borax (Disodium tetraborate decahydrate)	Other borates differing in degree of hydration
Acute oral toxicity	✓	✓	✓	✓(disodium octaborate tetrahydrate)
Acute dermal toxicity	✓	×	✓	✓ (disodium octaborate tetrahydrate)
Acute inhalation toxicity	✓	✓	✓	×
Skin irritation	✓	×	✓	✓(disodium octaborate tetrahydrate)
Eye irritation	✓	×	✓	✓(disodium octaborate tetrahydrate)

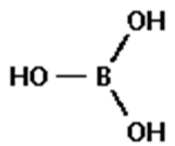
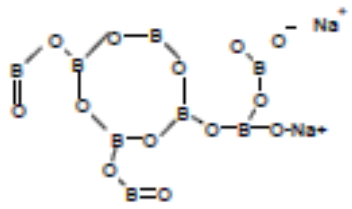
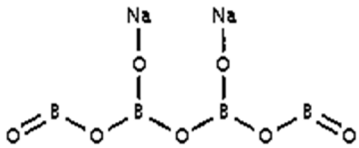
Toxicity endpoints	**Boric acid**	**Boric acid disodium salt (Disodium octaborate anhydrate)**	**Borax (Disodium tetraborate decahydrate)**	**Other borates differing in degree of hydration**
Respiratory irritation	✓	✓	×	×
Skin sensitisation	✓	×	✓	✓(disodium octaborate tetrahydrate)
Repeat dose toxicity (oral)	✓	×	✓	×
Genotoxicity	✓	×	×	×
Carcinogenicity	✓	×	✓	×
Reproductive toxicity	✓	×	✓	×

✓*Existing data point* × *Missing data point*

1.2 Chemical identity

The following chemical identity information in Table A1.2 was obtained from ChemID*plus* (2012), Agency for Toxic Substances and Disease Registry (ATSDR) (2010) and RIVM (2013).

Table A1.2 Chemical properties

	Boric acid	**Boric acid disodium salt**	**Borax**
Synonyms	Boric acid (H_3BO_3) Boracic acid Boron hydroxide Boron trihydroxide Orthoboric acid	Boron sodium oxide ($B_8Na_2O_{13}$) Disodium octaborate anhydrate Boric acid ($H_2B_8O_{13}$) Disodium salt Sodium borate	Borax ($Na_2(B_4O_7).10H_2O$) Disodium tetraborate, decahydrate Sodium borate, decahydrate Sodium tetraborate Sodium tetraborate, decahydrate
Structural formula			
Molecular formula	BH_3O_3	$B_8Na_2O_{13}$	$B_4Na_2O_7.10H_2O$
Molecular weight	61.83	340.47	381.37

	Boric acid	**Boric acid disodium salt**	**Borax**
Appearance and odour	Colourless, transparent crystals or white granules or powder. Odourless.	Solid white powder. Odourless.	White crystalline solid. Odourless.
SMILES notation	B(O)(O)O	B(O{-})(O{-})O{-}_B(O{-})(O{-}.[Na]{+})O{-}.[Na]{+}	Not available
Conversion factors to boron equivalents	0.175	0.254	0.113

1.3 Physical properties

Information on the physical properties in Table A1.3 was obtained from ATSDR (2010) and RIVM (2013). In the absence of information available for disodium octaborate anhydrate, information is provided for disodium octaborate tetrahydrate.

Table A1.3 Physical properties

	Boric Acid	**Boric acid disodium salt**	**Borax**
Melting point	170.9 °C	813 °C	75 °C (decomposes)
Boiling point	No data	No data	No data
Density	1.44 x 10^3 kg/m^3 at 15 °C	1.87 x 10^3 kg/m^3	1.73 x 10^3 kg/m^3
Water solubility	50 g/L at 25 °C	223.7 g/L at 20 °C	59.3 g/L at 25 °C
pK_a	9.42	No data	No data
Log K_{ow}	0.175	No data	No data
Vapour pressure	Negligible at 20 °C	No data	Negligible

1.4 Current regulatory controls

1.4.1 *Hazard classification for occupational health and safety*

Boric acid and borax are classified as hazardous for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) with the following risk phrases:

- Toxic to reproduction (Repr.) Cat. 2; R60 (May impair fertility)
- Repr. Cat. 2; R61 (May cause harm to the unborn child)

Mixtures containing boric acid and borax are classified as hazardous with the following risk phrases based on the concentration (conc) of the chemicals in the mixtures.

- Boric acid: Conc ≥5.5%: Toxic (T); R60; R61

- Borax: Conc ≥8.5%: T; R60; R61.

Disodium octaborate anhydrate is currently not classified.

1.4.2 *Occupational exposure standards*

1.4.2.1 Australia

There are no specific exposure standards for boric acid or disodium octaborate anhydrate. However, the permissible exposure limits (as the time weighted average (TWA)) for dusts apply (10 mg/m^3 measured as inspirable dust) (Safe Work Australia 2013b).

The exposure standard for borax is 5 mg/m^3 TWA (Safe Work Australia 2013a).

1.4.2.2 International

The following exposure standards were identified (Galleria Chemica 2013):

- Boric acid
  - Canada 2 mg/m^3 TWA, 6 mg/m^3 Short-term exposure limit (STEL) (borate compounds)
  - Germany 10 mg/m^3 TWA; 1 mg/m^3 STEL
  - Spain 10 mg/m^3 TWA (insoluble particles)
  - US 2 mg/m^3 TWA; 6 mg/m^3 STEL (borate compounds), 5 mg/m^3 TWA (particulates, respirable fraction)
- Disodium octaborate anhydrate
  - Canada 10 mg/m^3 TWA, (insoluble particles)
  - Spain 10 mg/m^3 TWA (particulates, inhalable fraction)
  - US 5 mg/m^3 TWA (particulates, respirable fraction)
- Borax
  - Canada 1 to 5 mg/m^3 TWA, 6 mg/m^3 STEL (inorganic borate compounds)
  - Denmark 1 to 2 mg/m^3 TWA
  - Germany 0.5 mg/m^3 TWA
  - Spain 5 mg/m^3 TWA
  - Sweden and UK 2 mg/m^3 TWA
  - US 2 mg/m^3 TWA (inorganic borate compounds); 5 to 10 mg/m^3 TWA.

1.4.3 *Australian food standards*

No Australian food standards were identified for the chemicals.

1.4.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values exist specifically for boric acid, disodium octaborate anhydrate or borax. However, the guidelines note that boron in the environment is likely to be predominantly in the form of boric acid and that based on health considerations, the concentration of boron in drinking water should not exceed 4 mg/L (NHMRC 2011).

1.4.5 *Additional controls*

1.4.5.1 Australia

Boric acid and borax are listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedule 5 with the following entry:

- Boric acid (excluding its salts) and borax except:
    a) when included in Schedule 4
    b) in preparations, other than insect baits, containing 1 per cent or less of boron or
    c) in hand cleaning preparations.

1.4.5.2 International

According to the European Commission Cosmetics Directive Annex III (List of Restricted Substances), restrictions exist for boric acid, borates and tetraborates for certain types of cosmetic products in the European Community (European Commission 2013).

- The maximum concentration for boric acid, borates and tetraborates in talc cosmetic products is 5% (as boric acid). These are not to be used in products for children under three years of age and not to be used on peeling or irritated skin if the concentration of free soluble borates exceeds 1.5% (as boric acid).
- For oral cosmetic products, the maximum concentration is 0.1% (as boric acid). These are not to be used in products for children under three years of age.
- For other cosmetic products, the maximum concentration is 3% (as boric acid). These are not to be used in products for children under three years of age and not to be used on peeling or irritated skin if the concentration of free soluble borates exceeds 1.5% (as boric acid).

Additional restrictions apply specifically for tetraborates in cosmetic products.

- The maximum concentration for tetraborates in bath products is 18% (as boric acid). These are not to be used in products for children under three years of age.
- The maximum concentration for tetraborates in hair products is 8% (as boric acid).

1.5 Use

The use of these chemicals in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

1.6 Health hazard characterisation

The information in sections A1.6.1 to A1.6.9 on health hazards is obtained from the following comprehensive reviews of boron and its compounds:

- World Health Organisation (WHO) (1998)
- United States Environment Protection Agency (US EPA) (2004)

- ATSDR (2010)
- European Chemicals Agency (ECHA) (2010)
- RIVM (2013).

Unless otherwise noted, references to individual studies below are taken from these reviews.

1.6.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

In aqueous solutions at physiological and acidic pH, low concentrations of simple borates such as boric acid, disodium octaborate anhydrate and borax will exist predominantly as undissociated boric acid. Above pH 10, the metaborate anion $B(OH)_4$ becomes the main species in solution. The toxicokinetics and toxicological effects of these three borates will therefore be similar on a boron equivalents basis.

It is noted that dissolution from simple borates to boric acid takes about 15 minutes, potentially leading to differences in acute toxicity and local toxic effects between borates. However, for comparative purposes, dose levels of borates can still be expressed generally as boron equivalents based on the fraction of boron on a molecular weight basis. Conversion factors to boron equivalents are provided above in Table A1.2.

1.6.1.1 Oral absorption

Boric acid and simple sodium borates administered orally are readily and completely absorbed in humans and animals as shown by levels of boron in urine, blood or tissues. Animals investigated include rats (Ku et al. 1991), rabbits (Draize and Kelly 1959), sheep (Brown et al. 1989) and cattle (Owen 1944; Weeth et al. 1981). In rats fed ^{10}B at a dose of 20 µg, 95% and 4% were recovered from urine and faeces respectively within 24 hours, indicating rapid absorption (Vanderpool et al. 1994).

Several studies of boron uptake following oral ingestion in human volunteers have also been conducted (ATSDR 2010; WHO 1998). Reports describing human ingestion of boric acid with fatal consequences also provide evidence of rapid and complete oral absorption. A review of the literature indicates oral absorption fractions of 81 to 92% for humans and 95% for rats (Dourson et al. 1998). For human risk assessment purposes, 100% oral absorption is assumed.

1.6.1.2 Dermal absorption

Across intact skin, dermal absorption of borates is insignificant in rats (Nielsen 1970) and rabbits (Draize and Kelley 1959). However, borates have been demonstrated in these studies to penetrate damaged or abraded skin.

In human volunteers, 0.23% of an applied dose of 1.8 mL of 5% boric acid aqueous solution to intact skin was shown to be absorbed after 24 hours (Wester et al., 1998). Dermal absorption of borates in ointment (3% boric acid) is similarly insignificant across intact skin in new-born infants (Friis-Hansen et al. 1982) and adults (Stüttgen et al. 1982). Minimal differences were found in borate absorption (5% boric acid in talcum powder 7 to 10 times per week) in infants with or without nappy rash (Vignec and Ellis 1954).

For human risk assessment purposes, a dermal absorption rate of 0.5% is assumed based on rounding and statistical variation within the data.

1.6.1.3 Inhalation absorption

In rats following inhalation, an anhydrous boric acid aerosol was readily absorbed, which was identified through increased levels of boron excreted in urine (Wilding et al. 1959). It is not clear if the inhaled amount of boron was absorbed entirely by the respiratory tract or whether swallowed particles cleared from the respiratory tract may have contributed to systemic uptake. Production workers exposed to sodium borate dusts were found to have approximately an order of magnitude higher blood and urine concentrations of boron at the end of a work shift compared to at the beginning, suggesting that inhaled boron is absorbed and systemically distributed (Culver et al. 1994). For human risk assessment purposes, an inhalation absorption rate of 100% is assumed.

1.6.1.4 Distribution

Absorbed boron rapidly distributes throughout water in the body. In animal studies, there is no evidence of boron accumulation, although bone contains higher levels than other tissues, but the boron is slowly eliminated from bone. Following oral administration, boron evenly distributed to liver, kidney, brain, muscle, adrenals, epididymis, testes, seminal vesicles and blood (but not fat) of male rats fed 61 mg boron/kg/day as boric acid for 1 to 28 days (Ku et al. 1991; Moseman 1994; Treinen and Chapin 1991), reaching steady-state by four days. Blood and testes boron levels were similar in rats fed 26 to 68 mg boron/kg/day as boric acid for nine weeks (Ku et al. 1991). However, boron accumulated in bone in male rats fed 61 mg boron/kg/day (as boric acid) for nine weeks, with achievement of steady-state at four weeks. Bone levels were approximately three-fold higher than soft tissue levels (Moseman 1994).

1.6.1.5 Metabolism

Inorganic borate compounds convert to (and are present at physiological pH within the body as) boric acid. Boric acid is not metabolised in either animals or humans due to the high energy level required to cleave the B-O bond (Emsley 1989). Studies of inhalation and oral exposure of animals and humans to borates have consistently only reported recovery of the parent borate in the blood, tissues and urine (Culver et al. 1994b; Draize and Kelley 1959; Jansen et al. 1984; Ku et al. 1991; Moseman 1994; Treinen and Chapin 1991).

1.6.1.6 Excretion

In both humans and animals, boron is excreted in the urine with a half-life of less than 24 hours. Boron is slowly eliminated from bone (Chapin et al. 1997; Moseman 1994). Since boric acid is excreted unchanged in the urine, the major determinant of excretion is expected to be renal clearance. Rats and mice generally have faster rates of renal clearance than humans since glomerular filtration rates as a function of body mass are generally higher in rats and mice than in humans. A comparison of the renal clearance between rats and humans in terms of body surface area indicated that humans clear boric acid slightly faster than rats while a comparison by bodyweight indicates that humans clear boric acid more slowly than rats (Pahl et al. 2001; Vaziri et al. 2001).

1.6.1.7 Summary of toxicokinetics

The toxicokinetics of boric acid and sodium borates are similar in rats and humans with respect to absorption, distribution and metabolism. A difference in renal clearance is the major determinant of differences between excretion in animals and humans. For risk assessment purposes, 0.5% absorption for dermal exposure and 100% absorption for oral

and inhalation exposures are assumed for boric acid, disodium octaborate anhydrate and borax.

1.6.2 *Acute toxicity*

1.6.2.1 Oral

Borates are of low acute toxicity in mammals, including rats and mice.

For boric acid, an oral median lethal dose (LD50) of 3765 mg/kg bw (659 mg boron/kg bw) was reported in Sprague-Dawley rats (Keller 1962; Weir and Fisher 1972).

An acute oral toxicity study in rats conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401 of disodium octaborate tetrahydrate reported an LD50 of 2550 mg/kg bw (535 mg boron/kg bw) (Doyle 1988).

For disodium tetraborates (anhydrous, pentahydrate and decahydrate (borax)), LD50 values of >2500 mg (>538 mg boron)/kg bw, 3305 mg (489 mg boron)/kg bw and 5560 mg (628 mg boron)/kg respectively were reported in rat studies (Denton 1996; Reagan and Becci 1985a; Meyding and Foglhian 1961).

The main symptoms of toxicity in species tested were central nervous system (CNS) depression, ataxia and convulsions.

1.6.2.2 Dermal

In an acute dermal toxicity study in rats performed with disodium octaborate tetrahydrate the LD50 value was >2000 mg/kg bw (European Commission 2000). The other borates also appear to have low acute dermal toxicity. In a study in rabbits, the dermal LD50 value for boric acid was >2000 mg/kg bw/day (Weiner et al. 1982). Acute dermal toxicity studies with disodium tetraborate decahydrate (borax) and disodium tetraborate pentahydrate revealed no deaths at a limit dose of 2000 mg/kg bw/day (Reagan and Becci 1985a,c). It was noted that these studies may be flawed since the test material was not moistened, so good contact with the skin was not ensured.

1.6.2.3 Inhalation

The four-hour acute median lethal concentration (LC50) for boric acid, borax and disodium borates is reported to be >2 mg boron/m^3 (Hubbard 1998).

An inhalation study in rats conducted to OECD TG 403 with boric acid reported an oral median lethal concentration (LC50) of ≥2.03 mg/L (Wnorowski 1994a). A similar study with disodium octaborate anhydrate reported an LC50 of ≥2.01 mg/L (Wnorowski 1994b).

1.6.2.4 Observation in humans

A review of more than 700 cases of acute boric acid exposures in adults and children found 88% of cases were without symptoms (Litovitz et al. 1988). In general, only limited information on dose was provided. However, symptomatic cases had doses ranging from 100 mg to 55 g boric acid.

There are case reports of lethal oral exposures of humans to boron primarily involving accidental or intentional exposures to high levels of boric acid. Deaths have been recorded in children following accidental ingestion of 4.5 to 14 g boric acid (0.8 to 2.5 g boron) (Wong et al. 1964). Death occurred in a 77-year-old male following ingestion of 30 g boric acid (85 mg boron) (Ishii et al. 1993) and in a 45-year-old male following ingestion of

approximately 280 g boric acid (49 g boron) (Restuccio et al. 1992). In both instances, clinical signs were similar: vomiting, diarrhoea, erythema, cyanotic extremities, acute renal failure, cardiopulmonary hypertension and death from cardiac insufficiency.

1.6.3 *Irritation / Corrosivity*

1.6.3.1 Skin irritation

Borates have low skin irritation potential.

In rabbit studies, boric acid did not cause skin irritation when applied to intact or abraded skin at a dose of 0.5 g (Roudabush et al. 1964) or only caused very mild irritation when applied as 5 mL of 10% boric acid (Weiner et al. 1982).

There were no data available for disodium octaborate anhydrate.

Very mild irritation was observed with disodium octaborate tetrahydrate when applied to the skin of rabbits at a dose of 0.5 g (Doyle 1989c).

In rabbit studies, borax did not cause skin irritation when applied at a dose of 0.5 g (Reagan and Becci 1985b) or only caused very mild irritation when applied as 10 mL of 5% borax in water (Roudabush et al. 1964).

1.6.3.2 Eye irritation

In rabbits, boric acid induced reversible conjunctival redness and chemosis and minor effects on the iris (Doyle 1989a). Effects were reversible within seven days.

No data were available for disodium octaborate anhydrate.

Reversible iris and conjunctival irritation was observed with disodium octaborate tetrahydrate when applied to the eye of rabbits (Doyle 1989d). Irritation was possibly due to the crystalline nature of the compound (RIVM 2013).

In rabbits, borax was found to induce reversible conjunctival redness and chemosis and related effects on the cornea and iris (Doyle 1989b). Irritation was possibly due to the crystalline nature of the compound (RIVM 2013).

1.6.3.3 Respiratory irritation

In inhalation studies in rats, nasal and ocular discharge was noted in association with boric acid (Wnorowski 1994a) and ocular discharge was noted in association with disodium octaborate anhydrate (Wnorowski 1994b).

In tests in mice examining depression of respiratory frequency in response to sensory irritants, exposure to 300 mg/m^3 boric acid as an aqueous aerosol resulted in a 20% reduction in respiratory rate. It was concluded that boric acid acts as a sensory irritant (Krystofiak and Schaper 1996).

1.6.3.4 Observation in humans

Acute respiratory effects have been extensively documented in humans (workers) following inhalation of boric acid and other borates as dusts in a number of studies (ATSDR 2010; WHO 1998). Effects include nasal and eye irritation, throat irritation, cough and breathlessness. These effects were regarded as sensory irritant effects that would typically be seen in normal populations in the absence of respiratory hypersensitivity. A No Observed Adverse Effect Concentration (NOAEC) of 0.8 mg boron/m^3 was identified (ECHA 2009).

1.6.4 *Sensitisation*

1.6.4.1 Skin sensitisation

Boric acid and borax were tested in a Buehler skin sensitisation test conducted according to OECD TG 406 (Wnorowski 1994c, 1994d). Test substances were applied at a concentration of 95% in water during both induction and challenge. No signs of skin sensitisation were seen.

No data were found for disodium octaborate anhydrate.

A Buehler skin sensitisation test similar to those above was reported for disodium octaborate tetrahydrate with negative results (RIVM 2013).

1.6.4.2 Respiratory sensitisation

No data were available.

1.6.4.3 Observation in humans

There has been no reported evidence of skin or respiratory sensitisation in humans exposed occupationally to borates (ECHA 2009; RIVM 2013).

1.6.5 *Repeat dose toxicity*

1.6.5.1 Oral

The following key rodent data relating to the repeated dose oral toxicity of boric acid and borax (Table A1.4) were summarised from ECHA (2009) and RIVM (2013). No studies were found for disodium octaborate anhydrate.

Table A1.4 Repeated dose toxicity studies

Test substance	Method	Results	Remarks	Reference
Boric acid	Rat, 13 weeks, diet. Doses: equivalent to 0, 2.6, 8.8, 26, 88 and 260 mg boron/kg bw/day	Lowest Observed Adverse Effect Levels (LOAEL) = 26 mg boron/kg bw/day NOAEL = 8.8 mg boron/kg bw/day	Bodyweight reduction, clinical signs of toxicity, testicular atrophy at ≥88 mg boron/kg bw/day. Testicular atrophy in one animal at 26 mg boron/kg bw/day.	Weir (1962)
Boric acid	Rat, 2 year, diet. Doses: equivalent to 0, 5.9, 17.5, 58.5 mg boron/kg bw/day	LOAEL = 58.5 mg boron/kg bw/day NOAEL = 17.5 mg boron/kg bw/day	Bodyweight reduction, clinical signs of toxicity, testicular atrophy and reductions in red cell volume and haemoglobin.	Weir (1966a)
Boric acid	Mouse, 13 weeks, diet. Doses: equivalent to 0, 34, 71, 142,	LOAEL = 142 mg boron)/kg bw/day (males) NOAEL = 71 mg	Extramedullary haematopoiesis of the spleen at all doses (minimal and prevalence within	National Toxicology Program (NTP)

Test substance	Method	Results	Remarks	Reference
	284, 568 mg boron/kg bw/day (males); 0, 47, 98, 196, 392, 784 mg boron/kg bw/day (females).	boron/kg bw/day (males)	historical controls at lowest dose; Degeneration and atrophy of seminiferous tubules at ≥142 mg boron/kg bw/day.	(1987)
Borax	Rat, 30 and 60 days, drinking water. Doses: equivalent to 0, 25, 50, 100 mg boron/kg bw/day.	LOAEL = 25 mg boron/kg bw/day (lowest dose tested)	Decreased epididymal weight in all dose groups after 30 days; Increased plasma FSH and decreased diameter of seminiferous tubules. 60 days: decreased testes and liver weight at ≥50 mg boron/kg bw/day; changes in testicular enzyme activity. 30 - 60 days: testicular atrophy and loss of germinal elements ≥50 mg boron/kg bw/day (60 days >30 days). Changes in testicular enzyme activities ≥50 mg boron/kg bw/day.	Dixon et al. (1979)
Borax	Rat, 2 year, diet. Doses: equivalent to 0, 5.9, 17.5, 58.5 mg boron/kg bw/day.	LOAEL = 58.5 mg boron/kg bw/day NOAEL = 17.5 mg boron/kg bw/day	58.5 mg boron/kg bw/day: decreased bodyweight, clinical signs of toxicity, reductions in red cell volume and haemoglobin; testicular atrophy.	Weir (1966b)

Boric acid and borax induced consistent effects on the testes (decreases in weight and testicular atrophy) and on blood parameters indicative of increased red blood cell destruction. Overall, a NOAEL for effects on the testes and the blood system of 17.5 mg boron/kg bw/day (LOAEL of 58.5 mg boron/kg bw/day) was derived from two 2-year studies of boric acid and borax in rats (Weir 1996a; Weir 1996b; RIVM 2013). These NOAELs were the equivalent of 100 mg boric acid/kg bw/day and 155 mg borax/kg bw/day. Similar effects were observed in dogs (Weir and Fisher 1972, data not tabled).

1.6.5.2 Dermal

No data were available.

1.6.5.3 Inhalation

No data were available.

1.6.5.4 Observation in humans

In addition to numerous acute poisoning incidents with boric acid described under Section A1.6.2, some data were available on effects from repeated doses of boric acid or borax as treatments for medical conditions. Multiple exposures via the oral and dermal routes result in a variety of symptoms including dermatitis, alopecia, loss of appetite, nausea,

vomiting, diarrhoea and focal or generalised CNS effects or convulsions (ECHA 2009; RIVM 2013).

1.6.6 *Genotoxicity*

In vitro genotoxicity studies of boric acid include:

- a bacterial reverse mutation test with *Salmonella typhimurium*
- *in vitro* mammalian cell gene mutation tests with mouse lymphoma cells
- an *in vitro* mammalian chromosome aberration test in Chinese hamster ovary cells.

All studies were negative (ECHA 2009; RIVM 2013).

Similarly, one *in vivo* mouse bone marrow micronucleus test with boric acid concluded that boric acid did not induce chromosome aberrations (ECHA 2009; RIVM 2013).

No studies were available for disodium octaborate anhydrate or borax. A comet assay in workers exposed to boron showed no correlation between blood boron levels and DNA strand breaks in sperm (ECHA 2009; RIVM 2013).

Overall, it was concluded that boric acid is unlikely to be genotoxic.

1.6.7 *Carcinogenicity*

In two-year dietary studies on boric acid and borax in rats (Weir 1966a; Weir 1966b) (described under Section A1.6.5) no signs of carcinogenicity were observed. It has been noted that less than one third of treated animals (10 animals per sex) were used for macroscopic and histopathological examination in these studies (ECHA 2009; RIVM 2013).

In a subsequent two-year dietary carcinogenicity study of boric acid in mice, animals received 0, 446 or 1150 mg boric acid (0, 75 or 200 mg boron)/kg bw /day (NTP 1987). High-dose males showed testicular atrophy and interstitial cell hyperplasia. No signs of carcinogenicity were observed.

No data were available for disodium octaborate anhydrate.

1.6.8 *Reproductive toxicity*

The following key rodent data (Table A1.5) on fertility and developmental toxicity of boric acid and borax were summarised from WHO (1998), ECHA (2009) and RIVM (2013). No studies specifically investigating the effects on fertility were reported. However, effects on the male reproductive organs in rats were reported in repeated dose toxicity studies (see Table A1.5).

No studies were found for disodium octaborate anhydrate.

Table A1.5 Reproductive toxicity studies

Test substance	Method	Results	Remarks	Reference
Boric acid	Mouse, 13 weeks, diet. Doses: equivalent to 0, 34, 71, 142, 284, 568 mg	LOAEL = 142 mg boron)/kg bw/day (males) NOAEL = 71 mg boron/kg bw/day	Degeneration and atrophy of seminiferous tubules at ≥142 mg boron/kg bw/day	NTP (1987)

Test substance	Method	Results	Remarks	Reference
	boron/kg bw/day (males); 0, 47, 98, 196, 392, 784 mg boron/kg bw/day (females)	(males)		
Boric acid	Rat, 2 year, diet. Doses: equivalent to 0, 5.9, 17.5, 58.5 mg boron/kg bw/day.	LOAEL = 58.5 mg boron/kg bw/day NOAEL = 17.5 mg boron/kg bw/day	Testicular atrophy at 58.5 mg boron/kg bw/day	Weir (1966a)
Borax	Rat, 30 and 60 day, drinking water. Doses: equivalent to 0, 25, 50, 100 mg boron/kg bw/day.	LOAEL = 25 mg boron/kg bw/day (lowest dose tested)	Decreased epididymal weight in all dose groups after 30 days; Increased plasma FSH and decreased diameter of seminiferous tubules; 60 days: decreased testes and liver weight at ≥50 mg boron/kg bw/day; changes in testicular enzyme activity. 30 - 60 days: testicular atrophy and loss of germinal elements ≥50 mg boron/kg bw/day (60 days >30 days); Changes in testicular enzyme activities ≥50 mg boron/kg bw/day.	Dixon et al. (1979)
Borax	Rat, 2 year, diet. Doses: equivalent to 0, 5.9, 17.5, 58.5 mg boron/kg bw/day.	LOAEL = 58.5 mg boron/kg bw/day NOAEL = 17.5 mg boron/kg bw/day	Testicular atrophy and seminiferous tubule degeneration at 58.5 mg boron/kg bw/day.	Weir (1966b)
Boric acid	Rat, prenatal developmental toxicity study (compliant with OECD TG 414)	Dams: NOAEL = 25 mg boron/kg bw/day. Foetuses: NOAEL = 9.6 mg boron/kg bw/day.	Dams: no toxicity. Foetuses: at 13.3 mg boron/kg bw d, reduced bodyweight, short 13th rib, wavy rib; not seen postnatally.	Price et al. (1996a)
Boric acid	Rabbit prenatal developmental toxicity study (compliant with OECD TG 414)	Dams: NOAEL = 21.8 mg boron/kg bw/day. Foetuses: NOAEL = 21.8 mg boron/kg	Dams: at 43.5 mg boron/kg bw/day, reduced bodyweight and food intake with abortions and resorptions. Foetuses: at 43.5 mg boron/kg bw/day,	Price et al. (1996b)

Test substance	Method	Results	Remarks	Reference
		bw/day.	resorptions and cardiovascular malformations	

Studies of reproductive toxicity and repeated dose toxicity of boric acid and borax in mice, rats and dogs (data not tabled), indicate that boron impairs fertility through effects on the testes (ATSDR 2010; WHO 1998). Based on data from the two-year feeding studies with boric acid and borax in rats, the overall NOAEL for fertility is 17.5 mg boron/kg bw/day (equivalent to 100 mg boric acid/kg bw/day and 155 mg borax/kg bw/day). The LOAEL was 58.5 mg boron/kg bw/day.

Developmental toxicity (malformations) was observed in studies in mice, rats and rabbits (Table 5). The rat was the most sensitive species. There was no information to suggest that developmental effects were secondary to other toxic effects or to exposures via lactation. The NOAEL for developmental effects was 9.6 mg boron/kg bw/day (equivalent to 55 mg boric acid/kg bw/day. The LOAEL was 13.3 mg boron/kg bw/day.

1.6.9 *Other health effects*

No additional health effects were identified.

1.7 Health hazard summary

1.7.1 *Critical health effects*

Toxicity testing has been conducted on several borate compounds. In physiological conditions, aqueous solutions of simple borates will exist predominantly as un-dissociated boric acid. Therefore, the chemical and toxicological properties of boric acid, disodium octaborate anhydrate and borax are expected to be similar on a mol boron/L equivalent basis when dissolved in water or biological fluids at the same pH and low concentration. Accordingly, reading across toxicity testing results between these borate species and from other similar borate species differing only in extent of hydration was applied and testing results were expressed as boron equivalents.

Borates were found to be of low acute toxicity and low skin irritation potential. Mild eye irritation observed in animal studies may be due to the crystalline nature of the compounds tested. In inhalation testing in animals, borates were found to be sensory irritants. Sensory irritation from inhalation of borates has also been documented in humans. Borates were shown not to be skin sensitisers, genotoxic or carcinogenic.

Repeated exposures to boron as boric acid and borax induced effects on fertility (testes), development and the blood system. The NOAEL for effects on fertility and the blood system was 17.5 mg boron/kg bw/day with a LOAEL of 58.5 mg boron/kg bw/day. This NOAEL was the equivalent of 100 mg boric acid/kg bw/day, 69 mg disodium octaborate anhydrate/kg bw/day and 155 mg borax/kg bw/day.

The most sensitive endpoint was effect on development with a NOAEL of 9.6 mg boron/kg bw/day. The LOAEL was 13.3 mg boron/kg bw/day. This NOAEL was the equivalent of 55 mg boric acid/kg bw/day, 38 mg disodium octaborate anhydrate/kg bw/day and 85 mg borax/kg bw/day.

1.7.2 *Hazard classification*

This hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) for boric acid and borax. The listings below do not consider physical or environmental hazards. The chemicals are recommended by NICNAS to Safe Work Australia for classification under the adopted Globally Harmonised System (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) (Table A1.6). These NICNAS recommendations do not consider physical or environmental hazards.

Table A1.6 Hazard classification recommended by NICNAS to Safe Work Australia for boric acid and borax

	GHS[a] classification
Boric acid Reproductive toxicity	May damage fertility. May damage the unborn child - Cat. 1B (H360FD)
Borax Reproductive toxicity	May damage fertility. May damage the unborn child - Cat. 1B (H360FD)

[a] *Globally Harmonised System (UNECE 2009)*

Disodium octaborate anhydrate is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria and adopted GHS (Table A1.7). These NICNAS recommendations do not consider physical or environmental hazards.

Table A1.7 Hazard classification recommended by NICNAS to Safe Work Australia for disodium octaborate anhydrate

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Reproductive toxicity	Repr. Cat. 2; May impair fertility (T; R60) Repr. Cat, 2; May cause harm to the unborn child (T; R61)	May damage fertility. May damage the unborn child - Cat. 1B (H360FD)

[a] *Approved Criteria for Classifying Hazardous Substances (NOHSC 2004);* [b] *Globally Harmonised System (UNECE 2009)*

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A2 Calcium chloride

CAS No.	CAS Name
10043-52-4	Calcium chloride ($CaCl_2$)

2.1 Chemical identity

The information on chemical identity was obtained from ChemID*plus* (2012) and the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier of the chemical (REACH 2013). Details of the chemical identity are provided in Table A2.1.

Table A2.1 Chemical identity

	Calcium chloride
Synonyms	Calcium chloride anhydrous Calcium dichloride
Structural Formula	Cl—Ca—Cl
Molecular formula	$CaCl_2$
Molecular weight	110.98
Appearance and odour	Odourless white powder
SMILES notation	[Ca]{2+}_Cl{-}_Cl{-}

2.2 Physical properties

The following physical properties were obtained from OECD (2002). Details are provided in Table A2.2.

Table A2.2 Physical Properties

Property	**Value**
Melting point	772 °C
Boiling point	>1600 °C
Density	2.16 g/cm^3 at 25 °C
Vapour pressure	Negligible
Water solubility	745 g/L at 20 °C

Calcium chloride is an inorganic salt with hygroscopic and deliquescent properties that readily dissociates in water to calcium and chloride ions.

2.3 Current regulatory controls

2.3.1 *Hazard classification for occupational health and safety*

The chemical is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) with the following risk phrase:

- Xi; R36 (Irritating to eyes)

Mixtures containing calcium chloride are classified as hazardous based on the concentration (Conc) of the chemical in the mixtures. The risk phrase is:

- Conc ≥20%: Xi; R36

2.3.2 *Occupational exposure standards*

2.3.2.1 Australia

There are no specific exposure standards for this chemical. However, the permissible exposure limits for dusts apply (10 mg/m^3 Time Weighted Average [TWA] measured as inspirable dust) (Safe Work Australia 2013).

2.3.2.2 International

There are no specific exposure standards for this chemical. However, the following exposure standards (TWA) for particulates are identified (Galleria Chemica 2013):

- 10 mg/m^3 [Canada, Ireland, Spain]
- 5 mg/m^3 [US]
- 2 mg/m^3 [Latvia].

2.3.3 *Australian food standards*

The Australian and New Zealand Food Standards Code Standard 1.3.1 provides an upper limit on calcium chloride in foods for infants of 750 mg/kg (Food Standards Australia New Zealand 2013).

2.3.4 *Australian drinking water guidelines*

The *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011) state that based on aesthetic considerations, the chloride concentration in drinking water should not exceed 250 mg/L. No health-based guideline value has been proposed for chloride concentration.

2.3.5 *Additional controls*

2.3.5.1 Australia

No additional controls were identified.

2.3.5.2 International

No additional controls were identified.

Calcium chloride was evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) to be a food substance of very low toxicity not requiring the establishment of an

acceptable daily intake (ADI) (JECFA 1974; JECFA 2001). It has also been considered as a Generally-Recognised-As-Safe (GRAS) substance by the US Food and Drug Administration (SCOGS 1975).

2.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

2.5 Health hazard characterisation

The following health hazard information is derived from an Organisation for Economic Co-operation and Development (OECD) SIDS Initial Assessment Report on calcium chloride (OECD 2002) and a Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier (REACH 2013).

2.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

Calcium chloride readily dissociates in water to calcium and chloride ions. Once absorbed, the calcium and chloride ions are regulated separately and health effects in animals are attributable to either or both ions (OECD 2002). Calcium and chloride toxicokinetics have been well reviewed in standard textbooks.

2.5.1.1 Oral absorption

Calcium chloride is of low molecular weight and high water solubility. It readily dissociates in water to calcium and chloride ions. Calcium and chloride ions are absorbed efficiently from the intestine (OECD 2002).

For human risk assessment purposes, an oral absorption of 100% is assumed.

2.5.1.2 Dermal absorption

No data were available on dermal absorption of calcium chloride. Absorption of ionic salts by the skin is essentially negligible (Schaefer and Redelmeier 1996). Calcium chloride is not expected to be absorbed from the skin and be systemically available.

2.5.1.3 Inhalation absorption

Reliable information on inhalation absorption of calcium chloride is not available. For human risk assessment purposes, an inhalation absorption of 100% is therefore assumed.

2.5.1.4 Distribution

Calcium and chloride ions are essential body constituents in all animal species (OECD 2002). Calcium is the most abundant inorganic constituent of all animal species with most of its content located in the skeleton. It is an essential ion for formation and maintenance of bone and teeth, and for regulation of several important physiological functions such as blood coagulation, neuromuscular activity, enzyme activity and regulation of acid-base balance. Hormonal systems regulate plasma calcium concentrations at approximately 100 µg/mL by controlling intestinal absorption of dietary calcium, release from bone and renal absorption/excretion.

Chloride is the most abundant anion in animals and is important for maintenance of osmotic and acid-base balance (OECD 2002). In the body, most chloride is located in extracellular fluids. Plasma concentrations are maintained at 3.6 to 3.9 mg/mL.

2.5.1.5 Metabolism

No data were available.

2.5.1.6 Excretion

Excess calcium is excreted in the urine via glomerular filtration (OECD 2002). The renal tubules are able to excrete as well as reabsorb calcium. A significant increase in the calcium concentration in plasma will only occur after high calcium intake in conjunction with other disorders such as renal insufficiency or primary hyperthyroidism. Chloride is excreted from the renal tubules by active transport systems as well as by passive diffusion.

2.5.2 *Acute toxicity*

2.5.2.1 Oral

The acute toxicity of calcium chloride has been reported in several studies summarised below (Table A2.3). The acute oral lethal median doses (LD50s) are also indicated for males and females. Values for oral LD50 range from 2 120 to 3798 (male) and 2361 to 4179 (female) mg/kg bw in rats to 2 045 (male) and 1 940 (female) mg/kg bw in mice. LD50 values in rabbits were 500 to 1 000 mg/kg bw.

Table A2.3 Acute oral toxicity studies for males (M) and females (F)

Species	Substance form	Vehicle	LD50 (mg/kg bw)	Reference
Rat, Wistar	Anhydride powder	5% Arabic gum	3798(M)-4179(F)	Akatsuka, Hashimoto and Takeuchi (1977)
Rat, Crj:CD(SD)	Solid (chips)	Water	2120(M)- 2361(F)	REACH (2013)
Mouse, ICR-SLC	Anhydride powder	5% Arabic gum	2045(M)-1940F	Akatsuka, Hashimoto and Takeuchi (1977)
Rabbit, New Zealand White (NZW)	33% solution	Gelatin capsule	500-1000(M)	Koopman and Pot (1986a)
Rabbit, NZW	Dihydrate powder	Water	1000(M)	Koopman and Pot (1986b)
Rabbit, NZW	Hexahydrate powder	Gelatin capsule	755(M)	Koopman and Pot (1986c)
Rabbit, NZW	Hexahydrate powder	Gelatin capsule	507(M)	Koopman and Pot (1986d)

2.5.2.2 Dermal

A study on acute dermal toxicity was conducted in male/female rabbits (Carreon et al. 1981). No animal deaths were observed at 5000 mg/kg bw, indicating that the dermal LD50 for male/female rabbits is >5000 mg/kg bw. No adverse effects were observed following treatment. No significant change was found either at gross necropsy examination or at the site of application except for some skin lesions (see Section A2.5.3.1 below).

2.5.2.3 Inhalation

An acute inhalation toxicity study in rats has been reported (Sukhanov et al. 1990). However, the reliability of this study is questioned due to insufficient information on methodology. Animals were exposed to 40 and 160 mg/m^3 calcium chloride for 4 hours. Signs of irritation of the trachea were observed in the animals. No deaths were reported.

There are insufficient data to reliably determine acute inhalation toxicity.

2.5.2.4 Observation in humans

Cases of gastrointestinal lesions including death have been described from single gavage administration of 3 to 4 g of calcium chloride in water in newborn babies as a treatment for tetany (Durlacher et al. 1946).

2.5.3 *Irritation / Corrosivity*

2.5.3.1 Skin irritation

In studies conducted to OECD or national test guidelines, no or only slight skin irritation was observed in rabbits from 4-hour exposures to either one of anhydride powder, 33% solution, dihydrate powder or hexahydrate powder (Norris 1971a, 1971b; Koopman and Pot 1986e-h). Exposure of rabbits for 24 hours to anhydride powder, dihydrate powder or 38% solution caused slight to moderate irritation on intact skin (Norris 1971a, 1971b; Carreon et al. 1981) and more severe irritation on abraded skin (Norris 1971a, 1971b).

2.5.3.2 Eye irritation

In studies conducted to OECD or national test guidelines, severe irritation to eyes of rabbits was observed with several forms of calcium chloride (anhydride, dihydrate, tetrahydrate and hexahydrate powders, and 33% and 38% solutions) (Norris 1971a, 1971b; Koopman and Pot 1986i-l).

2.5.3.3 Respiratory irritation

No data were available. However, signs of irritation of the trachea observed in animals in an acute inhalation study (Sukhanov et al. 1990) indicate that calcium chloride is likely to be a respiratory irritant.

2.5.3.4 Observation in humans

No data were available.

2.5.4 *Sensitisation*

2.5.4.1 Skin sensitisation

No data were available.

2.5.4.2 Respiratory sensitisation

No data were available.

2.5.4.3 Observation in humans

No data were available.

2.5.5 *Repeat dose toxicity*

2.5.5.1 Oral

In a study which used dose levels sufficiently dissimilar to oral LD50 values and also reported results from autopsy examination, calcium chloride was administered to 40-day-old rats via diet (20 mg calcium chloride /g diet) for 12 months (Pamukcu et al. 1977). No differences in food consumption, weight gain or mortality were observed between test and control animals. From food consumption data (22 g diet/d), the daily intake of calcium chloride was estimated to be 440 mg, corresponding to up to approximately 2000 mg/kg bw/day for young rats.

2.5.5.2 Dermal

No data were available.

2.5.5.3 Inhalation

No data were available.

2.5.5.4 Observation in humans

Cases of skin lesions including necrosis, ulceration and calcinosis have been described from incidental repeated contact with calcium chloride powder or concentrated solutions (Heppleston 1946; Zackheim and Pinkus 1957; Sneddon and Archibald 1958; Botvinick et al. 1961; Saeed et al. 1997).

Following inhalation of calcium chloride aerosols (2 to 5% aqueous solution) as therapy for pulmonary tuberculosis, several patients reported irritation of mucous membranes of the pharynx and throat (Vinnikov et al. 1962).

2.5.6 *Genotoxicity*

Two *in vitro* bacterial genotoxicity studies conducted in a similar fashion to OECD TG 471 were available (Fujita and Sasaki 1987). Doses of calcium chloride up to 5 mg/plate were examined in a *Salmonella* mutation test using TA92, TA94, TA98, TA100, TA1535 and TA1537 with metabolic activation (Ishidate et al. 1984). In another *Salmonella* mutation test, doses up to 10 mg/plate were examined using TA97 and TA102 with or without metabolic activation. No significant increases in mutation frequencies were observed in either study.

Two additional bacterial genotoxicity studies that were not conducted to OECD test guidelines have also been reported. In a *Bacillus subtilis* mutagenicity assay, no DNA damage was reported at calcium chloride concentrations up to 0.5 M (Kanematsu et al. 1980). In *Escherichia coli*, no SOS responses were noted at calcium chloride concentrations up to 1 mM (Olivier and Marzin 1987). The SOS response is a response to DNA damage in which normal cell processes cease and DNA repair and mutagenesis are induced.

An *in vitro* chromosome aberration test comparable to OECD test guidelines using Chinese hamster lung cells (CHL) has also been reported (Ishidate et al. 1984). Cells were exposed to calcium chloride at doses up to 4 mg/mL for 48 h without metabolic activation. No significant increases in polyploid formation or structural chromosome aberration were observed.

2.5.7 *Carcinogenicity*

No data were available, except for a 12-month study in rats in which no neoplastic lesions were observed in the gastrointestinal tract, urinary tract, liver, heart, brain or the spleen of treated animals (Pamukcu et al. 1977).

2.5.8 *Reproductive toxicity*

2.5.8.1 Fertility

No data were available.

2.5.8.2 Developmental toxicity

The effects of calcium chloride on embryo lethality and teratogenicity were studied in mice, rats and rabbits in developmental toxicity studies conducted in a comparable fashion to OECD TG 414 (Food and Drug Research Laboratories 1974). Test conditions are outlined below (Table A2.4).

Table A2.4 Developmental toxicity studies (Food and Drug Research Laboratories 1974)

Species, strain	Number of animals	Vehicle	Doses (mg/kg bw/day)	Period of administration (gestation day)	Caesarian section (gestation day)
Mouse, CD-1	25	Water	1.89, 8.78, 40.8, 189	6-15	17
Rat, Wistar	25	Water	1.76, 8.18, 38.0, 176	6-15	20
Rabbit, Dutch	16-22	Water	1.69, 7.85, 35.6, 169	6-15	29

Positive and negative controls were included. At Caesarian section, numbers of implantation sites, resorption sites and live and dead foetuses were recorded. All foetuses were subject to gross examination, one third was subject to detailed visceral examination and the remainder were assessed for skeletal defects. Calcium chloride had no discernible effect on implantation or on maternal or foetal survival. There were no differences in numbers of abnormalities in soft or skeletal tissues between test and control animals. The studies concluded that calcium chloride up to 189 mg/kg bw/day in the mouse, 176 mg/kg bw/day in the rat and 169 mg/kg bw/day in the rabbit had no developmental toxic effects.

2.5.9 *Other health effects*

No data were available.

2.6 Health hazard summary

2.6.1 *Critical health effects*

The oral and dermal LD50 values for calcium chloride are >2000 mg/kg bw. Calcium chloride is slightly irritating to the skin and severely irritating to the eye. Observations in humans suggest that calcium chloride may be a slight respiratory irritant. It is not a skin sensitiser.

From limited repeat dose data in rats, intakes of up to 2000 mg/kg bw/day via diet were without effect. Calcium chloride is neither genotoxic nor carcinogenic, nor a developmental toxicant.

2.6.2 *Hazard classification*

This hazard assessment confirms the existing hazard classification under the current Approved Criteria for Classifying Hazardous Substances (NOHSC 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A2.5. This recommendation does not consider physical or environmental hazards.

Table A2.5 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Irritation	Eye irritation – Cat. 2 (H319)

**Globally Harmonised System (UNECE 2009)*

2.7 References

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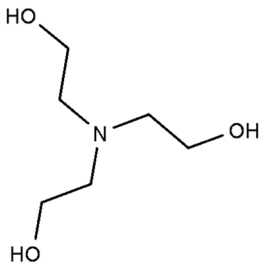
A3 Triethanolamine

CAS No.	CAS Name
102-71-6	Ethanol, 2,2',2''-nitrilotris-

3.1 Chemical identity

The information on chemical identity was obtained from ChemID*plus* (2012) and the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier of the chemical (REACH 2013). Details are provided in Table A3.1.

Table A3.1 Chemical identity

	Triethanolamine
Synonyms	Triethanolamine 2,2',2''-Nitrilotriethanol 2-[Bis(2-hydroxyethyl)amino]ethanol
Structural formula	
Molecular formula	$C_6H_{15}NO_3$
Molecular weight	149.19
Appearance and odour	Clear to slightly yellow liquid with aminic odour
SMILES notation	OCCN(CCO)CCO

3.2 Physical properties

The physical properties of the chemical are presented in Table A3.2. The information was obtained from the Organisation for Economic Cooperation and Development (OECD) (2001) and REACH (2013).

Table A3.2 Physical properties

Property	**Value**
Melting point	17-21.6 °C
Boiling point	153 °C at 0.1007 kPa 192.87 °C at 0.7996 kPa 236.69 °C at 5.01 kPa

Property	Value
	320 °C at 101 kPa
Density	1120 kg/m^3 at 20 °C 1113.6 kg/m^3 at 40 °C
Vapour pressure	1.9 x 10^{-3} at 20 °C 5 x 10^{-6} kPa at 40 °C
Water solubility	>1000 g/L at 20 °C (miscible)
Partition coefficient n-octanol/water (log K_{ow})	-1.9 at 25°C

3.3 Current regulatory controls

The document from now on refers to Ethanol, 2,2',2''-nitrilotris- (CAS No. 102-71-6) as 'triethanolamine', one of the synonyms of the chemical.

3.3.1 *Hazard classification for occupational health and safety*

Triethanolamine is listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) with a recommended Exposure Standard.

3.3.2 *Occupational exposure standards*

3.3.2.1 Australia

The following occupational exposure standard was identified (Safe Work Australia 2013).

- Time Weighted Average (TWA) of 5 mg/m³.

3.3.2.2 International

The following exposure standards (TWA) were identified (Galleria Chemica 2013):

- 5 mg/m³ [Belgium, Finland, Iceland, New Zealand, Peru]
- 0.5 mg/m^3 [Denmark].

3.3.3 *Australian food standards*

Triethanolamine is listed in Standard 1.3.3 of the Australia New Zealand Food Standards Code as a permitted processing aid in bleaching agents, washing and peeling agents, water used as an ingredient in other foods, and miscellaneous functions under the conditions of Good Manufacturing Practice (GMP) (Food Standards Australia New Zealand 2013).

3.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for triethanolamine in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

3.3.5 *Additional controls*

3.3.5.1 Australia

The chemical is listed as a precursor in the manufacture of weapons (Australian Government Foreign Affairs and Trade 1994).

The chemical is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedule 5 with the following entry:

- Schedule 5:
  - TRIETHANOLAMINE (excluding its salts and derivatives) except in preparations containing 5 per cent or less of triethanolamine.

3.3.5.2 International

The Canadian Government indicated that triethanolamine is a precursor chemical and is listed in Schedule 3 (chemicals that can be used for the production of chemical warfare agents but that are produced in large quantities for commercial use) (Foreign Affairs, Trade and Development Canada 1998).

Triethanolamine is a 'Chemical of Interest' according to the United States Department of Homeland Security (US DHS) with a screening threshold quantity (STQ) of 220 pounds (100 kg) (US DHS 2007).

Triethanolamine is classified in accordance with the New Zealand Hazardous Substances and New Organisms (HSNO) regulations as acutely toxic (oral), mildly irritating to the skin and irritating to the eye (New Zealand Environmental Protection Authority 2013).

3.4 Use

The use of triethanolamine in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

3.5 Health hazard characterisation

The following information on health hazards was obtained from OECD (2001) and REACH (2013). Unless otherwise noted, references to individual studies below are taken from these reviews.

3.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

3.5.1.1 Oral absorption

No data were available. The chemical is absorbed in the gastrointestinal tract based on liver and kidney changes observed in repeat oral dose toxicity studies (Section A3.5.5).

For the purposes of risk assessment, 100% oral absorption in humans is assumed.

3.5.1.2 Dermal absorption

In female Fischer 344 rats, following semi-occlusive application of 68 or 276 mg/kg bw radiolabelled [^{14}C]-triethanolamine, 20 to 30% of the applied dose was absorbed after 72 hours (REACH 2013). In C3H mice exposed to [^{14}C]-triethanolamine, 90 to 98% of the radioactivity was absorbed from dermal doses of up to 2000 mg/kg bw triethanolamine (Stott et al. 2000). In another study in C3H mice, dermal absorption was 94.5 and 97.8% after application of 1000 and 2000 mg/kg bw [^{14}C]-triethanolamine (REACH 2013). Approximately 60 to 80% of the radioactivity was absorbed after 72 hours following semi-occlusive applications of 79 or 1120 mg/kg bw [^{14}C]-triethanolamine in female B6C3F1 mice (REACH 2013).

For the purposes of risk assessment, 100% dermal absorption in humans is therefore assumed.

3.5.1.3 Inhalation absorption

No data were available. The chemical is absorbed based on liver and kidney changes observed in repeat inhalation dose toxicity studies (Section A3.5.5.3).

For the purposes of risk assessment, 100% inhalation absorption in humans is therefore assumed.

3.5.1.4 Distribution

Intravenous administration of 3 mg/kg bw [^{14}C]-triethanolamine to Fischer 344 rats resulted in 0.9% of the dose being present in the tissues 72 hours after dosing (REACH 2013). In another intravenous administration study, radioactivity was present in the heart, liver, kidney, lung and spleen of female B6C3F1 mice given 3 mg/kg bw [^{14}C]-triethanolamine (REACH 2013).

3.5.1.5 Metabolism

Triethanolamine as the parent compound was recovered after 24 hours in urine and faeces at 53% and 20%, respectively, of the administered dose from oral dosing of 2 to 3 mg/kg bw in rats (strain not specified) (Kohri et al. 1982). An unspecified amount, indicated in the study as ‘small’, of glucoronide conjugate of triethanolamine was also found in the urine. Forty-eight hours following dermal application of 1000 mg/kg [^{14}C]-triethanolamine in mice (strain not specified), approximately 60% and 20% was recovered as the parent compound in the urine and faeces, respectively (Waechter and Rick 1988). Less than 10% of the radioactivity was also recovered at the site of application. Intravenous administration of 3 mg/kg bw [^{14}C]-triethanolamine in Fischer 344 rats reported no change in the metabolic profile of the chemical after 72 hours of dosing (REACH 2013).

3.5.1.6 Excretion

Oral, dermal and intravenous administration of radiolabelled triethanolamine in rodents (REACH 2013; Stott et al. 2000; Kohri et al. 1982; Waechter and Rick 1988) indicated that the chemical is primarily excreted in the urine with up to 98% of the administered dose being excreted within 72 hours.

3.5.2 *Acute toxicity*

3.5.2.1 Oral

Several acute oral toxicity studies were cited in OECD (2001). Eight studies in rats (strain not specified) administered unspecified doses of triethanolamine reported that the acute oral median lethal doses (LD50s) ranged from 4190 to 11 300 mg/kg bw triethanolamine. Two studies in mice (strain not specified), two studies in rabbits (strain not specified), and three studies in guinea pigs (strain not specified) reported acute oral LD50s of 5400 to 7800, 2200 to 5200, and 2200 to 8000 mg/kg bw, respectively. No information on the effects was provided.

The studies demonstrate that triethanolamine has low acute oral toxicity in rodents, rabbits, and guinea pigs.

3.5.2.2 Dermal

Two acute dermal toxicity studies in rabbits (strain not specified) reported acute dermal LD50s of >2000 mg/kg bw (OECD 2001).

The studies demonstrate that triethanolamine has low acute dermal toxicity in rabbits.

3.5.2.3 Inhalation

No data were available that established the acute median lethal concentration (LC50) from acute inhalation toxicity of triethanolamine.

An inhalation risk test in rats (strain not specified) exposed to saturated triethanolamine (concentration not specified) for 8 hours reported no mortality and no clinical signs (REACH 2013).

3.5.2.4 Observation in humans

No data were available.

3.5.3 *Irritation / Corrosivity*

3.5.3.1 Skin irritation

Studies conducted similarly to OECD Test Guideline (TG) 404 reported minimal irritation, based on irritation scores, in Vienna White rabbit skin from application of up to 100% triethanolamine for a maximum of 20 hours' contact (REACH 2013). Several studies cited in OECD (2001) reported triethanolamine as non-irritating to rabbits (strain not specified) at up to 100%. No other details were provided.

The studies demonstrate that triethanolamine is not a skin irritant in rabbits.

3.5.3.2 Eye irritation

Several studies cited in OECD (2001) conducted in rabbits from 1946 to 1982 showed equivocal results on the eye irritancy potential of the chemical. The studies only indicated whether the chemical was not irritating, moderately irritating, irritating or corrosive. No other information was provided.

The REACH Dossier of the chemical presented irritation scores for four eye irritation studies, all conducted similarly to OECD TG 405. Two studies indicated that undiluted

triethanolamine is not irritating to New Zealand White (Griffith et al. 1980) and Vienna White (cited in REACH 2013) rabbits. Based on mean irritation scores, two studies indicated that undiluted triethanolamine is irritating to Vienna White (cited in REACH 2013) and albino (1967 study in REACH 2013) rabbits. Mucosal bleeding was observed in the animals from both studies. The mean irritation scores were 1.08, 1.08, and 1 for redness, chemosis, and corneal opacity, respectively (1966 study with four animals), and 2, 1.75, and 1 to 2 for redness, chemosis, and corneal opacity, respectively (1967 study with two animals). All the effects were reversible after eight days for both studies.

The studies demonstrate that triethanolamine is irritating to the eyes.

3.5.3.3 Respiratory irritation

No data were available. However, in the repeated dose inhalation studies (see section A 3.5.5.3), minimal to slight acute inflammation of the larynx was observed in rats and mice (NTP 1985a, 1985b). In a more recent 28-day inhalation study, minimal to moderate focal inflammation in the submucosa of the larynx was observed in rats (Gamer et al. 2008).

On the basis of these studies, triethanolamine is considered to be a respiratory irritant.

3.5.3.4 Observation in humans

Slight erythema was observed at the start of a study of one of six individuals on semi-occlusive application of triethanolamine for 24 hours (BASF AG 1930). After patch removal, no signs of irritation were seen in any of the individuals. The concentration of the chemical was not specified in this study (BASF AG 1930). No skin reactions were reported in five individuals following application of 50% triethanolamine in olive oil (BASF AG 1934).

The Cosmetic Ingredient Review (CIR) (2011) reported that, in clinical provocative tests using 5 to 10 ‘hyperreactors’ 100% triethanolamine produced an irritant reaction on non-scarified skin, 10% triethanolamine was a marked irritant on scarified skin and 5% triethanolamine in ethanol was slightly irritating to scarified skin.

The New Zealand Environmental Protection Authority (NZ EPA) reported a study (referenced as ICI Chemicals and Polymers Limited Runcorn, Cheshire) on 50 healthy volunteers, in whom increasing concentrations of the chemical were applied for 48 hours (NZ EPA 2013). The highest non-irritant concentration of the chemical from evaluation of skin reactions at 48 and 72 hours after patch removal was stated as 50% triethanolamine.

Based on the available data from human studies, the chemical is considered a skin irritant.

3.5.4 *Sensitisation*

3.5.4.1 Skin sensitisation

Triethanolamine, applied undiluted during induction and at a 10% concentration during the challenge phase, was negative for skin sensitisation in a well-documented guinea pig maximisation test conducted in accordance with OECD TG 406 (REACH 2013). Unpublished studies from various companies cited in OECD (2001) reported the chemical (unspecified concentrations) as negative for skin sensitisation in guinea pig patch tests. No other details were provided.

The studies demonstrate that triethanolamine is not a skin sensitiser.

3.5.4.2 Respiratory sensitisation

No data were available.

3.5.4.3 Observation in humans

Triethanolamine, at 1% concentration in an unknown vehicle, was not sensitising to 64 individuals following semi-occlusive application (induction and challenge patch testing) in the upper arm for three weeks (OECD 2001). Positive results were reported in 41of 1357 patients with eczematous contact dermatitis symptoms on patch testing with triethanolamine and its compounds (specific compounds and concentrations not indicated) (Scheuer 1983). However, 29 out of the 41 patients used topical anti-inflammatory medications which may have contributed to the sensitisation to the chemical.

3.5.5 *Repeat dose toxicity*

3.5.5.1 Oral

Fischer 344 rats and B6C3F1 mice were administered 0, 500, 1000, 2000, 4000 or 8000 mg/100 mL triethanolamine in drinking water (NTP 1990). Water consumption was reduced at the top two doses. No other details were provided.

In a 91-day study conducted in accordance with OECD TG 408, Cox CD rats were administered 88.5% triethanolamine in the diet at doses of 0, 250, 500 or 1000 mg/kg bw/day (REACH 2013). There were no significant dose-dependent changes in bodyweight, organ weight, histopathology, pathology and haematology. No Lowest Observed Adverse Effect Level (LOAEL) or No Observed Adverse Effect Level (NOAEL) can be established for this study.

In a 90-day study, rats (strain not specified) were administered doses of 5 to 2610 mg/kg bw/day triethanolamine in the diet (Smyth et al. 1951). The study reported microscopic lesions and mortality at doses of 730 mg/kg bw/day and above. The authors indicated the NOAEL as 80 mg/kg bw/day. No other details were provided.

In 60- and 120-day studies in rats (strain not specified) given 200 to 1800 mg/kg bw/day triethanolamine, effects observed included liver changes at all treatment doses after 60 and 120 days administration, kidney changes at 400 mg/kg bw/day after 60 and 120 days administration, and kidney damage at >800 mg/kg bw/day after 60 and 120 days administration (Kindsvatter 1940). The specific changes in the liver and kidney were not described. No other details were provided. The LOAEL for this study was 200 mg/kg bw/day.

3.5.5.2 Dermal

The key animal data on repeat dermal dose toxicity of triethanolamine are summarised from OECD (2001) and REACH (2013) and presented in Table A3.3. The LOAELs and NOAELs are indicated for each study.

Table A3.3 Repeat dermal toxicity studies with triethanolamine

Species	Duration Doses	Results	Remarks	Reference
Fischer 344 rats	14 days 0, 140, 280, 560, 1130 or	LOAEL and NOAEL cannot be established.	Necrotising inflammation of the skin at site of application. No other details provided.	NTP (1990)

Species	Duration Doses	Results	Remarks	Reference
	2250 mg/kg bw/day			
Rats (strain not specified)	16 days 100-2000 mg/kg bw/day	LOAEL and NOAEL cannot be established.	Study reported no overt signs of toxicity. No other details provided.	Melnick et al. (1988)
Fischer 344 rats	90 days (similar to OECD TG 411) 0, 125, 250, 500, 1000 or 2000 mg/kg bw/day	LOAEL = 250 (m) and 500 (f) mg/kg bw/day NOAEL = 125 (m) and 250 (f) mg/kg bw/day	Systemic effects observed included 32.8% ↓bodyweight gain in males at 2000 mg/kg bw/day, >20% ↓bodyweight gain in females at 1000 and 2000 mg/kg bw/day, significant changes in organ to bodyweight ratios (↑kidney at ≥250 mg/kg bw/day in males and ≥1000 mg/kg bw/day in females, ↑spleen at ≥1000 mg/kg bw/day in males, ↑thymus at 2000 mg/kg bw/day in males, ↑liver at 500 and 1000 mg/kg bw/day in males, ↑testes at 2000 mg/kg bw/day, and ↑epididymis at 2000 mg/kg bw/day in males), and clinical chemistry and urine protein changes in males at ≥250 mg/kg bw/day and in females at ≥500 mg/kg bw/day. Treatment-related local effects included inflammation and acanthosis at the site of application seen at ≥250 in males and ≥500 mg/kg bw/day in females.	REACH (2013)
C3H mice	14 days 1, 2.5, 5, 10, 25, 50 or 100%	No systemic LOAEL and NOAEL. LOAEL and NOAEL for local effects are 25 and 10%, respectively.	No clinical signs observed. Mild epidermal hyperplasia at 25% and above.	Union Carbide (1984a)
B6C3F1 mice	14 days 0, 210, 430, 840, 1690 or 3370 mg/kg bw/day	LOAEL and NOAEL cannot be established.	Necrotising inflammation of the skin at application site. No other details provided.	NTP (1990)
Mice (strain not specified)	16 days 200-3000 mg/kg bw/day	LOAEL and NOAEL cannot be established.	No overt signs of toxicity. No other details provided.	Melnick et al. (1988)
C3H mice	90 days 0, 10. 33 or 100%	LOAEL and NOAEL cannot be established.	No clinical signs observed. Mild epidermal hyperplasia in all treatment groups.	Union Carbide (1984b)

Species	Duration Doses	Results	Remarks	Reference
B6C3F1 mice	90 days (similar to OECD TG 411) 0, 250, 500, 1000, 2000 or 4000 mg/kg bw/day	LOAEL = 250 mg/kg bw/day (m, f) NOAEL cannot be established.	Systemic effects observed included significant changes in organ to bodyweight ratios (↑liver at 250 and 2000 mg/kg bw/day in males and at 4000 mg/kg bw/day in females, ↑right kidney at ≥2000 mg/kg bw/day in males and at 250 and 2000 mg/kg bw/day in females, ↑thymus at 2000 mg/kg bw/day in females, ↑heart at 4000 mg/kg bw/day in both sexes), clinical chemistry changes in females at 1000 and 2000 mg/kg bw/day. Inflammation of treated skin seen in all treatment groups.	REACH (2013)
Guinea pigs (strain not specified)	17 days 8000 mg/kg bw/day	LOAEL and NOAEL cannot be established.	Mortality reported within 2 days of application with damage to kidney, liver, lungs and adrenal glands.	Kindsvatter (1940)

↑ = increased; ↓ = decreased; m = males; f = females

Repeated dermal dose toxicity with triethanolamine application was consistently associated with inflammation at the treatment site. Systemic effects included changes in bodyweight and organ to bodyweight ratios. The critical study for determining the effects of repeated dermal exposures to the chemical is the 90-day study cited in REACH (2013) conducted similarly to OECD TG 411. The NOAELs for this study are 125 mg/kg bw/day for males and 250 mg/kg bw/day for females.

3.5.5.3 Inhalation

Fischer 344 rats were exposed to 0, 125, 250, 500, 1000 or 2000 mg/m^3 triethanolamine for 16 days (NTP 1985b). The effects observed included decreased bodyweight at 2000 mg/m^3 for both sexes, increased liver weight in males at 2000 mg/m^3, increased kidney weight in males at concentrations ≥500 mg/m^3, and increased kidney weight in females at concentrations ≥250 mg/m^3. Minimal to slight acute inflammation of the larynx was reported but the doses for which this effect was seen were not specified. The Lowest Observed Adverse Effect Concentrations (LOAECs) are 500 mg/m^3 in males and 250 mg/m^3 in females. The No Observed Adverse Effect Concentrations (NOAECs) are 250 and 125 mg/m^3 in males and females, respectively.

Wistar rats were exposed through the head and nose to 0, 0.02, 0.1 or 0.5 mg/L aerosolised triethanolamine in a 28-day study conducted in accordance with OECD TG 412 (Gamer et al., 2008). There were no treatment-related effects seen on bodyweight, haematology, clinical chemistry and neurobehavioural parameters. Local effects, such as minimal to moderate focal inflammation in the submucosa of the larynx region, were reported at all treatment concentrations. The LOAEC and NOAEC for systemic effects cannot be established. The LOAEC for local effects is 0.02 mg/L.

B6C3F1 mice exposed to 0, 125, 250, 500, 1000 or 2000 mg/m^3 triethanolamine for 14 days showed minimal acute inflammation of the laryngeal submucosa (NTP 1985a). The doses for which this effect was seen were not specified.

3.5.5.4 Observation in humans

No data were available.

3.5.6 *Genotoxicity*

The chemical was negative with and without metabolic activation in a number of *in vitro* studies such as the bacterial reverse mutation, chromosome aberration in Chinese hamster ovary cells, mammalian cell gene mutation, and unscheduled deoxyribonucleic acid (DNA) synthesis (OECD 2001; REACH 2013).

One *in vivo* study showed that the chemical was negative for the induction of sex-linked recessive mutation (OECD 2001).

Triethanolamine is not considered to be genotoxic based on the available data.

3.5.7 *Carcinogenicity*

Animal data on carcinogenicity of triethanolamine are summarised from OECD (2001) and REACH (2013), and presented in Table A3.4.

Table A3.4 Carcinogenicity studies with triethanolamine

Species Method	Doses	Effects	Reference
Fischer 344 rats Two-year dermal application (similar to OECD TG 451)	0, 32, 63 or 125 mg/kg bw/day (m); 0, 63, 125 or 250 mg/kg bw/day (f)	At the interim evaluation period of 15 months and at the end of the study, dermal effects at the site of application included increased incidence of acanthosis at the top dose in males, increased incidence of acanthosis, inflammation, ulceration and erosion at the mid- and top doses in females. There were no treatment-related changes in the incidence of tumours in the kidney, thyroid gland, uterus and pituitary gland.	1999 study cited in REACH (2013)
Fischer 344 rats Two-year drinking water study	0, 500 or 1000 mg/kg bw/day	No significant increase in primary tumour incidences. There was an observed positive trend in hepatic neoplasms in males and uterine endometrial sarcomas and renal cell adenomas in females.	Maekawa et al. (1986)
Fischer 344 rats Two-year drinking water study	0, 333, 667 or 1333 mg/kg bw/day	No significant increase in tumour incidences compared to controls. Increase in nephrotoxicity was seen in both sexes which may have affected the life expectancy of the animals. Mineralisation of the renal papilla, nodular hyperplasia of the pelvic mucosa and pyelonephritis were also reported. The doses for which the effects were observed were not specified.	1986 study cited in REACH (2013)
B6C3F1 mice 82-week drinking water study	0, 1 or 2%	Neoplasms were reported for all animals, including controls, there was no dose-related increase of the tumour incidences. No other information provided.	Konishi et al. (1992)

Species Method	Doses	Effects	Reference
C3H mice 78-week dermal application	0 or 22%	Increase, not statistically significant, in proliferative liver lesions compared to controls. No other information provided.	Borriston Lab (1982)
B6C3F1 mice Two-year dermal application (similar to OECD TG 451)	0, 200, 630 or 2000 mg/kg bw/day (m); 0, 100, 300 or 1000 mg/kg bw/day (f)	Skin irritation with visible crusts at the site of application was observed at all doses for both sexes. Carcinogenic activity, such as increased incidence of hepatocellular adenoma and carcinoma, was seen, a dose-dependent trend was not observed in the study.	2004 study cited in REACH (2013)
ICL-ICR mice Lifetime dietary study	0, 40 or 450 mg/kg bw/day	Significant increase in total incidence of lymphomas in females only but no correlation between doses and time for the first tumour to appear. However, the control mice did not present spontaneous tumours expected for this mice strain based on historical control data.	Hoshino and Tanooka (1978)

m = males; f = females

The animal studies show that triethanolamine is not carcinogenic.

The International Agency for Research on Cancer (IARC) concluded that there is inadequate evidence for the carcinogenicity of triethanolamine in experimental animals and humans. Triethanolamine is listed in Group 3 (Not classifiable as to its carcinogenicity in humans) (IARC 2000).

3.5.8 *Reproductive toxicity*

3.5.8.1 Fertility

In a reproduction/developmental toxicity screening test conducted in accordance with OECD TG 421, Wistar rats were administered 0, 100, 300 or 1000 mg/kg bw/day triethanolamine by gavage (REACH 2013). The animals were treated during pre-mating (two weeks for both sexes), mating (maximum of two weeks for both sexes), post-mating (one week in males), and the entire gestation period and four days of lactation in females. There were no parental systemic effects reported in all of the treated animals. Most of the animals treated at the top dose showed transient salivation, which could be attributed to the unpalatability of the chemical or local irritation of the upper digestive tract. There were no effects on fertility observed in any of the treated animals. The parental LOAEL and NOAEL for local effects are 1000 and 300 mg/kg bw/day, respectively. The LOAEL and NOAEL for fertility cannot be established.

There were no effects observed in the reproductive organs of the animals treated with the chemical from repeated oral, dermal and inhalation toxicity studies previously described (refer to Section A3.5.5).

Based on these results, triethanolamine is not considered to be toxic to fertility.

3.5.8.2 Developmental toxicity

In a previously described reproduction/developmental toxicity screening test (REACH 2013), effects at the top dose included decreased number of implantation sites, increased post-implantation loss and lower average litter size. Local irritant effects for most of the dams were reported at the top dose. The maternal LOAEL and NOAEL for local effects are 1000 and 300 mg/kg bw/day, respectively. The developmental LOAEL and NOAEL are 1000 and 300 mg/kg bw/day, respectively.

A dye formulation containing 0.15, 1.5 or 2% triethanolamine was applied to the shaved skin of CD-1 rats (Burnett et al. 1976). The application occurred seven times during the gestation period. There were no systemic or local effects observed. No developmental effects were reported.

Triethanolamine is not considered to be a developmental toxicant.

3.5.9 *Other health effects*

No data were available.

3.6 Health hazard summary

3.6.1 *Critical health effects*

Triethanolamine has low acute oral and dermal toxicity but may cause eye and respiratory irritation.Triethanolamine was non-irritating to the skin in rabbit studies, whilst studies in humans indicate that the chemical can cause skin irritation. The chemical is not a skin sensitiser.

The most appropriate NOAELs for risk assessment, determined from the 90-day repeat dermal dose toxicity study cited in REACH (2013) are 125 (males) and 250 (females) mg/kg bw/day based on systemic effects.

The chemical is neither genotoxic, carcinogenic nor a reproductive toxicant.

3.6.2 *Hazard classification*

While available data indicate that triethanolamine is not classified as an eye irritant according to the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004), the data meet classification criteria under the adopted Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (UNECE 2009) (Table A3.5).

The chemical is also classified as a skin and respiratory irritant under the current Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) and the adopted GHS(UNECE 2009) as shown in Table A3.5. NICNAS has recommended that Safe Work Australia adopt these hazard classifications. These NICNAS recommendations do not consider physical or environmental hazards.

Table A3.5 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation / Corrosivity	-	Causes serious eye irritation – Cat. 2A (H319)
	Irritating to skin (X_i; R38)	Causes skin irritation – Cat. 2

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
	Irritating to respiratory system (X_i; R37)	(H315) May cause respiratory irritation – Specific target organ toxicity, single exposure – Cat. 3 (H335)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

3.7 References

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A4 Ethylene glycol

CAS No.	CAS Name
107-21-1	1,2-Ethanediol

4.1 Chemical identity

The information on chemical identity was obtained from ChemID*plus* (2012) and OECD (2009). Details are provided in Table A4.1.

Table A4.1 Chemical identity

	Ethylene glycol
Synonyms	Ethylene glycol Glycol Monoethylene glycol
Structural formula	
Molecular formula	$C_2H_6O_2$
Molecular weight	62.07
Appearance and odour	Clear, colourless, odourless liquid
SMILES notation	C(O)CO

4.2 Physical properties

The physical properties of the chemical are presented in Table A4.2. The information was obtained from NTP-CERHR (2004) and OECD (2009).

Table A4.2 Physical properties

Property	**Value**
Melting point	-13 °C
Boiling point	197 °C
Density	1108 kg/m^3 at 20 °C
Vapour pressure	0.0104 kPa at 25 °C
Water solubility	Miscible at 20 °C
Partition coefficient n-octanol/water (log K_{ow})	-1.36
Flash point	111-116 °C

4.3 Current regulatory controls

The document from now on refers to 1,2-Ethanediol (CAS No. 107-21-1) as ethylene glycol, one of the synonyms of the chemical.

4.3.1 *Hazard classification for occupational health and safety*

Ethylene glycol is classified as hazardous for human health in the *Hazardous Substances Information System* (HSIS) (Safe Work Australia 2013) with the following risk phrases:

- X_n (Harmful); R22 (Harmful if swallowed)

Mixtures containing ethylene glycol are classified as hazardous with the following risk phrase based on the concentration (Conc) of the chemical in the mixtures. The risk phrase for this chemical is:

- Conc ≥25%: X_n (Harmful); R22 (Harmful if swallowed)

4.3.2 *Occupational exposure standards*

4.3.2.1 Australia

a. The following occupational exposure standards were identified (Safe Work Australia 2013).

Time Weighted Average (TWA):

- 52 mg/m³ (20 ppm) (vapour)
- 10 mg/m³ (particulate)

Short-Term Exposure Limit (STEL):

- 104 mg/m³ (40 ppm)

4.3.2.2 International

The following exposure standards were identified (Galleria Chemica 2013):

TWA:

- 52 mg/m³ (20 ppm) [Belgium, Hungary, UK, Finland]
- 26 mg/m³ (10 ppm) [Denmark, Iceland, Sweden]
- 25 to 50 mg/m³ (63 to 125 ppm) [Mexico, Norway]
- 5 mg/m³ [Russia]

STEL:

- 20 to 40 mg/m³ (50 to 104 ppm) [Belgium, Hungary, UK, Finland, Peru, Sweden]
- 10 mg/m³ [Russia]

4.3.3 *Australian food standards*

No Australian food standards relating to ethylene glycol were identified.

4.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for ethylene glycol in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

4.3.5 *Additional controls*

4.3.5.1 Australia

The chemical is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedules 5 and 6, and Appendix C with the following entries:

- Schedule 5: ETHYLENE GLYCOL (excluding salts and derivatives) in preparations containing not less than 10 mg/kg of denatonium benzoate as a bittering agent except:
  - in paints or paint tinters
  - in toothpastes or mouthwashes containing more than 0.25% of ethylene glycol or
  - in other preparations containing 2.5% or less of ethylene glycol.
- Schedule 6: ETHYLENE GLYCOL (excluding salts and derivatives) except:
  - when included in Section 5
  - in paints or paint tinters
  - in toothpastes or mouthwashes containing more than 0.25% of ethylene glycol or
  - in other preparations containing 2.5% or less of ethylene glycol.
- Appendix C: ETHYLENE GLYCOL for use in toothpastes or mouthwashes except in preparations containing 0.25% or less of ethylene glycol.

4.3.5.2 International

Ethylene glycol (and mixtures containing 10% or more by weight) is a hazardous substance under Section 3(b) of the United States Federal Hazardous Substances Act as designated by the Consumer Product Safety Commission (CPSC 2013).

Ethylene glycol is listed as a hazardous substance under Section 102(a) of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), commonly known in the US as Superfund (US EPA 2012b).

Health advisories (HA) exist for ethylene glycol in the United States Drinking Water Standards. The health advisory is 'an estimate of acceptable drinking water levels for a chemical substance based on health effects information' (US EPA 2012a). The one-day and 10-day HAs for a 10 kg child are 20 and 6 mg/L, respectively. The lifetime HA for a 70kg adult is 14 mg/L.

The US Agency for Toxic Substances and Disease Registry (ATSDR) calculated minimal risk levels (MRLs) for ethylene glycol. An MRL is defined as *'an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (non-carcinogenic) over a specified duration of exposure... when reliable and sufficient data exist...*'. The following MRLs were derived for the chemical: 2 mg/m^3 for acute duration

(14 days or less) inhalation exposure; and 0.8 mg/kg bw/day for acute duration (14 days or less) and intermediate duration (15 to 364 days or less) oral exposure (ATSDR 2010).

4.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

4.5 Health hazard characterisation

The information on health hazards is obtained from the following comprehensive reviews of ethylene glycol: WHO (2002), NTP-CERHR (2004), OECD (2009), ATSDR (2010), and Environment Canada/Health Canada (2010). Unless otherwise noted, references to individual studies below are taken from these reviews.

4.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

4.5.1.1 Oral Absorption

Ingested ethylene glycol is rapidly absorbed in rats, reaching peak blood levels within 1 hour after single gavage doses of 150 to 20 000 mg/kg bw (Frantz et al. 1996a; Frantz et al.1996c; Pottenger et al. 2001; Winek et al. 1978). Similar rapid absorption was observed in other animals, with peak blood levels reaching within 1 to 3 hours after gavage exposure in mice, monkeys, dogs, and pregnant rabbits (Carney et al. 2008; Frantz et al. 1996a; Frantz et al. 1996b; Grauer et al. 1987; Hewlett et al. 1989; McChesney et al. 1971). Peak plasma concentrations were observed in rats and mice within 1 to 4 hours, with an absorption rate of 90–100% of the administered dose within 24 hours (Frantz et al. 1996a, 1996b). In addition, after gavage doses of 10 and 1000 mg/kg bw ethylene glycol to these rats and mice, the areas under the ethylene glycol plasma level versus time curves were similar to those observed with equivalent intravenous doses, suggesting near complete absorption of the ingested chemical in rats and mice. Pregnancy does not change the absorption kinetics in rats administered once on gestation day 10, with no difference in the time course and peak plasma concentrations of ethylene glycol between pregnant and non-pregnant Sprague-Dawley rats given 10 or 2500 mg/kg bw by gavage (Pottenger et al. 2001).

Limited reporting indicated the presence of ethylene glycol in human blood (levels from 14.5 to 650 mg/dL) following acute poisonings (Hewlett et al. 1986; Jacobsen et al. 1988). However, the amounts ingested in the events were unknown and may not be useful for estimating the rate of oral absorption in humans.

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

4.5.1.2 Dermal Absorption

In Sprague-Dawley rats exposed to occluded dermal doses of 10 or 1000 mg/kg bw ethylene glycol or 1000 mg/kg bw of a 50% ethylene glycol solution, applied to the thoracic dorsal area after light fur clipping, apparent absorption of 26 to 32% of the administered doses was observed from radioactivity recovered in body tissues, excreta and exhaled air (Frantz et al. 1996b).

Similarly, CD-1 mice treated with 100 or 1000 mg/kg bw ethylene glycol or 1000 mg/kg bw of 50% ethylene glycol showed apparent absorption of 60 to 84% (Frantz et al. 1996b).

In limited dermal absorption information in humans, following occluded application of 0.8 mL ethylene glycol for 4 to 6 hours to the forearm of three volunteers, the appearance of ethylene glycol and glycolic acid levels in serum and urine were assessed. Absorption of 1.0 to 1.3% and an estimated skin permeability constant of 0.000027 cm/hour were reported (Upadhyay et al. 2008).

For the purposes of risk assessment, 100% dermal absorption in humans is therefore assumed.

4.5.1.3 Inhalation absorption

Rats exposed (nose only) to 32 mg/m^3 ethylene glycol vapour for 30 minutes or 184 mg/m^3 ethylene glycol aerosol for 17 minutes showed absorption of between 75% and 85% of the [^{14}C]ethylene glycol radioactivity into the systemic circulation (Marshall and Cheng 1983). It is estimated that 60 to 90% of the inhaled dose was absorbed in this study (NTP-CERHR 2004).

Limited reporting showed that ethylene glycol is absorbed in the human respiratory tract from the detection of glycolic acid in the plasma and urine of two male volunteers after inhaling 0.96 and 1.51 mg/kg bw ethylene glycol vapour (Carstens et al., 2003) with similar results from two other volunteers (Upadhyay et al. 2008). In another study, no increase in serum or urinary levels of ethylene glycol was observed in males exposed to 17 to 49 mg/m^3 ethylene glycol for 30 days (Wills et al. 1974). The NTP-CERHR (2004) stated that the analytical techniques utilised in the serum and urine analysis of ethylene glycol may not have been sufficiently sensitive to detect a difference in the levels.

For the purposes of risk assessment, 100% inhalation absorption in humans is therefore assumed.

4.5.1.4 Distribution

The analysis of tissue, plasma and urine in humans, rats, mice, monkeys and dogs (Carstens et al. 2003; Marshall and Cheng 1983; Jacobsen et al. 1988; Frantz et al. 1996b; Frantz et al. 1996c; McChesney et al. 1971; Carney et al. 1998; Carney et al. 2008) showed that ethylene glycol is readily distributed within total body water.

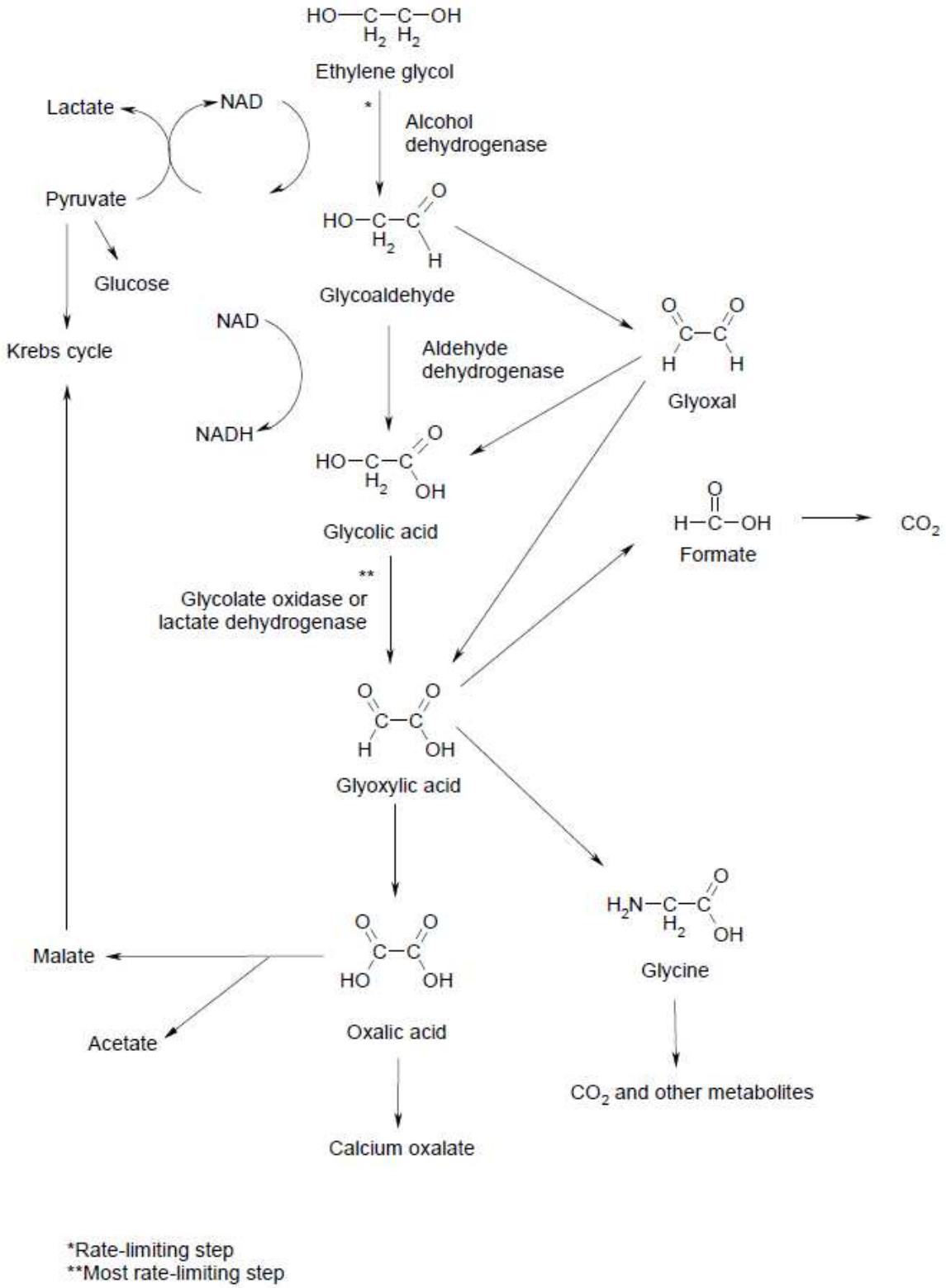
4.5.1.5 Metabolism

Figure A4.1 shows an outline of the metabolic pathway of ethylene glycol that is similar (qualitatively) in humans, monkeys, dogs, rabbits, rats and mice (ATSDR 2010).

The first major metabolic step is the conversion of ethylene glycol to glycoaldehyde by nicotinamide adenine dinucleotide (NAD)-dependent alcohol dehydrogenase (ADH) in a rate-limiting reaction. Glycoaldehyde has a short half-life and is rapidly converted to glycolic acid and to a lesser extent, glyoxal. Because of the fast metabolism of glycoaldehyde, minimal amounts are found in plasma. Glycolic acid is a major metabolite in humans and its potential to accumulate is of toxicological importance (NTP-CERHR 2004).

The second major metabolic step is the oxidation of glycolic acid to glyoxylic acid in a rate limiting reaction (NTP-CERHR 2004). Further metabolism of glyoxylic acid leads to the formation of formate, glycine and oxalic acid. Glycolic acid and oxalic acid have been observed in the blood and urine of unexposed individuals from the normal metabolism of proteins and carbohydrates, with the following ranges of background levels:

0.0044 to 0.0329 mM in plasma and 0.075 to 0.790 mM in urine for glycolic acid; and 0.002 to 0.0233 mM in plasma and 0.086 to 0.444 mM in urine.



Sources: NTP-CERHR (2004); Slikker et al. (2004).

Figure A4.1 Metabolic pathway for Ethylene glycol

In studies in rats, mice and dogs, ethylene glycol and the metabolite glycolic acid have been observed in plasma, urine and / or blood (Frantz et al. 1996b; Frantz et al. 1996c; Hewlett et al. 1989; Rofe et al. 1986; Corley and Soelberg 2005).

In vitro data show that humans could metabolise glycolic acid at a higher rate than rats (Corley et al. 2005; Booth et al. 2004). Clinical reports from poisoning cases showed that glycolic acid is a major metabolite with levels in plasma significantly higher than the parent compound. In addition, *in vivo* data possibly indicate the similarity of the rates of production of glycolic acid between rats and humans (NTP-CERHR 2004).

4.5.1.6 Excretion

The elimination of ethylene glycol from plasma in humans and laboratory animals was found to be rapid following oral exposure. The elimination half-lives in blood ranged from 1 to 4 hours in rats, mice, monkeys and dogs (Frantz et al. 1996a; Frantz et al. 1996b; Pottenger et al. 2001, McChesney et al. 1971; Hewlett et al.1989). In laboratory animals, the main excretion pathways were exhaled air and urine, independent of the exposure route.

Human elimination data of the chemical mostly sourced from cases of accidental poisonings established half-lives in blood ranging from 2.5 to 8.4 hours, and minimal concentrations of the chemical can be detected in urine or tissue after 24 to 48 hours (NTP-CERHR 2004).

4.5.2 *Acute toxicity*

4.5.2.1 Oral

Oral median lethal doses (LD50s) for ethylene glycol were 4000 to 10 020 mg/kg bw in rats, 6610 to 8200 mg/kg bw in guinea pigs, 5500 to 8350 mg/kg bw in mice, 5000 mg/kg bw in rabbits, and >8000 mg/kg bw in dogs (NTP-CERHR 2004; WHO 2002). The minimum lethal oral dose (LD_{min}) in rats was reported to be 3800 mg/kg bw (Clark et al. 1979). The toxicity demonstrated by ethylene glycol included central nervous system depression, metabolic acidosis, cardiopulmonary effects and renal toxicity (NTP-CERHR 2004).

The studies show that ethylene glycol has low acute toxicity by the oral route in rodents, guinea pigs, rabbits and dogs.

4.5.2.2 Dermal

A dermal LD50 of 10 600 mg/kg bw was reported in rabbits (WHO 2002). No other details were provided of how this was determined. The study shows that ethylene glycol has low acute toxicity by the dermal route in rabbits.

4.5.2.3 Inhalation

Lethal concentrations of >200 mg/m^3 were observed in rats and mice after a two-hour inhalation exposure to ethylene glycol (WHO 2002). No other details were provided for how this was determined.

The study shows that ethylene glycol has low acute toxicity by the inhalation route in rabbits.

4.5.2.4 Observation in humans

Acute toxicity data from observations in humans were primarily sourced from NTP-CERHR (2004). Mortality has been observed in humans following intentional or accidental ingestion of ethylene glycol, with the lethal oral doses estimated to be 1400 to 1600 mg/kg bw. The estimated range of acute lethal doses is uncertain since the

ingested amount was not well quantified. The toxic effects were characterised by distinct stages that possibly overlap. During the first stage (0.5 to 12 hours after intake), symptoms included central nervous system depression with ataxia, slurred speech, somnolence, convulsions and gastrointestinal upset. During the second stage (12 to 72 hours after intake), symptoms included metabolic acidosis with reductions in blood pH and bicarbonate levels and cardiopulmonary effects such as tachypnoea, hyperpnoea, tachycardia, cyanosis, pulmonary oedema and cardiac failure. During the third stage (24 to 72 hours after intake) renal toxicity was observed possibly from deposition of calcium oxalate crystals in the kidney. Histological investigation of the kidneys showed tubular necrosis and presence of oxalate crystals. A possible fourth stage (six or more days after intake) presented symptoms of deafness, facial paralysis and other neurologic effects.

The observations show that ethylene glycol has moderate toxicity by the oral route in humans.

4.5.3 *Irritation / Corrosivity*

4.5.3.1 Skin irritation

Mild dermal irritation was induced in rabbits and guinea pigs (Clark et al. 1979; Guillot et al. 1982; Anderson et al. 1986). No dermal effects were observed in female CD-1 mice administered 3549 mg/kg bw/day ethylene glycol under occlusion for 6 hours/day on GD6-15 (Tyl 1988; Tyl et al.1995).

The studies show that ethylene glycol is a mild skin irritant in animals.

4.5.3.2 Eye irritation

Minimal conjunctival irritation, without permanent corneal damage, was observed in rabbits following single ocular application of liquid or vapour ethylene glycol (McDonald et al. 1972; Clark et al. 1979; Guillot et al. 1982; Grant and Schuman 1993).

The studies show that the chemical is a mild eye irritant in animals.

4.5.3.3 Respiratory irritation

No data were available in animals.

4.5.3.4 Observation in humans

A clinical study of 20 male volunteers exposed to 0.8 to 6.7 and 6.7 to more than 200 mg/m^3 aerosolised ethylene glycol for 30 days (20 to 22 hrs/day) reported nasal/throat irritation at 140 mg/m^3; tolerance time of up to 15 minutes at 188 mg/m^3; tolerance time of up to one minute at 244 mg/m^3; tolerance time of 1 to 2 seconds at 303 mg/m^3 (Wills et al. 1974). Severe irritation of the tracheobronchial tree and pain were observed at concentrations >200 mg/m^3.

4.5.4 *Sensitisation*

4.5.4.1 Skin sensitisation

No evidence of skin sensitisation was observed in a guinea pig maximisation test (Kurihara et al. 1996).

The chemical is not considered to be a skin sensitiser.

4.5.4.2 Respiratory sensitisation

No data were available.

4.5.4.3 Observation in humans

No data were available.

4.5.5 *Repeat dose toxicity*

4.5.5.1 Oral

The key animal data on oral repeat dose toxicity of ethylene glycol are summarised from OECD (2009) and are presented in Table A4.3. The Lowest Observed Adverse Effect Levels (LOAELs) and No Observed Adverse Effect Levels (NOAELs) are indicated for each study. In addition, the Klimisch scores (Klimisch et al. 1997) (1 = reliable without restrictions; and 2 = reliable with restrictions) for each study are indicated.

Table A4.3 Repeat oral toxicity studies with ethylene glycol

Species	Method, study duration and doses	Results	Remarks	Reference
Fischer 344/N rats	Diet, 13 weeks 0, 0.32, 0.63, 1.25, 2.5, 5%	LOAEL = 2.5% (estimated 1200–2000 mg/kg bw/day) NOAEL = 1.25% (estimated 600-1000 mg/kg bw/day)	Males in 2.5 and 5% dose groups: decrease in mean bodyweight gain, increased left kidney weight, increased serum urea nitrogen and creatinine levels and kidneys with rough or granular appearance. Females in 2.5 and 5% dose groups: increased left kidney weight and increased creatinine levels. At the highest dose, brains contained cluster of cystals (males) and nephrosis seen (females)	Melnick (1984) Klimisch = 2
Sprague-Dawley rats	Drinking water, 90 days 0, 205, 407, 947, or 3134 mg/kg bw/day in males 0, 597, 1145, 3087, or 5744 mg/kg bw/day in females	LOAEL = 947 mg/kg bw/day (male); 597 mg/kg bw/day (female) NOAEL = 407 mg/kg bw/day (male); none (female)	The changes in the control group were not reported. Effects in males: kidney lesions and increased kidney weight at top two doses and decreased heart, liver and lung weights at top dose. Effects in females: decreased leukocyte levels at all doses, and kidney lesions at the top two doses. Renal changes included tubular dilation, tubular degeneration, acute inflammation, birefringent crystals in tubules and pelvic epithelium.	Robinson et al. (1990) Klimisch = 2
Wistar and F344 rats, males	Diet, 16 weeks 0, 150, 500, or 1000 mg/kg	LOAEL = 500 mg/kg bw/day for both strains NOAEL = 150	At the top dose, clinical observations of emaciation and dermal atonia and macroscopic findings of changes in kidneys (pale, calculi) and crystal nephropathy, small seminal vesicles.	WIL Research Laboratories Inc (2002)

Species	Method, study duration and doses	Results	Remarks	Reference
only	bw/day	mg/kg bw/day for both strains	At mid dose, decreased bodyweight gain, macroscopic findings of pale kidneys, presence of calculi, and dilated pelvis.	Klimisch = 1
Wistar Han rats, males only	Diet, 12 months 0, 50, 150, 300, or 400 mg/kg bw/day	LOAEL = 300 mg/kg bw/day NOAEL = 150 mg/kg bw/day	At 300 and 400 mg/kg bw/day dose groups, mortality and moribundity were reported. Additional effects were occasional absent/decreased faeces, blood in the cage, red perioral and perinasal soiling, increased absolute and relative kidney weights, decreased bodyweight gain, gross pathological observations in the kidney and urinary bladder, secondary lung observations. The observed severity of nephropathy in the kidney is discussed further below.	Wilson et al. (2005); also Corley et al. (2008) Klimisch = 1
Fischer 344 rats	Diet, 24 months 0, 40, 200, or 1000 mg/kg bw/day	LOAEL = 1000 mg/kg bw/day NOAEL = 200 mg/kg bw/day	Effects in females at the top dose: increased absolute and relative kidney weight, urine calcium oxalate crystals and mild fatty changes in the liver. Effects in males at the top dose: kidney and liver weight changes, microscopic lesions in the kidney, mineralisation of the heart, and alterations in clinical chemistry and urinary parameters.	DePass (1986a) Klimisch = 2
B6C3F$_1$ mice	Diet, 13 weeks 0, 0.32, 0.63, 1.25, 2.5, 5%	LOAEL = 2.5% (est. 1200-2000 mg/kg bw/day) NOAEL = 1.25% (est. 600-1000 mg/kg bw/day)	Renal lesions, such as tubular dilation, cytoplasmic vacuolisation, and regenerative hyperplasia, were seen in male mice at the 2.5 and 5% dose groups.	Melnick (1984) Klimisch = 2
B6C3F$_1$ mice	Diet, 103 weeks 0, 1500, 3000, 6000, or 12 000 mg/kg bw/day	LOAEL = 3000 mg/kg bw/day NOAEL = 1500 mg/kg bw/day	Centrilobular hepatocellular hyaline degeneration and nephropathy were seen at the top three doses (males) and top two doses (females). Medial hyperplasia of small pulmonary arteries observed in females at top three doses.	NTP (1993) Klimisch = 1

The critical study for determining the effects of repeated exposures to the chemical is the well-conducted study (Klimisch = 1) by Wilson et al. (2005), also cited as Corley et al. (2008) as this study is of a longer duration and the effects in the kidneys were studied in more detail. The severity of nephropathy in the kidneys was scored on a scale of 0 (no crystal nephropathy) to 5 (end-stage nephropathy indicative of impending renal failure) to determine the renal effects of ethylene glycol. At 400 mg/kg bw/day severity ranged from 3 (moderate)

to 5 and at 300 mg/kg bw/day, severity ranged from 1 (minimal) to 4 (marked). Treatment-related nephropathy was not seen at the two lowest doses. The concentrations of glycolic acid and oxalate were increased at 300 and 400 mg/kg bw/day indicating that the accumulation of calcium oxalate in the kidneys correlated with renal toxicity (ATSDR 2010).

Repeated oral exposure to ethylene glycol was consistently associated with adverse effects on the kidney such as crystal nephropathy. Fatty degeneration and hyaline degeneration of the liver were not seen consistently at the doses at which renal effects were observed.

4.5.5.2 Dermal

No data were available.

4.5.5.3 Inhalation

No data were available.

4.5.5.4 Observation in humans

No evidence of renal effects was observed in a small group of aircraft workers exposed to ethylene glycol vapour or mist during de-icing activities, although some were wearing protective breathing equipment (Gerin et al. 1997). Repeated human oral exposure studies of ethylene glycol are available; however, the NTP-CERHR (2004), WHO (2002), and Environment Canada/Health Canada (2010) noted that there were several limitations in the studies which did not allow dose quantification.

4.5.6 *Genotoxicity*

In vivo studies showed negative results for dominant lethal mutations in F344 rats after administration of up to 1000 mg/kg bw/day ethylene glycol in a 155-day multi-generational study (DePass et al. 1986b). Negative chromosomal aberration results were observed in Swiss mice exposed to 638 mg/kg bw/day for two days (WHO 2002).

Ethylene glycol yielded negative results in an Ames assay for reverse mutation for several *Salmonella typhimurium* strains (Clark et al. 1979; Kubo et al. 2002; McCann et al. 1975; Pfieffer and Dunkelberg 1980; Zeiger et al. 1987); gene mutation in the yeast *Schizosaccharomyces pombe* (Abbondandolo et al. 1980); and aneuploidy induction in the fungus *Neurospora crassa* (Griffiths 1979, 1981). The chemical did not induce growth inhibition in *Escherichia coli* repair-deficient strains (McCarroll et al. 1981) and did not induce gene mutations in L5178Y mouse lymphoma cells (McGregor et al. 1991) or deoxyribonucleic acid (DNA) strand breaks in primary rat hepatocytes (Storer et al. 1996).

Based on the available studies, ethylene glycol is not considered to be genotoxic.

4.5.7 *Carcinogenicity*

Histopathological investigations showed no evidence of carcinogenicity in Sprague-Dawley rats administered ≤3000 mg/kg bw/day in the diet for two years (Blood 1965), F344 rats administered 1000 mg/kg bw/day in the diet for one year (DePass et al. 1986a; Woodside 1982), B6C3F1 mice administered ≤12 000 mg/kg bw/day in the diet for two years (Melnick 1984), or CD-1 mice administered ≤1000 mg/kg bw/day in the diet for two years (DePass et al. 1986a; Woodside 1982).

Based on the available data, ethylene glycol is not considered to be carcinogenic.

4.5.8 *Reproductive toxicity*

4.5.8.1 Fertility

In a two-generation reproductive toxicity study conducted in accordance with the United States National Toxicology Program (NTP) Fertility Assessment by Continuous Breeding method, COBS Crl:CD1 mice were given 0, 410, 840 or 1640 mg/kg bw/day ethylene glycol in drinking water during pre-mating, pairing, cohabitation, segregation and weaning periods (Lamb et al. 1985). The same doses were administered to the parent (P) and first filial (F1) generation. No clinical signs of toxicity were observed in the P generation at any of the doses. At the 840 mg/kg bw/day group, two deaths occurred which could be attributed to oxalate crystal deposition in the kidney. Slight, but statistically significant, effects were reported at the highest dose on the number of F1 litters, number of live pups, and live pup weight. For the F1 generation, skeletal defects such as abnormally shaped or missing sternebrae and vertebrae, twisting of the spine, fused ribs, and shortened frontal, nasal and parietal bones and unusual facial features (shorter snout and wide set eyes) were observed in the second filial (F2) generation pups of the F1-treated mice at the highest dose. The NOAEL was 840 mg/kg bw/day based on fertility effects at the LOAEL of 1640 mg/kg bw/day.

In a three-generation reproductive toxicity study, Fischer F344 rats were administered ethylene glycol in the diet at doses of 0, 40, 200 or 1000 mg/kg bw/day (DePass et al. 1986b). There were no treatment-related effects on bodyweight, food consumption, appearance, behaviour and histopathology of major organs in the parents of all generations. There were no treatment-related effects on the fertility index, gestation index, gestation survival index, pup weight, appearance, behaviour and histopathology of major organs. The NOAEL for this study was 1000 mg/kg bw/day.

4.5.8.2 Developmental toxicity

The reproductive toxicity of ethylene glycol has been investigated in a number of adequate studies in mice and rats. The key animal data on developmental toxicity of ethylene glycol are summarised from OECD (2009) and presented in Table A4.4. The LOAELs and NOAELs, as well as the Klimisch scores (Klimisch et al. 1997) (1 = reliable without restrictions; and 2 = reliable with restrictions) for each study are indicated.

Table A4.4 Developmental toxicity studies with ethylene glycol

Species	Method, exposure period and doses	Results	Remarks	Reference
CD rats	Oral (gavage), GD6-15 0, 50, 150, 500, 1000, or 2500 mg/kg bw/day	*Maternal* NOAEL = 1000 mg/kg bw/day *Developmental* LOAEL = 1000 mg/kg bw/day NOAEL = 500 mg/kg bw/day	At 2500 mg/kg bw/day, dams had decreased bodyweight, decreased uterine weight, and increased kidney and relative liver weights. At 1000 mg/kg bw/day, developmental effects included extra or missing ribs, missing arches and poor ossification in thoracic and lumbar centra. At 2500 mg/kg bw/day, developmental effects were skeletal malformations, gastroschisis, hydrocephaly, dilated lateral ventricle, umbilical hernia, and	Neeper-Bradley et al. (1995) Klimisch = 2

Species	Method, exposure period and doses	Results	Remarks	Reference
			atelectasis.	
CD rats	Oral (gavage), GD6-15 0, 1250, 2500, or 5000 mg/kg bw/day	*Maternal* LOAEL = 1250 mg/kg bw/day *Developmental* LOAEL = 1250 mg/kg bw/day NOAEL not established	At the lowest dose, dams had treatment-related decreased bodyweight gain. At the mid- and top doses, dams had increased relative kidney weight and decreased gravid uterine weight. Live litter size was decreased at the top dose. Foetal bodyweight was decreased in the mid- and top doses. Litters with malformed foetuses were seen in all doses.	Price et al. (1985) Klimisch = 2
Fischer 344 rats	Oral (diet), GD6-15 0, 200, 400, or 1000 mg/kg bw/day	*Maternal* NOAEL = 1000 mg/kg bw/day *Developmental* LOAEL = 1000 mg/kg bw/day NOAEL = 400 mg/kg bw/day	No apparent treatment-related maternal toxicity at all doses. At the top dose, increased incidences of skeletal alterations (vertebral ossification) were reported. The number of animals and magnitude of effects were not specified.	Maronpot et al. (1983) Klimisch = 2
CD-1 mice	Oral (gavage), Gestation days (GD) 6-15 0, 50, 150, 500, or 1500 mg/kg bw/day	*Maternal* NOAEL = 1500 mg/kg bw/day *Developmental* LOAEL = 500 mg/kg bw/day NOAEL = 150 mg/kg bw/day	No apparent treatment-related maternal toxicity at all doses. At 1500 mg/kg bw/day, effects were fused ribs and arches, poor ossification in thoracic and lumbar centra, and increased occurrence of an extra rib. At 500 mg/kg bw/day, effects included slight reductions in foetal bodyweight and increased occurrence of extra rib.	Neeper-Bradley et al. (1995) Klimisch = 2
CD-1 mice	Oral (gavage), GD 6-15 0, 750, 1500, or 3000 mg/kg bw/day	*Maternal* NOAEL = 750 mg/kg bw/day *Developmental* LOAEL = 750 mg/kg bw/day NOAEL not established	At the mid-dose, dams had treatment-related decreased bodyweight gain, uterine weight and liver weight. Decreased number of implantation sites per litter was seen at the mid-dose. Litters with increased malformed foetuses and decreased foetal bodyweight gain were reported at all doses.	Price et al. (1985) Klimisch = 2
Swiss Crl:CD-1 mice	Oral (gavage), cohabitation for 3 days + GD8-14 0, 250, 700, or 2500 mg/kg bw/day	*Maternal* NOAEL = 2500 mg/kg bw/day *Developmental* LOAEL = 2500 mg/kg bw/day NOAEL = 700	No apparent treatment-related maternal toxicity at all doses. Fewer live implants and more dead implants, and lower total litter weights at the top dose.	Harris et al. (1992) Klimisch = 2

Species	Method, exposure period and doses	Results	Remarks	Reference
		mg/kg bw/day		
CD-1 mice	Cutaneous, GD6-15 0, 404, 1677, or 3549 mg/kg bw/day Positive control at 3000 mg/kg bw/day	*Maternal* NOAEL = 3549 mg/kg bw/day *Developmental* LOAEL = 3549 mg/kg bw/day NOAEL = 1677 mg/kg bw/day	No apparent treatment-related maternal toxicity at all doses. Significant skeletal malformations were reported at the top dose and the positive control groups.	Tyl et al. (1995) Klimisch = 2

The developmental toxicity studies summarised above (Table A4.4) demonstrate that ethylene glycol causes developmental effects (implant viability, weight of live foetuses, skeletal variations and / or malformations) at minimum doses of 500 mg/kg bw/day in mice and 1000 mg/kg bw/day in rats.

Developmental toxicity may not be attributed directly to ethylene glycol but from the accumulation of glycolic acid, which is a metabolic breakdown product of the ethylene glycol. The Expert Panel of the NTP Centre for the Evaluation of Risks to Human Reproduction (NTP-CERHR) evaluated all the available data from animal studies and *in vitro* metabolism studies and determined the levels of ethylene glycol that could saturate glycolic acid metabolism. The Expert Panel concluded that *'there is negligible concern of adverse developmental toxicity in humans from ethylene glycol at exposure levels below 125 mg/kg bw/day*' (NTP-CERHR 2004). In rats, the ethylene glycol level of metabolism saturation was estimated to be 500 mg/kg bw/day.

4.5.9 *Other health effects*

No data were available.

4.6 Health hazard summary

4.6.1 *Critical health effects*

Ethylene glycol demonstrates acute oral toxicity, is a mild skin and eye irritant and a respiratory irritant in humans. The chemical is not a skin sensitiser.

Consistent adverse effects associated with repeated exposure to ethylene glycol in animals are the kidney effects, characterised by calcium oxalate crystal deposition and consequent renal lesions. The NOAEL, determined from the 12-month dietary exposure study by Wilson et al. (2005) and Corley et al. (2008), is 150 mg/kg bw/day based on renal toxicity at the LOAEL of 300 mg/kg bw/day.

The chemical is not genotoxic or a carcinogen based on the available data discussed in previous sections. Developmental effects (implant viability, weight of live foetuses, skeletal variations and / or malformations) were observed in animals but were considered to be due to the accumulation of one of the chemical's metabolites, glycolic acid. From the evaluation

of all available developmental toxicity data from animal studies and *in vitro* metabolism studies:

> *'…there is negligible concern of adverse developmental toxicity in humans from ethylene glycol at exposure levels below 125 mg/kg bw/day…' (NTP-CERHR 2004).*

This level is taken as the NOAEL for developmental toxicity in humans.

4.6.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A4.5. This NICNAS recommendation does not consider physical or environmental hazards.

Table A4.5 Recommended hazard classification

	GHS* classification
Acute toxicity	Harmful if swallowed – Cat. 4 (H302)

** Globally Harmonised System (UNECE 2009)*

4.7 References

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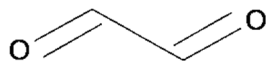
A5 Ethanedial

CAS No.	CAS Name
107-22-2	Ethanedial

5.1 Chemical identity

Details of the chemical identity were obtained from the Hazardous Substances Data Bank (HSDB) (2013) and a European Commission Scientific Committee on Consumer Products (SCCP) report on glyoxal (European Commission 2005). Details are provided in Table A5.1.

Table A5.1 Chemical identity

	Ethanedial
Synonyms	Glyoxal 1,2-Ethanedione Biformal Diformal Oxalaldehyde
Structural formula	 Ethanedial can undertake rotational isomerisation between the planar *cis* and *trans* conformations. The *trans* conformation (depicted above) is the most stable.
Molecular formula	$C_2H_2O_2$
Molecular weight	58.04
Appearance and odour	Light yellow liquid with a mild odour at ambient temperatures; yellow crystals at 15 °C.
SMILES notation	C(=O)C=O

5.2 Physical properties

The physical properties of ethanedial were obtained from HSDB (2013) and a European Commission Scientific Committee on Consumer Products (SCCP) report on glyoxal (European Commission 2005). Details are presented inTable A5.2.

Table A5.2 Physical properties

Property	**Value**
Melting point	15 °C
Boiling point	50.4 °C

Property	Value
Density	1.14 x 10^3 kg/m^3 at 20 °C
Vapour pressure	29.33 kPa at 20 °C
Water solubility	600 g/L at 25 °C
Partition coefficient n-octanol/water (log K_{ow})	0.85

5.3 Current regulatory controls

5.3.1 *Hazard classification for occupational health and safety*

Ethanedial is classified as hazardous for human health in the *Hazardous Substances Information System* (HSIS) with the following risk phrases (Safe Work Australia 2013):

- Muta. Cat. 3 (Mutagenic Substances, Category 3)
- R68 (Possible risk of irreversible effects)
- Xn; R20 (Harmful by inhalation)
- Xi; R36/38 (Irritating to eyes and skin)
- R43 (May cause sensitisation by skin contact)

5.3.2 *Occupational exposure standards*

5.3.2.1 Australia

No specific exposure standards were available.

5.3.2.2 International

The following exposure standards are identified (Galleria Chemica 2013).

Time Weighted Average (TWA):

- 0.1 mg/m³ [Belgium, Columbia, Canada (Alberta, British Columbia, Saskatchewan), Italy, Nicaragua, Portugal, Spain, United States of America]
- 0.5 mg/m³ (0.2 ppm) [Denmark].

Short Term Exposure Limit (STEL):

- 0.3 mg/m³ [Canada (Saskatchewan)].

5.3.3 *Australian food standards*

No Australian food standards were identified.

5.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

5.3.5 *Additional Controls*

5.3.5.1 Australia

No additional controls were identified.

5.3.5.2 International

According to the European Commission Cosmetics Directive Annex III (List of Restricted Substances) (European Commission 2013), the maximum allowable concentration for ethanedial in finished cosmetic products in the European Community is 100 mg/kg.

5.4 Use

The use of ethanedial in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

5.5 Health hazard characterisation

The following information on health hazard characterisation is obtained from:

- an Organisation for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS) Initial Assessment Report (OECD 2003)
- a World Health Organization (WHO) Concise International Chemical Assessment Document (CICAD) (WHO 2004)
- a European Commission Scientific Committee on Consumer Products (SCCP) report (European Commission 2005)
- an industry dossier on ethanedial submitted under the EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (REACH 2013a).

Unless otherwise noted, references are taken from these sources.

5.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

5.5.1.1 Oral absorption

There is limited information on oral absorption of ethanedial. Absorption is indicated on the basis of distribution to target organs and observed toxicological effects following acute and subchronic oral administration (BUA 1997; Ueno et al. 1991). However, the extent of absorption is unclear.

For human risk assessment purposes, and consistent with the low molecular weight (MW) of the chemical (<100), an oral absorption of 100% is therefore assumed.

5.5.1.2 Dermal absorption

Toxic effects in several organs have been observed following dermal application indicating that absorption occurs via this route (Ito 1963). Additionally, positive skin sensitisation data indicate that ethanedial is absorbed across the skin (see Section A 5.5.4.1) . However, the extent of absorption is unclear.

For human risk assessment purposes, and consistent with the low MW of the chemical and moderate partition coefficient (log K_{ow} of 0.85), a dermal absorption of 100% is therefore assumed.

5.5.1.3 Inhalation absorption

Acute and short term repeated inhalation exposures are associated with local effects on eyes and respiratory organs (Sections A5.5.3.2 and A5.5.2.3). However, the extent of systemic absorption inferred from these local effects is unclear.

For human risk assessment purposes, an inhalation absorption of 100% is therefore assumed.

5.5.1.4 Distribution

In aqueous biological media, less than 10% of ethanedial present is unbound in the form of free ethanedial and hydrates. Most of the reactive carbonyl groups are reversibly bound to cysteinyl, lysyl and arginyl residues of proteins (Thornalley 1995).

Data on distribution of ethanedial following absorption are limited. After oral administration, distribution occurs to erythrocytes, liver, lung, kidney, pancreas, and adrenal glands (BUA 1997; Ueno et al. 1991). After dermal administration, degenerative changes in liver, kidney, and pancreas have been observed (Ito 1963).

Limited distribution data are available for glutaraldehyde, a five carbon homologue of ethanedial. Following intravenous administration, distribution of radiolabelled glutaraldehyde occurs to a greater extent via the cellular blood fraction than the plasma fraction, due to cellular incorporation (Ranly and Horn 1990). In more recent toxicokinetics studies of glutaraldehyde outlined in a REACH dossier, radioactivity was detected in all tissues and organs following administration of radiolabelled glutaraldehyde by gavage or by intravenous injection (REACH 2013b).

5.5.1.5 Metabolism

Ethanedial is produced endogenously during normal cellular metabolism by several enzyme-independent mechanisms. These include the spontaneous reaction of amino groups in proteins with reducing sugars (Maillard reaction), sugar autoxidation, DNA oxidation, peroxidation of polyunsaturated fatty acids, UV photodamage and in conditions of oxidative stress and depletion of glutathione (GSH). Studies have reported plasma levels of ethanedial of 67 ng/mL (approximately 1.16 µmol/L) (Odani et al. 1999), 0.23 µmol/L (Agalou et al. 2002) and 0.3 µmol/L (Lapolla et al. 2003).

The cytosolic GSH-dependent glyoxalase system is the major pathway for the metabolism of ethanedial which is ultimately metabolised to carbon dioxide via the intermediate metabolite glyoxylate. Endogenous concentrations of ethanedial in human tissues and body fluids, as with other *α*-oxoaldehydes, are limited by the high catalytic efficiency of the glyoxalase system (Thornalley 1995), as well as by the rapid reaction of glyoxal with proteins (Sady et al. 2000).

5.5.1.6 Excretion

Information on the excretion of ethanedial is limited. Ethanedial has been detected in the urine of normal human subjects (Epsinosa-Mansilla et al. 1998).

5.5.2 *Acute toxicity*

5.5.2.1 Oral

The acute oral toxicity of ethanedial has been reported in a number of studies using various concentrations in different species including rats, mice, rabbits and cats. With 40% ethanedial, oral LD50 values of 640 to 8979 mg/kg bw in rats and an LD50 of 4064 mg/kg bw in mice have been reported (European Commission 2005; WHO 2004). Symptoms included decreased activity, apathy, abnormal posture, decreased respiratory rate, dyspnoea, ruffled fur, tremor, diarrhoea, equilibrium disturbances, reduced or absent reflexes and paresis. It is not always clear whether the LD50 data in these studies refer to the solutions as tested or to the active ingredient (OECD 2003).

Dossiers on ethanedial submitted by industry under REACH contain guideline studies of acute toxicity with additional information on active ingredient concentrations (REACH 2013a). In a study in rats reported in 1984 and 2008 conducted to OECD Test Guideline (TG) 401, the LD50 for a 40% ethanedial aqueous solution was reported as 3300 mg/kg bw, corresponding to 1320 mg/kg bw active ingredient. In a 1985 limit study conducted in rats in a similar fashion to OECD TG 401, a 40% ethanedial aqueous solution was tested at two doses – 2000 mg/kg bw and 5000 mg/kg bw. At 2000 mg/kg bw all animals survived. At 5000 mg/kg bw all animals died. Consequently, an LD50 value of >2000 to <5000 mg/kg bw, corresponding to >800 to <2000 mg/kg bw active ingredient, was reported.

In conclusion, ethanedial is moderately toxic via the oral route on an active ingredient basis. In a guideline oral toxicity study, the oral LD50 for 40% ethanedial as an aqueous solution was 3300 mg/kg bw, corresponding to 1320 mg/kg bw for the active ingredient.

5.5.2.2 Dermal

No deaths or signs of systemic toxicity were reported in an acute dermal toxicity test in 1985 with 40% ethanedial in rats conducted in a similar fashion to OECD TG 402 (REACH 2013a). The LD50 was >2000 mg/kg bw (corresponding to >800 mg/kg bw active ingredient). No deaths or signs of systemic toxicity were reported in 1984 in a similar guideline study in rabbits (REACH 2013a). The reported LD50 was >2000 mg/kg bw. The concentration of ethanedial in the applied test solution in this latter study was not reported.

In conclusion, ethanedial is of low acute dermal toxicity. An LD50 of >2000 mg/kg bw, corresponding to >800 mg/kg bw active ingredient, was reported.

5.5.2.3 Inhalation

An acute inhalation toxicity study in 1984 conducted in accordance with OECD TG 403 was reported with a 40% ethanedial aqueous solution (REACH 2013a). Signs of toxicity included irregular and noisy breathing, nasal discharge, intermittent respiration, gasping, narrowed eyelids, sneezing, retracted flanks, piloerection, prone position, drowsiness and, upon necroscopy, macroscopic findings in the lungs. The LC50 was 2.44 mg/L (active ingredient). No mortality was observed in a similar guideline study where rats were exposed to the highest technically possible concentration of ethanedial as dust (80% active ingredient) (REACH 2013a). Only signs of respiratory tract irritation (irregular breathing, sneezing, bloody lacrimation) were observed. The LC50 was >1.3 mg/L (active ingredient).

5.5.2.4 Observation in humans

No data were available.

5.5.3 *Irritation / Corrosivity*

5.5.3.1 Skin irritation

In a skin irritation test in 1985 in rabbits conducted to OECD TG 404, a 40% ethanedial aqueous solution showed no signs of irritation directly after 4 hour semi-occlusive exposure, or during a 72 hour observation period (REACH 2013a). However, in a series of earlier studies in which rabbits were exposed to 30 to 40% ethanedial solutions for periods ranging from one minute to 20 hours, slight to pronounced irritation was reported depending on the application period (REACH 2013a). Exposure for 20 hours caused occasional strong erythema and oedema, with scaling, scab formation and superficial necrosis observed after eight days (REACH 2013a).

In the acute dermal toxicity study in rats discussed in Section A 5.5.2.2, erythema was observed in all animals following 24 hour exposure to a 40% ethanedial aqueous solution at a dose corresponding to 800 mg/kg bw.

5.5.3.2 Eye irritation

In early studies, instillation of 50 µL of 30 to 40% aqueous solutions of ethanedial into the conjunctival sacs of rabbits was reported to cause slight to strong reddening, mild oedema and inflammation as well as hazy clouding of the cornea (BASF 1956, 1963a, 1963b). Changes subsided within one to two weeks.

In a study conducted to OECD TG 405, ethanedial was reported to be irritating (IFREB 1982). No other details were available. In a subsequent study conducted to OECD TG 405 (BASF 1985), 0.1 mL of a 40% aqueous solution of ethanedial caused definite conjunctival erythema and chemosis in three rabbits (one male, two females), 1 hour after instillation in the eye. After 24 hours, two animals exhibited slight to definite chemosis of the conjunctiva. Slight conjunctival reddening and chemosis were still observed 72 hours after administration. The symptoms subsided after eight days.

5.5.3.3 Observation in humans

No data were available.

5.5.4 *Sensitisation*

5.5.4.1 Skin sensitisation

In a Magnusson and Kligman maximisation test based on OECD TG 406, 20 female Pirbright-White guinea pigs were administered 0.1 mL of a 20% aqueous ethanedial solution intradermally into the shoulder area, and one week later were administered approximately 0.3 g of a 40% ethanedial solution epicutaneously under occlusion (BASF 1987). Challenge was conducted by epicutaneous application (under occlusion) of 0.15 g of a 10% aqueous ethanedial solution on the shaven flank on days 19 and 26 after intradermal induction. One guinea pig died inexplicably after the intradermal induction. In surviving animals, the intradermal induction produced necrotic skin changes and oedema.

After the first challenge, 1/19 animals showed slight erythema and 6/19 animals showed distinct erythema (one of which additionally had a slight oedema). Thus, a positive response was observed in 7/19 animals in total. After the second challenge, a total of 11/19 animals showed a positive skin response; 7/19 animals showed slight erythema and 4/19 animals showed distinct erythema (one of which additionally had a slight oedema). No skin reactions

were observed in the control group at any time. Thus, ethanedial showed a sensitising effect on the skin of guinea pigs.

Another Magnusson and Kligman maximisation test with ethanedial was conducted on female Dunkin-Hartley guinea pigs (Foussereau et al. 1992). Intradermal and dermal inductions were conducted with 10% aqueous solution and dermal challenge was conducted with 5% aqueous solution. While no data on actual animal numbers were provided, the report stated that 86% of the guinea pigs showed a strong positive reaction.

In a Bühler sensitisation test on guinea pigs, 40% ethanedial was shown to be sensitising, although no further details were provided (American Cyanamid Company 1988). A positive result for ethanedial was also reported in a murine Local Lymph Node Assay (LLNA) (Basketter et al. 1994).

5.5.4.2 Respiratory sensitisation

No data were available.

5.5.4.3 Observation in humans

Data were available for the sensitising effects of ethanedial in humans. A maximisation test was conducted on 24 male volunteers, each of whom received five 48-hour occlusive applications of patches soaked with 10% ethanedial solution (no data on vehicle) (Kligman 1966). Following a rest period of 24 hours, challenge was conducted with one 48 hour application of 2% ethanedial. Slight irritation was observed with induction applications. With challenge, skin reactions assessed as extreme were reported in all volunteers. Accordingly, ethanedial was concluded to be sensitising.

In contrast, a repeat insult patch test in 55 volunteers with ethanedial as a powder showed no sensitising effects (Monsanto 1969). Powdered ethanedial was applied to each subject via 15 occlusive patches for 24 hours separated by 24 hour rest periods, three times/week for a total of 15 applications. Following a 14 day period without induction, challenge was achieved by application of a single occlusive patch applied for 24 hours. No skin reactions were observed in any subject at any time point up to 48 hours after challenge patch removal.

Between 1965 and 1990, 65 cases of allergies to formaldehyde, glutaraldehyde and ethanedial were observed among the employees of a skin clinic, who were exposed to the chemical in its use as a sterilant for surgical instruments (Foussereau et al. 1992). Patch tests produced positive results for 41 persons. Among them, six individuals reacted positively only to ethanedial, four to ethanedial and formaldehyde, eight to ethanedial and glutaraldehyde and two to all three compounds. Cross reactions thus apparently existed for 12 persons.

In a German multicentre study of dermal sensitivity, the records of 31 849 health care workers from 24 allergy departments between 1992 and 1995 were evaluated (Schnuch et al. 1998). Of the 774 female patients working in the medical profession, 4.2% were found to show positive reactions to ethanedial patch testing, whereas only 1.4% of the control group (1895 persons not in the medical profession) were found to be positive.

Several individual case reports also describe sensitisation to ethanedial following occupational exposures (Ito 1963; Hindson and Lawlor 1982; Kanerva et al. 2000).

5.5.5 *Summary of acute toxicity*

Ethanedial is considered moderately toxic via the oral route on an active ingredient basis. The oral LD50 for 40% ethanedial as an aqueous solution was 3300 mg/kg bw,

corresponding to 1320 mg/kg bw for the active ingredient. Ethanedial is also moderately toxic via inhalation. An LC50 of 2.44 mg/L (active ingredient) was reported.

Via the dermal route, ethanedial is of low acute toxicity. An LD50 of >2000 mg/kg bw, corresponding to >800 mg/kg bw active ingredient, was reported.

Data from irritation studies and observations from a dermal toxicity test indicate that ethanedial is a skin irritant. Similarly, eye irritation studies indicate that it is an eye irritant. Ocular effects were reversible within one to two weeks. Studies in animals and data from patch testing in humans show that ethanedial is also a skin sensitiser.

5.5.6 *Repeat dose toxicity*

5.5.6.1 Oral

Several oral repeated dose studies of various durations were available for ethanedial. The following table (Table A5.3) of oral repeat dose studies is adapted from OECD (2003).

Table A5.3 Oral repeat dose studies for ethanedial (adapted from OECD 2003)

Test substance	Species and route of dosing	Exposure period	Doses	NOAEL (mg/kg bw/day)	NOAEL (mg/kg bw/day (active substance)	Reference
Ethanedial (40%)	Rat, diet	90 days	Male: 0, 32.7, 63.2, 132, 253 mg/kg bw/day Female: 0, 32, 63.2, 127, 271 mg/kg bw/day	125	50	Union Carbide (1966)
Ethanedial (40%)	Rat, drinking water	28 days	0, 100, 300, 1000 mg/kg bw/day	100	40	Société Française Hoechst (1987)
Ethanedial (40%)	Rat, drinking water	12 or 24 months	0, 25, 75 and 300 mg/kg bw/day (active substance)	25	25	REACH (2013a)
Ethanedial (100%)	Rat, drinking water	30, 60, 90 days	0, 2000, 4000, 6000 mg/L (active substance)	Not derived. LOAEL = 107	Not derived. LOAEL = 107	Ueno et al. (1991)
Ethanedial (no data)	Rat, mice, drinking water	90 days	0, 1000, 2000, 4000, 8000, 16 000 mg/L	Not derived.	Not derived.	NTP (1991)
Ethanedial (100%)	Dog, diet	90 days	0, 31, 65, 115 mg/kg bw/day (active substance)	115	115	Union Carbide (1966)

The most recent and long term repeat dose toxicity study is a combined chronic toxicity/carcinogenicity study reported in 2012 conducted in accordance with OECD TG 453 (REACH 2013a). In this test, 10 rats per sex per group (satellite groups) and 50 rats per sex per group (main groups) were exposed via drinking water to 40% ethanedial at nominal doses of 0, 25, 75 and 300 mg/kg bw/day (active substance) for 12 (satellite groups) or 24 months (main groups). There was no observed increase in mortality related to treatment. Changes in water consumption were observed and thought to be likely related to the taste of the test substance. No further details were provided. There were no effects on food consumption.

Treatment-related effects on body weight and changes in body weight were observed in high dose animals. Mean terminal body weight of high dose males of the satellite group (12 months) was decreased by 8%. Mean terminal body weight of high dose males and females of the main group (24 months) were decreased by 11% and 12% respectively. These decreases were regarded as reflecting a systemic adverse toxic effect.

Decreased alanine aminotransferase (ALT) activity was observed in high dose animals. Lower cholesterol and globulin values were also observed in high dose animals as well as in intermediate dose males. Increases in erosions/ulcers in the glandular stomach were noted in high dose and intermediate dose females. No other details on clinical chemistry or pathological findings were provided. No additional treatment-related gross lesions or changes in organ weights were observed. This minimally reported study concluded a NOAEL of 25 mg/kg bw/day (active substance) based on treatment-related changes in body weight, clinical chemistry and pathological findings commencing at 75 mg/kg bw/day (active substance) (LOAEL). It should be noted that the extent to which such erosions/ulcers are relevant to humans is unclear. There are anatomical differences in this portion of the gastrointestinal tract between rats and humans, and it has been noted that the general lack of comparative data on the ulcerative potential of drugs in patients makes interpretation of such changes in animals difficult (Greaves 2007).

Although of shorter duration, the critical study for repeat dose toxicity is a 90 day rat dietary study and a 28 day rat drinking water study conducted to OECD TG 407 by Société Française Hoechst (1987). In this study, six rats per sex per dose received ethanedial via drinking water at doses of 100, 300 and 1000 mg/kg bw/day (40, 120 and 400 mg/kg bw/day active substance). No deaths were reported in this study. Body weight gain was retarded in a dose-dependent fashion commencing at the intermediate dose. Reduced body weight coincided with reduced food consumption. A dose-dependent decrease in water consumption was noted for male animals commencing at the lowest dose and for female animals commencing at the intermediate dose. Slight increases in erythrocyte counts in high dose male rats were attributed to reduced water consumption. Effects on organ weights in high dose animals were attributed to reduced body weights. No substance-related effects on haematological, clinical chemistry or urinalysis parameters were seen. No macroscopic or histolopathologic changes were detected in any organ at any dose.

The study established a NOAEL of 100 mg/kg bw/day (40 mg/kg bw/day for active substance), based on dose-related decreases in body weight gain commencing at the intermediate dose of 300 mg/kg bw/day (120 mg/kg bw/day for active substance). This NOAEL is higher than the NOAEL but lower than the LOAEL established in the longer term combined chronic toxicity/carcinogenicity study (25 and 75 mg/kg bw/day for active substance respectively).

5.5.6.2 Dermal

No data were available.

5.5.6.3 Inhalation

The subacute inhalation toxicity of ethanedial was investigated in groups of five male and female Wistar rats given nominal concentrations of 0, 0.4, 2.0 and 10 mg/m³ ethanedial as an aerosol for 6 hours daily, 5 times per week over a period of 29 days (nose only, total of 20 exposures) (Hoechst 1995). Exposures were tolerated by all groups without any visible signs of toxicity. There were no differences in body weight gain, food and water intake, haematological, urinalysis or clinical chemistry findings for treated animals compared to controls. Autopsies at the end of the study showed no substance-related differences compared to the controls.

Histopathologically, animals of the intermediate and high concentration groups showed a minimal squamous metaplasia of the epiglottal epithelium in the larynx accompanied by minimal submucous lymphoid cell infiltration. No substance-related histopathological changes were noted in rats at the lowest dose.

A NOEL for local effects was established at 0.4 mg/m³ for active substance. Due to a lack of systemic toxic effects even at the highest dose, no NOAEL was derived.

5.5.6.4 Observation in humans

No data were available.

5.5.7 *Genotoxicity*

Numerous studies have examined the genotoxicity of ethanedial (OECD 2003; WHO 2004; European Commission 2005). *In vitro*, reverse mutation assays with *Salmonella typhimurium* have shown consistently positive results with strains TA 100, 102, 104 and 2638 and single positive results with TA 98 and 1535. In separate studies, both positive and negative results were reported with *Escherichia coli*. When tested, metabolic activation was shown to weaken observed mutagenic effects. Some (but not all) studies using mammalian somatic and germ cells *in vitro* have shown ethanedial able to produce gene mutations, chromosome aberrations and DNA damage.

In vivo, no gene mutations or chromosome damage were observed in tests with fruit flies (sex-linked recessive lethal test; dominant lethal test) or with mice (micronucleus test). A single poorly documented study reported chromosome aberrations in the duodenum, testes and spleen in mice following oral administration. Also in separate studies in mice, oral administration induced unscheduled DNA synthesis in the pyloric mucosa but not in hepatocytes while DNA strand breaks were reported in the pyloric sphincter and liver. These findings were interpreted as ethanedial possessing mutagenic activity at the point of entry within the gastro intestinal tract and in immediate downstream organs (liver) but not in more remote tissues (OECD 2003).

In conclusion, ethanedial was shown to be mutagenic in both bacterial and mammalian cells *in vitro*.

5.5.8 *Carcinogenicity*

Ethanedial was tested in 2012 in a combined chronic toxicity/carcinogenicity study in rats conducted in accordance with OECD TG 453 (see Section A5.5.6 on repeat dose toxicity). No treatment-related neoplastic lesions were observed in either males or females at 12 or 24 months (REACH 2013 a).

Ethanedial was tested for carcinogenic effects with dermal application in mice. Two groups of 40 male C3H/HeJ mice were each treated on clipped, back skin with a 1:8 dilution of 40%

ethanedial in water three times weekly for approximately 18 months (American Cyanamid Company 1982). Mortality was not affected and no skin tumours related to treatment were found in any mice treated with ethanedial. Skin irritation was observed in some mice but no skin or subcutaneous neoplasms were reported. A fibrosarcoma was observed in one animal but based on historical control data was not regarded as treatment-related. The study concluded that ethanedial showed no carcinogenic potential with lifetime dermal application in mice.

In a tumour initiation study with ethanedial conducted in mice, groups of 20 female CD-1 mice received 0.1 mL ethanedial (37 to 43%) to the clipped back skin twice weekly for five weeks (initiation phase), and following a one week pause, then received 12-*o*-tetradecanoylphorbol-13-acetate (TPA) to back skin as a promoter for 47 weeks (Miyakawa et al. 1991). The total initiation dose was 30 mg/mouse. 7,12-dimethylbenzo(a)-anthracene (DMBA) and dimethylsulfoxide (DMSO) were used as positive and negative controls respectively. All animals survived until the end of the study. Two of 20 mice treated with ethanedial showed papillomas. With DMBA, all 20 mice showed skin tumours – a total of 99 papillomas and 31 squamous cell carcinomas. No tumours were seen in DMSO treated mice. The study concluded that ethanedial was not a tumour initiator.

A tumour initiation/promotion study was also conducted in rats (Takahashi et al. 1989). In the initiation phase, two groups of 30 male Wistar rats each received100 mg/L N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in drinking water for eight weeks and simultaneously a diet containing 10% sodium chloride. From the eigth to 40th week, the first group was administered drinking water with 0.5% ethanedial and the second group, drinking water without ethanedial. A third group of 10 animals received a diet and drinking water without additives in the first eight weeks and then received drinking water with 0.5% ethanedial from the eigth to 40th week. In rats pre-treated with MNNG and sodium chloride, ethanedial caused a significant increase in adenocarcinomas of the glandular stomach (12 out of 28 animals). Lesions were localised predominantly in the pylorus region, where mucosal hyperplasia was also observed. In comparison, five tumours (five out of 30 animals) were observed for initiation treatment without subsequent administration of 0.5% ethanedial in the drinking water. The study concluded that ethanedial possesses local tumour-promoting properties on the glandular stomach of the rat.

Another initiation/promotion study was conducted in F344 rats (Hasegawa and Ito 1992). For the initiation phase, rats were injected intraperitoneally with 200 mg/kg bw diethylnitrosamine. Commencing two weeks later, they received 5000 ppm (corresponding to 333 mg/kg bw/day) ethanedial in the diet for six weeks. After a feeding time of one week, rats underwent a two-thirds hepatectomy. At the end of the study after a total of eight weeks, the GST-P (placental glutathione-S-transferase) positive foci in the liver were evaluated. A significant increase in the number of foci, compared to controls treated only with diethylnitrosamine, was regarded as indicative of carcinogenic potential. Ethanedial caused no increase in the number of foci.

Ethanedial was also investigated in cell transformation assays in which a mouse embryonic cell line was cultured with 40% ethanedial at concentrations of 0.0013 to 0.195 µL/mL (American Cyanamid Company 1980a, 1980b, 1980c). The highest concentrations were shown to be cytotoxic. Ethanedial did not induce cell transformations in these assays.

Based on these studies, ethanedial is not regarded as a human carcinogen. Ethanedial produced no cell transformation in mouse embryonic cell lines *in vitro*. *In vivo*, no carcinogenic effects were detected in lifelong dermal carcinogenicity studies or in tumour initiation studies in mice or in one of two tumour initiation/promotion studies in rats. The finding of increased tumours in the glandular stomach in rats in one study is not applicable to humans as humans have no such comparable tissues.

5.5.9 *Reproductive toxicity*

5.5.9.1 Fertility

No studies were available specifically examining effects of ethanedial on fertility, although some fertility results can be obtained from other studies in which fertility was not a focus.

In one 90-day repeat dose study, epididymal hypospermia with atypical cells and slight degenerative changes of the germinal epithelium in the testes occurred in male rats at the highest concentration administered via drinking water (16 000 mg/L) (NTP 1991). However, it was not clear whether these changes were related to treatment or were a consequence of reduced food and water consumption. In other 90 day repeat dose studies, no treatment-related changes in organ weights, macroscopic or histopathological changes in reproductive organs were noted in either male or female rats (Ueno et al. 1991; Union Carbide 1966) or dogs (Union Carbide 1966).

More recently, a two generation reproduction toxicity study was performed in 2011 in rats in accordance with OECD TG 416 (cited in REACH 2013a). Ethanedial 40% was administered to groups of 25 male and 25 female rats (F0 parental generation) via drinking water at nominal doses of 0, 25, 100 and 400 mg/kg bw/day (active ingredient). Dosing commenced in the F0 parental generation pre mating and continued to weaning of F1 pups. Mid and high dose parental animals showed treatment-related clinical signs (no additional detail was provided) and minor changes in clinical chemistry. The study reported no evidence from clinical, macroscopic or histopathological examinations that ethanedial at any dose adversely affected fertility or reproductive performance in F0 or F1 parental animals. The NOAEL for fertility effects for F0 and F1 parents was the highest dose (400 mg/kg bw/day).

5.5.9.2 Developmental toxicity

A prenatal developmental toxicity study was performed in 2001 in accordance with OECD TG 414 (BASF and Clariant 2001). Female rats received ethanedial via gavage at nominal doses of 0, 5, 25 or 125 mg/kg bw/day (active ingredient) from gestation day 6 to 19. Maternal toxicity (transient sporadic salivation post gavaging, reduced food consumption and body weight gain) were observed at the highest dose. No treatment-related changes in conception rate, mean number of corpora lutea, implantation sites, pre- and post-implantation losses, number of resorptions, or in viable foetuses were observed even at the highest dose of 125 mg/kg bw/day.

Developmental toxicity was also examined in 2011 in the two generation reproduction toxicity study conducted in rats in accordance with OECD TG 416 (cited in REACH 2013a) referred to in Section A5.5.9.1. Ethanedial 40% was administered to groups of 25 male and 25 female rats (F0 parental generation) via drinking water at doses of 0, 25, 100 and 400 mg/kg bw/day (active ingredient). Dosing commenced in the F0 parental generation prior to mating and continued to weaning of F1 pups.

One low dose female animal died during delivery. All other test animals survived treatment. A reduction of the terminal body weights of high dose males (F0 and F1 generation) was regarded as treatment-related. Mid and high dose parental animals also showed minor treatment-related clinical signs (no additional detail was provided) and changes in clinical chemistry. For all liveborn pups of F0 and F1 parents, no test substance-related signs of developmental toxicity were noted up to and including the mid dose (100 mg/kg bw/day). No further details were provided. Postnatal survival as well as post-weaning development of offspring of these test groups until sexual maturity remained unaffected. Furthermore, clinical and / or gross necropsy examinations of the F1 and F2 pups revealed no adverse findings. The study concluded that ethanedial did not induce developmental toxicity in the absence of

maternal toxicity. The NOAEL for developmental effects was considered the highest dose (400 mg/kg bw/day) (REACH 2013a).

Two developmental toxicity studies in rats and rabbits were also available for the chemical ethanedial, trimer, dihydrate (CAS No. 4405-13-4), which is an alternative source of ethanedial in aqueous solutions. In rats, ethanedial, trimer, dihydrate was administered by gavage on gestation days 6 to 15 at doses of 0, 50, 150 and 300 mg/kg bw/day (NTP 1994). Maternal toxicity (slight reduction in food consumption and body weight) was observed at the highest dose. No developmental toxicity was observed in the study even at this highest dose. A similar study was conducted in rabbits in which ethanedial, trimer, dihydrate was administered by gavage on gestation days 6-19 at doses of 0 and 50 mg/kg bw/day (NTP 1993). Mild maternal toxicity (transient reduction of food consumption and body weight) but no developmental toxicity was observed at 50 mg/kg bw/day.

5.5.10 *Other health effects*

No data were available.

5.6 Health hazard summary

5.6.1 *Critical health effects*

Ethanedial is moderately toxic via the oral and inhalation routes. In a guideline study in rats, an oral LD50 for a 40% ethanedial aqueous solution was reported at 3300 mg/kg bw. This corresponds to 1320 mg/kg bw/day for the active ingredient. An LC50 for inhalation toxicity was established at 2.44 g/L (active ingredient). Ethanedial is therefore considered to be of low dermal toxicity.

Animal studies indicate that ethanedial is a skin and eye irritant Based on both animal and human studies, ethanedial is also considered a skin sensitiser.

From an oral 28 day repeat dose toxicity test conducted in accordance with OECD TG 407 a NOAEL was established at 40 mg/kg bw/day (active substance), based on dose-related changes in body weight gain at higher doses. A single inhalation toxicity study in rats revealed no systemic toxicity even at the highest dose of 0.4 mg/m^3.

Ethanedial was shown to be mutagenic in both bacterial and mammalian cells *in vitro*. Unscheduled DNA synthesis was reported in one study in mice *in vivo*, but only within the pyloric sphincter and liver and not in more remote organs.

Results from several carcinogenicity studies, tumour initiation/promotion studies and *in vitro* cell transformation assays show that ethanedial is not carcinogenic. Also, available data on ethanedial and an analogue of ethanedial present in aqueous solutions suggest no effects on fertility or developmental toxicity in the absence of material toxicity.

5.6.2 *Hazard classification*

This hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) for acute inhalation toxicity, irritation, sensitisation and genotoxicity. Ethanedial is also recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances for acute oral toxicity and the adopted Globally Harmonised System of Classification (GHS (United Nations Economic Commission for Europe (UNECE) 2009) for acute oral toxicity, acute inhalation toxicity, irritation, sensitisation

and genotoxicity as shown in Table A5.4. These NICNAS recommendations do not consider physical or environmental hazards.

Table A5.4 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful if swallowed (X_n; R22) Harmful by inhalation (X_n; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled – Cat. 4 (H332)
Irritation / Corrosivity	Irritating to eyes and skin (X_i; R36/38)*	Causes skin irritation – Cat. 2 (H315) Causes serious eye irritation - Cat. 2A (H319)
Sensitisation	May cause sensitisation by skin contact (X_i; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat. 3 - Possible risk of irreversible effects (X_n; R68)*	Suspected of causing genetic defects – Cat. 2 (H341)

*[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b]Globally Harmonised System (UNECE 2009); * Existing hazard classification. No change recommended by NICNAS to this classification.*

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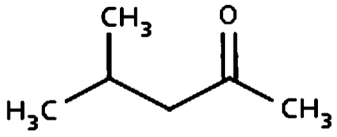
A6 Methyl isobutyl ketone

CAS No.	CAS Name
108-10-1	2-Pentanone, 4-methyl-

6.1 Chemical identity

The identity information was obtained from the Organisation for Economic Cooperation and Development (OECD) (2011) and ChemID*plus* (2012). A description of the chemical identity is provided in Table A6.1.

Table A6.1 Chemical identity

	Methyl isobutyl ketone
Synonyms	MIBK 4-Methyl-2-pentanone Isopropyl acetone Isobutyl methyl ketone
Appearance and odour	Colourless liquid with a faint ketonic and camphor odour
Structural formula	
Molecular formula	$C_6H_{12}O$
Molecular weight	100.16
SMILES notation	C(C)(=O)CC(C)C

6.2 Physical properties

The following information on physical properties was obtained from the World Health Organisation (WHO) (1997) and OECD (2011) (Table A6.2).

Table A6.2 Physical properties

Property	**Value**
Melting point	-84.7 °C
Boiling point	116.1 °C
Density – kg/m^3	8.02 x 10^2 (20 °C)
Vapour pressure	2.0 kPa (20 °C)
Water solubility	17-20.4 g/L (20 °C)
Partition coefficient (log K_{ow})	1.38

Property	Value
Flash Point	14 °C
Conversion factor	1 ppm = 4.1 mg/m^3; 1 mg/m^3 = 0.24 ppm

6.3 Current regulatory controls

Hereinafter the document refers to 2-pentanone, 4-methyl- as MIBK, one of the synonyms of the chemical.

6.3.1 *Hazard classification for occupational health and safety*

MIBK is classified as hazardous for human health in the *Hazardous Substances Information System* (HSIS) with the following risk phrases (Safe Work Australia 2013):

- X_n (Harmful); R20 (Harmful by inhalation)
- X_i (Irritant); R36/37 (Irritating to eyes and respiratory system)
- R66 (Repeated exposure may cause skin dryness or cracking)

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures. The risk phrases for this chemical are:

- Conc ≥25%: X_n: R20, R36/37
- 20% ≤Conc <25%: X_i: R36/37

6.3.2 *Occupational exposure standards*

6.3.2.1 Australia

The chemical has an exposure standard of 205 mg/m^3 (50 ppm) Time Weighted Average (TWA) and 307 mg/m^3 (75 ppm) Short-Term Exposure Limit (STEL).

6.3.2.2 International

The following exposure standards were identified for the chemical (Galleria Chemica 2013).

TWA:

- 80 to 208 mg/m^3 (20 to 50ppm) [Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Korea, Netherlands, New Zealand, Norway, Poland, Portugal, Spain, Sweden, Switzerland, Turkey, UK, US].

STEL:

- 164 to 416 mg/m^3 (40 to 104ppm) [OECD countries as above].

6.3.2.3 Australian food standards

No Australian food standards were identified (Food Standards Australia New Zealand 2013).

6.3.2.4 Australian drinking water guidelines

No aesthetic or health-related guidance values were identified in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

6.3.3 *Additional controls*

6.3.3.1 Australia

The chemical is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedule 5 (CAUTION) with the following entry:

- METHYL ISOBUTYL KETONE, except in preparations containing 25% or less of designated solvents.

The chemical is included in the Australian Dangerous Goods Code Edition 7 (ADG7) (National Transport Commission 2007) with an entry for methyl isobutyl ketone (UN Number 1245) listed as a 'Flammable Liquid' in Class 3. The ADG7 contains detailed provisions for the packaging, transport and marking of containers in Class 3.

6.3.3.2 International

MIBK is currently regulated under the Canadian Department of Justice, Hazardous Products Act, Ingredient Disclosure List (SOR/88-64) with the maximum authorised concentration of 1% (Canadian Department of Justice 2013).

6.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

6.5 Health hazard characterisation

Information on MIBK was sourced primarily from the Environmental Protection Agency (US EPA 2003), the WHO (1990 1991), the European Chemistry Industry Ecology and Toxicology Centre (ECETOC 1987) and the OECD (2011). Additional sources of hazard information for the chemical include the Registration Evaluation Authorisation of Chemicals (REACH 2013) dossier for the chemical, the National Toxicology Program (NTP 2007) and the International Agency for Research on Cancer (IARC 2012). Unless noted, references to individual studies below are taken from these reviews.

6.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

6.5.1.1 Oral absorption

Following oral exposure in rats, the chemical was rapidly absorbed with a maximum concentration observed at approximately 15 minutes and only very low levels at 9 hours post-dosing (Gingell et al. 2003). Plasma MIBK concentrations were 5.3, 8.4 and 16.1 µg/mL in rats at 1 hour after the last of three daily gavage exposures to 1.5, 3.0 and 6.0 mmol/kg

MIBK (150, 300 or 601 mg/kg bw/day) respectively, indicating rapid and dose-related oral absorption into the bloodstream (Duguay and Plaa 1995).

For the purposes of risk assessment, 100% oral absorption in humans is assumed.

6.5.1.2 Dermal absorption

The percutaneous uptake rate in guinea pigs exposed epicutaneously to MIBK peaked at 10 to 45 minutes after the onset of a 150-minute exposure and then started to decline in spite of continuing exposure (Hjelm et al. 1991). The maximum uptake rate ranged from 0.11 to 2.0 µmol/min/cm and averaged 1.1 µmol/min/cm.

For the purposes of risk assessment, 100% dermal absorption in humans is assumed.

6.5.1.3 Inhalation absorption

In rats, plasma MIBK concentrations were 5.0, 8.1 and 14.3 µg/mL immediately following the last of three daily four-hour inhalation exposures to 200, 400, or 600 ppm MIBK (819, 1639, or 2458 mg/m^3), indicating rapid and dose-related respiratory absorption into the bloodstream (Duguay and Plaa 1995). In human volunteers exposed to the chemical at 10 to 200 mg/m^3 for 2 hours during light exercise, relative uptake of the inhaled chemical ranged from 56.3 to 61.7% (Hjelm et al. 1990).

For the purposes of risk assessment, 100% inhalation absorption of MIBK in humans is assumed.

6.5.1.4 Distribution

Human blood/air and oil/air partition coefficients for MIBK indicate significant blood and lipid solubility (Sato and Nakajima 1979). MIBK partitions approximately equally between red blood cells and plasma in rat and human blood; in plasma, MIBK is associated primarily with proteins rather than being dissolved in plasma (Lam et al. 1990). Concentrations of MIBK and its principal metabolite, 4-hydroxy-4-methyl-2-pentanone (HMP) in rat plasma, liver, and lung tissue were positively related to exposure levels shortly after the last of three daily oral or inhalation exposures (Duguay and Plaa 1995). Malyscheva (1988) showed dermal absorption followed by systemic distribution as evidenced by toxicity in many organs; inhalation studies producing hepatic and renal changes are similarly suggestive of extensive distribution (MacEwen et al. 1971; Vernot et al. 1971).

MIBK accumulated rapidly in brain tissue of mice after a single intraperitoneal dose of 5 mmol MIBK/kg, peaking at 30 minutes post-exposure (Granvil et al. 1994). This signifies that the chemical is able to pass the blood-brain barrier.

6.5.1.5 Metabolism

Following oral exposure in rats, the chemical was rapidly metabolised (within 3 hours) to the major metabolite, HMP, with a peak (maximum) concentration (Cmax) of 2.03 mmol/L at 9 hours. HMP remained detectable at 12 hours post dosing. No compounds other than HMP and the chemical were detected in the blood (Gingell et al. 2003). HMP was also identified as the major metabolite in guinea pigs following a single intraperitoneal administration of the chemical. Serum half-life and clearance times of 66 minutes and 6 hours, respectively, were estimated for the chemical in this study (DiVincenzo et al. 1976). Several studies have shown that MIBK can induce microsomal enzyme metabolism in the liver (MacEwen et al. 1971; Vernot et al. 1971; Vezina et al. 1985; Abou-Donia et al. 1985). It is expected that a hydroxylation product like the metabolite HMP would be further metabolised to an O-sulfate or O-glucuronide conjugate. However very low levels were detected in urine and it has been

postulated that HMP may either undergo further metabolism to be eliminated as CO_2 via the lungs or intermediate metabolites may be incorporated into tissues.

6.5.1.6 Excretion

The elimination of MIBK from plasma in rodents was found to be rapid following oral or intraperitoneal exposure. The elimination half-lives in blood ranged from 66 minutes for guinea pigs (DiVincenzo et al. 1976) and 90 minutes for mice (Granvil et al. 1994), administered the chemical intraperitoneally for 210 minutes in rats following oral exposure (Gingell et al. 2003).

In humans, elimination of MIBK from blood following cessation of a 2 hour inhalation exposure during light exercise was biphasic, with a half-life of 11 to 13 minutes during the first 30 minutes post-exposure in subjects exposed to 100 or 200 mg/m^3 (Hjelm et al. 1990). The half-life in blood during the second elimination phase was 59 and 74 minutes in subjects exposed to 100 and 200 mg/m^3, respectively. The O-sulfate or O-glucuronide conjugate were only detected in the urine at low concentration within a 3 hour post-exposure period. Another study reported biphasic urinary elimination of MIBK from human volunteers, although the major route of elimination was by exhalation (Ogata et al. 1995).

6.5.1.7 Summary of toxicokinetics

Studies have shown that MIBK is rapidly and extensively absorbed after oral, dermal, intraperitoneal or inhalation administration. The chemical is likely to be widely distributed in the body because of its high blood and lipid solubility and it has been measured in plasma, liver, lung and brain. In animals, MIBK is rapidly and predominantly metabolised to the water-soluble species, HMP, and can induce metabolic activation in the liver. The chemical was reported to be eliminated via a rapid and slow phase predominantly by exhalation, with urinary excretion at much lower levels.

6.5.2 *Acute toxicity*

The acute toxicity of MIBK is summarised in Table A6.3 (ECETOC 1987; OECD 2011).

Table A6.3 MIBK: Summary of acute lethality studies

Route	Species	Result (mg/kg bw)	Reference
Oral	Rat	LD50 = 4570 mg/kg	Smyth et al. (1951)
	Rat	LD50 = 4600 mg/kg	Batyrova (1973)
	Mouse	LD50 = 2850 mg/kg	Batyrova (1973)
	Mouse	LD50 = 1900 mg/kg	Zakhari et al. (1977)
Dermal	Rat	LD50 >1900 mg/kg	REACH (2103)
Inhalation	Rat	LD50 = 2000-4000 ppm (4-h exposure)	Smyth et al. (1951); Smyth (1956)
	Mouse	LD50 = 5000 ppm (2-h exposure)	Batyrova (1973)

6.5.2.1 Oral

Acute oral median lethal dose (LD50) values from studies with rats were between 4570 mg/kg to 4600 mg/kg (Smyth et al. 1951; Batyrova 1973) and 1900 mg/kg to 2850 mg/kg for mice (Batyrova 1973; Zakhari et al. 1977).

6.5.2.2 Dermal

Acute dermal toxicity was reported to be >2000 mg/kg bw; however, no further details were provided (REACH 2013).

6.5.2.3 Inhalation

There were no median lethal concentration (LC50) data available. Six rats survived a 4 hour exposure to 2000 ppm (8200 mg/m^3) of MIBK but another group of six animals died within 14 days of a 4 hour exposure to 4000 ppm (16 400 mg/m^3) MIBK (Smyth et al. 1951; Smyth 1956).

In two pre-OECD guideline studies, guinea pigs were exposed to MIBK concentrations of 4100, 69000, and 115 000 mg/m^3 for up to 24 hours (Specht 1938; Specht et al. 1940). At 4100 mg/m^3 there was decreased respiratory rate during the first 6 hours of exposure, which was attributed to a narcotic effect. At the higher doses, signs of eye and nose irritation, followed by salivation, lacrimation, ataxia, progressive narcosis and death were reported. Histopathological investigations showed fatty livers and congestion of the brain, lungs and spleen.

6.5.2.4 Observation in humans

In studies where volunteers were exposed to high vapour concentrations of MIBK, a transient anaesthetic effect, which was reversible upon termination of exposure, was noted (Hjelm et al. 1990; Dick et al. 1992; Elkins 1959). Similarly, vapours of MIBK inhaled at concentrations greater than 1000 ppm produced central nervous system (CNS) depression and narcosis (Krasavage et al. 1982). Symptoms, such as headache, nausea or vertigo, also occurred at 10 to 410 mg/m^3 (2.4 to 100 ppm). Gastrointestinal pain and hepatic toxicity may occur with exposure to high concentrations (WHO 1991).

6.5.3 *Irritation / Corrosivity*

6.5.3.1 Skin irritation

A single, 10 hour occluded application of undiluted MIBK to the shaved skin of rabbits produced erythema for up to 24 hours, while daily applications of 10 mL on 10 cm^2 skin for seven days caused flaking and drying of the skin (Krasavage et al. 1982).

The chemical produced no dermal irritation to rabbit skin in a study conducted according to OECD Test Guideline (TG) 404 (REACH 2013).

The chemical is not irritating to the skin but is capable of causing flaking and dryness on repeat application.

6.5.3.2 Eye irritation

In a well-conducted test, in accordance with OECD TG 405, instillation of MIBK into the conjunctival sac of three rabbits caused changes of the conjunctivae that resolved within 24 hours and disturbance of the corneal epithelium that resolved within 48 hours (REACH 2013). Similarly, undiluted MIBK caused inflammation and conjunctival swelling within 8 hours of instillation in the rabbit eye; the inflammation, swelling and exudate present at 24 hours had disappeared by 60 hours (Krasavage et al. 1982).

Overall, the chemical is irritating to the eyes of animals in the reported studies.

6.5.3.3 Respiratory irritation

In a brief report, an irritation threshold of 60 to 120 ppm in cats was identified following a 15 minute exposure to the chemical (Batyrova 1973). The respiratory irritation potential of MIBK has been assessed in the mouse (De Ceaurriz et al. 1981), although details were limited. The RD50 value, the exposure concentration causing a 50% reduction in the respiratory rate, was estimated to be 13 100 mg/m^3 (3195 ppm).

Overall, the animal data available are insufficient to determine the respiratory irritation potential of the chemical.

6.5.3.4 Observation in humans

In several briefly reported human studies, exposure to MIBK resulted in sensory irritation.

Exposure to a concentration of 820 mg MIBK/m^3 (200 ppm) for a 15 minute period caused eye irritation in 12 human volunteers (Silverman et al. 1946), while Shell (1957) also reported undiluted MIBK splashed in the eyes may cause painful irritation.

Workers exposed to 410 mg MIBK/m^3 (100 ppm) have complained of respiratory irritation (Elkins 1959). In human volunteers, irritation, particularly of the nose and throat, was reported following 2 hours' exposure to 10, 100, and 200 mg/m^3 (Hjelm et al. 1990).

Groups of volunteers were exposed via full face mask to 402, 915, 1393, 1680, 2301 or 2827 mg/m^3 of MIBK during a seven minute exposure period. Transient eye, nose and throat irritation reported throughout the exposures generally increased with exposure level; the threshold for irritation was reported to be 1393 mg/m^3 (Esso Research and Engineering Company 1965; Hazleton Laboratories, Inc. 1965).

These human studies indicate liquid MIBK and vapour at concentrations above 10 mg/m^3 are an irritant to the eyes and the upper respiratory tract.

6.5.4 *Sensitisation*

6.5.4.1 Skin sensitisation

No data were available. The chemical does not contain any functional groups that are known to be associated with skin sensitisation.

6.5.4.2 Respiratory sensitisation

No data were available.

6.5.4.3 Observation in humans

No data were available.

6.5.5 *Repeat dose toxicity*

6.5.5.1 Oral

Rodent studies on the repeat dose oral toxicity of MIBK are summarised from US EPA (2003) and OECD (2011), and are presented in Table A6.4. The Lowest-Observed Adverse-Effect Levels (LOAELs), No Observed Adverse Effect Levels (NOAELs) and Klimisch scores (Klimisch et al. 1997) (1 = reliable without restrictions; 2 = reliable with restrictions) are indicated for each study.

Table A6.4 Repeat oral toxicity studies with MIBK

Species	Treatment	Results	Remarks	Reference
Wistar rats (f)	Drinking water, 7 days 0.5, 1% (estimated at 300 or 900 mg/kg bw/day)	No NOAEL established LOAEL = 0.5%	At the top dose, reduced body weight gain and pale or mottled kidneys. At the low dose, pale or mottled kidneys. No control group used.	Carnegie-Mellon Institute of Research, (1977a) Klimisch = 3
Wistar rats (f)	Drinking water, 120 days 0, 1.3% (estimated at 1040 mg/kg bw/day)	No LOAEL or NOAEL established	Increased relative and absolute kidney weights with no related histological changes.	Carnegie-Mellon Institute of Research, (1977a,b) Klimisch = 2
SD rats	Gavage, 13 weeks 0, 50, 250, 1000 mg/kg bw/day	LOAEL = 250 mg/kg bw/day NOAEL = 50 mg/kg bw/day	At the top dose, increased relative and absolute liver and kidney weights were observed. Associated altered clinical chemistry and urinalysis parameters were sex specific with the exception of increased serum cholesterol. Mild nephropathy. Increased relative adrenal and testis weights. At the mid dose, slight increase in terminal absolute or relative kidney weights.	Levine et al., (1987) Klimisch = 1

A number of effects suggestive of liver and kidney toxicity have been observed in animals following repeated oral exposures (Levine et al. 1987). A variety of clinical blood chemistry, urine chemistry and organ weight changes in addition to nephropathy observed at the top dose of 1000 mg/kg bw/day in this study suggest adverse hepatic and renal changes. Absolute or relative increases in kidney weights (6 to 12%), observed at the mid dose of 250 mg/kg bw/day, were also considered as early indications of an adverse effect and corroborative of the abnormal function and histopathological changes seen in the kidney at the top dose. Therefore, a NOAEL of 50 mg/kg bw/day was established for this study, which is regarded in this assessment as the critical study.

6.5.5.2 Dermal

No data were available.

6.5.5.3 Inhalation

The key animal data on the inhalation repeat dose toxicity of MIBK are summarised from OECD (2011), US EPA (2003) and NTP (2007) and presented in Table A6.5. The Lowest-Observed-Adverse-Effect-Concentrations (LOAECs) and No-Observed-Adverse-Effect-Concentrations (NOAECs) are indicated for each study, along with their Klimisch scores.

Table A6.5 Repeat inhalation toxicity studies with MIBK

Species	Treatment	Results	Remarks	Reference
CR rats	2 weeks (4 weeks) 0, 750 (or 4530) mg/m^3	No LOAEC or NOAEC established	At 4530 mg/m^3 (4 weeks), no treatment-related effects. At 750 mg/m^3 (2 weeks), increased relative kidney weights (males).	Hazelton Laboratories (1966, 1968) Klimisch = 2
SD rats	Neurotoxicity test, 13 weeks 0, 250, 750, or 1500 ppm (0, 1024, 3073, or 6146 mg/m^3)	LOAEC = 750 ppm NOAEC = 250 ppm	At the mid- and top dose, increased relative kidney and liver weights and reduced activity during the first 8-10 weeks of treatment. No cumulative neurotoxic effects as assessed by operant behaviour parameters.	David et al. (1999) Klimisch = 1
Fischer 344 rats	14 weeks 0, 50, 250, or 1000 ppm (0, 205, 1033, or 4100 mg/m^3)	LOAEC = 250 ppm(m) NOAEC = 50 ppm (m) LOAEC = 1000 ppm(f) NOAEC = 250 ppm (f)	At the top dose, in males, increased liver weights (absolute and relative) and increased platelet number, urine glucose, serum cholesterol and proteinuria. Hyaline droplet lesions in kidneys. At the top dose, in females, increased urine glucose and decreased eosinophil number. At the mid dose, in males, increased serum cholesterol, urinary glucose and hyaline droplets in kidneys.	Phillips et al. (1987) Klimisch = 1
Fischer 344 rats	2 years 0, 450, 900, or 1800 ppm (0, 1845, 3690, or 7380 mg/m^3)	LOAEC = 450 ppm	Increased mortality and incidence of adrenal medulla hyperplasia in males at the top dose; At all dose levels, chronic nephropathy (both sexes), renal papilla mineralisation, renal tubule hyperplasia and transitional epithelial hyperplasia of the renal pelvis (males).	NTP (2007) Klimisch = 1
B6C3F1 mice	14 weeks 0, 50, 250, or 1000 ppm	No LOAEC or NOAEC established	No adverse treatment-related effects.	Phillips et al. (1987) Klimisch = 1

Additional repeated dose inhalation studies in rats and mice (nine days to five months) have either resulted in no effects or increased liver and kidney weights and hyaline droplet formation (OECD 2011). Some evidence of slight narcosis and transient reduced activity has also been reported. While exposure of MIBK to dogs at 410 mg/m^3 for 90 days had no effect, one of the two monkeys exposed for the same time period to the same concentration had focal chronic renal inflammation (OECD 2011).

In the critical study for determining the effects of repeated exposures to the chemical liver and kidney effects were reported in rats (Phillips et al. 1987). The LOAEC and NOAEC established from the study were 250 ppm and 50 ppm respectively (equivalent to 212 and 42 mg/kg bw/day respectively) in male rats, based on increased serum cholesterol and urinary glucose. Renal hyaline droplet formation noted at the mid- and top dose is considered a male rat-specific lesion that is probably not relevant to humans. In female rats, the NOAEC was 250 ppm established for a LOAEC of 1000 ppm based on clinical blood and urine chemistry changes.

Serious kidney effects (e.g. nephropathy, renal tubular hyperplasia, papillary mineralisation, epithelial hyperplasia of the renal pelvis) seen at doses of 450 ppm and above in a two year carcinogenicity study (NTP 2007) were not reported in shorter term studies. Such findings indicate the possibility that longer term exposure could result in the development of these lesions.

6.5.5.4 Observation in humans

Neurotoxicity observed in humans exposed to MIBK is presented in Section A6.5.9.

6.5.6 *Genotoxicity*

Genotoxicity studies were sourced from OECD (2011), US EPA (2003) and REACH (2013).

MIBK tested negative (with and without metabolic activation) in several bacterial reverse mutation assays and in a gene mutation assay with *Saccharomyces cerevisiae*. The chemical also tested negative in a cell transformation assay using BALB/3T3 mouse embryo cells, in an unscheduled DNA synthesis assay in rat primary hepatocytes and in a micronucleus cytogenetic assay in mice administered chemical intraperitoneally. Although the chemical tested negative in a mouse lymphoma cell forward mutation assay (conducted using mouse cell line L5178Y tk+/tk-) with metabolic activation, results were equivocal in this mouse cell assay conducted without metabolic activation.

Overall, the chemical is not considered to have genotoxic potential.

6.5.7 *Carcinogenicity*

The potential carcinogenicity of MIBK has been examined in a chronic inhalation study conducted in accordance with OECD TG 451 (NTP 2007). Fischer 344 rats and B6C3F1 mice were exposed to the chemical at concentrations of 0, 450, 900, or 1800 ppm for 6 hours/day, 5 days/week for 2 years. Survival was significantly decreased in males at 1800 ppm compared to the controls. Chronic progressive nephropathy (CPN) was observed in all rats (including controls) but there were treatment-related significant increases in both the incidence and severity in all exposed groups. In male rats, there were also increases in renal tubular hyperplasia at all concentrations and in renal tubular adenoma and adenoma/carcinoma (combined) at 1800 ppm; these lesions are thought to represent a continuum in the progression of proliferative lesions in the renal tubular epithelium, resulting in increased severity of CPN, either through α2µ-globulin-dependent or -independent mechanisms. An α2µ-globulin-induced nephropathy is suggestive of a mechanism leading to xenobiotic-induced renal carcinogenesis which is specific to the male rat and not relevant to humans. Increases in the incidence of CPN were also observed in female rats at all exposure concentrations, indicating that CPN was increased by mechanisms in addition to those related to α2µ-globulin. There were also renal mesenchymal tumours in two female rats at 1800 ppm not seen in the historical controls. There was a positive trend in the incidences of mononuclear cell leukaemia in males and the incidence in the 1800 ppm group was significantly increased. In mice, the incidence of hepatocellular adenomas and hepatocellular adenoma/carcinoma (combined) were increased in both sexes exposed to 1800 ppm.

Based on this study, the International Agency for Research on Cancer (IARC) has evaluated the chemical as possibly carcinogenic to humans (Group 2B) (IARC 2012). It was also concluded that the chemical-induced tumours probably occur through a non-genotoxic mechanism. This is supported by the findings outlined in Section A6.5.6.

Overall, there is sufficient evidence in rodents for the carcinogenicity of MIBK through the inhalation route. Under the test conditions, the chemical caused cancer of the liver in male

and female mice. Increases in mononuclear cell leukaemia in male rats and mesenchymal tumours in the kidney of female rats may also have been related to exposure to MIBK.

6.5.8 *Reproductive toxicity*

6.5.8.1 Fertility

In a two-generation inhalation reproduction toxicity study, rats were exposed (whole body) to MIBK at 0, 500, 1000, or 2000 ppm (0, 2050, 4100, or 8200 mg/m^3) for 6 hours per day for 70 days prior to and through mating (Nemec et al. 2004). There were no effects on reproductive parameters, offspring growth and developmental landmarks at any exposure level. The NOAEC for parental systemic toxicity (apart from male nephropathy) was considered to be 1000 ppm (4100 mg/m^3), based on transient reduced body weight gain and food consumption. No NOAEC was identified for effects of MIBK on reproductive parameters or the sexual maturation of pups.

6.5.8.2 Developmental toxicity

In a developmental toxicity study (OECD TG 414), female rats and mice were exposed (whole body) to vapours of the chemical at 0, 300, 1000 or 3000 ppm (0, 1230, 4100 or 12 300 mg/m^3) on gestational days six through to 15, for six hours per day (Tyl et al. 1987). Foetal toxicity was observed only in the presence of maternal toxicity. The NOAEC for maternal toxicity was 1000 ppm (4100 mg/m^3) in both species, based on clinical signs of toxicity, increased kidney weights and decreased food consumption (rat only) and increased liver weights (mice only) at 3000 ppm. The NOAEC for foetotoxicity was 1000 ppm (4100 mg/m^3) in both species, based on reduced foetal body weights, increased occurrence of retarded ossification and an increased incidence of dead foetuses (mice only) at the LOAEC of 3000 ppm (12 300 mg/m^3). There was no evidence of treatment-related maternal, embryo or foetal toxicity (including malformation) at 300 or 1000 ppm in either species.

6.5.9 *Other health effects*

6.5.9.1 Neurotoxicity

Acute inhalation exposure of humans to MIBK resulted in neurological effects. The threshold for odour was reported to be 402 mg/m³ and an index of the prevalence and intensity of neurological symptoms was significantly increased in a group exposed to 200 mg/m³, as compared to a 10 mg/m³ group (Esso Research and Engineering Company 1965; Hazleton Laboratories, Inc. 1965).

In a more detailed study in humans, volunteers were exposed to the chemical in an exposure chamber at 10, 100 or 200 mg/m³ on three separate occasions for two hours under conditions of light exercise (Hjelm et al. 1990). It was noted that the index of reported neurological symptoms (headache, nausea and vertigo) generally increased with exposure level and decreased rapidly after cessation of exposure.

Studies of workers exposed repeatedly to mixtures of solvents that included MIBK reported various associated neuropathies and decrements in neurobehavioural performance tests with exposure (US EPA 2003). However, the results are not sufficient for establishing causality or characterising an inhalation exposure-response relationship in humans. This is because the exposure levels for individual solvents were not reported and the degree to which MIBK contributed to the observed effects was uncertain.

Several studies in animals have also been conducted to examine the potential of the chemical to induce neurotoxicity. Although some studies have reported evidence of

neurobehavioural effects, this was not the case in several other studies designed specifically to measure neurotoxicity (OECD 2011). MIBK has also been shown to enhance the known peripheral neurotoxicity of hydrocarbons such as n-hexane (Abou-Donia et al. 1985, 1991).

6.6 Health hazard summary

6.6.1 *Critical health effects*

In animals, MIBK is of low acute toxicity by the oral, dermal and inhalation routes. Reversible depressant effects on the central nervous system have been observed in humans after inhalation exposure and the chemical causes eye and respiratory tract irritation. Following repeated dermal application, flaking and drying of the skin could also occur but MIBK is not expected to be a sensitiser.

A number of effects suggestive of liver and kidney toxicity have been observed in animals following repeated oral exposures. The most appropriate NOAEC for risk assessment determined from the 14-week inhalation study by Phillips et al. (1987) is 42 mg/kg bw/day based on liver and kidney effects in male rats at the LOAEC of 212 mg/kg bw/day.

MIBK is not genotoxic but there is sufficient evidence in rodents for the carcinogenicity of inhaled MIBK under conditions of repeated exposure at high dose levels. The primary target organ for carcinogenicity was the kidney in rats and the liver in rats and mice.

Results of fertility and developmental toxicity studies in animals indicate that the chemical is foetotoxic at a LOAEC of 3000 ppm, where maternal toxicity is also evident, but is not a developmental toxicant at a NOAEC of 1000 ppm.

6.6.2 *Hazard classification*

This hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) for acute toxicity and irritation. MIBK is also recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances for carcinogenicity and the adopted Globally Harmonised System of Classification (GHS (United Nations Economic Commission for Europe (UNECE) 2009) for acute toxicity, irritation and carcinogenicity as shown in Table A6.6. These NICNAS recommendations do not consider physical or environmental hazards.

Table A6.6 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful by inhalation (X_n; R20)*	Harmful if inhaled – Cat. 4 (H332)
Irritation/ Corrosivity	Irritating to eyes (X_i; R36)* Irritating to respiratory system (X_i; R37)* Repeated exposure may cause skin dryness or cracking (R66)*	Causes serious eye irritation – Cat. 2A (H319) May cause respiratory irritation – Specific target organ toxicity, single exposure - Cat. 3 (H335) Repeated exposure may cause skin dryness or cracking (AUH066)

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Carcinogenicity	Carc. Cat. 3 – Limited evidence of a carcinogenic effect (X_n; R40)	Suspected of causing cancer – Cat. 2 (H351)

*[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009); * Existing hazard classification. No change recommended by NICNAS to this classification*

6.7 References

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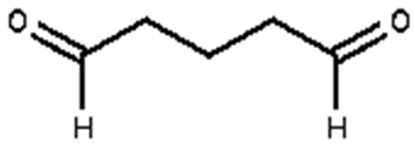
A7 Glutaraldehyde

CAS No.	CAS Name
111-30-8	Pentanedial

7.1 Chemical identity

The following chemical identity information was obtained from ChemID*plus* (2012) and National Industrial Chemicals Notification and Assessment Scheme (NICNAS 1994). Table A7.1 provides details of the chemical identity.

Table A7.1 Chemical identity

	Glutaraldehyde
Synonyms	Glutaraldehyde 1,3-diformylpropane Glutaric dialdehyde 1,5-pentanedione
Structural formula	
Molecular formula	$C_5H_8O_2$
Molecular weight	100
Appearance and odour	Colourless oily liquid with a pungent smell
SMILES notation	O=CCCCC=O

7.2 Physical properties

The physical properties of glutaraldehyde are presented in Table A7.2. This information was obtained from NICNAS (1994).

Table A7.2 Physical properties

Property	Value
Melting point	Not applicable
Boiling point	188 °C
Density	0.72 kg/m^3 at 25 °C
Vapour pressure	2.03 x 10^{-3} kPa at 25 °C (50% solution)
Water solubility	Soluble in all proportions in water and ethanol

Property	Value
Partition coefficient n-octanol/water (log K_{ow})	-0.01 (50% solution).

7.3 Current regulatory controls

7.3.1 *Hazard classification for occupational health and safety*

Glutaraldehyde is classified as hazardous in the Hazardous Substances Information System (HSIS) with the following risk phrase (Safe Work Australia 2013):

- T (Toxic); R23/25 (Toxic by inhalation and if swallowed)
- C (Corrosive ; R34 (causes burns)
- R42/43 (May cause sensitisation by inhalation and skin contact).

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures. The risk phrases for this chemical are:

- Conc ≥50%: T; R23/25; R34; R42/43 (Toxic; toxic by inhalation and if swallowed; causes burns; may cause sensitisation by inhalation and skin contact)
- ≥25% Conc <50%: T; R23; R22; R34; R42/43 (Toxic; toxic by inhalation, harmful if swallowed, causes burns; may cause sensitisation by inhalation and skin contact)
- ≥10% Conc <25%: C; R20/22; R34; 42/43 (Corrosive; harmful by inhalation and if swallowed; causes burns; may cause sensitisation by inhalation and skin contact)
- ≥2% Conc <10%: Xn; R20/22; R37/38; R41; R42/43 (Harmful; harmful by inhalation and if swallowed; irritating to respiratory system and skin; risk of serious eye damage; may cause sensitisation by inhalation and skin contact)
- ≥1% Conc <2%: Xn; R36/37/38 R42/43 (Harmful; Irritating to eyes, respiratory system and skin; may cause sensitisation by inhalation and skin contact)
- ≥0.5% Conc <1%: Xi; R36/37/38; R43 (Irritating; irritating to eyes, respiratory system and skin; may cause sensitisation by skin contact)

7.3.2 *Occupational exposure standards*

7.3.2.1 Australia

The chemical has an exposure standard of 0.41 mg/m³, 0.1 ppm; Time Weighted Average (TWA).

7.3.2.2 International

The following exposure standards are identified in Galleria Chemica (2013):

- Occupational Exposure limit (TWA) of 0.2 mg/m^3 [Canada, China, Denmark, Japan, Korea, UK]
- 0.4 mg/m^3 TWA [Sweden]
- 0.8 mg/m^3 TWA [US (NIOSH), Greece].

7.3.3 *Australian food standards*

No Australian food standards relating to the chemical have been identified (Food Standards Australia New Zealand 2013).

7.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the *Australian Drinking Water Guidelines*. (National Health and Medical Research Council (NHMRC) 2011).

7.3.5 *Additional controls*

Glutaraldehyde is included in Schedule 2, Schedule 5 and Schedule 6 of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014)

- Schedule 2: GLUTARALDEHYDE for human therapeutic use
- Schedule 5: GLUTARALDEHYDE in preparations containing 5% or less of glutaraldehyde except:
    a) when included in Schedule 2 or
    b) in preparations containing 0.5% or less of glutaraldehyde when labelled with the statements: IRRITANT; and Avoid contact with eyes.
- Schedule 6: GLUTARALDEHYDE except:
    a) when included in Schedule 2 or 5 or
    b) in preparations containing 0.5% or less of glutaraldehyde when labelled with the statements: IRRITANT; and Avoid contact with eyes.

Glutaraldehyde is not included in the Australian Dangerous Goods Code Edition 7(ADG7) (National Transport Commission 2007).

7.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

7.5 Health hazard characterisation

The information on health hazards is obtained from the Organisation for Economic Cooperation and Development (OECD 1995); Registration, Evaluation, Authorisation and Restriction of Chemicals dossiers on glutaraldehyde (REACH 2013) and NICNAS (1994). Unless otherwise noted, references to individual studies below are taken from these sources.

7.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

7.5.1.1 Oral absorption

In a detailed toxicokinetics study conducted in 2004 (REACH 2013), absorption, tissue distribution and excretion of glutaraldehyde were studied in male and female Wistar rats following oral administration. The radiolabelled test substance was administered by single gavage at doses 5 and 75 mg/kg bw.Faeces and urine were collected at six, 12 and 24 hours and thereafter at 24-hour intervals for up to 168 hours and CO_2 in exhaled air was determined throughout this period and checked for radioactivity. After 168 hours, liver, kidney, heart, lung, brain, gonads, spleen, pancreas, adrenals, thyroid, stomach, stomach contents, gut, gut contents, blood cells and plasma, uterus, muscle tissue, skin, bone, bone marrow, fat and remaining carcass were checked for radioactivity content. The mean total radioactivity recovery for both doses was more that 91%. In the 5 mg/kg bw group, 45% and 49% of the administered dose was excreted in faeces in males and females, respectively, indicating that more than 50% of the administered dose was absorbed from the intestine and excreted through urine, carbon dioxide and bile. At the higher dose (75 mg/kg bw), reduced absorption through the intestine (around 40%) was noted.The results of distribution and excretion of glutaraldehyde are discussed under sections A7.5.1.4 and A7.5.1.6, below.

In another toxicokinetics study, male Fischer 344 rats were administered 68.5 mg/kg bw radiolabelled glutaraldehyde in 0.25 mL solution by gavage (REACH 2013). Urine and faeces were collected separately at 24 and 48 hours following treatment. Results showed that only 23% of the radioactivity was eliminated via faeces, indicating significant absorption of the administered glutaraldehyde through the gastrointestinal tract.

Based on these observations, 100% absorption of glutaraldehyde by the gastrointestinal tract will be assumed for human risk assessment purposes.

7.5.1.2 Dermal absorption

Dermal absorption of glutaraldehyde is low (NIOSH 2011). In a dermal absorption study, 2.5 mL of 0.75 and 7.5% radiolabelled glutaraldehyde solution was applied to the dorsal clipped skin of New Zealand White rabbits under occluded conditions (McKelvey et al. 1992). Blood samples (0.1 to 0.3 mL) were taken at regular intervals. Only a small fraction of the radiolabelled chemical was detected in the blood. The absorption rate constants were low, with average values ranging from 0.2 to 2.0/hour. The estimated percutaneously absorbed dose of glutaraldehyde in rabbits ranged from 2.5% to 15.6%.

In an *in vitro* skin penetration study using isolated human epidermis (chest and abdomen) and human stratum corneum (blister tops from the sole), 2.8% to 4.4% penetration of glutaraldehyde in the isolated epidermis and 3.3% to 13.8% penetration through the thin stratum corneum were reported 1 hour after application of 10% glutaraldehyde aqueous solution (Reifenrath et al. 1985). Glutaraldehyde did not penetrate the thick stratum corneum.

Based on these observations, a dermal absorption rate of 10% for glutaraldehyde will be used for human health risk assessment.

7.5.1.3 Inhalation absorption

Information on inhalation absorption of glutaraldehyde is not available. In the absence of data on inhalation absorption, a 100% absorption by this route is assumed for human health risk assessment.

7.5.1.4 Distribution

Glutaraldehyde administered orally is rapidly absorbed and distributed to almost all tissues and organs in the body. In the 2004 toxicokinetics study described previously (Section

A7.5.1.1) and other similar studies described in the REACH dossier on glutaraldehyde (REACH 2013), radioactivity was detected in all tissues and organs following administration of radiolabelled glutaraldehyde by gavage or by intravenous injection. In most organs, highest concentrations of glutaraldehyde were detected 1 hour after administration, following which the radioactivity declined.

7.5.1.5 Metabolism

Metabolism of glutaraldehyde to CO_2 has been investigated in a number of *in vivo* and *in vitro* studies (Ballantyne 1986; Karp et al. 1987; Beauchamp et al. 1992). These studies have suggested that the glutaraldehyde metabolic pathway involves a series of oxidation, decarboxylation and hydration reactions. The initial step is believed to be oxidation of glutaraldehyde to glutaric semialdehyde, followed by oxidation to glutaric acid, which can undergo further metabolism by synthesis of a Coenzyme A thioester. The glutaryl CoA produced is then oxidised by glutaryl CoA dehydrogenase to give glutaconyl CoA, which is subsequently decarboxylated to crotonyl CoA (Besrat et al. 1969). The crotonyl CoA is converted by enoyl CoA hydratase to β-hydroxybutyryl CoA, which can subsequently be used for synthesis of acetoacetate or be degraded to acetate and then to CO_2 (US DHHS 1993).

7.5.1.6 Excretion

Orally administered glutaraldehyde is rapidly excreted via faeces, urine and expired air (CO_2). In the 2004 toxicokinetics study described earlier in the report (REACH 2013), recovery of radioactivity in exhaled air ($^{14}CO_2$) reached 19.5% in male rats within 72 hours and 20.6% in females within 96 hours following dosage with 75 mg/kg bw test substance. Radioactivity recovery in urine was almost complete after 48 hours. During the first 48 hours following dosage, radioactivity recovery in faeces was 58.5% for males and 51.3% for females. Total biliary excretion was about 2.6% of the administered radioactivity. The maximum excretion was reached within the first 6 hours following dosage for both sexes; thereafter the biliary excretion declined continuously.

7.5.2 *Acute toxicity*

7.5.2.1 Oral

Several acute oral toxicity studies with glutaraldehyde have been reported in rats and other species. In one reliable study, administration of 0.2, 0.3, 0.5, 1.0, 1.7 mL/kg bw glutaraldehyde (corresponding to 226, 339, 565, 1130 and 1921 mg/kg bw, respectively) to male/female Wistar rats by gavage gave a median lethal dose (LD50) of 226 mg/kg bw (REACH 2013). Necropsy of animals that died during the observation period revealed congestion of the lungs and the abdominal viscera. In another study in Sprague-Dawley rats, the oral LD50 was 316 mg/kg bw for males and 285 mg/kg bw for females, when 10 mL of 2.15, 3.16, 4.64, 14.7% glutaraldehyde (corresponding to 215, 316, 464 and 1470 mg/kg bw) was administered by oral gavage (REACH 2013).

In a separate study using different strengths of glutaraldehyde, Ballantyne (1986) showed that the oral LD50 for glutaraldehyde in rats varied with the concentration of the glutaraldehyde used. By using different concentrations of glutaraldehyde solutions (1% to 50%) and varying the administration volume to maintain a constant dose, oral LD50 in the range 66 to 733 mg/kg bw were obtained.

These studies indicate that glutaraldehyde has high acute oral toxicity.

7.5.2.2 Dermal

Of the 18 acute dermal toxicity studies reported in REACH (2013) dossiers, results from 14 studies indicated LD50 higher than 2000 mg/kg bw. In four other studies, LD50 ranged between 250 and 1432 mg/kg bw. These studies however did not follow international guidelines and have low reliability.

Based on these studies, glutaraldehyde is considered to have low acute dermal toxicity.

7.5.2.3 Inhalation

In a well-defined study, 10 male and 10 female Sprague-Dawley rats per dose group were exposed to glutaraldehyde as liquid aerosol at 0.22, 0.31 and 0.63 mg/L for 4 hours (REACH 2013). Exposure was followed by an observation period of 14 days. During the exposure period slight nasal discharge, snout wiping, flank respiration and irregular to intermittent respiration were reported in rats. During the post-exposure period, bloody nasal discharge, red crusts surrounding the nose, whooping or gasping respiration with rasping sounds and a tremulous gait were observed. These symptoms disappeared in the surviving animals within 5 to 9 days post-exposure. Mortalities were noted in all treated groups. The determination of the LC50 values was based on the Probit Analysis. An LC50 of 0.48 mg/L was calculated for both male and female rats.

In another acute inhalation study conducted in a similar manner to the above study, Sprague-Dawley rats, 10 rats per sex per dose group, were exposed to 0.1, 0.18, 0.28, 0.39 and 0.44 mg/L glutaraldehyde as liquid aerosol for 4 hours (REACH 2013). During and after exposure, mortality and clinical signs of toxicity were recorded at regular time intervals. The LC50 in this study was established as 0.28 mg/L for females and 0.39 mg/L for males.

Based on the above studies, glutaraldehyde is considered to have high acute inhalation toxicity.

7.5.2.4 Observation in humans

No deaths in humans due to glutaraldehyde exposure have been reported. The most common symptoms reported for cases of dermal exposure were skin irritation/burning, rash, itching, skin discoloration/redness (US EPA 2007). Inhalation exposure is reported to cause headache, dizziness, nausea, stomach ache, sore throats, numbness of limbs, and cardiac effects, such as heart palpitations and tachycardia (US EPA 2007).

7.5.3 *Irritation / Corrosivity*

7.5.3.1 Skin irritation

Several studies on the skin irritant effects of glutaraldehyde in rabbits have been reported (REACH 2013, NICNAS 1994). Almost all studies produced positive results for skin irritation. Erythema, edema and skin necrosis were commonly observed in animals treated with 25% or 50% glutaraldehyde solution (REACH 2013). In a skin irritation study conducted according to OECD guidelines, 0.5 mL of 50% glutaraldehyde solution was applied to the shaved skin of New Zealand White rabbits. After a period of 4 hours, under semi-occlusive conditions, the dressing was removed and the animals were observed at one, 24, 48 and 72 hours and seven days post application. All rabbits showed moderate to severe erythema and oedema. After 24 hours, necrosis was minor in three and well-defined in one case. After 48 hours, all rabbits displayed necrosis, which was well-defined in three cases. Fissuring of the skin was observed in one rabbit after 72 hours and on a further two after seven days. In addition to the well-defined necrosis, desquamation of the skin at the application site was reported for all

animals at day seven; in one case this was accompanied by scab formation. After 10 days, all rabbits displayed scabs and alopecia, although erythema and edema had subsided.

In another skin irritation study, severe skin reactions (erythema and edema extending beyond treated area) were reported in Vienna White rabbits following application of 50% glutaraldehyde under occlusive conditions for 4 hours. No reversibility was noticed and pronounced necrosis was seen at the end of the observation period of eight days, thus indicating that the test material was corrosive to the skin of rabbits under the test conditions used (REACH 2013).

Based on these observations, glutaraldehyde is concluded to be corrosive to skin.

7.5.3.2 Eye irritation

In an eye irritation study published by Ballantyne et al. (1997), 0.1 mL of 2.2% glutaraldehyde solution was instilled into the conjunctival sac of one eye of New Zealand White rabbits (three males and three females). The untreated eye in each rabbit served as a control. The eyes were examined for signs of irritation after 1 hour and 1, 2, 3, 7, 10, 14 and 21 days, or until healing. All animals showed necrosis and haemorrhage of the nictitating membrane on day two. Moderate to severe conjunctival hyperaemia was observed in treated eyes and lasted until day 14. Moderate chemosis was also seen after one day and lasted until day three. The animals also developed iritis and corneal opacity that lasted 7 to 10 days. Corneal neovascularisation was seen only in some cases.

In another study conducted according to a method equivalent to the OECD Test Guideline (TG) 405 (Acute Eye Irritation/Corrosion), 0.1 mL of 25% glutaraldehyde was applied to the eyes of Vienna White rabbits (REACH 2013). The eyes were left unwashed and were examined after 1 hour, 24 hours, 48 hours, 72 hours, 96 hours and at day eight. After 1 hour, corrosion of the mucosa with redness, marked edema and corneal opacity were noted. Observation at 24 hours revealed corrosion in the eyes as well as severe oedema. No change in the condition was noted eight days after treatment and the changes were irreversible. Control eyes treated with physiological saline remained free from effects. The authors of the study concluded that glutaraldehyde was corrosive.

Several other studies have reported similar results (cited in REACH 2013). Based on all these studies, glutaraldehyde was considered to be corrosive to the eye.

7.5.3.3 Respiratory irritation

Glutaraldehyde vapour has been identified as an irritant to the respiratory system in mice as measured by its effect on the respiratory rate (BRRC 1993). In the respiratory irritation study, conducted according to Method E981-84 of the American Society for Testing and Materials (ASTM), male ND4 Swiss Webster mice were exposed (head only) to concentrations of glutaraldehyde vapour ranging from 1.64-36.7 ppm for 30 minutes, with a seven-day recovery period after exposure. The glutaraldehyde vapour concentrations were generated by passing compressed air through a bubbler containing 50% aqueous glutaraldehyde solution. The respiratory rate (breaths/minute) of each animal was measured every 15 seconds and compared with the pre-exposure rate. No mortality occurred during the study and no clinical signs of toxicity were observed. The respiratory rate decreased sharply at all concentrations within three minutes of exposure, with the depression maintained throughout the 30 minute period. The decrease in respiratory rate was due to a lengthening of the expiratory phase of breathing. Under the conditions of the study, respiratory irritation in mice, as measured by decrease in respiratory rate, was observed at all vapour concentrations, significant even at the lowest concentration. The RD50, the concentration which produces a 50% decrease in respiratory rate, was calculated to be 13.8 ppm glutaraldehyde.

Respiratory irritant effects of glutaraldehyde at low vapour concentrations were also observed in test animals during acute inhalation studies (REACH 2013). Signs of irritation included laboured and audible breathing and wetness and encrustation around the nose.

7.5.3.4 Observations in humans

Human evidence has shown that glutaraldehyde is an irritant to the skin, eyes and respiratory system, consistent with those demonstrated in experimental animals. Several cases of dermatitis have been reported for workers exposed to glutaraldehyde solutions (OECD 1995). Contact dermatitis and eye and respiratory problems were observed in nurses who were regularly exposed to glutaraldehyde during the disinfection of instruments such as endoscopes and bronchoscopes, and radiologists, who used glutaraldehyde as a fixative in their x-ray developing solutions (NICNAS 1994). Facial dermatitis has resulted from the use of glutaraldehyde in spray form.

In a South Australian study, hand dermatitis was reported in dental assistants and facial irritation was reported in egg collectors spraying eggs with a glutaraldehyde sanitising solution (NICNAS 1994). In several cases of dermatitis, sensitisation to glutaraldehyde has been demonstrated by patch testing (NICNAS 1994).

Irritation of the nose and throat and general tightness of the chest have been experienced by workers exposed to glutaraldehyde vapours. In a study of Swedish hospital workers, nose and throat irritation was experienced at vapour concentrations below 0.2 ppm (NICNAS 1994). Eye irritation was observed in workers exposed to glutaraldehyde vapours above disinfectant solutions. Human evidence indicates that skin and respiratory irritant effects are exacerbated on repeated exposure to glutaraldehyde (OECD 1995).

7.5.4 *Sensitisation*

7.5.4.1 Skin sensitisation

In a maximisation test (NICNAS 1994) conducted according to the OECD TG 406, 2% aqueous glutaraldehyde was found to be a moderate to strong skin sensitiser in guinea pigs.

In a Local Lymph Node Assay (LLNA) using either acetone or dimethylformamide (DMF) as the application vehicle glutaraldehyde gave positive reaction at all tested concentration levels except for the lowest tested concentration of 0.1%; the stimulation indices ranged from 3 to 18, with 18 having been reported for the highest test concentration (Hilton et al. 1998).

Glutaraldehyde also tested positive in several mouse-ear swelling tests, proposed for the detection of skin allergens (REACH 2013).

Glutaraldehyde was considered to be a skin sensitiser.

7.5.4.2 Respiratory sensitisation

In a mouse Immunoglobulin E (IgE) test, regarded as a test for respiratory sensitisation potential, glutaraldehyde induced a slight increase in total serum IgE levels which was only significant at higher concentrations of glutaraldehyde (Potter and Wederbrand 1995).

7.5.4.3 Observation in humans

The skin sensitising effect of glutaraldehyde in workers exposed to the chemical is well documented with numerous cases of allergic skin reactions reported in the scientific literature.

A hospital cleaner, a surgical instruments nurse and a hospital maintenance employee, all without any personal or family history of atopy or dermatitis developed dermatitis of the hands and fingers and around the mouth and eyes after exposure to 2% or less glutaraldehyde solutions (NICNAS 1994). Patch testing with glutaraldehyde gave positive results at 48 and 72 hours. In another report (Nethercott et al. 1988), allergic contact dermatitis of the hands was found in 13 health care workers, comprising five dental assistants, three endoscopy nurses, two supply nurses, a veterinarian, a respiratory technician and an embalmer, who were exposed regularly to glutaraldehyde. At least seven of the workers had no history of atopy. The patients were patch tested to standard procedures on the upper back with 1% glutaraldehyde, the patch being in place for 48 hours and readings taken soon after removal (30 to 60 minutes) and at 96 hours. Nine of the workers showed a positive response at the first reading and all 13 showed positive responses at 96 hours.

According to a review by the Dutch Expert Committee on Occupational Standards (2005), glutaraldehyde can cause asthmatic symptoms, such as wheezing, coughing, chest tightness, breathing difficulties and non-specific hyper responsiveness. The asthmatic symptoms were considered to be indicative of a respiratory sensitising potential for glutaraldehyde. Based on immunological tests in humans and the few animal studies and indications that glutaraldehyde may cause allergic skin sensitisation, the Dutch Committee concluded that glutaraldehyde should be considered as a respiratory sensitiser.

To summarise, glutaraldehyde is readily absorbed by the gastrointestinal tract but only sparingly absorbed by the skin. Information on the inhalation absorption rate of glutaraldehyde is not currently available. It has high acute oral and inhalation toxicity and moderate acute dermal toxicity. Glutaraldehyde is corrosive to the skin and eyes. Vapours of glutaraldehyde are irritant to respiratory tract. It has skin and respiratory sensitisation potential.

7.5.5 *Repeat dose toxicity*

7.5.5.1 Oral

A subchronic oral toxicity study in rats was carried out with UCARCIDE 250 Antimicrobial (50% w/v glutaraldehyde) by a method similar to the OECD TG 408 (BRRC 1985). Four groups, each of 20 male and 20 female Fischer 344 rats, received 0, 50, 250 or 1000 ppm w/v glutaraldehyde in their drinking water over 13 weeks. The approximate daily intakes were 5, 25, or 100 mg/kg bw/day for male rats, and 7, 35 or 120 mg/kg bw for females.

Food consumption was significantly reduced in male and female rats in the high dose group, paralleled by reduction in body weight. No haematological effects were observed. A significant dose-related increase in kidney weight relative to final body weight occurred in males and females in the 250 and 1000 ppm groups, however histologic examination of tissues revealed no treatment-related findings. A No Observed Adverse Effect Level (NOAEL) could not be established in this study.

In another subchronic oral study conducted according to OECD guidelines, male and female Fischer 344 rats were given glutaraldehyde in drinking water for 13 weeks (BRRC 1985). The three dose levels tested were 50, 250, 1000 ppm (5, 25, 100 mg/kg bw/day in males and 7, 35, 120 mg/kg bw/day in female rats).

No mortality or clinical signs of toxicity were observed. Necropsy revealed a dose-related increase in kidney weight relative to the final body weight at 250 and 1000 ppm for the males. In females, the absolute and relative kidney weights as well as the kidney weights

relative to the brain were increased in a dose-related manner at 250 and 1000 ppm. The increase in kidney weight was considered to be treatment-related and a NOAEL of 50 ppm (5 mg/kg bw/day in males and 7 mg/kg bw/day in females) was established.

In a chronic 12-month study conducted according to OECD TG 452 (Chronic Toxicity Studies), glutaraldehyde was administered to male and female Wistar rats in drinking water (REACH 2013). The concentration of glutaraldehyde in the water was 100 ppm, 500 ppm or 2000 ppm corresponding to 6.4, 30.5 and 116.6 mg/kg bw/day in males and 9.6, 46.0, 153.2 mg/kg bw/day in females. No treatment-related mortalities occurred and no changes in hematology, clinical chemistry or histology were observed in any dose group. The following effects, considered to be treatment-related, were reported in the highest dose group (2000 ppm): decrease in food consumption and body weight (up to –11.2%), lesions within the glandular stomach (both sexes showed erosion/ulceration of the glandular stomach), increased incidence of clear cell foci in the liver (males) and a single case of slight diffuse squamous metaplasia in the epithelium of the larynx in a male rat. A NOAEL of 500 ppm (30.5 mg/kg bw/day in males and 46 mg/kg bw/day in females) was established in this study.

A two-year chronic study was conducted in male and female Fischer 344 rats (NICNAS 1994). Groups of 100 male and 100 female rats were administered 0, 50, 250, or 1000 ppm w/v glutaraldehyde in drinking water (4, 17 and 64 mg/kg bw/day for the males and 6, 25 and 86 mg/kg/day for the females). The mortality rate over the treatment period was 25 to 30% for males and 19 to 23% for females with no dose-related increase. The major cause of death in all rats (control and dose groups) was large granular cell lymphatic leukaemia (LGLL).

Small dose-related decreases in absolute body weight and body weight gain occurred at 250 and 1000 ppm in males and at 1000 ppm in females. Dose-related decrease in urine volumes and associated increase in osmolality were observed in higher dose animals. At necropsy at 52, 78 and 104 weeks, the only statistically significant changes in organ weights were for the kidney. Relative kidney weights were increased for males and females at 52 and 78 weeks. A significant dose-related increase in kidney weight relative to final body weight occurred for males and females in the 250 and 1000 ppm groups, including an increase in absolute kidney weight for the female rats. Changes in final body weights and the weights of other organs were minor and / or sporadic and were unlikely to be related to glutaraldehyde exposure.

The total leucocyte count was significantly increased at week 104 in males at 250 and 1000 ppm, and in females at 250 ppm only. The variation in counts was large, possibly due to the large monocyte count at 250 and 1000 ppm. Changes in clinical chemistry parameters included decreases in the activities of some enzymes at 250 and 1000 ppm and occasional decreases in total protein, globulin and phosphorous; these were probably due to reduced food consumption and body weight.

Gross pathology showed evidence of gastric inflammation, particularly in rats sacrificed at the end of the study, with irritation observed as ulceration, a multifocal colour change and thickening of the mucosa (dose groups not specified). Histologic examination of the tissues revealed squamous epithelial hyperplasia and keratinised cysts and oedema.

The increased incidence of LGLL in treated rats is discussed in Section A7.5.7 *Carcinogenicity*. Based on the observations, a NOAEL of 4 mg/kg bw/day for males and 6 mg/kg bw/day for females was established in this study.

For the purpose of human health risk assessment, the lowest NOAEL (4 mg/kg bw/day) established in the two-year chronic study in rats will be used.

7.5.5.2 Dermal

In a subacute dermal study (Ballantyne 1986), male C3H mice were dermally treated with glutaraldehyde solution for two weeks (10 applications per animal). 50 µL of test solution (100%, 50%, 10%, 5%, 1%, 0.5%, and 0.1% glutaraldehyde) were applied to the clipped dorsal skin of mice (five animals per group).

All animals receiving 50% and 100% of test material lost weight and died after four to nine applications, indicating that toxicity is possible by repeated dermal contact with the test material. However, no consistent features were seen on necropsy of these animals. Mice receiving 10% glutaraldehyde had decreased body weights after four and six doses, but not thereafter. There was no evidence of short-term toxicity in mice treated with glutaraldehyde concentrations less than 10%. A dermal NOAEL of 5% glutaraldehyde was suggested by the study authors. For a 100 g mouse, the NOAEL is estimated to be 25 mg/kg bw.

In a subchronic dermal study conducted according to OECD TG 411, male/female Sprague-Dawley rats (10 per sex per group) were dermally treated with 2 mL/kg bw/day of a test material containing 50% glutaraldehyde (REACH 2013). Three concentrations of the test material (5%, 10% or 15%) were applied which corresponded with 25, 50 or 75 mg/kg bw/day glutaraldehyde. The test solution was applied to the clipped dorsal skin of each animal following which the application site was covered with gauze held in place with a semi-occlusive dressing for 6 hours. The animals were treated five days a week over a period of 13 weeks, implying 67 days of test substance-administration.

Signs of local irritation, including scabs, desquamation and very slight or well-defined erythema, were noted at the application site of almost all treated animals. Slight to moderate acanthosis, together with the presence of inflammatory cells in the dermis was reported for the skin.

Slight decrease in body weights and changes in hematological parameters were noted in treated animals which were considered to be of no biological/ toxicological relevance. Differences in organ weights were minimal and not related to dose or microscopic findings. No systemic effects were noted in any of the treated groups. Lesions in the liver included coagulative hepatocellular necrosis, interlobular fibroplasia, tension lipidosis and macrophages with yellow pigment contents. These findings were in accordance with the macroscopical findings in the liver and were found with similar incidence and severity in both, treated and control animals.

A NOAEL could not be established as no effects were seen even at the highest dose tested.

7.5.5.3 Inhalation

The following key rodent data on the repeat dose inhalation toxicity of glutaraldehyde in Table A7.3 have been summarised from REACH (2013) and NICNAS (1994).

Table A7.3 Repeated dose inhalation studies

Test substance	Method	Results	Remarks	Reference
Glutaraldehyde	Male/female rats; 9-days; 0, 0.3, 1.1, 3.1 ppm	NOAEL = 0.3 ppm.	Atrophy of the liver and mortality (7/12) at 3.1 ppm; respiratory irritation, nasal cavity lesions and changes in urine and blood	BRRC (1983)

Test substance	Method	Results	Remarks	Reference
			parameters at 1.1 and 3.1 ppm. Small increase in lung weight for males at 0.3 ppm.	
Vapors from 50% Glutaraldehyde	Wistar rats; 28 days, 6 /day, 5 days/week 0.025 ppm and 0.1 ppm (0.0001, 0.0004 mg /L)	NOAEL = 0.0001 mg/L	Pronounced morphological changes in lung tissue at 0.1 ppm after a post-exposure period of 24 hours and several foci of collagen fibres observed 7 days post-exposure	Halatek et al. (2003)
Glutaraldehyde 50% aq. solution	Fischer 344 rats 14 weeks 6 h/day, 5 days/week 0, 0.02, 0.05, 0.2 ppm (0.00008, 0.0002, 0.0008 mg/L)	NOAEL = 0.02 ppm (0.00008 mg/L. LOAEL = 0.05 (0.0002 mg/L)	Reduced body weight, signs of irritation with perinasal discharge and encrustation at 0.05 ppm and above.	Ballantyne et al. (1985)
Glutaraldehyde	Wistar rats; 13 weeks; 0, 0.062, 0.125, 0.25, 0.5, 1.0 ppm	NOAEL = 0.125 ppm	No exposure-related mortality. Dose-related lesions of nasal cavity and, reduced body weight gain at 0.25 ppm.	NTP (1993)
Glutaraldehyde vapors	B6C3F1 mice; 2 years; 6 h/day, 5 days/week 0, 0.062, 0.125, 0.250 ppm (0, 0.00025, 0.0005, 0.001 mg/L).	NOAEL for local effects= 0.062 ppm (0.00025 mg/L air) LOAEL = 0.125 ppm (0.0005 mg/L air)	Squamous metaplasia in the respiratory epithelium at 0.0005 mg/L air	van Birgelen et al. (2000)

In these studies, glutaraldehyde induced consistent respiratory irritation with nasal cavity lesions. Mortality occurred at 2.6 ppm and above. Morphological changes in lung tissue and urine and hematology parameters were also affected by repeat inhalation exposure.

The highest reported NOAEL was 0.062 ppm for respiratory irritation and nasal discharge. This is equivalent to 0.00025 mg/L air.

7.5.5.4 Observation in humans

Glutaraldehyde is an irritant to skin, eyes and respiratory system in humans, consistent with the effects noted in animal tests. Many cases of dermatitis have been reported in workers exposed to glutaraldehyde solutions, usually at 2% or higher (NICNAS 19994).

Human evidence indicates that skin and respiratory irritant effects are exacerbated on repeated exposure to glutaraldehyde. Irritation of the nose and throat and general tightness of the chest have been experienced by workers exposed to glutaraldehyde vapours. In a

study of Swedish hospital workers, nose and throat irritation was experienced at concentrations below 0.2 ppm (NICNAS 19994).

Limited epidemiological data is available on the long term effects of glutaraldehyde and only the irritant and skin sensitising effects of glutaraldehyde have been confirmed. There was no evidence of adverse reproductive health effects on exposure to glutaraldehyde, consistent with the results of animal testing. A mortality study did not reveal any increased incidence of cancer deaths (NICNAS 19994).

7.5.6 *Genotoxicity*

Glutaraldehyde has been extensively tested for genetic activity *in vitro* and *in vivo*, however there is disagreement in the literature regarding glutaraldehyde's genetic activity (Zeiger et al. 2005). While all *in vivo* genotoxicity tests with glutaraldehyde gave negative results, mixed results were reported for *in vitro* mutagenicity tests. Early *in vitro* tests were negative (Watts 1984), but some recent bacterial assays and tests in mammalian cells indicated that glutaraldehyde could be mutagenic *in vitro*.

A series of reverse mutation assays was carried out with various *Salmonella typhimurium* strains, with and without metabolic activation (REACH 2013). All assays with TA 100, 1535, 1537 and 98 were negative. Some assays with TA 102 and 104 gave positive results. Tests with *Escherichia coli* also yielded both positive as well as negative results.

Glutaraldehyde induced sister chromatid exchanges in CHO cells with and without S9 metabolic activation in one laboratory, but was negative without S9 and only weakly positive with S9 in the second laboratory (NICNAS 1994). The difference in the results was attributed to slight differences between the data evaluation systems used in the two laboratories.

Glutaraldehyde was not mutagenic in any of the *in vivo* assays such as peripheral blood micronucleus test, rat bone marrow chromosomal aberration assay and the Drosophila melanogaster sex-linked recessive lethal test (NICNAS 1994; REACH 2013). Chromosome aberrations in bone marrow cells were reported in only one out of eight studies using rats and mice, micronuclei were not induced in bone marrow cells of mice, and dominant lethal mutations were not induced in mice. Glutaraldehyde did not induce cell transformation in Syrian hamster embryo cells *in vitro* (Zeiger et al. 2005). *In vivo*, inhalation of glutaraldehyde induced cell proliferation in nasal tissue in rats and mice, but did not induce DNA damage at these sites.

Based on these observations, it is concluded that glutaraldehyde is not a genotoxin.

7.5.7 *Carcinogenicity*

In a two-year chronic/carcinogenicity study by Van Miller et al. (2002), groups of 100 male and 100 female Fischer 344 rats were treated with 0, 50, 250, or 1000 ppm w/v glutaraldehyde in drinking water. The mean glutaraldehyde consumption for each of the three groups was 4, 17 and 64 mg/kg bw/day for the males and 6, 25 and 86 mg/kg bw/day for the females.

The mortality rate during the study period was 25 to 30% for males and 19 to 23% for females and was not dose-related. Gross pathology showed evidence of gastric inflammation.

The main finding of the study was an increased incidence of large granular lymphocytic leukaemia (LGLL) in the spleen and liver of male and female rats in all groups, including the control group. Treated females showed a significantly increased incidence of LGLL and

analysis for dose-response trend for the severity of LLGL revealed an increased severity in females at the higher dosages (53% in spleen and 54% in liver versus respectively 20% and 23% in untreated females) while no such observation were made for the males. No other significant oncogenic effects were observed during the study.

Occurrence of LGLL was seen in all groups including controls; the incidence of LGLL in the 1000 ppm group was high compared to controls but no clear dose-response relationship was evident, and LGLL mainly affected treated females whereas the incidence in treated males was within the control range (REACH 2013).

Historical control data for untreated Fischer 344 rats in NTP studies also indicates that the ranges for this tumour are 10 to 72% in males and 6 to 31% in females (REACH 2013). The control data in the Van Miller et al. study fitted in with the historical control data reported from NTP studies. The variability in control data for LGLL and the wide variation reported in the literature makes a definitive conclusion difficult.

Base on this study, glutaraldehyde was considered not to be carcinogenic.

7.5.8 *Reproductive toxicity*

7.5.8.1 Fertility

In a two-generation reproductive toxicity study conducted according to OECD TG 416, Wistar rats were administered glutaraldehyde through drinking water (REACH 2013). The doses were 0, 100, 500, 2000 ppm (0, 12, 58, 199 mg/kg bw/day) with 27 animalsper sex per group. Male and female rats from the same dose group were paired and the females were allowed to litter and rear their pups (FI generation pups) until day four or 21 post-parturition. After weaning of FI pups the F0 generation parental animals were sacrificed. Selected F1 pups were exposed continuously to the test substance at the same dose level as their parents from their growth into adulthood until they were sacrificed.

No mortality or treatment-related clinical symptoms or disturbances of general behaviour were observed in F0 and F1 male and female rats. In F0 rats the relative kidney and spleen weight of the 2000 ppm group were statistically significantly increased compared to the control group. Animals of all treated groups showed gross lesions in the liver, kidneys, testes or the ovaries. However, histopathology revealed no adverse treatment-related effects. In F1 animals, the mean terminal body weight of the 2000 ppm males was significantly reduced. Absolute and relative weights of some organs, such as liver and kidneys, were also higher than those in the control group. Gross treatment-related lesions were reported for the glandular stomach and consisted of small erosions and ulcers within the mucosa.

Mating index was normal in all dose groups in F0 and F1 rats. Pup viability and mortality was not affected. The mean body weight of the F1 pups (males and females) of the 2000 ppm group on day 21 were statistically significantly reduced compared to control. The F1 pups showed no treatment-related clinical symptoms of toxicity. Decrease in absolute weights were reported for the thymus, brain and the spleen of the F1 pups from the 500 and the 2000 ppm groups when compared to those of the controls.

F1 litter revealed no treatment-related abnormalities. The mean number of delivered F2 pups per dam and the rate of live born and stillborn pups were not affected by the treatment. The mean body weight of the F2 pups of the 2000 ppm group was statistically significantly reduced compared to control from day 14 post-parturition upwards. The F2 pups showed no treatment-related clinical symptoms of toxicity. Absolute and relative organ weights were noted in 2000 ppm F2 pups when compared to those of the control group.

A NOAEL of 500 ppm (58 mg/kg bw/day) for systemic toxicity was established based on reduced body weights and / or retarded body weight gains during the premating periods in F0 and F1 parental males and during premating, gestation and lactation in parental females observed at the highest tested dose of 2000 ppm. In addition, necropsy of the high dose F1 animals revealed an increased number of erosions/ulcers with microscopic erosion(s) or inflammatory oedema in the mucosa/submucosa of the glandular stomach.

A NOAEL for reproductive or developmental toxicity was not established.

In another similar two-generation reproductive toxicity study (Neeper-Bradley and Ballantyne 2000), Crj: CD(SD) rats were given 50, 250 or 1000 ppm glutaraldehyde (4.53, 21.95, and 71.08 mg/kg bw/d for males and 6.72, 29.57, and 99.56 mg/kg bw/d for females) in drinking water. No mortality or clinical symptoms of toxicity were reported for the parental F0 and F1 males and females. Body weights and body weight gains were significantly reduced for F0 and F1 male and female rats at 250 and 1000 ppm. No gross or histological treatment-related abnormalities were seen. The reproduction parameters were inconspicuous for both F0 and F1 generations. Effects on number of live-born pups, survival and viability were inconspicuous. No treatment-related adverse effects were reported in F1 and F2 offspring. For F1 and F2 offspring of the 1000 ppm group, body weight was reduced from day 21 to day 28 of lactation. A NOAEL for fertility could not be established in this study.

Glutaraldehyde was not considered to be toxic to fertility in animals.

7.5.8.2 Developmental toxicity

Further to the combined fertility-developmental studies discussed above, a number of studies in rats and rabbits focussing specifically on development, noted no treatment-related teratogenic effects when glutaraldehyde was administered either in drinking water or orally by gavage (REACH 2013).

No increased risk of spontaneous abortions and foetal malformations was found in Finnish hospital nurses and staff who used glutaraldehyde as a sterilising agent (Dutch Expert Committee on Occupational Standards 2005).

Based on these observations, glutaraldehyde is not considered to be a developmental toxicant.

7.5.9 *Other health effects*

No other health effects were identified.

7.6 Health hazard summary

7.6.1 *Critical health effects*

Glutaraldehyde has high acute oral and inhalation toxicity and low to moderate acute dermal toxicity. It is corrosive and the vapours are an irritant to the respiratory tract. It has skin and respiratory sensitisation potential. Glutaraldehyde has high repeat dose oral and inhalation toxicity with an oral NOAEL of 4 mg/kg bw/day and an inhalation NOAEL of 0.00025 mg/L. Glutaraldehyde is not genotoxic or carcinogenic. It did not have any adverse effects on the reproductive system of adult rats or on the development of foetuses.

The critical health effects of glutaraldehyde are corrosivity, skin and respiratory tract sensitisation and acute and repeat dose oral and inhalation toxicity.

7.6.2 *Hazard classification*

This hazard assessment confirms the existing hazard classification under the current *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A7.4. This NICNAS recommendation does not consider physical or environmental hazards.

Table A7.4 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Acute toxicity, oral	Toxic if swallowed – Cat 3 (H301)
Acute toxicity, inhalation	Fatal if inhaled – Cat 1 (H330)
Skin corrosion/Irritation	Causes severe skin burns and eye damage - Cat 1A (H314)
Eye damage/Irritation	Causes serious eye damage - Cat 1 (H318)
Respiratory irritation	May cause respiratory irritation - Specific target organ toxicity, single exposure – Cat. 3 (H335)
Sensitisation, skin	May cause allergic skin reaction - Cat 1 (H317)
Sensitisation, respiratory	May cause allergy or asthma symptoms, or breathing difficulties if inhaled - Cat 1 (H334)

**Globally Harmonised System (UNECE 2009)*

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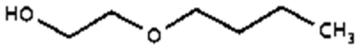
A8 Butoxyethanol

CAS No.	CAS Name
111-76-2	Ethanol, 2-butoxy-

8.1 Chemical identity

Details of the chemical identity provided in Table A8.1 were obtained from a NICNAS Priority Existing Chemicals assessment of 2-butoxyethanol (NICNAS 1996).

Table A8.1 Chemical identity

	Butoxyethanol
Synonyms	Butoxyethanol 2-Butoxyethanol Butylglycol Ethylene glycol monobutyl ether (EGBE) Ethylene glycol, mono-n-butyl ether Glycol butyl ether Monobutyl glycol ether
Structural formula	
Molecular formula	$C_6H_{14}O_2$
Molecular weight	118.19
Appearance and odour	Colourless liquid with an unpleasant odour
SMILES notation	C(CCC)OCCO

8.2 Physical properties

In this assessment, ethanol, 2-butoxy- (CAS No. 111-76-2) will be referred to by the synonym butoxyethanol.

The physical properties of butoxyethanol presented in Table A8.2 were taken from a NICNAS Priority Existing Chemicals assessment of 2-butoxyethanol (NICNAS 1996).

Table A8.2 Physical properties

Property	**Value**
Freezing point	-77 °C
Boiling point	170.8 °C
Density	900 kg/m^3 at 20 °C
Vapour pressure	0.12 kPa at 25 °C

Property	Value
Water solubility	Miscible
Partition coefficient n-octanol/water (log K_{ow})	0.81
Flash point (closed cup)	62 °C
Conversion factor (for vapour)	1 ppm = 4.9 mg/m^3

8.3 Current regulatory controls

8.3.1 *Hazard classification for occupational health and safety*

Butoxyethanol is classified as hazardous for human health in the *Hazardous Substances Information System* (HSIS) with the following risk phrases (Safe Work Australia 2013):

- Xn; R20/21/22 (harmful by inhalation, in contact with skin and if swallowed)
- Xi; R36/38 (irritating to eyes and skin)

Mixtures containing butoxyethanol are classified as hazardous with the following risk phrases based on the concentration (conc) of the chemical in the mixtures. The risk phrases for different concentration ranges are:

- Conc ≥25%: X_n: R20/21/22; R36/38
- ≥20% Conc <25%: Xi; R36/38.

8.3.2 *Occupational exposure standards*

8.3.2.1 Australia

Butoxyethanol is subject to the following Australian exposure standards (Safe Work Australia 2013):

- Time Weighted Average (TWA) of 96.9 mg/m^3 (20 ppm)
- Short-Term Exposure Limit (STEL) of 242 mg/m^3 (50 ppm).

The exposure standard is accompanied by a skin notation, indicating that absorption through the skin may be a significant source of exposure.

8.3.2.2 International

The following exposure standards were identified (Galleria Chemica 2013).

TWA:

- 5 ppm (24 mg/m^3) [US]
- 10 ppm (49 mg/m^3) [France, Germany, Norway, Sweden, Switzerland]
- 20 ppm (96.7 mg/m^3) [Canada, Chile, Estonia, Europe, Iceland, Ireland, Latvia, Malta, Spain, Turkey, US]
- 25 to 26 ppm (120 mg/m^3) [Greece, Iceland, Indonesia, Japan, Mexico, Singapore, South Africa, Taiwan, United Kingdom, US]
- 50 ppm (240 mg/m^3) [Canada, Phillipines, US].

STEL:

- 20 ppm (100 mg/m^3) [Sweden, Switzerland]
- 30 to 38 ppm (148 to 188 mg/m^3) [Canada, US]
- 50 ppm (246 mg/m^3) [Estonia, Europe, Iceland, Ireland, Latvia, Malta, Spain, Turkey, United Kingdom]
- 75 ppm (360 mg/m^3) [Mexico, US]
- 150 ppm (720 mg/m^3) [Canada].

8.3.3 *Australian food standards*

No Australian food standards were identified.

8.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

8.3.5 *Additional controls*

8.3.5.1 Australia

Butoxyethanol is currently listed in Schedule 6 (substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label) of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014):

- 2-BUTOXYETHANOL and its ACETATES except in preparations containing 10 per cent or less of such substances.

8.3.5.2 International

According to the European Commission Cosmetics Directive Annex III (List of Restricted Substances), the following restrictions exist for butoxyethanol in cosmetic products (European Commission 2013):

- Maximum concentration as a solvent in oxidative hair dye products – 4.0%
- Maximum concentration as a solvent in non-oxidative hair dye products – 2.0%
- Prohibited for use in aerosol dispensers (sprays).

In Canada, butoxyethanol is prohibited in hair dyes and nail products at concentrations greater than 10% (Health Canada 2011).

In the US, butoxyethanol is listed by the US Cosmetic Ingredient Review (CIR) program as a substance found safe, with qualifications – at up to 10% (Cosmetic Ingredient Review 2012).

8.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

8.5 Health hazard characterisation

The following information on health hazard was obtained predominantly from a US National Institute for Occupational Safety and Health review of butoxyethanol and butoxyethyl acetate (NIOSH 1990), a NICNAS *priority existing chemicals* assessment of butoxyethanol (NICNAS 1996), an EU *risk assessment report* on butoxyethanol (European Chemicals Bureau 2006) and an International Agency for Research on Cancer (IARC) monograph on butoxyethanol (IARC 2006). Unless otherwise noted, references to individual studies are taken from these review sources.

8.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

8.5.1.1 Oral absorption

From animal studies and incidences of human ingestion, oral absorption of butoxyethanol is rapid and extensive.

Radiolabelled butoxyethanol administered to male F344 rats by gavage at single doses of 125 or 500 mg/kg bw was reported to be excreted predominantly via urine within 24 hours, indicating rapid and extensive systemic absorption via the oral route (Ghanayem et al. 1987).

Poet et al. (2003) administered 250 mg/kg bw butoxyethanol by gavage and by intraperitoneal injection and 400 mg/kg bw by subcutaneous injection to B6C3F1 mice. They found no significant differences in blood concentrations of butoxyethanol or butoxyacetic acid (BAA) between the routes of administration. Butoxyethanol was rapidly eliminated and was no longer detectable 1 hour after treatment. The highest measured concentrations of BAA in blood (approx. 1 mM) were found in the samples obtained 0.5 hour after administration.

Several cases of ingestion of butoxyethanol from suicide attempts have been reported (IARC 2006). These indicate that butoxyethanol is well absorbed via the oral route in humans.

Overall, these data indicate that butoxyethanol is rapidly and extensively absorbed following oral administration. For human risk assessment purposes, an oral absorption of 100% is therefore assumed.

8.5.1.2 Dermal absorption

Studies have been conducted *in vivo* in animals and humans on the dermal absorption of butoxyethanol. Additionally, a series of *in vitro* studies in various species have been conducted.

In rats, dermal absorption was measured in a series of studies in which 200 mg/kg bw radiolabeled butoxyethanol was applied to the skin via non-occlusive conditions (Bartnik et al. 1987). Within 48 hours, approximately 20 to 23% of the applied radioactivity

was found in the urine. A dermal absorption of approximately 25 to 29% of the applied topical dose was determined. In another study in rats exposed dermally to up to 650 µmol radiolabeled butoxyethanol/rat (Sabourin et al., 1992b), 20 to 25% of the dermally applied dose was shown to be absorbed and metabolised. The majority of radioactivity was excreted in urine.

In guinea pigs exposed to 1 mL of undiluted butoxyethanol under occlusive conditions, blood concentrations rose rapidly and reached a plateau during the latter half of a 2 hour blood sampling period (Johanson and Fernström 1986). The mean absorption rate was 1.77 mg/cm^2/hour. In a subsequent study, higher absorption rates were noted for aqueous dilutions compared to undiluted butoxyethanol (Johanson and Fernström 1988).

The absorption of various concentrations of butoxyethanol was also studied *in vitro* using rat, pig and human skin (Bartnik et al. 1987). Through rat skin, butoxyethanol was shown to be almost completely absorbed at 16 hours following exposure. In human skin at 1 hour, 17% of the applied dose was absorbed. Data for subsequent time periods were not available. The rate of penetration through pig skin was comparable to human skin which were both less than through rat skin.

In human studies, five male volunteers were exposed to neat butoxyethanol for 2 hours via finger immersion. There was reportedly little or no delay in detecting butoxyethanol in the bloodstream. Estimates of dermal uptake indicated high variability (more than 10-fold variation). The geometric mean dermal absorption rate was reported as 0.14 mg/cm^2/hour (Johanson et al. 1988).

In another study by the same group, dermal absorption of butoxyethanol as a vapour was measured in four male volunteers whose skin was exposed to butoxyethanol at 50 ppm for 2 hours whilst in an inhalational chamber (Johanson and Borman 1991). Absorption rates were calculated from finger prick blood samples and compared to absorption rates from inhalation (mouth only) in the same volunteers. The mean dermal absorption rate was 227 mg/hour, compared to an inhalation absorption rate of approximately 70 mg/hour, suggesting that dermal uptake potentially accounts for a majority (75%) of the total uptake during whole-body exposures to butoxyethanol vapour. A subsequent repeat of this dermal/inhalation study (Corley et al. 1994) was conducted in which six male volunteers were exposed dermally to 50 ppm butoxyethanol vapours via one arm for two hours and in which blood was sampled from both finger prick of the exposed arm and compared to blood sampled from unexposed arms via a catheter. This study revealed the dermal absorption rate of the previous study to be a significant overestimate due to blood sampling from exposed fingers clearly overrepresenting systemic blood levels. In this latter study, dermal absorption of butoxyethanol vapour was calculated to account for no more than 21% of total uptake from a whole-body exposure.

Four volunteers were exposed to 50 ppm butoxyethanol vapour for two hours via whole body (two exposures) and skin only (two exposures) at different conditions of temperature and humidity (Jones and Cocker 2003). Measurements of total BAA in urine were used to assess absorption of butoxyethanol. The mean dermal absorption of butoxyethanol as a component of total absorbed butoxyethanol ranged from 11% (baseline conditions) to 39% (high humidity and temperature).

Overall, these data indicate that butoxyethanol is absorbed following dermal exposure. In rats, dermal absorption of liquid butoxyethanol varied between 20 and 30% of the applied dose. In volunteers, dermal absorption of butoxyethanol vapours as a proportion of total absorbed butoxyethanol ranged between 11% and 39%. Accordingly, for human risk assessment purposes, a conservative dermal absorption of 30% for butoxyethanol liquid and 39% for butoxyethanol vapour are therefore assumed.

8.5.1.3 Inhalation absorption

Inhalation absorption of butoxyethanol has been studied in animals and humans. In male rats exposed continuously (whole body) to 20 ppm or 100 ppm butoxyethanol for up to 12 days (Johanson 1994), the mean uptake rate was 3.5 mg/kg bw/hour and 17.8 mg/kg bw/hour respectively. The rate was independent of exposure duration. The measured urinary excretion of the metabolite BAA corresponded to 64% of the calculated respiratory uptake.

In a subsequent study, male rats were administered radiolabeled butoxyethanol by inhalation (nose only) for six hours at doses of 5, 50 or 450 ppm (Sabourin et al. 1992a). One group of five rats was used to determine the fractional uptake and body burden. At all exposure concentrations, the majority of radiolabel (up to 76%) was found in the urine. Less than 7% was exhaled and 10 to 20% remained in the carcass.

In a study carried out in an inhalational chamber (Johanson et al. 1986), seven male volunteers were exposed to 20 ppm butoxyethanol for two hours during light exercise. By analysing expired air samples, the mean respiratory absorption rate was estimated as 71.6 mg/hour, equivalent to 57.3% of the amount inhaled. The uptake was rapid and remained relatively constant during exposure.

In an inhalation study in male volunteers (Van Vlem 1987; noted by NIOSH 1990), 67 to 78% of the inhaled amount of butoxyethanol was absorbed during exposure to 12.6 or 25.2 ppm, either at rest or during light exercise. The volunteers wore face masks during the four hour exposure.

Overall, these animal and human data indicate that butoxyethanol is rapidly and extensively absorbed following inhalation. For human risk assessment purposes, an inhalation absorption of 75% is assumed.

8.5.1.4 Distribution

Following absorption, butoxyethanol is rapidly distributed to all tissues via the blood stream.

In a gavage study in F344 rats treated with a single dose of 125 or 500 mg/kg radiolabelled butoxyethanol (Ghanayem et al. 1987), radioactivity was detected 48 hours after dosing in the liver, kidney, spleen, lung, heart, forestomach, glandular stomach, skin, testes, muscle, blood and fat. The highest levels were found in the forestomach, followed by liver, kidneys, spleen and glandular stomach.

In a dermal study in male Wistar rats, radiolabeled butoxyethanol was distributed widely to all tissues, with the greatest level of radioactivity reported in the spleen and thymus, followed by the liver (Bartnik et al. 1987).

In an inhalational study, male Sprague-Dawley rats were continuously exposed to 20 or 100 ppm butoxyethanol for 12 days (Johanson 1994). Concentrations of butoxyethanol and BAA were quantified for blood, muscle, testes and liver. Highest concentrations of both were found in blood followed by liver.

8.5.1.5 Metabolism

The metabolism of butoxyethanol has been extensively studied in rodents, particularly in rats. Butoxyethanol is rapidly metabolised following absorption, with a plasma half-life in animals and humans of less than one hour (NICNAS 1996).

The principal products from metabolic processes in animals or humans are BAA and the glutamine or glycine conjugate of BAA (in humans). Other potential metabolic products, such

as the glucuronide conjugate of butoxyethanol, ethylene glycol (EG), butoxyacetaldehyde (BAL) and CO_2 are minor metabolites or are transitory in nature (e.g., BAL) and do not accumulate in blood, tissues, or excreta.

8.5.1.6 Excretion

Elimination of absorbed butoxyethanol, following metabolism, is rapid and occurs mainly via the urinary route (80 to 90% of the metabolites). In animals and humans, the plasma half-life of metabolites is approximately four hours (NICNAS 1996).

In a study in male F344 rats administered with radiolabelled butoxyethanol by gavage at single doses of 125 or 500 mg/kg bw, urine was found to be the major pathway of excretion and most of the radioactivity was excreted during the first 24 hours after dosing (Ghanayem et al. 1987). Faecal excretion of butoxyethanol ranged between 2% and 3% of the administered doses. The extent of enterohepatic recirculation was not determined.

8.5.2 *Acute toxicity*

The acute toxicity of butoxyethanol has been determined in a number of species. Details of well-conducted studies for different exposure routes below have been adapted from a NICNAS Priority Existing Chemicals assessment of butoxyethanol (NICNAS 1996) and an EU risk assessment report on butoxyethanol (European Chemicals Bureau 2006).

8.5.2.1 Oral

The acute median lethal doses (LD50) determined in various species by the oral route are provided in Table A8.3 (European Chemicals Bureau 2006). Numerous studies have been performed to assess the oral toxicity of butoxyethanol. In rats, the most tested species, LD50 values range from 530 to 2420 mg/kg bw, with most studies providing LD50 values in the range 1000 to 2000 mg/kg bw.

Table A8.3 Acute oral LD50 values for butoxyethanol determined in various species

Species	Toxicological effects	LD50 (mg/kg)
Rat	Narcosis - prostration	560-3000 (male); 530-2800 (female)
Rat	-	1950
Rat	Lethargy, laboured breathing, haemolysis, liver and kidney toxicity.	1590
Rat	Laboured breathing, sluggish and bloody salivation. Haemolysis, dark liver and red kidneys.	2420
Rat	Lethargy, laboured breathing, necrosis of the tail.	1000-2000
Rat	Inactivity, laboured breathing, anorexia, tremors, haemolysis.	1746
Mouse	-	1230
Mouse	Laboured breathing, anorexia, tremors, haemolysis.	1519 (fasted), 2005 (fed)
Rabbit	-	320-370

Guinea pig	-	1200
Guinea pig	Weakness, prostration, necrosis and haemorrhage of gastric mucosa.	1414

8.5.2.2 Dermal

The acute median lethal doses (LD50) determined in various species by the dermal route are provided in Table A8.4 (European Chemicals Bureau 2006).

Table A8.4 Acute dermal LD50 values for butoxyethanol determined in various species

Species	Experimental conditions	Toxicological effects	LD50 (mg/kg bw)
Rat	4 hours, occlusive	-	2275
Rat	24 hours, semiocclusive	No irritation, no signs of toxicity	>2000
Rat	24 hours, occlusive	No signs of irritation. Ataxia, pallor of extremities, lethargy, laboured breathing.	>2000
Guinea pig	-	-	6411
Guinea pig	-	-	208 (intact skin); 271 (abraded skin)
Guinea pig	-	-	450-1800
Guinea pig	24 hours, occlusive	No signs of irritation, no signs of toxicity	>2000
Rabbit	24 hours, occlusive	Haemolysis, renal, hepatic and splenic toxicity	560
Rabbit	24 hours, occlusive, dermal abrasion	Anorexia, depression, cyanosis, ataxia, laboured breathing, renal, hepatic and thymic toxicity.	580
Rabbit	8 hours	Haemolysis, narcosis, laboured breathing, skin irritation. Liver, splenic and kidney toxicity.	100
Rabbit	24 hours, occlusive	-	569
Rabbit	24 hours, occlusive	Anorexia, depression, cyanosis, ataxia, laboured breathing, renal, hepatic and thymic toxicity.	435
Rabbit	24 hours, semiocclusive	Signs of irritation mild to severe - necrosis at high doses. Lethargy, haemolysis, ataxia, Hepatic and renal toxicity.	>2000
Rabbit	24 hours, occlusive	Signs of irritation mild to severe - necrosis at high doses. Very slight systemic effects.	1060 (males); 667 (females)

Overall, significant differences were observed in acute dermal toxicity between the tested species. The rabbit appears to be the most sensitive species. Across a number of studies, the LD50 was approximately 500 mg/kg bw or >2000 mg/kg bw for occlusive versus non occlusive applications respectively.

8.5.2.3 Inhalation

The acute median lethal concentrations (LC50) determined in various species by the inhalation route are provided in Table A8.5 (European Chemicals Bureau 2006).

Table A8.5 Acute inhalation LC50 values for butoxyethanol determined in various species

Species	Toxicological effects	LC50 (mg/L)
Rat	Exposure to 800 ppm for 8 hours: 50% mortality; no mortality was observed with an exposure time of 4 hours. Exposure to 500 ppm (2.45 mg/L) for 8 hours: no mortality. One death (out of six) was seen with 500ppm for 4 hours. Older rats at 375 ppm: mortality in 11/ 13 animals and 23/23 after 7 hours of exposure	-
Rat	4 hour exposure: Laboured breathing, loss of coordination, tail necrosis, renal toxicity, haemolysis.	2.38 mg/L (486 ppm) (males); 2.2 mg/L (450 ppm) (females)
Rat	At 3 mg/L (617 ppm): Mortality 4/6 at 7 hour exposure; 1/6 at 3 hour exposure; no mortality at 1 hour exposure. Lethargy, necrosis of the tail and haemolysis.	-
Guinea pig	LT50: 7 hours at 6.37 mg/L (1300 ppm)	-
Guinea pig	1 hour exposure. No effects observed.	>3.39 mg/L (691 ppm) (males); >3.1 mg/L (633 ppm) (females)

Signs of toxicity from inhalation exposure include laboured breathing, ataxia, tail necrosis and haemolysis. In a good quality four hour inhalation toxicity study in rats, the LC50 was calculated as 2.38 mg/L for males and 2.2 mg/L for females (Bushby Run Research Centre 1980a).

8.5.2.4 Observation in humans

Several cases of ingestion of butoxyethanol from suicide attempts have been reported (IARC 2006). Symptoms included vomiting, lethargy, central nervous system depression, coma, depressed ventilation, hypotension, metabolic acidosis, hypokalaemia, anaemia, haematuria, haemoglobinuria, non-cardiogenic pulmonary oedema, hepatic and renal failure. A worst case estimation from a case report of non-lethal ingestion of butoxyethanol (McKinney et al. 2000) indicates a human LOAEL for oral intake of approximately 400 mg/kg bw based on induction of metabolic acidosis (European Chemicals Bureau 2006).

Headache, nausea, as well as irritation of eyes, nose and throat and disturbed taste were reported in whole body inhalation studies in which volunteers were exposed to up to 200 ppm butoxyethanol for four-hour periods (Mellon Institute of Industrial Research 1955; Carpenter 1956). Exposures to 100 ppm for eight hours resulted in headache and nausea. No effects on erythrocyte fragility were reported.

8.5.3 *Irritation / Corrosivity*

8.5.3.1 Skin irritation

Skin irritation (occasionally severe) has been noted in several dermal toxicity tests with butoxyethanol (see Section A8.5.2 *acute toxicity*).

In a skin irritation study performed according to the US *Code of Federal Regulations*, butoxyethanol was administered to abraded and intact skin of six rabbits for 24 hours under semi-occlusive conditions (Huntingdon Life science 1979b). Scoring was performed immediately and at 48 hours after the first reading. At the first reading, five out of six animals exhibited a slight to moderate erythema (score 1 to 2) and four out of six exhibited a slight oedema (score 1). At the second reading , four out of six animals exhibited slight to moderate erythema (score 1 to 2) and three out of six exhibited a slight oedema (score 1). In terms of severity of reactions, butoxyethanol was considered to be slightly irritating. Reactions were not reversed at the end of the 72 hour observation period.

In a comparative study of nine glycol ethers in rabbits and guinea pigs, undiluted material was applied under an occlusive dressing for 24 hours at the dose where enough animals survived to make an evaluation. Butoxyethanol was reported to be a moderate irritant in the rabbit (dose of 0.3 g/kg bw), and a strong irritant in the guinea pig (dose of 4.5 g/kg bw) (Eastman Kodak 1981).

In a study conducted in a similar fashion to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 404, 0.5 mL of undiluted butoxyethanol was applied to the clipped intact skin of six male New Zealand White rabbits for four hours under a patch (Rohm and Haas 1983). Skin reactions scored at five hours (one hour after patch removal), one day, three days and seven days were variable, with severe and persistent erythema with eschar and severe oedema observed in three rabbits and very slight oedema and erythema observed in the others. No oedema was observed in any rabbit after seven days. Under the conditions of the study, butoxyethanol was found to be irritating to the skin of rabbits.

Butoxyethanol and other ethylene glycols (purity >99%) were administered dermally to rabbits according to a European Economic Community (EEC) testing method (Jacobs and Martens 1985). Butoxyethanol (0.5 mL) was applied under an exposure chamber to the flank of five New Zealand White rabbits, for four hours. The maximal mean erythema score was 1.8 but the results per animal were variable, ranging from not irritating to very irritating.

Butoxyethanol and other glycol ethers were administered dermally to New Zealand White rabbits according to two cutaneous irritation test methods (Zissu 1995): the EEC testing method and the Draize protocol. Three rabbits were used in the EEC protocol and six in the Draize protocol. Butoxyethanol (0.5 mL) was applied occlusively to the flank of each animal for four hours for the EEC protocol and 24 hours for the Draize protocol (for the later, butoxyethanol was also applied to a second scarified flank). According to the EEC method and Draize method, butoxyethanol was classified as an irritant and severe irritant, respectively (no detailed observations were available).

In summary, several tests have reported positive irritation responses, with occasional severe irritation reported in individual animals. In an early study, reactions were shown not to be reversed at the end of the observation period (72 hours).

8.5.3.2 Eye irritation

An eye irritation study was performed according to the method described in the US *Code of Federal Regulations* (Huntingdon Life science 1979a). Undiluted butoxyethanol (0.1 mL) was instilled into the eyes of six animals. Effects were scored (Draize) at 24, 48 and 72 hours. Reactions on cornea were reported in five animals, conjunctivae in two and iritis in six out of the six animals at 24, 48 and 72 hours respectively (no other details were available).

In a study of five rabbits, 0.005 mL of undiluted butoxyethanol reportedly caused severe corneal injury and iritis; 0.5 mL of a 15% aqueous solution caused moderate corneal injury, and no effects were observed with 0.5 mL of a 5% solution (Bushy Run Research Center 1980c). An internal protocol was used and individual results for each animal were not reported.

In a study of a single rabbit, the instillation of 0.1 mL of undiluted butoxyethanol resulted in severe conjunctivitis, iritis and corneal opacity, with irritation still obvious 21 days after exposure (Carreon 1981).

Butoxyethanol (99% purity) was instilled in the right eye of six New Zealand White rabbits (Jacobs and Martens 1987). The test was performed in two phases. The first phase tested the chemical according to OECD TG 405 (1981 version). In the second phase, three other chemicals were tested and in addition to the clinical examination, corneal swelling was also measured. Erythema, chemosis, iritis and corneal opacity were scored (Draize) at 4, 24, 48, 72, 96 and 168 hours after treatment. The mean erythema, chemosis, iritis and corneal opacity values (average of the 24, 48 and 72 hour observations) were: 2.59, 0.78, 1.00 and 1.33, respectively. The mean corneal upper layer damage (loss of epithelium measured by fluorescein retention on the cornea) was 95% after four hours. Marked pannus was also seen in all six rabbits. The study was subsequently repeated using the same protocol (Jacobs 1992). Reported mean scores were similar, but slightly lower. The mean erythema, chemosis, iritis and corneal opacity values (average of the 24, 48 and 72 hour observations) were 2.47, 0.83, 0.83 and 1.73 respectively.

In a test performed according to OECD TG 405 (1981 version), pure butoxyethanol was instilled in the eye of three rabbits (ECETOC 1998). Erythema, chemosis, iritis and corneal opacity were scored (Draize) at 1, 2, 3, 7, 14 and 21 days after treatment. Scores for erythema, chemosis and corneal opacity values (average of the 24, 48 and 72 hour observation) were 2.33, 2.78 and 2.33 respectively. Opacity resolved in all three animals although very slight redness (score 1), remained in two animals and chemosis (score 1) remained in one animal.

In a well-conducted study performed in accordance with OECD TG 405, pure butoxyethanol was instilled into the eyes of three New Zealand White rabbits which were then observed for 21 days (BASF 2000). Eye washing was performed about 24 hours after treatment, before the 24 hour reading. At 24, 48 and 72 hours, all three animals showed no or only mild (score 1) corneal opacity and iritis. In contrast, at these timepoints, all three animals showed moderate to severe erythema and mild to moderate chemosis. For erythema, the mean scores for the three animals were 3, 2.33 and 2.33. For chemosis, the mean scores across these timepoint for the three animals were 2, 2 and 1.33.

In summary, a number of studies have revealed that butoxyethanol is an eye irritant, although most of these studies did not conform to test guidelines.

8.5.3.3 Respiratory irritation

An Alarie test in male mice exposed to vapour concentrations of up to approximately 1100 ppm, found the RD50 (the concentration which produces a 50% decrease in respiratory rate) for butoxyethanol of 13.84 mg/L (2825 ppm) (Kane et al. 1980). This test suggests that butoxyethanol is a weak upper respiratory tract irritant. A previously modelled estimate of the RD50 of butoxyethanol based on physico-chemical properties derived a similar value of 13.86 mg/L (2828 ppm) (Alarie et al. 1995).

8.5.3.4 Observation in humans

Immersion of the fingers of five male volunteers in neat butoxyethanol for two hours resulted in mild dermal effects consisting of wrinkled appearance of the digits with decreased finger volume and skinfold thickness (Johanson et al. 1988).

Irritation of eyes, nose and throat and disturbed taste were reported in whole body inhalation studies in which volunteers were exposed to up to 200 ppm butoxyethanol for four-hour periods (Mellon Institute of Industrial Research 1955; Carpenter 1956). The severity of responses was not reported. In contrast, no irritation to the eyes or respiratory tract was reported in a whole body inhalation study of volunteers exposed to lower doses of 20 ppm for two hours or 25 ppm for 25 minutes (Johanson et al. 1986).

8.5.4 *Sensitisation*

8.5.4.1 Skin sensitisation

In a Magnusson and Kligman maximisation study in guinea pigs conducted in a similar fashion to OECD TG 406, (Unilever Research 1989), a group of 10 animals was treated intradermally for induction with 0.5% butoxyethanol in 0.9% saline, followed by dermal application of a 25% solution (in 0.9% saline) seven days later under an occlusive wrap. The animals were then challenged topically twice with 10% butoxyethanol, firstly at 13 days after induction, and then a week later. A vehicle control group of four animals per sex was used in the study. In a preliminary occluded patch irritation test designed to determine dose levels for the main study, 25% butoxyethanol was irritating to the skin and a 10% solution was non-irritating. No evidence of sensitisation was seen at either challenge or re-challenge.

In another Magnusson and Kligman guinea pig maximisation study, none of the glycol ethers tested, including butoxyethanol, was a skin sensitiser (Zissu 1995). Challenge was conducted with 1% butoxyethanol. No other data were available.

8.5.4.2 Respiratory sensitisation

No data were available.

8.5.4.3 Observation in humans

The human sensitising potential of 10% butoxyethanol aqueous solution was assessed using 201 volunteers (TKL Research 1992). The induction phase consisted of nine consecutive occlusive applications each for 24 hours. Assessments of the sites of application were made at 48 hour intervals and after new patches were reapplied. Following the ninth evaluation, the subjects were rested for 14 days. The challenge phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the butoxyethanol solution. After 24 hours, these were removed and the sites graded 24 hours and 48 hours later. Re-challenge if required was to be performed whenever there was evidence of possible sensitisation. The re-challenge was to be conducted on naïve sites on the back under both

occlusive and semi-occlusive conditions approximately one or two weeks after challenge had been completed. Patches were to be applied for 24 hours and the sites evaluated 48, 72 and 96 hours after patch applications.

Re-challenge was not required for any subject. Only seven of the 48-hour evaluations and 12 of the 72-hour evaluations showed slight erythema. One subject at 72 hours had definite erythema. In conclusion, according to the study, none of the 201 subjects completing the study showed evidence of sensitisation.

8.5.5 *Summary of acute toxicity*

Numerous animal studies have examined the acute toxicity of butoxyethanol. For acute oral toxicity, LD50 values range from 530 to 2420 mg/kg bw, with most studies providing LD50 values in the range 1000 to 2000 mg/kg bw. Across a number of acute dermal toxicity studies, the LD50 was approximately 500 mg/kg bw for occlusive applications or more than 2000 mg/kg bw for non occlusive applications. For acute inhalation toxicity, the LC50 from a four-hour inhalation test in rats was calculated as 2.38 mg/L for males and 2.2 mg/L for females respectively. In humans, severe symptoms have been reported from oral exposures to butoxyethanol.

Several animal tests have reported positive skin irritation responses, with occasional severe irritation reported in individual animals. In an early study, cutaneous reactions were shown not to be reversed at the end of the 72 hour observation period. Dermal exposures of limited duration in humans resulted in only mild dermal effects.

In tests in rabbits, butoxyethanol is moderately to severely irritating to the eyes with effects on the conjunctivae, iris and cornea. In one early study, irreversible effects on the conjunctivae and cornea were observed at the end of the 72 hour observation period in at least one animal. A single test in mice suggests that butoxyethanol is only a weak upper respiratory tract irritant.

Mild ocular and respiratory tract irritation has been reported following inhalation exposures of humans to butoxyethanol.

The available data indicate that butoxyethanol is not a skin sensitiser in humans or animals.

8.5.6 *Repeat dose toxicity*

The repeat dose toxicity of butoxyethanol has been determined in a number of species. Details on reputable studies for different exposure routes below are adapted from a NICNAS Priority Existing Chemicals assessment of butoxyethanol (NICNAS 1996) and an EU risk assessment report on butoxyethanol (European Chemicals Bureau 2006).

8.5.6.1 Oral

Repeat dose toxicity studies of butoxyethanol via the oral route are outlined in Table A8.6.

Table A8.6 Oral repeat dose toxicity studies

Species, treatment and doses	Results	Toxic effects	Reference
Rat, 90 days, food 0.01, 0.05, 0.25 and 1.25%;	NOAEL = 0.05% (38 mg/kg bw/day) for males; 0.25% (222 mg/kg bw/day) for females	Decrease in food consumption and body weight gain in males at 0.25% and 1.25%, and in	Mellon Institute of Industrial Research

Species, treatment and doses	Results	Toxic effects	Reference
7, 38, 188 and 919 mg/kg bw/day (males); 9, 41, 222, and 976 mg/kg bw/day (females).		females at 1.25%. Testes atrophy at 0.25% and 1.25%.	(1963)
Rat, 6 weeks, gavage 0, 222, 443 and 885 mg/kg bw/day.	No NOAEL derived; LOAEL = 222 mg/kg bw/day	Haematological effects at all doses	Krasavage (1983)
Rat, 21 days, drinking water 0, 180 and 500 mg/kg bw/day for males and 200 and 444 mg/kg bw/day for females.	No systemic NOAEL derived.	No remarkable effects on the immune system	Exon et al. (1991)
Rat, 13 weeks, drinking water 0, 69, 129, 281, 367 and 452 mg/kg/day for males and 0, 82, 151, 304, 363 and 470 mg/kg/day for females.	No NOAEL derived. LOAEL = 69 and 82 mg/kg bw/day for males and females respectively.	Slight decrease in body weight gain at the two highest doses; haematological and liver effects at all doses.	NPT (1993)
Mouse, 14 weeks, drinking water 118, 223, 553, 676 and 694 mg/kg/day for males and 185, 370, 676, 861 and 1306 mg/kg/day for females.	NOAEL = 223 and 370 mg/kg bw/d for males and females respectively. LOAEL = 553 and 676 mg/kg bw/d for males and females respectively.	Decrease in body weight gain at the three highest doses.	NTP (1993)

Common effects observed following repeat oral administration of butoxyethanol in rodents were local irritation (gastrointestinal tract), reductions in body weight, haemolysis and hepatic effects. For the oral repeat dose toxicity, LOAELs of 69 and 82 mg/kg/day for male and female F344/N rats (respectively) were established in a 13 week drinking water study (NTP 1993). In this study, no NOAEL was established based on cytoplasmic alterations observed in hepatocytes in both males and females at these lowest doses.

8.5.6.2 Dermal

Repeat dose toxicity studies of butoxyethanol via the dermal route are outlined in Table A8.7.

Table A8.7 Dermal repeat dose toxicity studies

Species, treatment and doses	Results	Toxic effects	Reference
Rabbit, 9 days	NOAEL = 450 mg/kg bw/day.	Transient haematological	Bushy Run Research Center

Species, treatment and doses	Results	Toxic effects	Reference
0, 45, 225, 450, 900 mg/kg bw/day.	LOAEL = 900 mg/kg bw/day	effects (haemolysis) at the highest dose.	(1980b); Tyler (1984)
Rabbit, 13 weeks 0, 10, 50, 150 mg/kg bw/day	No NOAEL derived	Slight erythema noted intermittently; no systemic effects	Wil Research Laboratories Inc. (1983); Tyler (1984)
Mouse, 4 days 0, 100, 500, 1000, 1500 mg/kg bw/day.	NOAEL = 1000 mg/kg bw/day LOAEL = 1500 mg/kg bw/day	Effects on splenic cellularity at the highest dose	Singh et al. (2001)

Two studies in rabbits were available to assess the repeat cutaneous administration of butoxyethanol. A single mouse study was also available, but of very brief duration (four days). In the rabbit, systemic effects were only observed in one study of nine days duration (Bushy Run Research Center 1980b; Tyler 1984). This study reported signs of haemolysis consisting of decreases in erythrocyte counts, haemoglobin and increases in mean corpuscular haemoglobin concentrations at the highest dose, which had resolved by the end of a 14 day post-exposure observation period.

A second 13 week study in rabbits (Wil Research Laboratories Inc. 1983; Tyler 1984) reported slight local irritant effects, but no systemic toxicity, even at the highest dose of 150 mg/kg bw/day. Sporadic changes in haematology parameters and RBC fragility values were noted, but values were within normal ranges for the laboratory and therefore not regarded as directly treatment-related. Accordingly, no NOAEL was derived from this longer term study based on a lack of effects seen at this highest dose.

8.5.6.3 Inhalation

Repeat dose toxicity studies of butoxyethanol via the inhalation route are outlined in Table A8.8.

Table A8.8 Inhalation repeat dose toxicity studies

Species, treatment and doses	Results	Toxic effects	Reference
Rat 15 exposures (whole body) to 0, 20, 50 and 100 ppm. 4 exposures to 250 ppm.	NOAEC = 20 ppm	Haematological effects (no details available)	Gage (1970)
0, 20, 86, 245 ppm	NOAEC = 20 ppm	Haematological effects at 86 ppm and above; increased liver weight at 245 ppm and 86 ppm (females only); decreased body weight gain at 245 ppm	Bushy Run Research Center (1981a)
Rat, 6 hours/day,	NOAEC = 25 ppm	Haematological effects and	Bushy Run

Species, treatment and doses	Results	Toxic effects	Reference
13 weeks 0, 5, 25, 75 ppm (whole body)		transient decreased body weight gain at 75 ppm (females only)	Research Center (1981b)
Rat, 6 hours/day, 13 weeks 0, 31.2, 62.5, 125, 250, 500 ppm (whole body)	Males: NOAEC = 62.5 ppm. Females: No NOAEC derived; LOAEC = 31 ppm	Haematological effects in females at all doses and in males at 125 ppm and above	Nyska et al. (1999); Long et al. (2000); NTP (2000)
Rat, 104 weeks 0, 31.2, 62.5, 125 ppm (whole body)	No NOAEC derived LOAEC = 31 ppm	Haematological effects in males at 62.5 ppm and above and in females at 31.2 and 62.5 ppm. Liver effects (Kupffer cell pigmentation) in males at all doses and in females at 62.5 ppm and above.	NTP (2000)
Mouse, 30, 60 or 90 days 0, 100, 200, 400 ppm (whole body)	No NOAEC derived. LOAEC = 100 ppm	Haematological effects at all doses	Mellon Institute of Industrial Research (1955)
Mouse, 14 weeks 0, 31.2, 62.5, 125, 250, 500 ppm (whole body)	Males: NOAEC = 62.5 ppm. Females: No NOAEC derived; LOAEC = 31 ppm	Haematological effects in males at 125 ppm and above and in females at all doses. Irritant effects on the forestomach in females at 125 ppm and above.	NTP (2000)
Mouse, 104 weeks 0, 62.5, 125, 250 ppm (whole body)	No NOAEC derived LOAEC = 62.5 ppm	Haematological effects in males and females at all doses. Liver effects (Kupffer cell pigmentation) in males at 125 ppm and above and in females at all doses.	NTP (2000)
Guinea pig, male, 30 days 0, 375, 500 ppm (whole body)	No NOAEC derived	Mortality and increase in kidney weights at 375 ppm and 500 ppm. No effects on blood parameters.	Mellon Institute of Industrial Research (1955)
Dog, 12 weeks 415 ppm	No NOAEC derived	CNS depression, haemolytic anaemia.	Werner et al. (1943)
Dog, 2-90 days 0, 100, 200, 385, 615 ppm (whole body)	Data insufficient to establish effect levels.	Mortality and CNS depression at 385 ppm and 615 ppm. Congestion of lungs, liver at 385 ppm and lungs, kidneys at 615 ppm. Haematological effects at all doses (slight at 100 ppm).	Mellon Institute of Industrial Research (1955)
Monkey, 90 days	Data insufficient to establish	Transient haematological	Mellon

Species, treatment and doses	Results	Toxic effects	Reference
100, 200 ppm (whole body)	effect levels.	effects	Institute of Industrial Research (1955)

Inhalation repeat dose toxicity studies were available for several species (see Table A8.8, above). The predominant effect observed from repeat dose inhalation administration was haemolysis of erythrocytes, which is similar to that observed for other routes of exposure. This was observed consistently and associated occasionally with secondary hepatic effects (Kupffer cell pigmentation and liver weight increases).

From a 13 week (whole body) study in rats (Bushy Run Research Center 1981b), a NOAEC of 25 ppm was established based on haematological effects in females consisting of decreased erythrocyte counts, haemoglobin and haematocrit with slight increases in mean corpuscular haemoglobin at the highest dose of 75 ppm. At this dose, transient reduced body weight gain was also observed in female animals.

Similar haematological effects were noted in another 13week whole body inhalation study (NTP 2000) which reported dose-related decreases in haematocrit, haemoglobin and erythrocyte counts in all exposed female animals including at the lowest dose of 31.2 ppm and in males commencing at the intermediate dose of 125 ppm. A longer 104 week whole body study (NTP 2000) also reported similar haematological effects in rats and mice. In this longer study, the LOAEC for both male and female rats was 31 ppm, based on increased incidence of Kupffer cell pigmentation in males and haematological effects in females. In both these studies, no NOAEC was established.

Overall, a NOAEC of 25 ppm (121 mg/m^3) with a LOAEC of 31 ppm (150 mg/m^3) was established for inhalation repeat dose toxicity from these separate rodent studies.

8.5.6.4 Observation in humans

Whole body inhalation exposures of volunteers to 195 ppm for two four-hour periods resulted in irritation of the eyes, nose and throat, unpleasant taste and headache (Carpenter et al. 1956).

Episodes of repeated inhalation exposures to butoxyethanol via occupational use of solvent products containing butoxyethanol have been reported (Foo et al. 1994; Denkhaus et al. 1986). Although neurobehavioural, biochemical and haematological effects as well as atmospheric exposures of butoxyethanol have been assessed in these studies, coexposure with other solvents in the products confounds any conclusions regarding adverse effects linked with butoxyethanol exposures alone.

8.5.7 *Comparative studies of haemotoxicity*

Early *in vivo* studies by Werner et al. (1943) and Carpenter et al.(1956) reported transient haemoglobinuria in a variety of species exposed to butoxyethanol. Some species displayed more sensitivity compared to others. For example, haemoglobinuria was observed in rats and mice exposed to 200 ppm for seven hours, but not in guinea pigs exposed to 665 ppm for eight hours. The greater sensitivity of rats to the haemolytic effects of butoxyethanol compared to guinea pigs was confirmed in subsequent gavage studies (Ghanayem and Sullivan 1993). A gavage study in rats administered butoxyethanol and selective inhibitors of

alcohol dehydrogenase and aldehyde dehydrogenase also confirmed BAA as the primary haemolytic agent (Ghanayem et al. 1987).

In contrast to these rodent studies, no haemolysis was observed in inhalation studies in humans exposed to 195 ppm for two four-hour periods (Carpenter et al. 1956).

A series of *in vitro* studies have been conducted and confirm a relatively low sensitivity of human erythrocytes to the haemolytic effects of butoxyethanol and butoxyethanol metabolites compared to those of animals. These are discussed below.

In human and rat red blood cell cultures (Bartnik et al. 1987), butoxyethanol caused haemolysis of rat cells at 175 to 200 mM and of human cells at 225 mM (for 60 minutes incubation). For the same incubation time, BAA caused total haemolysis of rat cells at 7.5 mM but no haemolysis of human cells (with a maximum concentration 15 mM). For an incubation time of 180 minutes, BAA caused total haemolysis of rat cells at 3.75 mM and no haemolysis of human cells at the maximum concentration of 15 mM.

In a study of red blood cells from human, rat, dog and rabbit blood, BAA lysed rat cells at 0.05% but cells from the other species were stable up to the maximum concentration of 2% BAA (Hext 1985).

In a comparative study of rat and human red blood cells, haemolysis was observed in rat cells exposed for four hours to BAA at the lowest dose (0.5 mM) (Ghanayem 1989). No effects were observed in human cells exposed to 2 mM BAA for four hours, but slight swelling of the cells was noted at 4 mM, and slight but significant haemolysis was observed at 8 mM BAA.

Similarly, red blood cells from humans and Fischer 344 rats were treated with BAA (Udden and Patton 1994). On exposure to 2 mM for four hours, the rat cells exhibited significant haemolysis, preceded by a large decrease in red cell deformability (noted at one hour); whereas no haemolysis or change in deformability occurred in human cells. On exposure to 0.2 mM for six hours, the rat cells exhibited very slight haemolysis and a significant decrease in red cell deformability (noted at four hours).

8.5.8 *Genotoxicity*

A large number of genotoxicity tests conducted in accordance with recognised test guidelines have been reported for butoxyethanol and selected metabolites and the results of these are outlined in detail in several peer-reviewed reports such as NICNAS (1996), European Chemicals Bureau (2006) and IARC (2006). An overview of conclusions summarised in these reviews is provided below.

8.5.8.1 *In vitro* studies

Butoxyethanol appears not to be mutagenic in bacteria, based on negative results in five strains of *Salmonella typhimurium* tested with or without metabolic activation. In one study, a positive response was observed with *Salmonella typhimurium* strain TA97a. However, this positive result was not replicated in a subsequent study by another group to investigate this finding. Neither BAL nor BAA was mutagenic in *Salmonella typhimurium*.

In mammalian cells, two of three cell mutation assays using Chinese hamster ovary (CHO) cells did not indicate any mutagenic activity for butoxyethanol. A positive result was obtained in one poorly reported study using Chinese hamster lung V79 cells exposed to high concentrations (20 mM). The same publication reported a positive result with BAL at 20 mM, whereas another study found no effects at concentrations up to 7.6 mM.

Inconsistent results have been reported for butoxyethanol in sister chromatid exchange (SCE) induction assays using CHO cells and cell transformation assays using Syrian hamster embryo cells. A single study of gap-junctional intercellular communication in Chinese hamster lung V79 cells suggested inhibition with butoxyethanol at non-cytotoxic doses, but neither BAA nor BAL showed any activity.

Several studies of chromosomal aberration using CHO cells, V79 cells or human lymphocytes showed no induction with butoxyethanol. A single study reported positive results for butoxyethanol and BAL but not BAA.

8.5.8.2 *In vivo* studies

In F344/N rats, there was no evidence of micronucleus induction by butoxyethanol in bone marrow cells or interactions between butoxyethanol and DNA from the brain, testes, liver, spleen or kidneys of Sprague-Dawley rats. Similarly, no evidence of micronucleus induction in bone marrow cells was reported in several studies of butoxyethanol in B6C3F1 mice or a study of BAA in CD-1 mice.

Overall, available data indicate that butoxyethanol is not regarded as genotoxic.

8.5.9 *Carcinogenicity*

The carcinogenic potential of butoxyethanol was assessed in a 104 week inhalation study in F344/N rats, exposed whole body to 0, 31.2, 62.5 or 125 ppm (0, 151, 302 or 604 mg/m3 butoxyethanol vapour for six hours each day, five days a week (NTP 2000). Survival of exposed animals was similar to controls and no clinical signs were attributed to exposure to butoxyethanol. At the end of the 104 week study, no significant neoplastic effects were observed in male or female rats. Two nasal tumours were found, a chondroma in a low dose male and an adenoma in a mid dose male. In the absence of any preneoplastic changes, these were regarded as incidental findings.

In female rats, the combined incidence of benign and malignant pheochromocytoma of the adrenal medulla was 3/50, 4/50, 1/49, and 8/49. The incidence in the high-dose group (16%) did not represent a statistically significant increase over the control group (6%), but did exceed the historical control prevalence range for this effect (6.4 ± 3.5%; range 2 to 13%). The primary criterion used to distinguish phaeochromocytomas from medullary hyperplasia was the presence of mild-to-moderate compression of the adjacent tissue. Most of the phaeochromocytomas were small and not substantially larger than the more severe grades of adrenal medullary hyperplasia. There was only one phaeochromocytoma that was graded as malignant.

The report concludes that there was no evidence for carcinogenicity in male rats and equivocal evidence for carcinogenicity in female rats due to the presence of small phaeochromocytomas, mostly not distinct from adrenal medullary hyperplasia, at the highest dose.

The carcinogenic potential of butoxyethanol was also assessed in a similar 104 week inhalation study in B6C3F1 mice (50 males and 50 females per group), which were exposed whole body to 0, 62.5, 125 or 250 ppm (0, 302, 604 or 1208 mg/m^3 butoxyethanol vapour for six hours per day, five days per week (NTP 2000).

Survival of male mice exposed to 125 or 250 ppm was significantly less than that of the control group, whereas survival in all other treated groups was similar to the control group. The mean numbers of survivors at the end of the experiment in each of the 0, 62.5, 125 and 250 ppm groups were 39, 39, 27 and 26 males and 29, 31, 33 and 36 females, respectively.

No clinical signs were attributed to exposure to butoxyethanol. Body weights of exposed male mice were generally less than those of the controls during the last 25 weeks of the experiment. Body weights of female rats of the 250 ppm group were generally 20% lower than those of the controls from week 30 until the end of the experiment. Body weights of the 62.5 and 125 ppm group females were generally lower than the chamber controls from about week 60 until the end of the experiment.

There was a dose-related increase in the incidence of forestomach squamous cell papilloma and squamous cell papilloma or carcinoma combined in female mice. The increased incidences were statistically significant at the highest dose (250 ppm), in which the only squamous cell carcinoma also occurred. These incidences also exceeded the historical control range for female mice. There was no significant increase in the incidence of these neoplasms in male mice, but incidences did exceed the historical control range for male mice. In male mice there was one squamous cell carcinoma, which occurred in the 125 ppm group.

In the liver, there was a dose-related increase in the incidence of haemangiosarcomas in male mice. The increased incidence was statistically significant at the highest dose, at which it also exceeded the historical control range for this tumour type. There was also a dose-related increase (statistically significant at the highest dose) in the incidence of hepatocellular carcinomas. There was, however, no change in the incidence of hepatocellular adenomas and carcinomas combined, because of a reduced incidence of hepatocellular adenomas in the treated groups. In female mice there was a single haemangiosarcoma in the low dose group, considered to be an incidental finding. Furthermore, the incidences of hepatocellular adenomas were reduced in the 125 and 250 ppm groups of female mice and there was no change in the incidence of hepatocellular carcinomas.

The NOAEC for carcinogenicity in mice was 125 ppm, based on an increased incidence of haemangiosarcomas in males and squamous cell papillomas or carcinomas in the forestomach in females at 250 ppm.

8.5.9.1 Hypothesised modes of action for carcinogenicity and relevance to humans

Modes of action (MOA) have been proposed for both the forestomach and liver tumours observed in rodents in these studies (European Chemicals Bureau 2006; IARC 2006; USEPA 2010). For forestomach tumours, the hypothesised key steps are metabolism to BAA, followed by tissue irritation and subsequent cytotoxicity, compensatory proliferation, and the induction of forestomach tumours.

For the liver tumours, the hypothesised key steps are metabolism of butoxyethanol to BAA, haemolysis of erythrocytes with release of haemoglobin and hepatic hemosiderin accumulation, followed by oxidative stress, modulation of gene expression and cell proliferation, promotion and neoplasm, leading to the formation of liver tumours.

Both of these MOAs are regarded as relevant to humans since the principal biological components and the processes by which they interact are present in humans. Collectively, however, the evidence suggests that both MOAs have only limited quantitative significance to humans, principally due to toxicokinetic/dynamic differences between humans and rodents.

In the case of forestomach tumours, although humans do not possess forestomachs, comparative squamous epithelial tissues are present in humans in the oral cavity and upper oesophagus (IARC 2003). The primary difference between mice and humans, therefore, is

not anatomic, but the degree of kinetics in the metabolising enzymes involved in the production and clearance of BAA.

In the case of the liver tumours, *in vitro* data suggest there is a significant difference in doses that produce haemolytic changes in human erythrocytes compared to those of rodents. This difference is supported by an *in vivo* study in which no changes in erythrocyte fragility were measured in humans at the highest tested concentration (195 ppm), despite increases in erythrocyte fragility measured in coexposed rats (Carpenter et al. 1956). Further, physiologically based pharmacokinetic (PBPK) modelling (Corley et al. 2005) predicts that given the vapour pressure of butoxyethanol, the maximum blood level of BAA that can be obtained from inhalation exposure would be lower than the predicted concentrations from bolus exposures that have not resulted in haemolytic effects and lower than concentrations that have been shown to produce effects on human erythrocytes *in vitro*.

In conclusion, given the species and sex specificities of the neoplastic responses and current evidence supporting the hypothesis of a mode of action based on haemotoxicity, butoxyethanol is not regarded as a human carcinogen.

8.5.10 *Reproductive toxicity*

8.5.10.1 Fertility

Some repeat dose studies in rodents have reported testicular effects. In an oral study in which rats were given 0, 0.01, 0.05, 0.25 or 1.25% (0, 7, 38, 188 and 919 mg/kg/day) butoxyethanol for 90 days via food (Mellon Institute of Industrial Research 1963), testicular atrophy was reported at the mid (0.25%) and high (1.25%) doses. At these doses, decreased appetite and body weight gain (at the high dose this was 50% less than control animals) were also observed. In contrast, no effects on the testes were reported in other 13-week oral repeat dose rodent studies at doses up to 470 mg/kg bw/day (rats) or 1306 mg/kg bw/day (mice) (NTP 1993). No effects on weights of testes, seminal vesicles or coagulating glands were observed in mice receiving gavage doses of butoxyethanol up to 2000 mg/kg bw/day for five weeks (Nagano et al. 1984).

In inhalation studies of 13 to 14 weeks or 104 weeks duration, no effects on the testes or epididymis were observed in surviving rats or mice that were exposed repeatedly to up to 500 ppm butoxyethanol (Busby Run Research Center 1981b; NTP 2000).

Multigenerational studies of the effects of butoxyethanol have also been conducted. In one study, male and female mice received butoxyethanol via drinking water at doses of 0, 0.5, 1.0 or 2.0% (equivalent to daily intakes of 0, 720, 1340 and 2050 mg/kg bw/day) during a continuous breeding phase with a seven-day pre-mating period and a 98-day cohabitation period (Morrissey et al. 1988, 1989; Heindel et al. 1990). A high number of deaths occurred in female mice(but not male mice) during the cohabitation period – more than half at the highest dose and approximately 30% in the 1% group.

At the completion of the continuous breeding phase, F0 breeding pairs were separated. When the last litters were weaned, males and females from the 1% group were mated with control animals in a one-week cross-over mating study during which butoxyethanol exposures were briefly discontinued. The proportion of successful copulations from the breeding pairs was similar in all groups, however, the number of fertile females was reduced in the group where treated females were mated with control males. Moreover, proportionally more females had extended oestrous cycles compared to controls. At necropsy, no significant differences were observed between control and treated animals for reproductive organ weights, sperm motility, morphology or average oestrous cycle length and frequency. However, male and female mice from this 1% group had significantly lower body weights and

increased relative kidney weights while females also had significantly increased relative liver weight. The results suggest that effects on fertility were confined to females. However, these effects appeared to be a consequence of systemic toxicity rather than a direct effect on reproductive organs.

Fertility was also assessed in F1 pups from parents in the 0.5% group from the continuous breeding phase. After rearing to sexual maturity, mice received 0.5% (equivalent to 950 mg/kg bw/day) butoxyethanol via drinking water and were then mated. No significant fertility or reproductive effects were observed in the F1 animals. No treatment-related effects on reproductive organ weights, sperm motility, morphology or oestrous cycle length and frequency were noted. However, a significant increase in relative kidney weight in females and a significant increase in relative liver weight in both males and females were observed.

Overall, fertility effects in females were observed at 1.0%. However, these were likely a consequence of systemic toxicity. A conservative NOAEL for fertility was established at 0.5% (720 mg/kg bw/day).

In *in vivo* studies with butoxyethanol metabolites, no morphological changes in the testes were observed following repeated gavage administration of BAA at 868 mg/kg bw/day for four days (Gray et al. 1985) or as a single dose (Foster et al. 1987). In contrast, metabolites of methoxyethanol (methoxyacetic acid) induced testicular toxicity at lower doses in both these studies.

8.5.10.2 Developmental toxicity

The developmental toxicity of butoxyethanol was tested in an NTP oral study in F344 rats (Sleet et al. 1989). Groups of animals were administered butoxyethanol via gavage to pregnant rats during the critical periods of cardiovascular development, with doses of 0, 30, 100 or 200 mg/kg/day on gestational days 9 to11 (group 1) or 0, 30, 100 or 300 mg/kg/day on gestational days 11 to13 (group 2). Except for the restricted exposure time, the procedure was similar to that of OECD Test Guideline 414.

Dose-related changes in haematological parameters including significant reductions in circulating erythrocytes, haematocrit and haemoglobin were observed in the dams of both groups at the two highest doses (100 and 200 mg/kg or 100 and 300 mg/kg). Additional signs of maternal toxicity included dose-related reductions in body weight gain and food and water consumption. Relative spleen weights were increased at 100 and 200/300 mg/kg, relative kidney weights were increased at 200/300 mg/kg and relative liver weights at 200/300 mg/kg. The NOAEL for maternal toxicity was 30 mg/kg/day.

An increase in non-viable and adversely-affected implants, post-implantation loss and resorptions per litter were observed at 200 mg/kg/day (group 1 only). In foetuses, a decreased platelet count was noted at 300 mg/kg/day (group 2 only). No foetal malformations, and in particular no cardiovascular malformations, were observed at any dose. A NOAEL for developmental toxicity was established at 100 mg/kg bw/day.

In prenatal and postnatal studies in pregnant CD-1 mice, butoxyethanol was administered via gavage at 0, 350, 650, 1000, 1500 or 2000 mg/kg/day on gestational days 8 to 14 (Wier et al. 1987). Mortality was observed at 1500 and 2000 mg/kg bw/day and signs of toxicity (haemolysis) were apparent at 650 mg/kg/day and above. The NOAEL for maternal toxicity was 350 mg/kg/day. An increased number of resorptions and a reduced number of viable foetuses were observed at 1000 and 1500 mg/kg. The NOAEL for embryotoxicity and foetotoxicity was 650 mg/kg/day. In the postnatal study, dams were treated with butoxyethanol via gavage at 650 or 1000 mg/kg bw/day on gestational days 8 to 14. Maternal

body weight was reduced at 1000 mg/kg bw/day. Pup growth or survival were unaffected by treatment. No statistically significant developmental effects were observed.

Inhalation developmental toxicity studies have also been conducted in pregnant Fischer 344 rats and New Zealand White rabbits (Tyl et al. 1984). Animals were exposed whole body to concentrations of 0, 25, 50, 100 or 200 ppm (0, 0.12, 0.25, 0.49 or 0.98 mg/L) for six hoursper day on gestational days 6 to 15 for the rat and gestational days 6 to 18 for the rabbit. In the rat, haematological effects, increased relative spleen weights and reduced body weight gain were observed in the dams at 100 and 200 ppm. The NOAEL for maternal toxicity was 50 ppm. Teratogenicity was observed at 100 and 200 ppm in the form of small retardations in skeletal ossification of vertebral arches or centra, sternebrae or phalanges. No other foetal effects were noted. A NOAEL for developmental toxicity was established at 100 ppm (0.49 mg/L).

In the rabbits, mortality, increased number of abortions and reduced uterus and body weight were observed at 200 ppm. However, no significant dose-dependent haematological changes were observed. The NOAEL for maternal toxicity was 100 ppm. Foetotoxicity was not observed at any dose, but a significantly lower number of total and viable implants per litter were noted at 200 ppm. The NOAEL for developmental toxicity was 100 ppm.

In an inhalation study in Sprague-Dawley rats, animals were exposed to butoxyethanol at 150 or 200 ppm for seven hours per day over gestational days seven to 15 (Nelson et al. 1984). Haemoglobinuria was noted in the dams at both doses on the first day only. No evidence of embryotoxicity, foetotoxicity or teratogenicity was observed.

These oral and inhalation studies in rats, mice and rabbits report developmental effects consisting of changes in numbers of total and viable implants, resorptions and live foetuses and, in one study, minor retardations of skeletal ossification. However, these effects were observed at maternally toxic doses. No developmental effects were noted in the absence of maternal toxicity.

8.5.11 *Other health effects*

No other data were available.

8.6 Health hazard summary

8.6.1 *Critical health effects*

Numerous animal studies have examined the acute toxicity of butoxyethanol. For acute oral toxicity, LD50 values range from 530 to 2420 mg/kg bw, with most studies providing LD50 values in the range 1000 to 2000 mg/kg bw. For dermal toxicity, the LD50 was approximately 500 mg/kg bw or >2000 mg/kg bw for occlusive versus non occlusive applications respectively. For acute inhalation toxicity, the LC50 from a four-hour inhalation test in rats was calculated as 2.38 mg/L for males and 2.2 mg/L for females respectively.

In humans, severe symptoms have been reported from acute ingestion of butoxyethanol, suggesting a human LOAEL for acute effects (metabolic acidosis) of 400 mg/kg bw.

Butoxyethanol is a skin irritant with occasional severe irritation reported in individual animals. Butoxyethanol is moderately to severely irritating to the eyes. Irreversible effects on the conjunctivae and cornea were observed at the end of the 72-hour observation period in one animal study. A single test in mice suggests that butoxyethanol is only a weak upper respiratory tract irritant. In humans, ocular and respiratory tract irritation (severity unknown) has been reported by participants in some inhalation tests, but not others.

No signs of skin sensitisation were observed in studies in animals or humans.

Repeat dose studies in a variety of animal species reveal haemotoxicity as a common effect following oral, dermal or inhalation exposures to butoxyethanol. Comparative *in vivo* and *in vitro* studies reveal that rats are more sensitive to the haemotoxic effects of butoxyethanol than humans. For oral repeat dose toxicity, LOAELs of 69 and 82 mg/kg/day for male and female rats respectively were established in a well-conducted 13-week drinking water study. No NOAELs were established from this study. For dermal repeat dose toxicity, a well-conducted 13-week study in rabbits reported no systemic effects at doses up to 150 mg/kg bw/day. For inhalation repeat dose toxicity, a NOAEC of 25 ppm (121 mg/m^3) with a LOAEC of 31 ppm (150 mg/m^3) was established from 13- and 104-week studies in rats and mice.

Butoxyethanol is not genotoxic. In carcinogenicity studies in rats, there was no evidence of carcinogenicity in males and equivocal evidence in females, based on combined incidences of pheochromocytoma of the adrenal medulla increased above historical controls. In mice, increased incidences of haemangiosarcomas in males and squamous cell papillomas or carcinomas in females were reported. These effects occurred at doses higher than those associated with repeat dose toxicity. Overall, given the species and sex specificities of these neoplastic responses, and current evidence supporting the hypothesis of a mode of action based on haemotoxicity, butoxyethanol is not regarded as a human carcinogen.

Reproductive studies revealed no direct effects of butoxyethanol on male or female reproduction in the absence of severe systemic toxicity. In a continuous breeding study in mice, effects were seen on female fertility only at doses associated with significant systemic toxicity. From this study a conservative NOAEL for fertility was established at 720 mg/kg bw/day. Similarly, studies in rats, mice and rabbits revealed developmental effects but only at maternally toxic doses. No developmental effects were noted in the absence of maternal toxicity.

Overall, the most sensitive effect from butoxyethanol exposures is repeat dose toxicity (haemotoxicity). For oral repeat dose toxicity, LOAELs of 69 and 82 mg/kg/day for male and females respectively, were established from a well-conducted 13 week rat drinking water study. No NOAELs were established from this study. A NOAEC of 25 ppm (121 mg/m^3) with a LOAEC of 31 ppm (150 mg/m^3) was established for inhalation repeat dose toxicity from well-conducted 13-week and 104-week studies in rats and mice.

8.6.2 *Hazard classification*

This hazard assessment confirms the existing hazard classification under the current *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004). The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A8.9. This NICNAS recommendation does not consider physical or environmental hazards.

Table A8.9 Hazard classification by NICNAS to Safe Work Australia

	GHS* classification
Acute toxicity	Harmful if swallowed – Cat. 4 (H302) Toxic in contact with skin or if inhaled – Cat. 3 (H311+H331)
Irritation	Causes skin irritation – Cat. 2 (H315) Causes serious eye irritation - Cat. 2A (H319)

[b] *Globally Harmonised System (UNECE 2009)*

8.7 References

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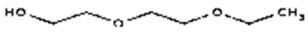
A9 Diethylene glycol ethyl ether

CAS no.	CAS Name
111-90-0	Ethanol, 2-(2-ethoxyethoxy)-

9.1 Chemical identity

The chemical identity information was obtained from ChemID*plus* (2012) and O'Neil (2001). A description of the chemical identity is provided in Table A9.1.

Table A9.1 Chemical Identity

	Diethylene glycol ethyl ether
Synonyms	Diethylene glycol ethyl ether Diethylene glycol monoethyl etherEthoxydiglycol Carbitol DGEE
Structural formula	
Molecular formula	$C_6H_{14}O_3$
Molecular weight	134.17
Appearance and odour	Colourless liquid with a mild, pleasant odour
SMILES notation	C(COCC)OCCO

9.2 Physical properties

The following information was obtained from ChemID*plus* (2012), Galleria Chemica (2013) and the Organisation for Economic Co-operation and Development (OECD 2007). Table A9.2 provides the physical properties of diethylene glycol monoethyl ether.

Table A9.2 Physical Properties

Property	Value
Melting point	-54 °C
Boiling point	196 °C
Density – kg/m^3	985 at 20 °C
Vapour pressure	0.017 kPa at 20 °C
Water solubility	1000 g/L at 20 °C

Property	Value
Partition coefficient (log K_{ow})	-0.69 (EPIWIN estimation)
Flash point	96 °C

9.3 Current regulatory controls

Hereinafter the document refers to ethanol, 2-(2-ethoxyethoxy) as DGEE, one of the synonyms of the chemical.

9.3.1 *Hazard classification for occupational health and safety*

DGEE is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

9.3.2 *Occupational exposure standards*

9.3.2.1 Australia

No specific exposure standards were available.

9.3.2.2 International

The following exposure standards (expressed as Time Weighted Average (TWA) or Short Term Exposure Limit (STEL)) were identified for DGEE (Galleria Chemica 2013).

TWA:

- 35 to 50 mg/m³ (6 ppm) [Austria, Germany, Spain, Switzerland]
- 80 mg/m³ (15 ppm) [Sweden]
- 145 to 165 mg/m³ (25 to 30 ppm) [Canada, US].

STEL:

- 100 mg/m³ [Spain, Switzerland]
- 140 to 170 mg/m³ (24 ppm) [Austria, Sweden].

9.3.3 *Australian food standards*

No Australian food standards were identified (Food Standards Australia New Zealand 2013).

9.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

9.3.5 *Additional controls*

9.3.5.1 Australia

The chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

9.3.5.2 International

DGEE is listed by the United States Food and Drug Administration (US FDA) under 21CFR 176.180 'Indirect Food Additives- Substances for Use Only as Components of Paper and Paperboard - Components of paper and paperboard in contact with dry food' with no restrictions.

DGEE is currently regulated under the Canadian Department of Justice, Hazardous Products Act, Ingredient Disclosure List (SOR/88-64) with the maximum authorised concentration of 1%.

DGEE is classified as a hazardous substance under the New Zealand Hazardous Substances and new Organisms (HSNO) Act as acutely toxic (oral), mildly irritating to the skin and irritating to the eye (EPA NZ 2012).

9.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

9.5 Health hazard characterisation

Information on DGEE was sourced primarily from the OECD assessment of the diethylene glycol ethers category (OECD 2007) and the European Commission's Scientific Committee on Consumer Safety (SCCS 2013). Additional sources of hazard information for the chemical include the World Health Organisation (WHO 2007) and the Hazardous Substances Data Bank (HSDB). Unless otherwise noted, references to individual studies below are taken from these reviews.

9.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

9.5.1.1 Oral absorption

The absorption of DGEE was investigated *in vivo* in two strains of rats, conducted according to OECD Test Guideline 417 (OECD TG 417), after a single oral dose of 20 mg [^{14}C]-DGEE/kg bw/day each. The absolute bioavailability of the radioactivity ranged from 79% to 95% (Gattefosse 2002a).

When a single oral dose of DGEE, approximately 20 mg/kg bw, was given to an adult human, 68% of the dose was excreted in the urine as 2-(2-ethoxyethoxy)acetic acid within 12 hours (Kamerling et al. 1977).

For human risk assessment purposes, 100% oral absorption is assumed.

9.5.1.2 Dermal absorption

The absorption of DGEE in human abdominal, whole skin has been tested *in vitro*. The rate of absorption was 0.125 mg/cm^2/hour and the permeability constant was 1.32 x 10^{-4} cm/hour. There was a trend of reducing absorption rate with increasing molecular weight or reducing volatility for the diethylene glycol series tested; 2-(2-methoxyethoxy) >2-(2-ethoxyethoxy) >2-(2-butoxyethoxy) (Dugard et al. 1984).

Up to 56% dermal absorption in human skin (abdomen and breast) was reported in a series of percutaneous absorption studies of DGEE in various cosmetic formulations (summarised by the SCCS 2013).

For human risk assessment purposes, 100% dermal absorption is assumed.

9.5.1.3 Inhalation absorption

No data were available. For human risk assessment purposes, 100% inhalation absorption is assumed.

9.5.1.4 Distribution

In vivo, the tissue distribution of DGEE was investigated (OECD TG 417) in two strains of rats after a single oral dose of 20 mg [^{14}C]-DGEE/kg bw/day each (Gattefosse 2002b). The distribution of the radioactivity was characterised by high concentrations observed in pituitary, thyroid, adrenals and bone marrow as compared to the concentrations observed in blood/plasma (100 to 1000 times less) at the same sampling time. The radioactivity measured in tissues was significantly decreased at 48 hours post administration.

9.5.1.5 Metabolism

The metabolic fate of DGEE was investigated in rats after a single oral dose of 1000 mg [^{14}C]-DGEE /kg bw/day by gavage (Gattefosse 2003a). Blood, urine and faecal samples were collected before administration and during the first 24 hours. After administration, ^{14}C-DGEE was extensively metabolised, as only 3% of the urinary excreted radioactivity corresponded to unchanged compound. The two major urinary metabolites were identified as ethoxyethoxyacetic acid and diethylene glycol, which represented 83% and 5.4% of the excreted urinary radioactivity, respectively. Consistent with urinary results, in plasma only ethoxyethoxyacetic acid and unchanged ^{14}C-DGEE were detected.

9.5.1.6 Excretion

The excretion of DGEE was investigated (OECD 417) *in vivo* in rats after a single oral or intravenous dose of 20 mg or 1000 mg (oral only) [^{14}C]-DGEE/kg bw/day each. Approximately 90% of the radioactivity was rapidly excreted in urine, irrespective of sex and route of administration (Gattefosse 2002b, 2003b).

When a single oral dose of approximately 20 mg/kg bw DGEE was given to an adult human, 68% of the dose was excreted in the urine as 2-(2-ethoxyethoxy)-acetic acid within 12 hours (Kamerling et al. 1977).

9.5.1.7 Summary of toxicokinetics

Available studies in rats indicate that DGEE is absorbed well by the oral route and that the principal metabolite, 2-(2-ethoxyethoxy)-acetic acid, is eliminated rapidly via the urine. Limited human data support similar conclusions.

9.5.2 *Acute toxicity*

9.5.2.1 Oral

Oral median lethal doses (LD50s) for DGEE were 6580 to 7410 mg/kg bw/day in mice, 3900 mg/kg bw/day in guinea pigs, 5400 to 10 500 mg/kg bw/day in rats and 3600 mg/kg bw/day in rabbits (SCCS 2013). Signs of acute rodent intoxication to DGEE

include inactivity, laboured breathing, rapid respiration, anorexia, slight to moderate weakness, tremors and prostration (Krasavage and Terhaar 1981a).

The studies show that DGEE has low acute toxicity by the oral route in rodents, guinea pigs and rabbits.

9.5.2.2 Dermal

Dermal LD50s were reported as 4200 to 9143 mg/kg bw/day for rabbits, 6000 mg/kg bw/day for rats and mice and 3200 mg/kg bw/day for guinea pigs (SCCS 2013). The studies show that DGEE has low acute toxicity by the dermal route in rodents and rabbits.

9.5.2.3 Inhalation

A median lethal concentration (LC50) of 5240 mg/m^3 was observed in rats after inhalation exposure to DGEE (BG Chemie 1993). However, no other details were provided for this determination.

The study shows that DGEE has low acute toxicity by the inhalation route in rats.

9.5.2.4 Observation in humans

In a case report, an adult male who ingested approximately 300 mL of a liquid containing 47% DGEE (approximately 2000 mg/kg bw) experienced severe symptoms of central nervous and respiratory effects such as dyspnoea, thirst, acidosis and albumin in the urine. The subject recovered following symptomatic treatment (Browning 1965).

9.5.3 *Irritation / Corrosivity*

9.5.3.1 Skin irritation

In a well-conducted study, no dermal effects were observed in male rabbits following application (occluded) of 50% DGEE for 24 hours (Gattefosse 1974).

Slight to no dermal irritation was induced in rabbits and guinea pigs (OECD 2007). However, in general, only limited information on study methodology and results are available.

9.5.3.2 Eye irritation

In a method comparable to OECD TG 405, ocular irritancy was tested by instilling 30% and 100% DGEE to the conjunctival sac of rabbits and evaluated over 72 hours. At the high dose, very slight reversible conjunctival reddening and chemosis were observed at 24 hours together with slight congestion that persisted for 48 hours. No irritation was observed at the low dose 24 hours after dosing (Gattefosse 1996a, 1996b).

Other older studies in rabbits noted no, slight or irritant effects on the eyes (OECD 2007).

9.5.3.3 Respiratory irritation

No data were available. In a 28 day nose only inhalation study in rats, mild local irritation of the larynx and nasal turbinates and foci of necrosis in the larynx were reported (Hardy et al. 1997). Based on these effects DGEE is likely to be a respiratory irritant.

9.5.3.4 Observation in humans

No irritation was noted in 25 subjects undergoing a closed patch test with 20% DGEE in petrolatum (Kligman 1972). Out of 60 subjects exposed dermally to DGEE of unknown purity

for 10 days, three showed signs of irritancy (Smyth et al. 1938). In a 48 hour occlusive patch test study, 45% of males exposed to 50% DGEE showed erythema and oedema however further details were not provided (Motoyoshi et al. 1984).

Patch testing of 10 females with undiluted DGEE over 48 hours induced very slight erythema in one individual. It was concluded that under conditions of the test DGEE was 'well tolerated' (Gattefosse 1992).

The results of these studies do not indicate a significant skin irritation potential.

9.5.4 *Sensitisation*

9.5.4.1 Skin sensitisation

No data were available for DGEE. Results of OECD Guideline studies for two other members of the diethylene glycol ether category were negative (OECD 2007). Based on this data it is concluded that DGEE is not a skin sensitiser.

9.5.4.2 Respiratory sensitisation

No data were available.

9.5.4.3 Observation in humans

In a study conducted in accordance with good laboratory practice (GLP), occlusive patches of undiluted DGEE were applied to the skin of 24 individuals for nine 24 hour periods over three weeks. None gave positive reactions on challenge 15 days after the final induction application (Gattefose 1993). A maximisation test conducted in 25 subjects with 20% DGEE in petrolatum was also negative (Kligman 1972).

9.5.5 *Repeat dose toxicity*

9.5.5.1 Oral

Animal data on oral repeat dose toxicity of DGEE were summarised from OECD (2007) and SCCS (2013) and are presented in Table A9.3. The Lowest-Observed-Adverse-Effect-Levels (LOAELs), No-Observed-Adverse-Effect-Levels (NOAELs) and Klimisch scores (Klimisch et al. 1997) (1 = reliable without restrictions; 2 = reliable with restrictions; and 3 = invalid) are indicated for each study.

Table A9.3 Repeat oral toxicity studies with DGEE

Species	Treatment	Results	Remarks	Reference
SD rats, males only	Gavage, 6 weeks 0, 1340, 2680, or 5360 mg/kg bw/day	LOAEL = 2680 mg/kg bw/day NOAEL = 1340 mg/kg bw/day	At the top dose, mortality, red urine, haematological and clinical chemistry effects including reduced red blood cell (RBC) count. At the mid dose, increased relative organ weights (liver, heart and kidney), hyperkeratosis of the stomach, and splenic congestion.	Krasavage and Vlaovic (1982) Klimisch = 2
CFE rats	Diet, 90 days 0, 250, or 2500 mg/kg	LOAEL = 2500 mg/kg bw/day NOAEL = 250	At the top dose, clinical observations of reduced growth, bodyweight, increased relative kidney (both sexes), spleen and thyroid (female) weights,	Gaunt et al. (1968) Klimisch = 2

Species	Treatment	Results	Remarks	Reference
	bw/day	mg/kg bw/day	and oxalate crystals in the urine. Histological changes in kidneys (calcification of the renal cortex, hydropic degeneration) and decreased haemoglobin (Hb) (both sexes), RBC count (females).	
Rats	Diet, 90 days 0, 200, 800, or 4000 mg/kg bw/day	LOAEL = 4000 mg/kg bw/day) NOAEL = 800 mg/kg bw/day)	At the top dose, clinical observations of mortality, reduced bodyweight and increased relative kidney weights. Histological changes including hydropic degeneration of the kidney and liver and fatty liver. Clinical chemistry observations were increased urinary aspartate transaminase and proteinuria (males). No changes at low or mid doses.	Hall et al. (1966) Klimisch = 2
Wistar rats	Drinking water, 2 years 0, 0.01, 0.04, 0.2, or 1%,	LOAEL = 1% (est. 950 mg/kg bw/day) NOAEL = 0.2% (est. 200 mg/kg bw/day)	At the high dose, pathological changes in the bladder and kidney.	Smyth et al. (1964) Klimisch = 3
CD-1 mice	Diet, 90 days 0, 0.2, 0.6, 1.8, 5.4%	LOAEL = 1.8% (est. 2700 mg/kg bw/day) NOAEL = 0.6% (est. 900 mg/kg bw/day)	At the top dose, mortality, hydropic degeneration and atrophy of the kidney, increased relative kidney weight (both sexes), liver cell hypertrophy. Males in top dose group: increase relative liver, heart and brain weights, reduction in RBCs, protein inclusions and submucosal inflammatory cell infiltration of the bladder At the 1.8% dose, the only effect noted was an increase in relative kidney weight in males.	Gaunt et al. (1968) Klimisch = 2
CD-1 mice	Drinking water, 14 weeks 0, 440, 2200, or 4400 mg/kg bw/day	LOAEL = 4400 mg/kg bw/day NOAEL = 2200 mg/kg bw/day	Reproduction study: At the top dose increased relative liver weight and decreased relative brain weight reported. Clinical chemistry not performed.	Williams et al. (1990) Klimisch = 1
Pigs	Diet, 90 days 0, 167, 500, 1000, or 1500 mg/kg bw/day Top dose decreased to 1000 mg/kg bw/day at	LOAEL = 500 mg/kg bw/day NOAEL = 167 mg/kg bw/day	Mortality and uraemia (both sexes) at the initial top dose. Males: hydropic degeneration of the liver and proximal tubules of the kidney, increased relative kidney weight at the 2 top doses. Reduced RBC count at the top dose. Females: hydropic degeneration of the liver and proximal tubules of the kidney	Gaunt et al. (1968) Klimisch = 2

Species	Treatment	Results	Remarks	Reference
	week 3.		at 500 mg/kg bw/day and above.	
Dogs, beagle	Gavage, 90 days 0, 400, 1000, 1500, or 2000 mg/kg bw/day Top dose decreased to 1500 mg/kg bw/day at week 3.	LOAEL = 1000 mg/kg bw/day NOAEL = 400 mg/kg bw/day	Mortality due to severe renal tubular degeneration at the initial top dose. Males: increased alkaline phosphatase at mid dose and above. Decreased urine sodium, chloride and creatine at all doses were not considered to be adverse. Females: Increased relative liver weights, elevated alkaline phosphatase and urine creatine at the mid dose and above.	Gattefosse (2007) Klimisch = 1

In short, medium and long term repeated oral toxicity studies in rats, mice, pigs and dogs, the kidney and liver are the critical organs for which effects have been observed across all experimental animals tested. In four rat studies, the NOAELs varied from 200 to 1340 mg/kg bw/day. In a two year and a 90 day rat study, NOAELs of 200 to 250 mg/kg bw/day were recorded based on pathological kidney changes at 5 to 10 times higher doses. A NOAEL of 900 mg/kg bw/day was found in one study with mice based on increased relative kidney weight. In a non-GLP, 90 day pig study, kidney damage was observed at 500 mg/kg bw/day and a NOAEL of 167 mg/kg bw/day was derived; however, it was of concern that relatively high concentrations of ethylene glycol were present in the test material.

The critical study for determining the effects of repeated exposures to the chemical is the well-conducted 90 day gavage study in dogs (Gatefosse 2007a). Decreased levels of urinary electrolytes and creatine, seen in one sex at the lowest dose, were considered to be non-adverse effects. Repeated exposure to DGEE at higher doses was associated with adverse effects on the liver such as increased relative weight and increases in alkaline phosphatase levels with severe renal tubular degeneration contributing to morbidity at the top dose. A NOAEL of 400 mg/kg bw/day was established based on hepatic toxicity at the LOAEL of 1000 mg/kg bw/day. Based on this NOAEL, the European Commission's Scientific Committee on Consumer Safety (SCCS) recommended that DGEE be used at a maximum concentration of 2.6% in cosmetic products (SCCS 2013).

9.5.5.2 Dermal

In a GLP study, undiluted DGEE was applied to the skin of rabbits (semi-occluded) for daily six hour periods over 28 days at doses up to 1000 mg/kg bw/day. The treatment-related effects observed were limited to barely perceptible erythema and / or oedema and desquamation (Gattefosse 1994).

In a poorly reported 12-week study in rabbits, DGEE at doses estimated at 100, 300, 1000 and 3000 mg/kg bw/day for five days/week resulted in increased blood urea nitrogen and severe kidney injury at the top dose (Dow Chemical Company 1950). A dose of 1000 mg/kg bw/day resulted in moderate kidney changes while no effects were observed at doses of 300 mg/kg bw/day or below. Kidney damage and mortality was reported in rabbits following dermal application of DGEE for 30 days; however, details of the study were limited (Hanzlick et al. 1947).

Overall, effects from a reliable dermal study using DGEE were limited to slight irritation at 1000 mg/kg bw/day. The data from other studies were limited and inconclusive and included

unspecified mortality (at unspecified doses in one of the studies), and some kidney and liver effects at high dose levels.

9.5.5.3 Inhalation

In a 28-day nose only inhalation study, rats were exposed to 16, 49, or 200 ppm (90, 270, 1100 mg/m^3) DGEE for six hours per day (Hardy et al. 1997). No systemic effects were observed. However, mild local irritation of the larynx and nasal turbinates was found in some rats and foci of necrosis in the larynx were observed in males inhaling 270 mg/m^3 or above. The NOAEL for local effects was determined to be 1100 mg/m^3.

In a poorly reported study in which rats were exposed for four months continuously to 0.2, 1 or 4 ppm (1, 5, or 25 mg/m^3) DGEE, changes in the functional state of the nervous system were claimed during both the treatment and the recovery periods in rats exposed to 5 mg/m^3 or more (Krotov et al. 1981). Haematological changes and increased liver weight were noted in some animals with investigators stating that 'the findings were confined mainly to rats receiving 5 mg/m^3 or more'. No conclusions could be drawn from this study due to the nature of exposure as well as the limited details available.

Overall, one reliable 28-day inhalation study with DGEE in rats showed only mild respiratory effects at 270 or 1100 mg/m^3

9.5.5.4 Observation in humans

No data were available.

9.5.6 *Genotoxicity*

Good quality Ames tests have been performed on DGEE in *S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537, and TA1538 (EI DuPont de Nemours 1989; Gattefosse 1999). Results of these studies were negative in the absence and presence of metabolic activation. Evidence for weak mutagenicity in *Saccharomyces cerevisiae* D7 and *S. typhimurium* strains TA1535, TA537 and TA1538 was discounted due to methodological deficiencies in the studies (Berte et al. 1986).

In an unscheduled DNA assay in rat liver (OECD 486), DGEE administered up to 2000 mg/kg bw did not induce DNA-damage (Gattefosse 1996c). Similarly, a mouse micronucleus study with DGEE (two daily doses of 1814 mg/kg bw/day, intraperitoneal) was negative but its reliability was considered to be limited (Berte et al. 1986).

Overall, it is concluded that DGEE is unlikely to be genotoxic.

9.5.7 *Carcinogenicity*

No adequate data were available. Investigators stated that tumours were not increased in rats exposed for 718 days to up to 950 mg/kg bw/day in drinking water (Smyth et al. 1964); however, the study was inadequate in design and inconclusive as to carcinogenic potential.

9.5.8 *Reproductive toxicity*

9.5.8.1 Fertility

The reproductive toxicity of DGEE has been investigated in a number of adequate studies in mice, rats and pigs. The key animal data were summarised from OECD (2007) and SCCS (2013) and presented in Table A9.4.

Table A9.4 Reproductive toxicity studies with DGEE

Species	Treatment	Results	Remarks	Reference
CD-1 mouse, 2-generation	Drinking water, 0, 440, 2200, or 4400 mg/kg bw/day for 14 weeks	NOAEL/P = 4400 mg/kg bw/day NOAEL /F1 reproduction= 2200 mg/kg bw/day NOAEL/F2 toxicity = 4400 mg/kg bw/day	F0: There was no treatment-related systemic effect. F1: There was no effect on fertility despite a decrease in sperm motility in males at 4400 mg/kg bw/day. Increased relative liver weight also seen at this dose.	Williams et al. (1990) Klimisch = 1
SD rats, fertility	Oral (gavage), 0, 300, 1000, or 2000 mg/kg bw/day for 65 days (males) or 21 days (females)	*Systemic toxicity* NOAEL = 1000 mg/kg bw/day *Fertility* NOAEL = 2000 mg/kg bw/day	There was no treatment-related effects on gonads, fertility or reproductive performance. A reduction in body weight gain and minor clinical findings at 2000 mg/kg bw/day in both sexes.	Gattefosse (2001) Klimisch = 1
SD male rats, exam of reproductive organs	Oral (gavage), 0, 1340, 2680, or 5360 mg/kg bw/day for 6 weeks	NOAEL = 5360 mg/kg bw/day	Testicular atrophy and degenerated spermatozoa and hypospermia in the epididymis of 1/10 rats at 2680 mg/kg bw/day. No effect at high or low dose.	Krasavage and Vlaovic (1982) Klimisch = 2
CFE rat, exam of reproductive organs	Oral (diet), 0, 250, or 2500 mg/kg bw/day for 90 days	NOAEL = 2500 mg/kg bw/day	There was no treatment-related effect on weights or histology of reproductive organs	Gaunt et al. (1968) Klimisch = 2
Rat, exam of reproductive organs	Oral (diet), 0, 205, 800, or 3988 mg/kg bw/day for 90 days	LOAEL = 3988 mg/kg bw/day NOAEL = 800 mg/kg bw/day	Testicular oedema in 5/12 males at 3988 mg/kg bw/day. No effect on testes at other doses.	Hall et al. (1966) Klimisch = 2
CD-1 mice, exam of reproductive organs	Oral (diet), 0, 300, 900, 2700 or 8100 mg/kg bw/day for 90 days	NOAEL = 8100 mg/kg bw/day	There was no treatment-related effect on histology of reproductive organs.	Gaunt et al. (1968) Klimisch = 2
Pig, exam of reproductive organs	Oral (diet), 0, 167, 500, 1000, or 1500 mg/kg bw/day	NOAEL = 1500 mg/kg bw/day	There was no treatment-related effect on weights or histology of reproductive organs	Gaunt et al. (1968) Klimisch = 2
SD rat, exam of reproductive organs	Inhalation, 0, 90, 270, or 1100 mg/m^3 for 28 days	NOAEL = 1100 mg/m3	There was no treatment-related effect on weights or histology of reproductive organs	Hardy et al. (1997) Klimisch = 2

The reproductive toxicity studies demonstrate that DGEE had no effect on fertility at 4400 mg/kg bw/day, the highest oral dose tested.

Results of the majority of reliable repeated-dose toxicity studies in which reproductive organs were examined indicate that DGEE did not cause toxicity to reproductive organs including the testes. However, two studies showed toxicity to sperm or testes at high doses.

In a two-generation study, although a 34% decrease in sperm motility was noted in mice treated with 4400 mg DGEE/kg bw/day for 14 weeks, sperm concentrations and morphology, histopathology of the testes and fertility were not affected (Williams et al. 1990). Additionally, a 90-day dietary study found testicular oedema at a dose of 4000 mg DGEE/kg bw/day (Hall et al. 1966). Since the purity of the material used in the studies that showed testicular toxicity is unknown, the OECD (2007) considered it possible that the toxicity was caused by an impurity, the known testicular toxicant, ethylene glycol monoethyl ether. Overall, potential testicular toxicity of DGEE is observed at high doses, but DGEE is considered not to have any significant effects on fertility.

9.5.8.2 Developmental toxicity

The key animal data on developmental toxicity of DGEE were summarised from OECD (2007) and SCCS (2013) and presented in Table A9.5.

Table A9.5 Developmental toxicity studies with DGEE

Species	Method, exposure period, doses	Results	Remarks	Reference
SD rats	Inhalation, GD7-15 0, 102 ppm (570 mg/m3), 7 h/day	Maternal NOAEL = 102 ppm Developmental NOAEL = 102 ppm	No apparent treatment-related maternal or foetal toxicity at the only dose tested.	Nelson et al. (1984) Klimisch = 2
SD rats	Dermal GD7-16 0, 1.4mL mg/kg bw/day (1385 mg/kg bw/day)	Maternal NOAEL = 1385 mg/kg bw/day Developmental NOAEL = 1385 mg/kg bw/day	No apparent treatment-related maternal or foetal toxicity at the only dose tested. Validity questionable as applications were not occluded	Hardin et al. (1984) Klimisch = 3
SD rats	Oral (gavage), Day 7-16 post coitum 0, 300, 1000, or 2000 mg/kg bw/day	Maternal NOAEL = 1000 mg/kg bw/day Developmental LOAEL = 2000 mg/kg bw/day NOAEL = 1000 mg/kg bw/day	At the top-dose, dams had decreased bodyweight gain, and reduced food consumption. At 2000 mg/kg bw/day, effects were minor skeletal findings mainly increased incidence of reduced ossification of cranial bones.	Gattefosse (2002b) Klimisch = 1
CD-1	Oral (gavage),	Maternal	Maternal toxicity (14% mortality and reduced	Schuler et al. (1984); Hardin et

Species	Method, exposure period, doses	Results	Remarks	Reference
mice	GD6-13 0, 5500 mg/kg bw/day	LOAEL = 5500 mg/kg bw/day Developmental NOAEL = 5500 mg/kg bw/day	weight gain) at the only dose tested.	al. (1987) Klimisch = 2

The developmental toxicity studies demonstrate that DGEE causes developmental effects (minor skeletal variations) at 2000 mg/kg bw/day in rats. These findings are not considered to be indicative of a developmental toxicity potential.

9.5.9 *Other health effects*

No additional health effects were identified.

9.6 Health hazard summary

9.6.1 *Critical health effects*

DGEE demonstrates low acute toxicity and is a mild eye irritant. The chemical is not a skin irritant or sensitiser. Based on a repeat dose study, it is likely to be a mild respiratory irritant.

Consistent adverse effects associated with repeated oral and dermal exposure to DGEE in animals are kidney and liver effects. The most appropriate NOAEL for risk assessment determined from the 90-day gavage study in dogs (Gattefosse 2007) is 400 mg/kg bw/day based on hepatic toxicity at the LOAEL of 1000 mg/kg bw/day.

The chemical is not genotoxic, but no reliable studies were identified regarding carcinogenicity. The weight of evidence also indicates the chemical is not a reproductive or developmental toxicant – whilst a few studies indicated some minor effects, the vast majority of studies indicated no effects, even up to relatively high doses.

9.6.2 *Hazard classification*

DGEE is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) and is not recommended by NICNAS for classification.

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A10 Precipitated silica, Amorphous silica

CAS No.	CAS Name
112926-00-8	Silica gel, preciptated, crystalline-free
7631-86-9	Silica

10.1 Chemical identity

Silicon dioxide exists as crystalline as well non-crystalline (amorphous) forms that are identical in composition but have different atomic arrangements. Silica, independent of its form and method of preparation, is found under the CAS No. 7631-86-9. To differentiate between the silica polymorphs, specific CAS registry numbers have been generated for each form of silica (Figure A10.1).

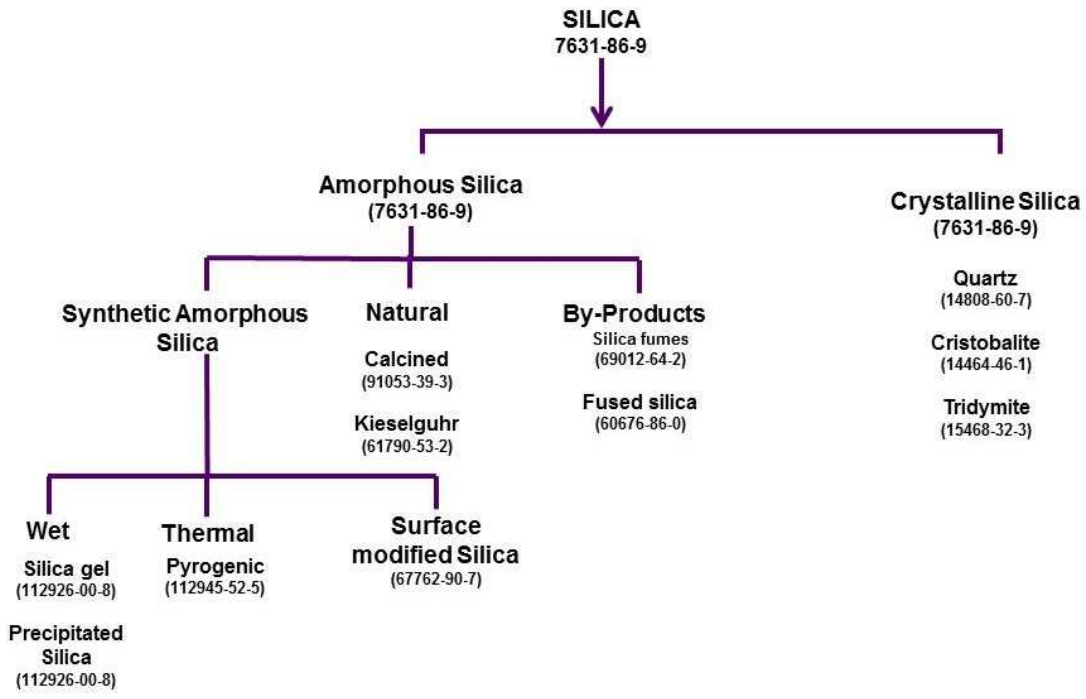

Figure A10.1. Polymorphs of silica (ECETOC 2006)

Amorphous silica can be naturally occurring, (e.g. diatomaceous earth, kieselgurh) or chemically synthesised under controlled conditions (synthetic amorphous silica, SAS). Commonly encountered synthetic amorphous silicas are silica gel, precipitated silica and fumed silica, differentiated according to their method of preparation. The most outstanding characteristics of synthetic amorphous silicas are their small ultimate particle size and high specific surface area, which determine their numerous applications (Stokinger 1981).

While one company reported the use of amorphous silica under the general CAS number 7631-86-9 (polymorph not specified), others reported the names and CAS numbers of the specific polymorphs of amorphous silica. The present report therefore deals with the hazard assessment of amorphous silica in general with specific toxicological data from studies conducted with silica gel/precipitated silica (CAS No. 112926-00-8). These two forms of synthetic amorphous silica have been specifically identified as being used in coal seam gas extraction in Australia. Both these forms of silicas are synthesised by reacting sodium silicate solution with a strong acid, such as hydrochloric acid. They both bear the CAS No. 112926-00-8.

The chemical identity information was obtained from the Organisation for Economic Cooperation and Development (OECD 2004) and the ECETOC (2006) and is provided in Table A10.1.

Table A10.1 Chemical identity

	Precipitated silica, Amorphous silica
Synonyms	Non-crystalline silica Synthetic amorphous silica (SAS) Amorphous precipitated silica Precipitated silica
Structural formula	O = Si = O
Molecular formula	SiO_2
Molecular weight	60.08
Appearance and odour	White solid (amorphous), odourless
SMILES notation	O=[Si]=O

10.2 Physical properties

The information on physical properties was obtained from OECD (2004) and is provided in Table A10.2.

Table A10.2 Physical properties

Property	**Precipitated silica/silica gel**
Melting point	Approx 1700 °C
Boiling point	No data
Density	2.2 g/cc
Vapour pressure	Negligible
Water solubility	Slightly soluble (15-68 mg/L)
Partition coefficient n-octanol/water (log K_{ow})	Not relevant

10.3 Current regulatory controls

10.3.1 *Hazard classification for occupational health and safety*

Precipitated silica and silica gel are listed on the Australian Hazardous Substances Information System (HSIS) as 'Silica amorphous [precipitated and gel]' (Safe Work Australia 2013); however, no hazard classification is provided.

10.3.2 *Occupational exposure standards*

10.3.2.1 Australia

The following occupational exposure standard is recommended for precipitated silica and silica gel in Australia (Safe Work Australia 2013):

- 10 mg/m³ (Time Weighted Average, TWA).

10.3.2.2 International

Occupational exposure limits for precipitated silica identified internationally are provided below (Galleria Chemica 2013).

TWA:

- 10 mg/m³ [Belgium, Canada].

Permissible exposure limit (PEL):

- 6 mg/m³ [US (Calif, Washington].

The US Department of Energy has designated the following Temporary Emergency Exposure Limits (TEEL) for precipitated silica/silica gel (Table A10.3) (Galleria Chemica 2013):

Table A10.3 Temporary Emergency Exposure Limits (TEEL) for precipitated silica/silica gel

TEEL-0	TEEL-1	TEEL-2	TEEL-3	Units
10	30	50	250	mg/m³

No other countries have established exposure limits specifically for the chemicals.

10.3.3 *Australian food standards*

Amorphous silica is included in Schedule 1 of FSANZ 'Permitted food additives' with an INS (International Numbering System for food additives) of 551. The maximum level of amorphous silica permitted in food is not specified (Food Standards Australia New Zealand 2013).

10.3.4 *Australian drinking water guidelines*

The *Australian Drinking Water Guidelines* state 'To minimise an undesirable scale build up on surfaces, silica (SiO_2) within drinking water should not exceed 80 mg/L' (National Health and Medical Research Council (NHMRC) 2011).

10.3.5 *Additional controls*

10.3.5.1 Australia

No additional controls were identified.

10.3.5.2 International

No additional controls were identified.

10.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

10.5 Health hazard characterisation

The following information on health hazards was obtained from the OECD (2004) and ECETOC (2006) reviews on amorphous silica. Unless otherwise noted, references to individual studies below are taken from these reviews.

10.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

Blood levels of silica (form of silica not specified) were determined in 264 unexposed human volunteers (ECETOC 2006). The mean value was 8.3 ng SiO_2/mL total blood. There was no significant influence of sex, age, employment, lung disease (dust lung) or other disease on blood levels.

10.5.1.1 Oral absorption

Intestinal absorption of amorphous silica following oral administration is insignificant in animals and humans. In a rat study, following daily oral administration of 1500 mg/kg bw of precipitated silica (FK700) as aqueous suspension for one month, there was no accumulation of silica in the organs: the average silica content in liver was 1.5 µg, in kidney 6.4 µg and in spleen 5.3 µg. The corresponding control values were 1.8, 7.2 and 7.8 µg silica, respectively (Degussa 1968).

In a similar experiment in rats receiving 20 daily oral doses of 100 mg SAS per animal (about 500 mg/kg bw), tissue values were slightly increased in liver and kidney: in liver 4.2 µg (control value 1.8 µg), in the spleen 5.5 µg (7.2 µg) and in the kidneys 14.2 µg (7.8 µg) (Klosterkoetter 1969).

In the above two studies, it is not clear if these values were expressed as ‘per gram tissue’ or ‘for the whole organ’.

No significant intestinal absorption of the silica gel (Syloid HC) was observed in a study in which six human volunteers were administered silica gel with their morning and evening meal. Starting with an oral dose of 1 g/day, the dose was increased daily by 1 g/day, up to a final dose of 16 g/day (Grace 1982).

In a human study described in more detail later in the report, most of 2500 mg precipitated silica administered orally was excreted in faeces and there was little indication of absorption

across the gut wall (Degussa 1966). Intestinal resorption appears to be insignificant in animals and humans.

A 0% oral absorption for amorphous silica will be assumed for human health risk assessment.

10.5.1.2 Dermal absorption

Information on dermal absorption of amorphous silica is not available. Considering the particulate nature of the amorphous silicas and their low solubility in water, dermal absorption is likely to be minimal and 0% dermal absorption will be assumed for human health risk assessment.

10.5.1.3 Inhalation absorption

Information on the inhalation absorption of amorphous silica, including precipitated silica/silica gel is not available. In many laboratory animal studies (OECD 2004; ECETOC 2006), the elimination of amorphous silica in lungs, following prolonged inhalation exposure, did not involve lymph nodes, indicating that amorphous silica is sparingly absorbed in the lungs.

In an inhalation study, Wistar rats (10 per sex per group) were exposed six hours/day for five days to 1, 5 and 25 mg/m^3 precipitated silica (Zeosil-45), silica gel (Syloid-74) and pyrogenic silica (Cab-O-Sil M5) (Arts and Kuper 2003; Arts et al. 2003). Additional groups were exposed similarly and kept for a recovery period of 1 or 3 months. One day after exposure, 64 to 86 µg silica was detected in lungs of high dose animals after Zeosil-45 exposure, 163 µg silica after Syloid-74 exposure and 92 µg silica after Cab-O-Sil M5 exposure. In all cases, the silica content of the lungs after one and threemonths of recovery was below the detection limit. No increased silica levels were observed in the lymph nodes at any concentration tested.

Rats were exposed by inhalation for five hours to 55 mg/m^3 precipitated SAS (FK700) (Degussa 1968b). The mean retention value (20 h later) was 0.138 mg SiO2/lung. The average silica content of the lungs was 1.022 mg after four months of exposure, and 3.443 mg after 12 months. The corresponding values for the mediastinal lymph nodes were 0.033 mg after four months, 0.052 mg after five months and 0.069 mg after 12 months. The average silica content of the lungs was 0.457 mg (elimination 87%) five months after exposure. This indicates that there was no significant elimination of SAS via the mediastinal lymph nodes, such as that observed with quartz.

In similar experiments, after 12 month's exposure to 50 – 55 mg/m^3 SAS, (approx. 30 mg/m^3 respirable), only 1% of administered total respirable dust was estimated to be retained in the lung (Klosterkoetter 1969). The increase in lung deposition was rapid at the initial exposure, then low from 18 weeks to 12 months of exposure (six weeks: 0.5 mg, 18 weeks: 1.2 mg, 12 months: 1.37 mg SiO_2). Mediastinal lymph nodes contained about 0.02 mg SiO_2 after six weeks and 0.13 mg SiO_2 after 12 months. After five months post-exposure, mean levels of SiO_2 were 0.16 mg/lung and 0.047 mg/lymph node, i.e. a reduction at some 88% in the lung and more than 50% in the lymph nodes.

The above studies indicate that very little silica is deposited in the lungs following inhalation exposure, the majority being expelled. The deposited silica particles are internalised by phagocytosis. Based on the small amounts of silica internalised by the lungs, 1% inhalation absorption for amorphous silica is assumed for human risk assessment.

10.5.1.4 Distribution

No data were available.

10.5.1.5 Metabolism

No data are available on metabolism. Amorphous silica is generally considered to undergo minimal metabolism with some conjugation reported (ECETOC 2006). Small amounts are expected to be hydrolysed to silicic acid under the influence of low pH, such as in gastric juices (OECD 2004).

10.5.1.6 Excretion

There was no accumulation of SAS in body tissues following oral ingestion. Rapid elimination occurred upon cessation of exposure (ECETOC 2006). In the two dietary studies described above (Degussa 1968; Klosterkoetter 1969), the majority of the swallowed SAS was excreted in the faeces.

In a human study, 12 volunteers were given precipitated silica in two portions of 1250 mg (each suspended in 250 mL apple juice) (Degussa 1966). Urine samples were analysed daily for the silica content prior and after treatment. No significant increase in renal excretion of silica was found. In 5/6 persons, the daily renal silica excretion was increased by 7 mg above the individual three-day baseline levels (average 16 mg). In 1/6 persons it was decreased. The median daily secretion of silica for the following three days was increased by only 4 mg (to 20 mg). The apparently small increases in the urinary output of silica in human volunteers (in relation to the high administered dose of 2500 mg silica) are consistent with the majority being excreted in the faeces. There was little indication of absorption across the gut wall.

10.5.2 *Acute toxicity*

10.5.2.1 Oral

The acute oral administration of various forms of SAS (aqueous suspension or gel) did not produce signs of toxicity or deaths in treated animals. Doses of up to 20 000 mg/kg bw by gavage in mice and rats, and up to 10 000 mg/kg bw in the diet for 24 hours did not cause mortality (OECD 2004). Median lethal dose (LD50 values) for the two types of oral exposures (gavage and dietary) were >20 000 mg/kg bw and >10 000 mg/kg bw, respectively.

10.5.2.2 Dermal

After acute dermal application of up to 5000 mg/kg bw of aqueous pastes of precipitated silica to the intact and abraded skin of rabbits for 24 hours under occlusive conditions, no mortality or signs of systemic toxicity were noted. It was concluded that SAS was not toxic by the dermal route (Degussa 1978). The dermal LD50 from this study was >5000 mg/kg bw.

10.5.2.3 Inhalation

For SAS, mean lethal concentration (LC50) values were higher than the highest technically achievable concentrations (2000 mg/m^3). Some mortality observed with hydrophobic SAS was due to suffocation associated with the extremely high particle numbers administered and not with any intrinsic toxicity of the SAS tested (ECETOC 2006).

Ten male Sprague-Dawley rats were exposed to 2200 mg/m3 of silica gel (Syloid 244) for one hour (nose-only). Only one animal died. The LC50 was determined to be >2200 mg/m^3 (Grace 1975).

10.5.2.4 Observations in humans

No major or long lasting effects have been reported in workers handling amorphous silica. A few cases describing dryness of the skin or degenerative eczema in workers with chronic contact with amorphous silica have been reported by occupational physicians (OECD 2004).

10.5.3 *Irritation / Corrosivity*

10.5.3.1 Skin irritation

Results from eight skin irritation studies in rabbits with precipitated silica were summarised in a report (ECETOC 2006). Up to 500 mg of precipitated silica was applied to abraded/intact skin for 4 or 24 hours under occlusive conditions. No irritating effects in test animals were reported in six studies and two studies showed very slight erythema (Draize score= 1) which was rapidly reversible.

Based on the above information, it was concluded that precipitated silica was not a skin irritant.

10.5.3.2 Eye irritation

Precipitated silica and silica gel, suspended in olive oil and instilled in rabbit eyes up to 100 mg, did not show any irritating effects (OECD 2004; ECETOC 2006). The slight eye irritation seen with SAS in some tests was completely and rapidly reversible. After washing the eyes, there was no irritation. In all tests, SAS was not an eye irritant.

It is concluded that precipitated silica/silica gel is not an eye irritant.

10.5.3.3 Respiratory irritation

No data were available. The amorphous forms of silica are classified as nuisance dusts and do not induce pneumoconiosis (ASCC 2006). Inflammatory reaction and irritation in the lung tissue was observed with SAS in some repeated inhalation studies in rats which could be related to respiratory irritation. However, no specific data have been reported for this endpoint (OECD 2004).

10.5.3.4 Observations in humans

Case reports of workers available from occupational physicians describe dryness or degenerative eczema of the skin in workers with chronic contact with amorphous silica (OECD 2004).

10.5.4 *Sensitisation*

10.5.4.1 Skin sensitisation

No data were available on the skin sensitisation effects of amorphous silica. Based on its structure and physico-chemical properties, SAS is not expected to cause skin sensitisation (ECETOC 2006). Data collected from industrial hygiene surveillance over the last 50 years do not indicate any potential for skin sensitisation (OECD 2004).

10.5.4.2 Respiratory sensitisation

No data were available.

Precipitated silica and silica gel have low acute toxicity. No mortalities were reported in acute oral, dermal or inhalation studies. They are not skin or eye irritants. Data on the skin sensitisation potential of these chemicals are not available. Based on the structure and physico-chemical properties, precipitated silica/silica gel are not expected to cause skin sensitisation.

10.5.4.3 Observations in humans

No data were available.

10.5.5 *Repeat dose toxicity*

10.5.5.1 Oral

Limited studies are available on the repeat oral dose toxicity of amorphous silica (OECD 2004; ECETOC 2006). In two short term repeat oral dose studies in rats, one each with precipitated silica (13 weeks) and silica gel (two weeks), no effects on physical appearance or gross and microscopic pathological abnormalities were observed (dosing details not provided). Silica gel up to 8980 mg/kg bw/day and precipitated silica up to 4000 mg/kg bw/day had no effect on the animals. No Observed Adverse Effect Limit (NOAEL) could not be established in this study (Degussa 1981).

In a chronic oral study, B6C3F1 mice and Fischer rats (40 per sex per group per species) were administered silica gel (Syloid 244) in the diet for 21 and 24 months, respectively. The dose in both species was 0, 1.25, 2.5 or 5.0% of diet (Takizawa et al. 1988). In mice there was a transient, slight but significant decrease in growth rate at higher doses between months 4 and 13. There were no significant differences in survival rates between the groups although the high dose group exhibited the greatest mean survival.

There was no evidence of altered haematology or in the treated groups. Significantly lower liver weights were observed for females only in the 2.5 and 5.0% dosage groups at 12 and 24 months. Abnormal atrophy or hypertrophy of the liver, spleen, heart and brain was sporadic between groups, but did not appear to be sex, dose or exposure duration-related.

The rats showed similar effects with dietary silica gel. There were some erratic variations in haematology and serum biochemistry in both males and females, but there was no pattern associated with sex, dose or time.

The authors concluded that no significant dose-related effects were seen at any dose level and that dietary administration of SAS silica gel, resulted in no long-term toxic effects. Neither a NOAEL nor a Lowest Observed Adverse Effect Level (LOAEL) was established in this study.

10.5.5.2 Dermal

No repeated dermal toxicity studies are available for amorphous silica.

10.5.5.3 Inhalation

Several short-term and long-term repeat dose studies have been conducted with precipitated silica and other forms of amorphous silica in various animal species, mostly rat, but also guinea pig, rabbit and monkey (Table A10.4). The available data confirm the absence of significant toxicity of precipitated silica and silica gel by the inhalation route. Unlike crystalline silica, no signs of classical nodular silicosis or lymphatic-type pneumoconiosis were observed following repeated inhalation exposure of rats to respirable particles of amorphous silica. In some species there was a time- and dose-related inflammatory response of the lung

tissue in animal studies. Nevertheless, all observed effects were reversible, although this was rather slow at high and prolonged exposure.

Chronic inhalation exposure to precipitated silica caused macrophage accumulation, reticulin fibre formation, nodule formation and some alterations in pulmonary function. Focal emphysematous lesions were noted in rats. These lesions resolved during recovery (post-exposure). There was no evidence of interstitial pulmonary fibrosis. In those studies that included a recovery period, pulmonary effects diminished with time (OECD 2004; ECETOC 2006).

Table A10.4 Repeat inhalation toxicity studies with precipitated silica and silica gel

Species	Method, study duration, doses	Results	Remarks	Reference
Silica gel				
Wistar rats, 10 males, 6 females	6 hours/day, 5 days; 1 and 3 months recovery; 0, 0.94, 5.13, 25.1 mg/m^3	NOAEL for systemic effects not established	No significant effects at 0.94 mg/m^3. Incidence of pulmonary inflammation at the mid and high doses. Observed changes tended to disappear during recovery.	Arts and Kuper (2003)
Precipitated Silica				
Wistar rats; 10 males, 10 females	6 hours/day; 5 days, recovery 1 and 3 months; 0, 1.16, 5.39, 25.2 mg/m^3	NOAEL for systemic effects not established	Incidence of pulmonary inflammation increased after exposure at the mid and high doses. Observed changes disappeared or tended to disappear during recovery. 1.16 mg/m^3 had no effect.	Arts et al. (2003)
Wistar rats 10 males, 10 females	6 hours/day, 5 days/wk for 2 wks; 0, 46, 180, 668 mg/m^3	LOAEL= 46 mg/m^3	Lungs of several animals at 668 mg/m^3 spotted and swollen. Increased septal cellularity, alveolar interstitial pneumonia and accumulation of alveolar macrophages in lungs of most males at 180 and 668 mg/m^3 and in all females. Early granulomata in mediastinal lymph nodes at 180 and 668 mg/m^3, and in one male at 46 mg/m^3	Degussa (1986)
Wistar rats; 70 males, 70 females	6 hours/day, 5 days/wk for 13 wks; 0 and 34.9 mg/m^3	LOAEL or NOAEL not established	Lung collagen content increased immediately after exposure, and returned to control levels by the 52 wk recovery period. Alveolar macrophage accumulation occurred at varying times post-exposure	Reuzel et al. (1991)

Species	Method, study duration, doses	Results	Remarks	Reference
Sprague-Dawley rats; 80 males	6 hours/day, 5 days/wk for 12 months; 0 and 6.9 mg/m^3 respirable	LOAEL or NOAEL not established	Small numbers of macrophage cell aggregates present. Interstitial fibrosis observed, but was also seen in control animals.	Groth et al. (1981)
Guinea pig, Hartley; 20 males			Small numbers of macrophage cell aggregates present.	
Monkey, Cynomolgus 10 males	5.5 hours/day, 5 days/wk for 18 months; 0 and 6.9 mg/m^3 respirable	LOAEL 6.9 mg/m^3	Large numbers of macrophage cell aggregates present. Reticulin fibres and small amounts of collagen present. Total lung capacity (TLC) and forced vital capacity (FVC) decreased.	
Rats (strain not stated)	6 h/day, 5 days/wk for 4 wks; 0, 10, 50, or 150 mg/m^3	NOAEL 10 mg/m^3	Silica-laden alveolar macrophages, neutrophilic infiltration, and Type II pneumocyte hyperplasia, enlarged tracheal (transient pulmonary inflammatory response). Disappears after exposure stopped.	Kelly and Lee (1990)
Fischer 366 rats	6 h/day, 5 days/wk for 3 and 8 months; 50 mg/m^3	NOAEL 50 mg/m^3	Transient pulmonary inflammatory response (as above) which returned to control levels after exposure stopped	Johnston et al. (2000)
Wistar rats, 57 (sex not stated)	8 hours/day, 7 days/wk for 15 months (6 months recovery) 126 mg/m^3	LOAEL or NOAEL not established	25 to 37% died from viral pneumonia. Particle-filled macrophages accumulated in alveoli, bronchioles and lymphoid tissue.	Schepers (1981)

No significant adverse effects were observed in any of the studies. A No Observed Adverse Effect Concentration (NOAEC) of 50 mg/m^3 was established in an 8-month rat inhalation study based on no adverse effects at 50 mg/m^3. This NOAEC will be carried forward for human health risk assessment.

10.5.5.4 Observations in Humans

Information on the short-term exposure effect of precipitated/gel silica in humans is not available.

Epidemiological data on workers in the amorphous silica industry are limited and in most studies appropriate control populations were lacking.

No cases of silicosis were observed in a study that evaluated medical records of 143 German workers manufacturing pyrogenic SAS from 1959 to 1985 (Degussa 1988). The exposure period ranged from 1 to >30 years. Fifty-four workers complained of pulmonary symptoms such as dry cough, sputum and shortness of breath or exhibited abnormalities in lung pathology or function. Of these 54 workers, 59% had a case history of disorders or of confounding exposure, 56% had a history of smoking, and only 22% had neither. Radiological examination did not show any signs of fibrotic disease. However, statistical analysis was not conducted to correlate exposure, smoking habits or other influencing factors with respiratory symptoms or lung pathology, and no attempt was made to calculate cumulative exposure. The study is therefore limited.

Medical records of 165 workers employed at two plants using precipitated SAS were reviewed (Wilson et al. 1981). Workers were exposed for a mean of 8.6 years to precipitated SAS. Dust levels at the workplace varied between <1 to 10 mg/m^3 with some higher intermittent levels. Forty four workers had been exposed to amorphous silica 18 years on average (range 10 to 35 years). Yearly decline of pulmonary function variables in these workers was similar to the overall group of 165 workers. Eleven workers had radiographic evidence of minimal pneumoconiosis, but this effect was biased by prior occupational exposure to limestone. Linear regression analysis of yearly change of all pulmonary function variables showed no correlation with either the dose of precipitated SAS or total years of exposure.

Company health records were reviewed for 78 males employed in the manufacture of precipitated SAS (Hi-Sil and Silene) in the US (Plunkett and DeWitt 1962). Duration of employment ranged from 1 year to 16 years and 7 months (average of 4.75 years). The percentage of time/employee exposed to SAS varied from less than 30% (7 employees), 50 to 90% (31 employees) to up to 100% (40 employees). Total SAS levels ranged from 0.3 to 204 mg SiO_2/m^3. Symptoms included mechanical irritation of (unprotected) skin, eyes, nose and throat from dry dust contact and thermal burns of skin and eyes from wet slurry. The workers did not exhibit silicosis or any other pulmonary disease based on annual X-ray examination.

A more recent descriptive report of a cross-sectional health survey of workers currently exposed to SAS, or who had left jobs where they were exposed to SAS, was reviewed (ECETOC 2006). The study was conducted in workers from five German factories. In three factories, the exposure was to pyrogenic SAS and in the other two the exposure was to precipitated SAS. A total of 510 currently exposed workers and 269 former workers with at least one month's exposure after 1980 were tested. Another 210 unexposed control workers also participated.The prevalence of chronic bronchitis was within expected ranges but somewhat higher in exposed subjects. There were minor differences between exposed and control subjects for the standard spirometric measurements. Chest radiographs showed no increased risk of pneumoconiosis of exposed subjects compared to controls and bronchial hyper responsiveness was within expected ranges for the study group. Pleural thickening was not observed in exposed subjects. The authors of the study (Merget and Kappler 2005) assume that the smoking habits in the exposed group were responsible for any small differences noted in these parameters. The results did not demonstrate a health risk due to SAS exposure.

10.5.6 *Genotoxicity*

SAS was not a gene point mutagen *in vitro*, using *Salmonella typhimurium*, *Escherichia coli* or *Saccharomyces cerevisiae*. SAS did not induce gene mutations in Chinese hamster ovary cells or chromosomal aberrations in cultured mammalian cells. Cytogenetic tests in bone morrow, dominant lethal tests in rat and host-mediated assays using S. typhimurium or S.

cerevisiae, were clearly negative, indicating that SAS is not genotoxic *in vivo* (ECETOC 2006).

There was no evidence that synthetic amorphous silica induced mutations either *in vitro* or *in vivo* using the standard methods (OECD 2004).

10.5.7 *Carcinogenicity*

In the chronic (12 months and 21 months) oral study in mice and rats discussed in Section A10.5.5.1, there was no significant increase in neoplastic or non-neoplastic lesions of the examined tissues, which included the lymphatic system, lungs, liver, adrenals, testes, mammary glands and prepuce (Takizawa et al. 1988).

The International Agency for Research on Cancer (IARC) considered the available literature on occupational exposure to amorphous silica, including diatomaceous earth and SAS. Since there was insufficient evidence of carcinogenicity in experimental animals and very little epidemiological evidence, IARC concluded that there is inadequate evidence in humans for the carcinogenicity of amorphous silica – 'Amorphous silica is not classifiable as to its carcinogenicity to humans (Group 3)' (IARC 1997).

10.5.8 *Reproductive toxicity*

10.5.8.1 Fertility

No data were available on reproductive effects of SAS.

10.5.8.2 Developmental toxicity

Pregnant albino CD-1 mice, Wistar rats and Golden hamsters were dosed daily by gavage with SAS gel (Syloid 244) suspended in water at doses ranging between 0 and 1350 mg/kg bw/day from day 6 to 15 of gestation (hamsters between 0 and 1600 mg/kg bw/day) (ECETOC 2006). No compound-related maternal deaths or significant variations of maternal body weight gain were reported in the studies. There were no significant differences in the number of corpora lutea (measured in rabbit only), percentage of implantation and / or resorption, and weight of live pups when compared to controls. The number of external, visceral or skeletal abnormalities in the test groups did not differ from controls.

It is concluded that precipitated silica/silica gel have no toxic effect on development.

10.5.9 *Other health effects*

No data were available.

10.6 Health hazard summary

10.6.1 *Critical health effects*

Precipitated silica and silica gel have low acute toxicity. No mortalities were reported in acute oral, dermal or inhalation studies. They are not skin or eye irritants. Data on skin sensitisation potential of these chemicals are not available; however, based on the structure and physico-chemical properties, precipitated silica and silica gel are not likely to be skin sensitisers.

Repeated oral exposure to amorphous silica (including silica gel and precipitated silica) had no adverse effect up to a dose of 4000 mg/kg. A common effect seen in inhalation studies with amorphous silica was an inflammatory response of the lung characterised by silica-

laden alveolar macrophages, neutrophilic infiltration, and Type II pneumocyte hyperplasia and enlarged tracheal and mediastinal lymph nodes. Most of these effects disappeared during the recovery period following cessation of exposure. The NOAEC for this effect was 50 mg/m^3 in an 8-month rat inhalation study.

10.6.2 *Hazard classification*

Based on the acute and chronic health effects, precipitated silica and silica gel are not recommended by NICNAS for classification and labelling under the current Approved Criteria and under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009).

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A11 Slaked lime

CAS No.	CAS Name
1305-62-0	Calcium hydroxide $Ca(OH)_2$

11.1 Chemical identity

The following chemical identity information was obtained from ChemID*plus* (2012) and Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013). Table A11.1 provides details of the chemical identity.

Table A11.1 Chemical identity

	Slaked lime
Synonyms	Limestone Hydrated lime Slaked lime
Structural formula	HO – Ca – OH
Molecular formula	Ca(OH)2
Molecular weight	74
Appearance and odour	Odourless, off-white powder
SMILES notation	[Ca+2].[OH-].[OH-]

11.2 Physical properties

Information on the physical properties of calcium hydroxide in Table A11.2 was obtained from REACH (2013).

Table A11.2 Physical properties

Property	**Value**
Melting point	580 °C
Boiling point	Decomposes at temperatures above 580 °C to give calcium oxide.
Density	2.21 kg/m3 at 25 °C
Vapour pressure	Negligible at 25 °C
Water solubility	1.73 g/L (20 °C)
Partition coefficient n-octanol/water (log K_{ow})	Not relevant

11.3 Current regulatory controls

11.3.1 *Hazard classification for occupational health and safety*

Calcium hydroxide is listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013). No risk phrases have been assigned to this chemical.

11.3.2 *Occupational exposure standards*

11.3.2.1 Australia

The chemical has an exposure standard of 5 mg/m³, Time Weighted Average (TWA) (Safe Work Australia 2013).

11.3.2.2 International

The following exposure standards are identified in Galleria Chemica (2013):

- Occupational Exposure Limit (TWA) of 5 mg/m^3 [Canada, Denmark, Korea, UK, US (NIOSH 1988)]
- Permissible Exposure Limits (PEL) of 15 mg/m^3 [US (OSHA 1995)].

11.3.3 *Australian food standards*

Calcium hydroxide is allotted the following International Numbering System (INS) of food additives number: INS 526 (Food Standards Australia New Zealand 2013).

11.3.4 *Australian drinking water guidelines*

Calcium hydroxide is used in water treatment to correct pH and adjust alkalinity, for coagulation optimisation, corrosion control and water softening. Typical calcium hydroxide concentrations used in drinking water treatment depend on the quality of the water to be treated, and the purpose of treatment (e.g. water softening, pH adjustment or alkalinity increase), and can vary from 5 to 500 mg/L (National Health and Medical Research Council (NHMRC) 2011).

11.3.5 *Additional controls*

11.3.5.1 Australia

Calcium hydroxide is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

11.3.5.2 International

No additional controls were identified.

11.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

11.5 Health hazard characterisation

The information on health hazards is obtained from REACH dossiers on the chemical (REACH 2013) and report by the Scientific Committee on Occupational Exposure Limits for Calcium Oxide and Calcium Hydroxide (SCOEL 2008). Unless otherwise noted, references to individual studies below are taken from these sources.

Data were read across from calcium lactate and calcium gluconate studies for systemic effects of calcium hydroxide. The rationale for using these analogues is that under physiological conditions the calcium ion (Ca^{2+}) is the chemical species of interest. After oral administration, the hydroxide ions released from calcium hydroxide are neutralised in the gastrointestinal tract and the lactate and gluconate moieties from calcium lactate and calcium gluconate, respectively, become integral components of mammalian energy metabolism and are therefore toxicologically not relevant (REACH 2013).

11.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

When systemically absorbed, calcium hydroxide dissociates into calcium ions and hydroxide ions. These are normal physiological components in humans that are subject to homeostatic mechanisms to regulate their levels in the body.

Calcium is the most abundant inorganic constituent of all animal species with most of the body content located in the skeleton. It is an essential ion for formation and maintenance of bone and teeth, and for regulation of several important physiological functions such as blood coagulation, neuromuscular activity, enzyme activity and acid-base balance. Hormonal systems regulate plasma calcium concentrations at approximately 100 µg/mL by controlling intestinal absorption of dietary calcium, the release from bone, and renal absorption/excretion (OECD 2005).

In healthy individuals, therefore, it is not biologically plausible for low level exposures to calcium hydroxide to affect internal organs (including reproductive organs) (SCOEL 2008; Geibel and Wagner 2006).

11.5.1.1 Oral absorption

Calcium hydroxide will hydrolyse in the acid pH of the stomach to generate calcium ions. Calcium ions are absorbed in the mammalian small intestine by two general mechanisms:

- a transcellular active transport process, located largely in the duodenum and upper jejunum
- a paracellular, passive process that functions throughout the length of the intestine (Bronner 2003).

Gastrointestinal absorption and bioavailability of orally administered calcium in the form of calcium gluconate, has been studied in rats (Sarabia et al. 1999). In the study, male rats were administered ^{45}Ca-labelled calcium gluconate (30 mg Ca/kg bw) by means of a syringe coupled to a gastric catheter, which allowed the intake volume to be standardised to one millilitre. Rats were placed in metabolic cages and urine and faeces were collected for a period of 12 days. Bioavailability was determined by measurement of ^{45}Ca excretion in urine, as a function of time, and expressed as percentage of the total amount of ^{45}Ca administered. Only 1.24 ± 0.5% of the administered labelled calcium was excreted in urine. Other excretion pathways (e.g. via faeces) were not investigated in this study.

Bioavailability of approximately 99.94% was derived based on the retention of 98.7% in the bone. The study concluded that 100% of calcium, when available in water-soluble form, is absorbable in the intestine.

For human risk assessment purposes, an oral absorption of 100% is assumed.

11.5.1.2 Dermal absorption

No data were available on dermal absorption of calcium hydroxide. Absorption of ionic salts by the skin is essentially negligible (Schaefer and Redelmeier 1996). Calcium hydroxide is not expected to be absorbed from the skin and be systemically available.

11.5.1.3 Inhalation absorption

Information on inhalation absorption of calcium hydroxide is not available. In the absence of data on inhalation absorption, a 100% absorption by this route is assumed for human health risk assessment purposes.

11.5.1.4 Distribution

In the study by Sarabia et al. (1999) described above, determination of the biological distribution of calcium was carried out 12 days after administration of ^{45}Ca-labelled calcium gluconate (30 mg Ca/kg bw) to rats. ^{45}Ca was found in blood, liver, spleen, bone, the gut including gut content, muscle, lungs, heart, brain and kidneys. The highest concentrations of radioactivity (98.7%) were found in bone.

11.5.1.5 Metabolism

Under physiological conditions, the hydroxyl-ions released from calcium hydroxide following oral administration are neutralised in the gastrointestinal tract and are therefore not relevant for consideration in toxicokinetics (REACH 2013). Calcium ions are not chemically transformed within the body as they are a simple inorganic ion, but rather are chelated in various ways for distribution via the blood and deposition in bone.

11.5.1.6 Excretion

Excess calcium is excreted in the urine via glomerular filtration. The renal tubules are able to excrete as well as reabsorb calcium. A significant increase in the calcium concentration in plasma will only occur after high calcium intake in conjunction with other disorders such as renal insufficiency or primary hyperthyroidism (REACH 2013).

11.5.2 *Acute toxicity*

11.5.2.1 Oral

A study on acute oral toxicity of calcium hydroxide in female rats was conducted by a scientifically accepted method (REACH 2013). Female rats were given calcium hydroxide suspended in polyethylene glycol by gavage at a dose of 2000 mg/kg bw. No animal deaths were observed at 2000 mg/kg bw, indicating that the oral median lethal dose (LD50) for rats is >2000 mg/kg bw. No adverse effects were observed following treatment. No macroscopic findings were observed at necropsy.

On the basis of available research, calcium hydroxide has low oral acute toxicity with an oral LD50 of >2000 mg/kg bw.

11.5.2.2 Dermal

An acute dermal toxicity study was conducted in male and female rabbits using calcium hydroxide slurry (REACH 2013). The test substance was applied to the skin under semi-occluded conditions. No animal deaths were observed at 2500 mg/kg bw $Ca(OH)_2$, indicating that the dermal (LD50 for male/female rabbits is >2500 mg/kg bw. However, some skin irritation effects were observed in the exposed rabbits. These effects are discussed in section A 11.5.3.1 of the report.

On the basis of available research, calcium hydroxide is considered to have low acute dermal toxicity.

11.5.2.3 Inhalation

No information was available.

11.5.2.4 Observation in humans

No information was available on the acute toxicity effects of calcium hydroxide in humans.

11.5.3 *Irritation / Corrosivity*

11.5.3.1 Skin irritation

In a skin irritation study conducted according to the Organisation for Economic Cooperation and Development (OECD) guidelines, 0.5 g un-moistened calcium hydroxide was applied to the shaved skin of New Zealand White rabbits (REACH 2013). After a period of four hours under semi-occlusive conditions the dressing was removed and the animals were observed at 1, 24, 48 and 72 hours later. Only slight skin irritation was observed at the application sites.

In a second skin irritation study, calcium hydroxide in putty form (60% H_2O, 40% $Ca(OH)_2$) was applied to the skin of three Himalayan rabbits (REACH 2013). After a maximum four-hour exposure, symptoms of skin irritation were observed during the subsequent 14-day observation period. Twenty four and 48 hours after termination of exposure, two rabbits showed well defined erythema (Draize score = 2) and one also had a slight oedema. These effects remained 72 hours after the termination of exposure. Seven days after exposure one animal was free of any skin reaction but the second animal still showed well defined erythema. Based on this study, the putty form of calcium hydroxide (60% H_2O, 40% $Ca(OH)_2$) was considered to be a skin irritant.

In the acute dermal toxicity study described earlier, 10 New Zealand White rabbits exposed to 2500 mg/kg bw of calcium hydroxide slurry for four hours showed erythema but no oedema. A mean Draize value of approximately two was calculated for erythema/eschar formation from the results.

Aqueous suspensions of CaO and $Ca(OH)_2$ are highly alkaline (pH~12 to 13) and can remove lipids from the skin and cause drying, cracking and irritant contact dermatitis. The effect from the high alkalinity can increase to ulcer formation and frank skin burn (SCOEL 2008; Winder and Carmody 2002).

On the basis of available research, calcium hydroxide is considered to be a moderate skin irritant.

11.5.3.2 Eye irritation

In a study conducted according to OECD test guidelines, TG 405, ocular irritancy of calcium hydroxide was tested by instilling 0.1 g of the compound into the left eye (conjunctival sac) of a New Zealand White rabbit while the right eye served as the untreated control (REACH 2013). One hour after administration, severe eye reactions were observed with pronounced chemosis (score: 3), necrotised appearance of the conjunctiva and total opacity of the cornea, showing a nacreous appearance. The iris was no longer visible. Given the seriousness of the eye lesions observed, the animal was put down for humane reasons. Maximum Draize scores of four and three for corneal opacity and chemosis, respectively, were considered for these effects.

On the basis of available research, calcium hydroxide is considered to be a severe eye irritant.

11.5.3.3 Respiratory irritation

No data were available.

11.5.3.4 Observation in humans

In a human study, 315 workers from 23 plants producing calcium oxide and calcium hydroxide from limestone were evaluated one day after exposure (Wegman et al. 1992). Workers exposed to $Ca(OH)_2$ had more eye, nose and throat irritation as well as acute cough than those exposed to neither of the compounds.

Patty's Industrial Hygiene and Toxicology (Clayton and Clayton 1993) states that calcium hydroxide, being a strong base, can cause irritation to all exposed surfaces of the body including the respiratory tract. Acute exposures may cause irritation along with coughing, pain, and possibly burns of the mucous membranes, and in severe acute exposures, pulmonary edema and hypotension with weak and rapid pulse.

The *US Occupational Health Guideline for Calcium Hydroxide* states that calcium hydroxide is a corrosive that affects all tissues it contacts (OSHA 1995). According to the guideline, calcium hydroxide can induce redness, tearing, irritation, or corrosion of the eyes, runny nose, upper respiratory tract irritation, bronchitis, pneumonia, and redness, rashes, irritation, or corrosion of the skin. Direct contact of the skin with calcium hydroxide causes skin irritation and may lead to corrosive chemical burns. Prolonged contact may cause skin desquamation and a vesicular rash, skin ulceration and corrosion in some cases (Parmeggiani 1983).

Overall, on the basis of available research, calcium hydroxide can be regarded as a respiratory irritant.

11.5.4 *Sensitisation*

11.5.4.1 Skin sensitisation

No data were available.

11.5.4.2 Respiratory sensitisation

No data were available.

11.5.4.3 Observation in humans

No data were available.

As per the previous discussion, calcium hydroxide has low acute oral and dermal toxicity. Information on acute inhalation toxicity is not available. It is considered to be a moderate skin irritant and a severe eye irritant, and human experience indicates that it is a respiratory irritant, which is consistent with its high alkalinity.

11.5.5 *Repeat dose toxicity*

11.5.5.1 Oral

Studies on the oral repeat dose toxicity of calcium hydroxide are not available. A number of repeat dose studies using analogues of calcium hydroxide (calcium carbonate, calcium gluconate) that investigate the effect of calcium ion on various metabolic functions in experimental animals are available. However, none of these studies are appropriate for derivation of a No Observed Adverse Effect Level (NOAEL) as they do not follow any international guidelines prescribed for NOAEL determination studies (REACH 2013).

The effects of long term mucosal exposure to $Ca(OH)_2$ were studied in relation to the common practice of consuming $Ca(OH)_2$ and betel leaves in some Asian countries. In a chronic study, 250 mg/day of $Ca(OH)_2$ was administered into hamster cheek pouches (Dunham et al. 1966). Control animals were treated similarly with a homogenous mixture of amylase and amylopectin derived from corn starch, together with 2% magnesium oxide. Animals were treated until they completed their life spans, i.e. they were found deceased or were euthanised when moribund. All six animals in the treated group had pouch lesions and two animals had bowel cancer. None of the four control animals showed these effects. In another group, six animals received 50 mg/kg of $Ca(OH)_2$ in the morning and 50 mg of starch mixture 3 to 5 hours later. All animals had pouch lesions and one animal had granulosa cell tumour of the ovaries. Additional groups were treated with $Ca(OH)_2$ and gambier or snuff. The hamsters in the $Ca(OH)_2$ groups had chronic inflammation and ulcers in the cheek pouch together with hyperplasia, hyperkeratosis, increased cells in stratum spinosum (acanthosis) and cellular atypia of the epithelium. The Scientific Committee on Occupational Exposure Limits has however cautioned that the test doses in this study were considerably high (assuming the body weight of a hamster is 100 g, the exposure would correspond to a $Ca(OH)_2$ dose of 0.5 to 2.5 g/kg/day) and also that the study had a low number of animals – only six in the treated group and even less in control group. A No Observable Adverse Effect Level (NOAEL) was not established in this study.

In another long-term study (Sirsat and Kandarkar 1968), the palate and buccal mucosa of 115 Wistar rats were painted five days/week with commercially available $Ca(OH)_2$ for betel chew. The controls (24 animals) were painted similarly but without $Ca(OH)_2$. Twelve months of treatment caused marked epithelial cell hyperplasia, cytoplasmic vacuolation, prominent stratum granulosum, hyperkeratosis, and epithelial cord invagination into the corium. The submucosal connective tissue showed proliferation of fibroblasts, oedema, connective tissue hyalinisation, chronic inflammatory exudation and dilated blood vessels. No epithelial malignancy was detected. The dose was not specified in this study.

11.5.5.2 Dermal

Repeat dose dermal studies for calcium hydroxide are not available.

11.5.5.3 Inhalation

No data were available.

11.5.5.4 Observation in humans

The Scientific Committee on Occupational Exposure Limits for Calcium Oxide and Calcium Hydroxide reviewed a study on the effects of occupational exposure to the two compounds (SCOEL 2008). About 580 workers from 31 plants producing CaO and $Ca(OH)_2$ from limestone were studied for chronic effects. Workers were exposed to CaO, $Ca(OH)_2$ or both compounds. Those usually exposed to $Ca(OH)_2$ had more chronic cough (Risk Ratio=1.5), phlegm (1.3), bronchitis (1.4), wheeze (2.2), chest tightness (1.7) and dyspnoea (2.2) than unexposed controls.

The effects of lime dust (calcium oxide and calcium hydroxide) have been studied in Finnish pulp-mill workers (Torén et al. 1996). In the lime kiln department, 15 workers were compared with 15 matched unexposed referents from the transportation and office departments. The mean total dust level among the kiln workers was 1.2 mg/m^3 (range: 0.4 to 5.8 mg/m^3). There was no statistically significant difference in self-reported symptoms, nasal bleeding, crusts in the nose, nasal blockage and nasal secretion. There was no statistically significant increase in inflammation in the nose and throat among the exposed workers, nor was any statistically significant difference observed in the Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1/FVC (%), nasal peak expiratory flow or in eosinophilic cationic protein, myeloperoxidase and hyaluronic acid in the nasal lavage fluid. In contrast, the nasal mucociliary clearance was significantly longer (mean and range: 13.4 min and 6.0 to 26 min) in the exposed group compared to the controls (10.0 min and 4 to 20 min), determined by the saccharin test. After rebuilding the kiln, the mean total dust level was reduced to 0.2 mg/m^3 (range: 0.1 to 0.6 mg/m^3) and the temperature to 28°C. The mean saccharin transition time normalised in the exposed workers (8.6 min and 1.4 to 15 min) and it was no longer different from the mean value in the controls (10.2 min and 5.5 to 20 min). The authors interpreted the normalisation to be due to the decrease in the lime dust level, but mentioned that some influence of reduced temperature cannot be excluded. Overall, the NOAEL for all effects, except the nasal mucociliary clearance, is 1.2 mg/m^3 total dust.

11.5.6 *Genotoxicity*

Calcium hydroxide was not mutagenic in bacterial reverse mutation assays using *Salmonella typhimurium* strains TA100, TA1535, TA1537 and TA98 or other *Escherichia coli* strains, with and without metabolic activation (REACH 2013). The chromosome aberration assay with calcium hydroxide was also negative. Results from mammalian cell gene mutation assay are not available.

Based on the bacterial reverse mutation assay results and chromosomal aberration assays, calcium hydroxide is not mutagenic.

11.5.7 *Carcinogenicity*

A long-term toxicity/carcinogenicity study with calcium lactate was undertaken in Fischer 344 (F344) rats (Maekawa et al. 1991). Calcium lactate, a food additive, was given in drinking water at levels of 0, 2.5 or 5% to groups of 50 male and 50 female rats for two years. The highest dose concentration of 5% corresponded to a calcium lactate dose of nearly 300 mg/kg bw/day in 250 g male rats. At the end of the dosing period, no specific dose-related changes in haematological or biochemical parameters were observed. Female rats of

the high-dose group exhibited significantly higher kidney and brain weights although no histological changes were detected.

A number of non-neoplastic lesions (myocardial fibrosis, bile-duct proliferation, hepatic microgranulomas and chronic nephropathy) were observed in all groups, with no difference in their incidence and / or degrees. None of the experimental groups showed any significant increase in the incidence of any specific tumours compared with the corresponding controls, neither was any positive trend noted in the occurrence of tumours.

The authors of the study concluded that calcium lactate did not cause toxicity or carcinogenic activity in F344 rats.

Based on the above observations, calcium hydroxide is not considered to be carcinogenic.

11.5.8 *Reproductive toxicity*

11.5.8.1 Fertility

No data were available.

11.5.8.2 Developmental toxicity

Developmental toxicity studies with calcium hydroxide are not available. Studies with related compounds, such as calcium oxide and calcium carbonate, did not show any developmental effects in rats (REACH 2013).

Based on the available data, calcium hydroxide is not considered to be a developmental toxicant.

11.6 Health hazard summary

11.6.1 *Critical health effects*

In summary for this chapter, calcium hydroxide has low acute oral and dermal toxicity, is a moderate skin irritant and a severe eye irritant. Epidemiologic studies indicate that calcium hydroxide is also a respiratory irritant. Calcium hydroxide is not genotoxic or carcinogenic and does not have any developmental effects in animals.

Given the constituent ions of calcium hydroxide, systemic health effects from repeated exposures to calcium hydroxide are not expected.

In an epidemiological study, no significant adverse effects were observed in lime-kiln workers exposed to 1.2 mg/m^3 lime dust. This atmospheric concentration was taken as an overall NOAEC for calcium hydroxide. This NOAEC will be carried forward for human health risk assessment.

The most critical health effects of calcium hydroxide are skin, eye and respiratory tract irritation.

11.6.2 *Hazard classification*

The chemical is recommended by NICNAS to Safework Australia for classification and labelling under the Approved Criteria for Classifying Hazardous Substances and adopted Globally Harmonised System (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A11.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A11.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation / Corrosivity	Risk of serious damage to eyes (X_i; R41)	Causes serious eye damage - Cat 1 (H318)
	Irritating to skin (X_i; R38)	Causes skin irritation (H315)
	Irritating to respiratory system (X_i; R37)	May cause respiratory irritation - Specific target organ toxicity, single exposure – Cat. 3 (H335)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

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A12 Lime

CAS No.	CAS Name
1305-78-8	Calcium oxide (CaO)

12.1 Chemical identity

The following chemical identity information was obtained from ChemID*plus* (2012) and Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013). Table A12.1 provides details of the chemical identity.

Table A12.1 Chemical identity

	Lime
Synonyms	Quicklime Calcium monoxide Calx Lime Unslaked lime
Structural formula	Ca = O
Molecular formula	CaO
Molecular weight	56.0
Appearance and odour	Greyish yellow, odourless, hygroscopic solid
SMILES notation	O=[Ca]

12.2 Physical properties

The following information on the physical properties of calcium oxide (Table A12.2) was obtained from REACH (2013).

Table A12.2 Physical properties

Property	**Value**
Melting point	2 572 °C
Boiling point	2 850 °C
Density	3.3 kg/m^3 at 25 °C
Vapour pressure	Negligible at 25 °C
Water solubility	1.19 g/L at 20 °C
Partition coefficient n-octanol/water (log K_{ow})	Not relevant

12.3 Current regulatory controls

12.3.1 *Hazard classification for occupational health and safety*

Calcium oxide is listed as hazardous in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013). No risk phrases have been assigned to this chemical.

12.3.2 *Occupational exposure standards*

12.3.2.1 Australia

The chemical has an exposure standard of 2 mg/m³, Time Weighted Average (TWA) (Safe Work Australia 2013).

12.3.2.2 International

The following exposure standards are identified in Galleria Chemica (2013):

- Occupational Exposure limit (TWA) of 2 mg/m^3 [Canada, Denmark, Korea, UK, US (NIOSH)]
- Permissible Exposure Limits (PEL) of 5 mg/m^3 [US (OSHA 1978)].

12.3.3 *Australian food standards*

Calcium oxide is allotted the following International Numbering System of food additives number: INS 529 (Food Standards Australia New Zealand 2013).

12.3.4 *Australian drinking water guidelines*

Calcium oxide is used in water treatment to correct pH and adjust alkalinity, for coagulation optimisation, corrosion control and water softening. Typical calcium oxide concentrations used in drinking water treatment depend on the quality of the water to be treated and the purpose of treatment (e.g. water softening, pH adjustment or alkalinity increase) and can vary from 5 to 500 mg/L (NHMRC 2011).

12.3.5 *Additional controls*

12.3.5.1 Australia

Calcium oxide is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

Calcium oxide (UN Number 1910) is included in the Australian Dangerous Goods Code Edition 7 (ADG7) (National Transport Commission 2007) under Class 8 and Packaging Group III. The ADG7 contains detailed provisions for the packaging, transport and marking of containers for Class 8 chemicals.

12.3.5.2 International

No additional controls were identified.

12.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

12.5 Health hazard characterisation

The information on health hazards is obtained from REACH dossiers on the chemical (REACH 2013). Unless otherwise noted, references to individual studies below are taken from these sources.

Data were read across from calcium hydroxide studies for the skin irritation and dermal toxicity endpoints, as calcium oxide reacts with water on the external surfaces of the body to form calcium hydroxide ($Ca(OH)_2$), which liberates OH- ions, affecting the skin and the mucous membranes.

Calcium lactate and calcium gluconate are considered as analogues of calcium oxide to read across for systemic effects of calcium oxide. The rationale for using these analogues is that under physiological conditions the calcium ion Ca^{2+} is the chemical species of interest. After oral administration, the hydroxyl-ions released from calcium oxide are neutralised in the GI tract and the lactate and gluconate moieties from calcium lactate and calcium gluconate, respectively, become integral components of mammalian energy metabolism and are therefore toxicologically not relevant (REACH 2013).

12.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

When systemically absorbed, calcium oxide dissociates into calcium ions and hydroxide ions. These are normal physiological components in humans that are subject to homeostatic mechanisms to regulate their levels.

Calcium is the most abundant inorganic constituent of all animal species, with most of the body content located in the skeleton. It is an essential ion for formation and maintenance of bone and teeth, and for regulation of several important physiological functions such as blood coagulation, neuromuscular activity, enzyme activity and acid-base balance. Hormonal systems regulate plasma calcium concentrations at approximately 100 µg/mL by controlling intestinal absorption of dietary calcium, the release from bone and renal absorption/excretion (OECD 2005). Hydroxide ions are a natural constituent of aqueous solutions arising from the self-ionisation reaction of water. Uptake of calcium oxide has the potential to increase the pH of the blood. However, pH is tightly regulated in the body and ingested calcium oxide is subject to neutralisation under the acidic conditions of the body.

Therefore, in healthy individuals, it is not biologically plausible for low level oral exposures to calcium oxide to affect internal organs (including reproductive organs) (Scientific Committee on Occupational Exposure Limits for Calcium Oxide and Calcium Hydroxide-SCOEL 2008); Geibel and Wagner 2006).

12.5.1.1 Oral absorption

Calcium oxide will gradually hydrolyse in the acid pH of the stomach to generate calcium ions and chloride ions. Calcium ions are absorbed in the mammalian small intestine by two general mechanisms:

- a transcellular active transport process, located largely in the duodenum and upper jejunum
- a paracellular, passive process that functions throughout the length of the intestine (Bronner 2003).

Gastrointestinal absorption and bioavailability of orally administered calcium in the form of calcium gluconate, has been studied in rats (Sarabia et al. 1999). In the study, male rats were administered ^{45}Ca-labelled calcium gluconate (30 mg Ca/kg bw) by means of a syringe coupled to a gastric catheter, which allowed the intake volume to be standardised to one millilitre. Rats were placed in metabolic cages and urine and faeces were collected for a period of 12 days. Bioavailability was determined by measurement of ^{45}Ca excretion in urine, as a function of time, and expressed as percentage of the total amount of ^{45}Ca administered. Only 1.24 ± 0.5% of the administered labelled calcium was excreted in urine. Other excretion pathways (e.g. via faeces) were not investigated in this study.

Bioavailability of approximately 99.94% was derived based on the retention of 98.7% in the bone. The study concluded that 100% of calcium, when available in water-soluble form, is absorbable in the intestine.

For human risk assessment purposes, an oral absorption of 100% is assumed.

12.5.1.2 Dermal absorption

No data were available on dermal absorption of calcium oxide. Absorption of ionic salts by the skin is essentially negligible (Schaefer and Redelmeier 1996). Calcium oxide is not expected to be absorbed from the skin and be systemically available.

12.5.1.3 Inhalation absorption

Information on inhalation absorption of calcium oxide is not available. In the absence of data on inhalation absorption, a 100% absorption by this route is assumed for human health risk assessment purposes.

12.5.1.4 Distribution

In the study by Sarabia et al. (1999) described above, determination of biological distribution of calcium was carried out 12 days after administration of ^{45}Ca-labelled calcium gluconate (30 mg Ca/kg bw) to rats. ^{45}Ca was found in blood, liver, spleen, bone, the gut including gut content, muscle, lungs, heart, brain and kidneys. The highest concentrations of radioactivity (98.7%) were found in bone.

12.5.1.5 Metabolism

Under physiological conditions, calcium oxide releases hydroxyl ions. These ions are neutralised in the gastrointestinal tract with calcium forming the systemically relevant species of calcium oxide.

Calcium ions are not chemically transformed within the body as they are a simple inorganic ion, but are chelated in various ways for distribution via the blood and deposition in bone.

12.5.1.6 Excretion

Excess calcium is excreted in the urine via glomerular filtration. The renal tubules are able to excrete as well as reabsorb calcium. A significant increase in the calcium concentration in

plasma will only occur after high calcium intake in conjunction with other disorders such as renal insufficiency or primary hyperthyroidism (OECD 2005).

12.5.2 *Acute toxicity*

12.5.2.1 Oral

A study on acute oral toxicity of calcium oxide in female rats was conducted by a scientifically accepted method (REACH 2013). Different doses of calcium oxide suspended in polyethylene glycol (0.2 g/mL) were administered to rats by gavage. No deaths were observed at 2000 mg/kg bw, indicating that the oral median lethal dose (LD50) for rats is >2000 mg/kg bw. No adverse effects were observed following treatment. No macroscopic findings were observed at necropsy.

Calcium oxide has low oral acute toxicity with an oral LD50 of >2000 mg/kg bw.

12.5.2.2 Dermal

Acute dermal toxicity studies with calcium oxide are not available. An acute dermal toxicity study was conducted in rabbits using moistened calcium hydroxide ($Ca(OH)_2$) (REACH 2013). As calcium oxide (CaO) is converted to $Ca(OH)_2$ in the presence of moisture, the test results for $Ca(OH)_2$ are also applicable for CaO. No animal deaths were observed at 2500 mg/kg bw $Ca(OH)_2$, indicating that the dermal LD_{50} for male/female rabbits is >2500 mg/kg bw. No adverse effects were observed following the treatment.

Based on the results with $Ca(OH)_2$, calcium oxide is considered to have low acute dermal toxicity.

12.5.2.3 Inhalation

No information is available.

12.5.2.4 Observation in humans

No information on the acute toxicity effects of calcium oxide in humans is available.

12.5.3 *Irritation / Corrosivity*

12.5.3.1 Skin irritation

Two skin irritation studies were conducted with minor variations to the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 404 (REACH 2013). In these studies, calcium oxide was not moistened before application as recommended in OECD TG 404, because, according to the authors, wetting the CaO would have transformed it into $Ca(OH)_2$, which is significantly more alkaline and therefore reactive to the skin. Dry calcium oxide (500 mg) was applied to the shaved skin of rabbits for four hours under semi-occluded conditions and the animals were observed at 1, 24, 48 and 72 hours after the dressing was removed. Only slight skin irritation was observed at the application sites.

Results from two skin irritation studies with calcium hydroxide (hydrated calcium oxide) indicated that calcium hydroxide causes skin irritation (REACH 2013). Further, aqueous suspensions of CaO and $Ca(OH)_2$ are highly alkaline (pH~12 to 13) and can remove lipids from the skin and cause drying, cracking and irritant contact dermatitis. The high alkalinity can also cause ulcers and frank skin burns (SCOEL 2008; Winder and Carmody 2002).

The US Occupational Health Guideline for calcium oxide states '*calcium oxide causes irritation of the eyes, nose, throat and skin. Severe burns may result from contact with this chemical*' (OSHA 1978).

These observations indicate that dry CaO is a slight skin irritant but can react with moisture on the external surface and produce skin irritation.

12.5.3.2 Eye irritation

In a study conducted according to OECD TG 405, ocular irritancy of calcium oxide was tested by instilling 0.1 g of the compound into the left eye (conjunctival sac) of a New Zealand White rabbit while the right eye served as the untreated control (REACH 2013). One hour after administration, severe eye reactions were observed with slight chemosis, necrotised appearance of the conjunctiva and total opacity of the cornea, showing a nacreous appearance. The iris was no longer visible. A purulent whitish substance was observed. Maximum Draize scores of four and two for corneal opacity and chemosis, respectively, were reported for these effects.

In addition to the generation of heat, calcium oxide, on reaching the eye, tends to react with the moisture and protein and form clumps of moist compound, which is very difficult to remove by the usual irrigation. Such clumps tend to lodge deep in the cul-de-sacs inferiorly and superiorly and act as reservoirs for the liberation of calcium hydroxide over long periods of time (Klaassen et al. 1995).

On the basis of available research, calcium oxide is considered to be a severe eye irritant.

12.5.3.3 Respiratory irritation

No data were available.

12.5.3.4 Observation in humans

In direct contact with moist tissues, calcium oxide can result in burns and severe irritation because of its high reactivity and alkalinity. The major complaints of workers exposed to lime dust include irritation of the eyes, inflammation of the respiratory passages, ulceration and perforation of the nasal septum, and even pneumonia, whichhave been attributed to inhalation of the dust (NIOSH 1988; Clayton and Clayton 1993). Exposure to a mixture of dusts containing calcium oxide at a concentration of approximately 25 mg/m^3 reportedly resulted in strong nasal irritation in workers (NIOSH 1988).

Industrial experience has shown calcium oxide to be very irritating to mucous membranes and moist skin as a result of local liberation of heat and dehydration of tissues upon slaking of the small size particles, and the resulting alkalinity of the slaked product, namely calcium hydroxide. Inflammation of respiratory passages and ulceration has been reported (Rom and Ryon 2011). Major complaints of workers exposed to lime consist of eye and skin irritation (ACGIH 1991).

The respiratory irritant effects of CaO were studied in 12 lightly exercising males exposed to 1 to 5 mg/m^3 CaO for 20 minutes (Cain et al. 2004). The parameters studied included nasal resistance, nasal secretion, mucociliary transport time and chemaesthetic magnitude, which was calibrated to pungency of CO_2. The CaO exposures caused an increase in irritation during the 20 minute exposure period and a steady state level was not reached within this time period. Sensitising feelings in the subjects were maximal in the nose, slightly lower in the throat and much lower in the eyes. In the nose, 2 mg/m^3 at the end of exposure gave rise to an effect which corresponded to the irritant effect of about 15% CO_2. The 5 mg/m^3 level had an effect equivalent to 20% CO_2. In comparison, the blank exposure (0 mg/m^3 CaO)

corresponded with irritant effects caused by about 7% CO_2. No significant effects occurred in nasal secretion and mucociliary clearance.

In another study (Cain et al. 2008), the effects of CaO on nasal airway were studied in six male and six female volunteers, aged 18 to 35 years, exposed to 2.5 mg/m^3 CaO for 45 minutes. Six concentrations of carbon dioxide ranging from just below detectable to concentrations producing sharply stinging effects provided subjects with references for their ratings. The sensory effects were highest in the nose, lower in the throat and lowest in the eyes. The maximum effect was reached about 30 minutes after the initiation of the exposure and stabilised thereafter (adaptation). The maximum effect in the nose corresponded to the effect of 17% CO_2. Dilution of CaO with $CaSO_4$ (1:9) showed that the effect was driven entirely by CaO.

On the basis of available research, calcium oxide is considered to be a respiratory irritant.

12.5.4 *Sensitisation*

12.5.4.1 Skin sensitisation

No data were available.

12.5.4.2 Respiratory sensitisation

Respiratory sensitisation data in experimental animals were not available.

Calcium oxide has low acute oral and dermal toxicity. Information on acute inhalation toxicity is not available. As per the previous discussion on irritation, calcium oxide is considered to be a skin and respiratory irritant and a severe eye irritant. Information on sensitisation effects is not available.

12.5.4.3 Observation in humans

No data were available.

12.5.5 *Repeat dose toxicity*

12.5.5.1 Oral

Studies on the oral repeat dose toxicity of calcium oxide are not available.

Several repeat dose studies using analogues of calcium oxide (calcium hydroxide, calcium carbonate, calcium gluconate) investigating the effect of calcium ions on various metabolic functions in experimental animals are available in the literature. However, all these studies were considered inappropriate for derivation of a No Observed Adverse Effect Level (NOAEL) by the study authors, as they did not follow any international guidelines (REACH 2013).

12.5.5.2 Dermal

No data were available.

12.5.5.3 Inhalation

No data were available.

12.5.5.4 Observation in humans

The systemic effects of CaO at normal occupational exposures are negligible (Flynn et al. 2003). Assuming an exposure level of 1 mg/m^3 CaO (equivalent to 0.71 mg Ca/m^3) at the workplace and an inhalation volume of 10 m^3 air during an eight-hour workday, the total inhalation dose would be 7.1 mg calcium/day. Since the Tolerable Upper Intake Level (TUIL) for calcium is 2500 mg/day, this occupational exposure would add a negligible body burden of calcium (Flynn et al. 2003).

The Scientific Committee on Occupational Exposure Limits for Calcium Oxide and Calcium Hydroxide reviewed a study on the effects of occupational exposure to the two compounds (SCOEL 2008). About 580 workers from 31 plants producing CaO and $Ca(OH)_2$ from limestone were studied for chronic effects. Workers were exposed to CaO, $Ca(OH)_2$ or both compounds. Those exposed to $Ca(OH)_2$ had more chronic cough (Risk Ratio=1.5), phlegm (1.3), bronchitis (1.4), wheeze (2.2), chest tightness (1.7) and dyspnoea (2.2) than unexposed controls. Results from exposure to CaO were not reported. The Committee, however, concluded that CaO will have a similar effect as it is strongly desiccating and forms more hydroxide ions per unit mass at hydration.

In a Belgian cross-sectional study, the effect of lime (i.e. calcium oxide) production was studied in 75 employees with a mean age of 46 years (Lahaye et al. 1987). The exposures were not well characterised, but the maximum dust level at one site was 620 mg/m^3. The study comprised clinical investigations, X-ray images of the thorax, electrocardiogram and lung function study. Prevalence of chronic bronchitis among the lime-exposed subjects was 6/13 (46%) as compared to 3/20 (15%) in individuals who were not exposed to lime. All exposed persons had residual volume and diffusion capacity within the respective normal ranges. Dust samples from the area contained 0.03 to 1% silica; however, no silicosis was observed among the individuals studied. As the exposure was not well characterised, it is not possible to conclude any effect limits.

The effects of lime dust (calcium oxide and calcium hydroxide) have been studied in Finnish pulp-mill workers (Torén et al. 1996). In the lime kiln department, 15 workers were compared with 15 matched unexposed referents from the transportation and office departments. The mean total dust level among the kiln workers was 1.2 mg/m^3 (range: 0.4 to 5.8 mg/m^3). There was no statistically significant difference in self-reported symptoms, nasal bleeding, crusts in the nose, nasal blockage and nasal secretion. There was no statistically significant increase in inflammation in the nose and throat among the exposed workers, nor was any statistically significant difference observed in the Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1/FVC (%), nasal peak expiratory flow or in eosinophilic cationic protein, myeloperoxidase and hyaluronic acid in the nasal lavage fluid. In contrast, the nasal mucociliary clearance was significantly longer (mean and range: 13.4 min and 6.0 to 26 min) in the exposed group compared to the controls (10.0 min and 4 to 20 min), determined by the saccharin test. After rebuilding the kiln, the mean total dust level was reduced to 0.2 mg/m^3 (range: 0.1 to 0.6 mg/m^3) and the temperature to 28°C. The mean saccharin transition time normalised in the exposed workers (8.6 min and 1.4 to 15 min) and it was no longer different from the mean value in the controls (10.2 min and 5.5 to 20 min). The authors interpreted the normalisation to be due to the decrease in the lime dust level, but mentioned that some influence of reduced temperature cannot be excluded. Overall, the NOAEL for all effects, except the nasal mucociliary clearance, is 1.2 mg/m^3 total dust.

12.5.6 *Genotoxicity*

Calcium oxide was not mutagenic in bacterial reverse mutation assays using *Salmonella typhimurium* strains TA100, TA1535, TA1537 and TA98 or other *Escherichia coli* strains, with

and without metabolic activation (REACH 2013). Results with chromosome aberration assay or mammalian cell gene mutation assay are not available.

Based on the bacterial reverse mutation assay results, it was concluded that calcium oxide is not mutagenic.

12.5.7 *Carcinogenicity*

No data were available.

A long-term toxicity/carcinogenicity study with calcium lactate was undertaken in Fischer 344 (F344) rats (Maekawa et al. 1991). Calcium lactate, a food additive, was given in drinking water at levels of 0, 2.5 or 5% to groups of 50 male and 50 female rats for two years. The highest dose concentration of 5% corresponded to a calcium lactate dose of nearly 300 mg/kg bw/day in male 250 g rats. At the end of the dosing period, no specific dose-related changes in haematological or biochemical parameters were observed. Female rats of the high-dose group exhibited significantly higher kidney and brain weights although no histological changes were detected.

A number of non-neoplastic lesions (e.g. myocardial fibrosis, bile-duct proliferation, hepatic micro granulomas and chronic nephropathy) were observed in all groups, with no difference in their incidence and / or degrees. None of the experimental groups showed any significant increase in the incidence of any specific tumours compared with the corresponding controls, neither was any positive trend noted in the occurrence of tumours.

The authors of the study concluded that calcium lactate did not cause toxicity or carcinogenic activity in F344 rats.

Using this study as a read across study, calcium oxide is considered not likely to be carcinogenic.

12.5.8 *Reproductive toxicity*

12.5.8.1 Fertility

No data were available.

12.5.8.2 Developmental toxicity

In two developmental toxicity studies conducted according to methods equivalent or similar to the OECD TG 414 (Prenatal Developmental Toxicity Study), calcium oxide was administered by gavage to pregnant female Wistar rats up to 680 mg/kg bw/day and CD-1 mice up to 440 mg/kg bw/day during gestation days 6 to 15 (10 consecutive doses) (REACH 2013). There were no clear discernible effects on implantation, maternal survival or foetal survival in any species at any of the doses. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ significantly from those occurring spontaneously in the controls. No NOAEL could be established for maternal toxicity or foetal developmental effects.

Based on the available data, calcium oxide is not considered to be a developmental toxicant.

12.5.9 *Other health effects*

No other health effects were identified.

12.6 Health hazard summary

12.6.1 *Critical health effects*

In summary for this chapter, calcium oxide has low acute oral and dermal toxicity, is a skin and respiratory irritant and a severe eye irritant. Calcium oxide is not genotoxic or carcinogenic and does not have any developmental effects in animals. Given the constituent ions of calcium oxide which are subject to tight homeostatic control in the body, repeated exposure to calcium oxide is regarded to have no significant systemic effects.

In an epidemiological study, no significant adverse effects were observed in lime-kiln workers exposed to 1.2 mg/m^3 lime dust. This atmospheric concentration was taken as an overall NOAEC for calcium oxide. This NOAEC will be carried forward for human health risk assessment.

The critical health effects of calcium oxide are skin and respiratory irritation and severe eye irritation.

12.6.2 *Hazard classification*

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the Approved Criteria for Classifying Hazardous Substances and adopted Globally Harmonised System (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A12.3. These recommendations do not consider physical or environmental hazards.

Table A12.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation / Corrosivity	Risk of serious damage to eyes (X_i; R41) Irritating to skin (X_i; R38) Irritating to respiratory system (X_i; R37)	Causes serious eye damage - Cat 1 (H318) Causes skin irritation (H315) May cause respiratory irritation - Specific target organ toxicity, single exposure – Cat. 3 (H335)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

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A13 Caustic soda

CAS No.	CAS Name
1310-73-2	Sodium hydroxide (Na(OH))

13.1 Chemical identity

Information on chemical identity was obtained from ChemID*plus* (2012) and OECD (2002). Details are provided in Table A13.1.

Table A13.1 Chemical identity

	Caustic soda
Synonyms	Caustic soda Sodium hydroxide Sodium hydrate Soda Lye
Structural formula	**Na – OH**
Molecular formula	NaOH
Molecular weight	40
Appearance and odour	Colourless to white deliquescent odourless solid.
SMILES notation	O{-}.[Na]{+} (eChemPortal 2013)

13.2 Physical properties

The physical properties of the chemical are presented in Table A13.2. The information was obtained from OECD (2002).

Table A13.2 Physical properties

Property	Value
Melting point	318 °C
Boiling point	1 388 °C
Density	2.13 kg/m^3 at 20 °C
Vapour pressure (kPa)	Negligible at 25 °C
Water solubility	520 g/L at 25 °C
Partition coefficient n-octanol/water (log K_{ow})	Not relevant

13.3 Current regulatory controls

13.3.1 *Hazard classification for occupational health and safety*

Sodium hydroxide is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) with the following risk phrase (Safe Work Australia 2013):

- C: R35 (Corrosive, causes severe burns)

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures. The risk phrases for this chemical are:

- Conc ≥5%: C; R35 (Corrosive, causes severe burns)
- 2% ≤Conc <5%: C; R34 (Corrosive, causes burns)
- 0.5% ≤Conc <2%: Xi; R36/38 (Irritant, irritating to eyes and skin).

13.3.2 *Occupational exposure standards*

13.3.2.1 Australia

Sodium hydroxide has an exposure standard of 2 mg/m³, Time Weighted Average (Safe Work Australia 2013).

13.3.2.2 International

The following exposure standards are identified in Galleria Chemica (2013):

- Occupational Exposure Limit (OEL) or limit values in working environment of 2 mg/m³ [Argentina, Belgium, Bulgaria, Canada, China, India, Japan and the US (NIOSH 1975)].
- Occupational exposure standard: 2 mg/m³ [Korea]
- Occupational exposure limit values: 0.5 mg/m³ [Latvia]
- Short Term Exposure Limit (STEL): 2 mg/m³ [UK]
- US Department of Energy Temporary Emergency Exposure Limits (TEELs) = 0.5 mg/m³ (TEEL-0 and TEEL-1), 5 mg/m³ (TEEL-2) and 50 mg/m³ (TEEL-3).

13.3.3 *Australian food standards*

The Australia New Zealand Food Standards code for sodium hydroxide has the following inclusion: Processing aids - Generally permitted - permitted for use as acidity regulator (FSANZ 2013). Sodium hydroxide is allotted an International Numbering System (INS) of food additives number: INS 524 (Food Standards Australia New Zealand 2013).

13.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for sodium hydroxide. However, since sodium hydroxide readily dissociates in water into sodium and hydroxyl ions, the *Australian Drinking Water Guidelines* for sodium state that, based on aesthetic considerations (taste), the concentration of sodium in drinking water should not exceed 180 mg/L (National Health and Medical Research Council (NHMRC) 2011). No health-based guideline value is proposed for sodium.

Medical practitioners treating people with severe hypertension or congestive heart failure are advised to be aware of the sodium concentration in the patient's drinking water exceeding 20 mg/L (NHMRC 2011).

13.3.5 *Additional controls*

13.3.5.1 Australia

Sodium hydroxide is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedule 5 and Schedule 6 and Appendix C:

- Schedule 5: SODIUM HYDROXIDE (excluding its salts and derivatives) in preparations containing 5 per cent or less of sodium hydroxide being:
    a) solid preparations, the pH of which in a 10 g/L aqueous solution is more than 11.5
    b) liquid or semi-solid preparations, the pH of which is more than 11.5 except in food additive preparations for domestic use.
- Schedule 6: SODIUM HYDROXIDE (excluding its salts and derivatives) except:
    a) when included in Schedule 5
    b) in preparations containing 5 per cent or less of sodium hydroxide being:
        i. solid preparations, the pH of which in a 10 g/L aqueous solution is 11.5 or less
        ii. liquid or semi-solid preparations, the pH of which is 11.5 or less.
    c) liquid or semi-solid food additive preparations, the pH of which is more than 11.5, for domestic use.
- Appendix C: SODIUM HYDROXIDE (excluding its salts and derivatives), in liquid or semi-solid food additive preparations, for domestic use, the pH of which is more than 11.5.

The SUSMP also recommends appropriate '*Warning Statements*' and '*Safety Directions*' for sodium hydroxide when used in consumer products.

Sodium hydroxide is included in the Australian Dangerous Goods Code Edition 7(ADG7) (National Transport Commission 2007), with separate entries for sodium hydroxide solid (UN Number 1823) and sodium hydroxide solution (UN Number 1824). Both forms are listed as 'Corrosive', in Class 8. The ADG7 contains detailed provisions for the packaging, transport and marking of containers in Class 8.

13.3.5.2 International

Sodium hydroxide is listed by the United States Food and Drug Administration (US FDA 2013) as a food processing substance that is '*Generally Recognised as Safe*' (GRAS) for its intended use (21 CFR 184.1763). According to the Select Committee on GRAS Substances (SCOGS), there is no evidence in the available information on sodium hydroxide that demonstrates, or suggests, reasonable grounds to suspect a hazard to the public when it is used as an ingredient of food packaging materials in the manner now practised or that might reasonably be expected in the future (USFDA 2013).

Sodium hydroxide is also included in the United States CWA (Clean Water Act) - List of Hazardous Substances and the United Kingdom Dangerous Goods Emergency Action Code List 2011 [Emergency Action Code (EAC): 2W] (National Chemical Emergency Centre-NCEC 2011).

13.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

13.5 Health hazard characterisation

The information on health hazards is obtained from the Screening Information Data Set Initial Assessment Report (SIAR) report on sodium hydroxide (OECD 2002). Unless otherwise noted, references to individual studies below are taken from this review.

13.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

When absorbed systemically, sodium hydroxide fully dissociates into sodium ions and hydroxide ions. Sodium is a normal constituent of the blood. Uptake of hydroxide ions has the potential to increase the pH of the blood. However, the blood pH (7.4 to 7.5) is efficiently regulated by mechanisms such as urinary excretion of bicarbonate and exhalation of carbon dioxide. Between 3.0 and 6.0 g of sodium is taken up via the food every day (Fodor et al. 1999).

13.5.1.1 Oral absorption

Sodium hydroxide is known to be corrosive. It can burn the lips, tongue, throat and stomach. Symptoms may include nausea, vomiting, stomach cramps and diarrhoea and can cause death (CCOHS 2013).

For the purposes of risk assessment, 100% oral absorption in humans is assumed.

13.5.1.2 Dermal absorption

No reliable data were available to evaluate the potential for sodium hydroxide to be absorbed through the skin or contribute to systemic toxic effects following dermal exposure to the substance. Sodium hydroxide is a corrosive substance. A 50% dermal sodium hydroxide solution caused a burn that was rapid and progressive in both depth and extent when applied to two square inches of the clipped backs of mice (Bromberg et al. 1965). It can be assumed from this observation that concentrated sodium hydroxide would penetrate the skin by destroying the tissue. Dermal absorption of non-irritating concentrations of sodium hydroxide is expected to be low due to the low absorption of ions by the skin. It is unlikely that sodium ions penetrate the skin to a considerable extent. In an extreme worst case assumption dermal absorption of these ions will be 1 to 10% (ECB 2008). For human health risk assessment purposes, 10% absorption of sodium hydroxide will be assumed.

13.5.1.3 Inhalation absorption

No data were available. Sodium hydroxide can be absorbed into the body by inhalation when in aerosol form (OECD 2002). For the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

13.5.1.4 Distribution

No data were available. Sodium hydroxide will rapidly dissociate on administration and the sodium and hydroxide ions will enter the body's electrolyte pool (Fodor et al. 1999). The body pool of these ions is large and regulated by processes well known from human physiology.

13.5.1.5 Metabolism

No data were available.

13.5.1.6 Excretion

A key regulator of sodium content in higher animals is the kidney. Although urine is the main route for excretion of sodium ions, small quantities are lost in the stool, sweat, tears, nasal mucus and saliva (Forbes 1962). With regard to hydroxide ions, changes in the pH of the body fluids caused by hydroxide ions are buffered and regulated within a narrow range to maintain homeostasis with respiratory excretion of carbon dioxide and bicarbonate regeneration through proton secretion in the urine (Ganong 2001).

13.5.2 *Acute toxicity*

13.5.2.1 Oral

No acute oral studies using international guidelines are available in animals to establish a median lethal dose (LD50) for sodium hydroxide. In a very old acute oral study in rabbits using 1 to 10% sodium hydroxide, an LD50 of 325 mg/kg bw was established (Naunyn-Schiedeberg 1937). Mortality was also observed when 1% sodium hydroxide was dosed but in this case the administered volume was relatively high (24 mL/kg bw).

An oral LD50 of 140 to 340 mg/kg in rats has also been reported (National Research Council 2011), however details of the study are not available.

13.5.2.2 Dermal

In an acute dermal study, mice were treated dermally with 50% sodium hydroxide, and the treated area was irrigated with water at various intervals (OECD 2002). The mortality of mice was 20, 40, 80 and 71% when they were irrigated at 30 minutes, one hour, two hours or not at all after the application. All animals developed rapidly progressive burns. No mortality or burns were observed when the treated area was irrigated immediately after the application.

A 5% aqueous solution of sodium hydroxide produced severe necrosis when applied to the skin of rabbits for four hours (Clayton and Clayton 1993).

A dermal LD50 of 1350 mg/kg has been reported in rabbits (National Research Council 2011), however details of the study are not available.

13.5.2.3 Inhalation

A median lethal concentration (LC50) for sodium hydroxide is not available. In an acute inhalation study, 10 Wistar rats were exposed to an aerosol of 40% aqueous sodium

hydroxide with particle size less than 1 µm in diameter (Clayton and Clayton 1993). After three weeks, two of the 10 rats died. Examination showed mostly normal lung tissue with foci of enlarged alveolar septa, emphysema, bronchial ulceration, and enlarged lymph adenoidal tissues.

13.5.2.4 Observation in humans

Cases of fatality due to ingestion of liquid sodium hydroxide have been reported in humans. Ingestion of sodium hydroxide causes oesophageal and gastric injury. A person who ingested 10 g of sodium hydroxide in water suffered transmural necrosis of the oesophagus and stomach and died three days after admission to the hospital (OECD 2002). A 42-year-old female swallowed approximately 30 mL of 16% sodium hydroxide in a suicide attempt. This resulted in a 9-cm stricture of the oesophagus which was treated by gastric antral patch oesophagoplasty (Hugh et al. 1991).

A fatal burn due to dermal exposure of a worker to sodium hydroxide at an aluminium plant has been reported (Lee and Opeskin 1995). The worker was found lying in a shallow pool of concentrated sodium hydroxide, which had been heated to ~95 °C.

Inhalation of aerosols of a product containing 5% sodium hydroxide by a 25-year-old female resulted in irreversible obstructive lung injury after working for one day in a poorly ventilated room (Hansen and Isager 1991). Besides sodium hydroxide, the product also contained smaller amounts of calcium carbonate, soft soap and protein.

A 14-year-old male accidentally put 30% sodium hydroxide solution into his mouth (IPCS 1996). Oesophagoscopy revealed mucosal lesions in the upper oesophagus. Serious inflammatory changes were observed with mediastinal emphysema and purulent pleuritis. On the 44th day after ingestion profuse bleeding was observed through the nasogastric tube. A right side thoracotomy showed a 4 to 5 mm rupture of the descending part of the aorta with bleeding into the left pleura. The aorta wall was fragile and could not be repaired. The patient died on the operating table.

Nine other cases of liquid sodium hydroxide ingestion that resulted in oesophageal and gastric injury have been reported (OECD 2002). One person who ingested 10 g of sodium hydroxide in water suffered transmural necrosis of the oesophagus and stomach and died three days after admission to the hospital.

13.5.3 *Irritation / Corrosivity*

On the basis of available research, sodium hydroxide is corrosive to the skin, eyes and respiratory tract, and corrosive on ingestion.

13.5.3.1 Skin irritation

On the basis of available research, sodium hydroxide is known to cause deep penetrating burns and necrosis. The skin is discoloured brown or black which may make initial assessment of the injury difficult. There may be recurring skin breakdown over a long period (O'Donoghue et al. 1996).

In a skin irritation test, 2N (8%), 4N (16%) and 6N (24%) sodium hydroxide were applied on the lower abdominal region of Yorkshire weanling pigs (Srikrishna and Monteiro-Riviere 1991). Gross blisters developed within 15 minutes of application 8% and 16% sodium hydroxide produced severe necrosis in all epidermal layers. A concentration of 24% produced numerous severe blisters with necrosis extending deeper into the subcutaneous tissue.

An *in vitro* test was also performed with isolated perfused skin flaps of Yorkshire weanling pigs using sodium hydroxide concentrations of 4N (16%) and 6N (24%). At both concentrations, sodium hydroxide produced severe necrosis of all epidermal cell layers and dermis. At times this lesion extended deep into the subcutaneous layers (OECD 2002).

Based on human data, sodium hydroxide concentrations of 0.5 to 4% are considered to be irritating for the skin (EC 2008). No human data on local effects to the eyes were available. The non-irritant level was 0.2 to 1.0%, while the corrosive concentration was 1.2%. The gastric erosive activity of sodium hydroxide was studied with rats using a maximum erosion score of 100. Sodium hydroxide concentrations of 0.4, 0.5 and 0.62% resulted in erosion scores of 10, 65 and 70%, respectively (Van Kolfschoten et al. 1983).

On the basis of available research, sodium hydroxide is considered to be highly corrosive.

13.5.3.2 Eye irritation

In an eye irritation study, 10 microlitres of 2 and 8% sodium hydroxide were directly applied to the cornea of the right eye of each test rabbit; the left eyes served as controls (Maurer and Parker 2000). Eyes and eyelids were macroscopically examined for signs of irritation beginning three hours after dosing and periodically until recovery or day 35. The macroscopic and microscopic changes were consistent with mild (2% sodium hydroxide) and severe (8% sodium hydroxide) eye irritancy.

A volume of 0.1 mL sodium hydroxide was placed in the lower conjunctival sac of the left eye of Stauffland Albino rabbits (Morgan et al. 1987). Both the left and the right eyes were evaluated for irritation and corneal thickness for up to 21 days. According to US Environmental Protection Agency (EPA) criteria, 0.001M (0.004%), 0.01M (0.04%) and 0.05M (0.2%) sodium hydroxide were considered non-irritant, while the irritation at 0.1M (0.4%) was mild and 0.3M (1.2%) was considered corrosive.

Instillation of a 1% solution into the conjunctival sac failed to cause ocular or conjunctival injury in rabbits, provided the eye was promptly irrigated with copious amounts of water (ACGIH 1991).

Animal data indicate that sodium hydroxide is corrosive to the eye with variations depending on the concentration (OECD 2002). The non-irritant level was 0.2 to 1.0%, while the corrosive concentration was 1.2% or higher.

13.5.3.3 Respiratory irritation

No data were available.

13.5.3.4 Observation in humans

A human skin irritation test with 0.5% sodium hydroxide was performed using exposure periods of 15, 30 and 60 minutes (OECD 2002). The treatment sites were assessed 24, 48 and 72 hours after patch removal. The results showed that after a maximum exposure of 60 minutes, 61% of the volunteers (20 of 33) showed a positive skin irritation reaction.

Sodium hydroxide induced irritation was studied in 34 volunteers by means of 24-hour patch testing at different concentrations and by a short-term test with exposure duration of 10 minutes (OECD 2002) . The 24-hour patch test with 4% sodium hydroxide revealed a classification of subjects in two categories: subjects who reacted normally (25 of 34) and hyper-reactors (9 of 34). Hyper-reactors showed an enhanced inflammatory response, a decreased dermal reflectivity and an increase in trans-epidermal water loss.

In conclusion, solid sodium hydroxide is considered to be corrosive. Depending on the concentration, solutions of sodium hydroxide range from non-irritating, irritating or corrosive and cause direct local effects on the skin, eyes and gastrointestinal tract. Based on human data, concentrations of 0.5 to 4.0% were irritating to the skin, while in animals a concentration of 8.0% was corrosive.

13.5.4 *Sensitisation*

13.5.4.1 Skin sensitisation

Skin sensitisation data were reported by Park and Eun (1995). The backs of male volunteers were exposed to sodium hydroxide concentrations of 0.063 to 1.0% (induction). After seven days the volunteers were challenged to a concentration of 0.125%. The irritant response correlated well with the concentration of sodium hydroxide, but an increased response was not observed when the previously patch tested sites were re-challenged. Based on this study, sodium hydroxide has no skin sensitisation potential and is not considered to be a skin sensitiser.

13.5.4.2 Respiratory sensitisation

Studies on the respiratory tract sensitisation effect of sodium hydroxide are not available.

13.5.4.3 Observations in humans

No data were available.

13.5.5 *Repeat dose toxicity*

13.5.5.1 Oral

No animal data were available on repeated dose toxicity studies by the oral route for sodium hydroxide. A limited oral drinking water study with rats revealed effects on growth (ECB 2008). This effect can be explained by sodium hydroxide neutralising the acid environment in the stomach, which decreases the digestion and the absorption of food.

13.5.5.2 Dermal

No animal data were available on repeated dose toxicity studies by the dermal route for sodium hydroxide.

13.5.5.3 Inhalation

In a repeat dose inhalation study, twenty seven white rats died within a month, mostly from bronchopneumonia, after being exposed twice weekly to an aerosol of unknown airborne concentration of sodium hydroxide, generated from an aqueous 40% sodium hydroxide solution (NIOSH 1975). When exposed to an aerosol generated from a 20% sodium hydroxide solution, the bronchi were dilated, the epithelial cover was thin and frequently desquamated, and the septa were dilated and cracked. A light round cell infiltration of the sub-mucus membrane tissue was also observed. Few changes occurred in a group of rats exposed to aerosols from 10% sodium hydroxide, but rats exposed to an aerosol of 5% sodium hydroxide had dilation of the bronchi and a slight degeneration of the mucus membrane and thickened strata of lymphadenoid tissue surrounding the bronchi. A No Observed Adverse Effect Level (NOAEL) could not be established in this study.

13.5.5.4 Observations in humans

Workers exposed to 0.24 to 1.86 mg/m^3 sodium hydroxide for 2 to 15 minutes reported throat irritation and watery eyes (NIOSH 1975). Based on the observations of the irritant effects on workers exposed to 1 to 40 mg/m^3 sodium hydroxide, it was concluded that 2 mg/m^3 represented a concentration that is '*noticeably but not extensively irritant*' (NIOSH 1975).

Obstructive airway disease has been reported following chronic occupational exposure to sodium hydroxide mist (IPCS 1996). The patient developed cough, dyspnoea and tachypnoea after a 20-year exposure to sodium hydroxide. The solution was used to clean jam containers which were boiled in it for two hours. He had a barrel chest with limited movement and diffused expiratory wheezing. A chest X-ray showed severe pulmonary hyperinflation.

13.5.6 *Genotoxicity*

Sodium hydroxide was assayed in the Ames reversion test with *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100 and in a DNA-repair test with *E. coli* strains WP2, WP67 and CM871 (De Flora et al. 1984). Based on the results of these tests, sodium hydroxide was considered to be non-genotoxic.

A mouse bone marrow micronucleus test using 15 mM sodium hydroxide at a dose of 10 mg/kg bw revealed no significant increase of nuclei (Morita et al. 1989). The test compound was administered as a single intraperitoneal dose to five males and five females at 30, 48 and 72h (Aaron et al. 1989). The clastogenic activity of sodium hydroxide was studied in an *in vitro* chromosomal aberration test using Chinese hamster ovary (CHO) K1 cells. No clastogenic activity was found at concentrations of 0, 4, 8 and 16 mM sodium hydroxide, which corresponded with initial pH values of 7.4, 9.1, 9.7 and 10.6, respectively.

Based on the results of these tests sodium hydroxide was considered non genotoxic (OECD 2002).

13.5.7 *Carcinogenicity*

No data were available.

13.5.8 *Reproductive toxicity*

The effect of sodium hydroxide on fertility is not known. No valid studies were identified regarding effects on fertility or developmental toxicity in animals after oral, dermal or inhalation exposure to sodium hydroxide.Sodium hydroxide is not expected to be systemically available in the body under normal handling and use conditions and for this reason it can be stated that the substance will not reach the foetus nor reach male and female reproductive organs (ECB 2008).

13.5.9 *Other health effects*

No data were available.

13.6 Health hazard summary

13.6.1 *Critical health effects*

In summary for this chapter, an oral LD50 of 325 mg/kg in rats and a dermal LD_{50} of 1350 mg/kg in rabbits were reported for sodium hydroxide. Lethality has been reported in animals at oral doses of 240 mg/kg bw. Inhalational LC50 is not available.

Based on available research, sodium hydroxide is corrosive to skin, eyes and gastrointestinal and respiratory tracts. Based on human data, concentrations of 0.5 to 4.0% are irritating to the skin, while a concentration of 8.0% is corrosive. Sodium hydroxide is not a skin sensitiser.

No animal data were available on repeated dose toxicity by oral or dermal routes for sodium hydroxide. In the single reported repeat dose inhalation study, a NOAEL could not be established.

Both *in vitro* and *in vivo* genetic toxicity tests indicated no evidence of a mutagenic activity. Information on reproductive and developmental toxicity and carcinogenicity of sodium hydroxide is not available.

In conclusion, due to dissociation into ions which are subject to homeostatic controls in the human body, systemic effects from repeated exposures to sodium hydroxide are not expected. The critical health effect of sodium hydroxide is its corrosive effect.

13.6.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification of sodium hydroxide under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A13.3. This NICNAS recommendation does not consider physical or environmental hazards.

Table A13.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation / Corrosivity	Causes severe burns (C; R35)*	Causes severe skin burns and eye damage - Cat 1A (H314) May cause respiratory irritation – Specific target organ toxicity, single exposure – Cat. 3 (H335)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b]Globally Harmonised System (UNECE 2009)

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A14 Ethanolamine

CAS No.	CAS Name
141-43-5	Ethanol, 2-amino-

14.1 Chemical identity

Information on chemical identity was obtained from ChemID*plus* (2013). Details are provided in Table A14.1.

Table A14.1 Chemical identity

	Ethanolamine
Synonyms	Ethanolamine 2-Aminoethanol Monoethanolamine
Structural formula	
Molecular formula	C_2H_7NO
Molecular weight	61.08
Appearance and odour	Colourless viscous liquid (or solid below 10°C), with unpleasant, fishy, ammoniacal smell.
SMILES notation	C(O)CN (eChemPortal 2013)

14.2 Physical properties

The physical properties of ethanolamine are presented in Table A14.2. The information was obtained from Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013).

Table A14.2 Physical properties

Property	**Value**
Melting point	10.3 °C
Boiling point	170.8 °C
Density	1.02 kg/m^3 at 20 °C
Vapour pressure	0.05 kPa at 20 °C
Water solubility	Miscible in water at 25 °C
Partition coefficient n-octanol/water (log K_{ow})	-1.31 at 25 °C

14.3 Current regulatory controls

14.3.1 *Hazard classification for occupational health and safety*

Ethanolamine is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) with the following risk phrases (Safe Work Australia 2013):

- C, R34 (Corrosive; causes burns)
- Xn, R20/21/22 (Harmful by inhalation, in contact with skin and if swallowed).

Mixtures containing ethanolamine are classified as hazardous with the following risk phrases based on the concentration (conc) of the chemicals in the mixtures. The risk phrases are:

- Conc ≥25%: C; R34; R20/21/22 (Corrosive, causes burns, harmful by inhalation, in contact with skin and if swallowed)
- 10% ≤Conc <25%: C; R34 (Corrosive, causes burns)
- 5% ≤Conc <10%: Xi; R36/37/38 (Harmful, irritating to eyes, respiratory system and skin).

14.3.2 *Occupational exposure standards*

14.3.2.1 Australia

The occupational exposure standards for ethanolamine are (Safework Australia 2013):

- Time Weighted Average (TWA): 7.5 mg/m³ (5 ppm)
- Short-Term Exposure Limit (STEL): 15 mg/m^3 (10 ppm).

14.3.2.2 International

Occupational exposure limits for ethanolamine identified internationally are provided below (Galleria Chemica 2013).

TWA:

- 7.5 mg/m³ (5 ppm) [Canada, Colombia, Japan]
- 2.5 mg/m³ (2 ppm) [Bulgaria, UK]
- 8 mg/m^3 [US]

STEL:

- 15 mg/m^3 (10 ppm) [Canada, Colombia, Japan, US]
- 7.5 mg/m^3 (5 ppm) [Bulgaria, UK].

14.3.3 *Australian food standards*

No Australian food standards have been identified.

14.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

14.3.5 *Additional controls*

14.3.5.1 Australia

Ethanolamine is included in Schedule 5 and Schedule 6 of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014):

- Schedule 5: Ethanolamine (excluding its salts and derivatives) in preparations containing 20 per cent or less of ethanolamine except:
    a) when included in Schedule 4
    b) in preparations containing 5 per cent or less of ethanolamine.
- Schedule 6: Ethanolamine (excluding its salts and derivatives) except:
    a) when included in Schedule 4 or 5
    b) in preparations containing 5 per cent or less of ethanolamine.

The SUSMP also recommends appropriate '*Warning Statements*' and '*Safety Directions*' for ethanolamine when used in consumer products.

14.3.5.2 International

Ethanolamine is included in Canada's Schedule 1, Toxic Substances List as '*Volatile organic compounds that participate in atmospheric photochemical reactions*' (Environment Canada 2013).

14.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

14.5 Health hazard characterisation

The information on health hazards is obtained from the European Commission (EC) (1992), REACH (2013) and Hazardous Substances Data Bank (HSDB) (2013). Unless otherwise noted, references to individual studies below are taken from these reviews.

14.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

14.5.1.1 Oral absorption

Early metabolic experiments in rats indicated that ethanolamine is absorbed from the gastrointestinal tract when administered through the diet (Weissbach and Sprinson 1953). A quantitative pattern of absorption by ingestion is not available. However, in an oral study in rats, from 6% to 48% of administered ethanolamine was recovered in rat urine within 24 hours on administration of 3.33 and 53 mg/100 g bw, respectively (ACGIH 2005). Details of

the oral study are not available, however these observations indicate that ethanolamine is moderately absorbed in the rat gastrointestinal tract.

For human risk assessment purposes, a 100% oral absorption for ethanolamine is assumed.

14.5.1.2 Dermal absorption

Klain et al. (1985) demonstrated that ethanolamine is absorbed through human skin. Four micrograms of radio-labelled ^{14}C-ethanolamine were applied topically to human skin grafted onto athymic nude mice and to non-grafted skin on nude mice. From the distribution and elimination data it was estimated that 60% of the applied dose was absorbed through the skin after 24 hours. Approximately 24.3% of the administered radioactive dose was recovered at the application site.

In the same study, an equal amount of ethanolamine was administered intraperitoneally to another group of mice for comparison. A time-lag of 30 minutes was noted before the appearance of $^{14}CO_2$ in exhaled breath after topical administration compared to the intraperitoneal route. This suggests that percutaneous absorption of ethanolamine is relatively rapid.

Skin penetration of ethanolamine was also tested *in vitro* with full thickness skin preparations from mice, rats, rabbits and humans (Sun et al. 1996). ^{14}C-ethanolamine was applied to skin discs as either an undiluted liquid or as an aqueous solution at target doses of 4 mg/cm^2. Within six hours the following amounts penetrated through whole skin: rat skin 5.98%, mouse skin 16.92%, rabbit skin 8.66% and human skin 0.61%.

Based on the observations in the *in vivo* study, 100% dermal absorption for ethanolamine will be used for human risk assessment.

14.5.1.3 Inhalation absorption

No quantitative information is available on the inhalation absorption of ethanolamine, although physiological effects of inhaled ethanolamine in animals indicate that it is absorbed by this route (Weeks et al. 1960). A continuous inhalation exposure experiment indicated that ethanolamine is '*perhaps ten times more toxic'* by this route than by ingestion (EC 1992).

For human risk assessment purposes, inhalation absorption of 100% is therefore assumed.

14.5.1.4 Distribution

Ethanolamine is widely distributed in the body with radioactivity detected in all the tissues and organs examined, and as exhaled CO_2 following oral administration of a radiolabelled dose (Klain et el. 1985). The highest levels of radioactivity derived from ^{14}C-ethanolamine were found in the liver (26%), exhaled CO_2 (over 18%) and kidneys (2.2%). Lungs, brain, and the heart contained 0.55, 0.27, and 0.15% of the dose, respectively.

In a rat study, eight hours after intra-peritoneal injection of ^{14}C-ethanolamine, 11.5% of the injected dose was recovered as $^{14}CO_2$ (Snyder 1990). Fifty per cent of the injected radioactivity was found in the liver, and significant amounts (>2% ^{14}C/g tissue) were detected in the spleen and brain. In the liver, >90% of the radioactivity was found in the lipid fraction; in the kidney, spleen and brain, the percentage in the lipid fraction was about 60, 30, and 54%, respectively. Radioactivity was also observed in hepatic phospholipids as the ethanolamine, serine, and choline bases, and in proteins and amino acids isolated from liver and skin sections.

14.5.1.5 Metabolism

Ethanolamine is a normal constituent of the human body. The main metabolic pathway for ethanolamine in rats involves its incorporation into phospholipids, presumably via exchange with serine in phosphatidylserine, resulting in the formation of phosphatidylethanolamine. Following condensation of ethanolamine with phospholipids to form phosphatidylethanolamine or phosphatidylcholine, it is incorporated into cellular membranes (EC 1992). It has been suggested that the incorporation of ethanolamine into phospholipids occurs via the cytidyldiphosphate-ethanolamine pathway (CDP-ethanolamine pathway) or by a base-exchange reaction (Massarelli et al. 1986).

The liver is a major site for metabolism of ethanolamine. In liver tissue, ethanolamine has also been demonstrated to be converted into amino acids, such as glycine and serine, which in turn are incorporated into hepatic proteins (EC 1992).

The molecule can also be deaminated, with the amine group eliminated from the body as nitrogenous waste either as urea or uric acid depending on the species. The remaining carbon skeleton is used as an energy source and oxidised fully to carbon dioxide (Snyder 1990). Ethanolamine is also metabolised in rat liver homogenates, yielding formaldehyde (Bingham et al. 2001).

14.5.1.6 Excretion

The major route of elimination of ethanolamine is through urine. Forty per cent of ^{15}N-labeled ethanolamine administered to rabbits was excreted as urea within 24 hours suggesting that ethanolamine is deaminated in the body (ACGIH 2005). Urinary excretion included radioactive ethanolamine, glycine, serine, uric acid, and choline. The whole blood half-life of ethanolamine in dogs was 19 days, and the total blood radioactivity after 24 hours was 1.68% of the administered dose (Rhodes and Case 1977). In this study, the percentage of the dose excreted in urine was 11%.

In humans, the excretion rate of ethanolamine in urine was slightly higher in females (7.7 to 35 mg/day) than in males (4.8 to 23 mg/day) (Bingham et al. 2001).

14.5.2 *Acute toxicity*

14.5.2.1 Oral

In a study conducted according to the Organisation for Economic Cooperation and Development (OECD) Test Guidelines (TG), Sprague-Dawley rats (five rats per sex) were administered 254, 509, 1018, 2036 and 4072 mg/kg bw/day ethanolamine by gavage, and the animals observed for 14 days (REACH 2013). Animals with high doses (2036 and 4072 mg/kg bw) displayed sluggishness and piloerection. All deaths occurred relatively rapidly after dosing (within two days), except for one male rat that died after 12 days following a dose of 509 mg/kg bw. Rats receiving ethanolamine at the maximum dosage died after three hours. The median lethal dose (LD50) values and the estimated LD50 slopes were calculated by the moving average method. An oral LD50 of 1089 mg/kg bw was established in this study.

The study shows that ethanolamine has moderate toxicity by the oral route in rats.

14.5.2.2 Dermal

In the only reported dermal toxicity study, ethanolamine at 1.0, 2.0, or 4.0 mL/kg (1010, 2020 or 4040 mg/kg bw) was applied to the clipped, intact skin of New Zealand White rabbits (five per sex) (REACH 2013). Gauze was wrapped around the trunk over the sample for the 24

hour exposure period. Observations for toxicity and skin reactions were made at one hour, seven days, and 14 days after the contact period. At death or termination, each animal was subjected to a gross pathologic evaluation. Erythema, oedema, necrosis and ecchymosis were common findings in all dose groups. Nearly all animals in the highest dose group died within 1 to 2 days.

The calculated LD50values for males and females were 2504 mg/kg and 2881 mg/kg, respectively.

The study shows that ethanolamine has low acute toxicity by the dermal route in rabbits.

14.5.2.3 Inhalation

In three separate studies that were reliable (with restrictions) (REACH 2013), rats were exposed to saturated vapour of ethanolamine generated by bubbling 200 l/hour air at 20°C through a column of test material (5 cm) above a fritted glass disc in a glass cylinder. Animals were exposed for eight hours and observed for seven days. No deaths occurred in any of the studies. Based on the atmospheric concentration of ethanolamine (1.3 mg/L air) derived from its theoretical saturated vapour concentrations at room temperature, the median lethal concentration (LC50) for ethanolamine was estimated as >1.3 mg/L.

14.5.2.4 Observation in humans

Information on the acute effects of ethanolamine on humans is not available.

14.5.3 *Irritation / Corrosivity*

14.5.3.1 Skin irritation

Ethanolamine was found to be corrosive to rabbit skin in three different skin irritation tests. One study had to be terminated as chemical burns were observed at the four hour observation period on all rabbits when 0.5 mL of 20% ethanolamine was applied to the shaved skin (REACH 2013). In two other studies, carried out according to OECD guidelines, ethanolamine was applied to 2.5 cm^2 shaved skin patches of rabbits (dose not provided) (REACH 2013). The chemical was washed after one minute, five minute, 15 minute and 20 hours' exposure. In the five and 15 minute exposure groups, pea sized brown erythematous lesions were observed at the application spots within 24 hours of application. At the end of eight days, brown red leather-like necrosis was observed in the animals. In the 20 hour exposure group, grey-brown erythematous lesions exceeding the area of application were observed, which turned to black brown hard necrosis by the end of the eighth day. Draize scores for erythema were three in the 20 hour exposure group at all time-points. Based on these observations, ethanolamine was considered to be corrosive to rabbit skin.

Continuous exposure of rats, guinea pigs and dogs to ethanolamine vapour, 24 hours per day, for 90 days produced skin irritation at concentrations as low as 5 ppm (13 mg/m^3) (Weeks et al. 1960). Exposure to high concentrations of 66 to 102 ppm (164 to 254 mg/m^3) ethanolamine resulted in severe lesions, including ulceration and necrosis of the dermal tissue that extended down to the level of the underlying muscle. The authors suggested that irritation of the skin could have been potentiated by contact of the skin with liquid ethanolamine that had condensed onto surfaces of the inhalation chamber.

Based on the available studies, ethanolamine is considered to be corrosive to animal skin.

14.5.3.2 Eye irritation

In an eye irritation study, five microlitres of undiluted ethanolamine was applied into the eyes of six New Zealand White rabbits (REACH 2013). The eyes were not washed. Severe corneal injury (average scores 2.5 and 2.7 for opacity and area), iritis (average score 1.0), and severe conjunctival irritation (average scores 2.8, 2.7 and 3.0 for redness, chemosis and discharge), with necrosis, were observed in all six animals by one hour of application. A red to brown ocular discharge was also noted in each animal. All animals exhibited haemorrhaging in addition to necrosis of the conjunctivae at 24 hours. Corneal vascularisation was noted in two animals by 72 hours and a third animal had vascularisation at 14 days. Irregularly shaped corneas characterised by surface bulges were evident in four animals by seven days. Severe irritation persisted in three animals through 21 days. Corneal opacity and area scores of four and two, respectively, were reported.

Three similar studies carried out prior to 1970 (1956, 1966 and 1967) in rabbits also concluded that ethanolamine was corrosive to the eyes (REACH 2013).

Based on the available studies, ethanolamine is considered to be corrosive to the rabbit eye.

14.5.3.3 Respiratory irritation

Information on respiratory irritation is not available. Based on the effects of ethanolamine on the skin and eyes of animals, the chemical is expected to be a respiratory irritant.

14.5.3.4 Observation in humans

The effects on humans are related primarily to the irritant local action of ethanolamine. A formulation of 11.5% ethanolamine (diluted 20 times) was applied to the upper arm of human volunteers (n=165) three times a week for three weeks (EC 1992). The authors concluded that the solution was irritating to the skin.

In a group of workers (64 males, 40 females) employed in a workplace where their hands and arms were often contaminated with a corrosion inhibitor containing ethanolamine, 13.5% were found to be suffering from occupational dermatoses (Tsyrkunov 1975). The author concluded that the clinical observations indicated that ethanolamine has moderate skin irritating properties.

14.5.4 *Sensitisation*

14.5.4.1 Skin sensitisation

The sensitisation effect of ethanolamine was tested in guinea pigs using the guinea pig maximisation test (GPMT) (REACH 2013). Groups of 15 animals were induced with 0.6% (intradermal) and 10.3% (epicutaneous) ethanolamine and then challenged after three weeks with 0.41, 2.05 and 4.1% ethanolamine. Prior to the topical induction, the animals were pre-treated with 10% sodium dodecyl sulphate. The challenge reactions were read blindly 48 and 72 hours after application of the patches (Finn chambers). Control groups of 12 animals were given the same treatment (Freund's Complete Adjuvant, vehicle, occlusion, etc.).

After the challenge with 4.1%, 2.05% and 0.41% ethanolamine, 3/15, 2/15 and 3/15 of the animals, respectively, reacted positively after 72 hours. Two out of 15 animals showed a reaction to the vehicle.

The study concluded that ethanolamine is not a skin sensitiser (REACH 2013).

14.5.4.2 Respiratory sensitisation

Information on respiratory sensitisation is not available.

14.5.4.3 Observation in humans

Repeated skin insult patch testing of human volunteers or chemical workers produced negative results. The overall evidence suggests ethanolamine is not allergenic (EC 1992).

Ethanolamine inhalation by humans has been reported to cause immediate allergic responses of dyspnoea and asthma and clinical symptoms of acute liver damage and chronic hepatitis. A case of occupational asthma in an industrial worker exposed to a detergent containing 8% ethanolamine was reported (CIR 2012).

Ethanolamine has moderate oral and dermal acute toxicity and is harmful by inhalation. It is corrosive to the eyes and skin. Tests with guinea pigs indicated that ethanolamine is not a skin sensitiser.

14.5.5 *Repeat dose toxicity*

14.5.5.1 Oral

In a 90-day sub-chronic oral study, rats were fed 320, 640 or 1280 mg/kg/day ethanolamine mixed in food (Smyth et al. 1951). No effects were observed in rats at 320 mg/kg bw/day ethanolamine. At 640 mg/kg/day, liver and kidney weights were altered and at the highest dose of 1280 mg/kg/day, death occurred. No further details of the study were available. The results indicated an oral NOAEL (No Observed Adverse Effect Level) of 320 mg/kg/day.

In a reproductive/development toxicity study (Hellwig and Liberacki 1997), pregnant rats were administered 0, 40, 120 and 450 mg/kg bw/day ethanolamine by gavage. Evidence of maternal toxicity such as reduced food consumption, lower mean body weights and impaired body weight gain were reported at 450 mg/kg/day. These observed effects were not sufficient to establish a NOAEL in this study.

The NOAEL from the 90-day study, 320 mg/kg bw/day, will be used for human risk assessment.

14.5.5.2 Dermal

Repeat dose dermal studies for ethanolamine are not available.

14.5.5.3 Inhalation

In a sub-acute inhalation study, rats were exposed to 10, 50 or 150 mg/m^3 ethanolamine aerosol, 6 hrs/day, 5 days/wk for 28 days (REACH 2013). The aerosol was generated with compressed air mixed with conditioned dilution air into the inhalation system using a two-component atomiser. The control group was exposed to conditioned air only.

No deaths were recorded throughout the study. No treatment-related changes in food intake, body weight or adverse changes in haematology or clinical chemistry parameters were observed. There were no gross lesions in treated male or female animals.

At 50 and 150 mg/m^3 all the animals developed submucosal inflammation at the base of the epiglottis, characterised by infiltrates of granulocytes and lymphoid cells. In addition, a focal squamous cell metaplasia was observed in some animals at 50 mg/m^3 and in all animals of the 150 mg/m^3 group. Some animals in the 150 mg/m^3 group also showed focal epithelial necrosis at the base of the epiglottis. A minimal focal epithelial hyperplasia also occurred in the 150 mg/m^3 group of rats. Histopathological changes such as squamous metaplasia in the trachea and mucous cell hyperplasia in the lungs were also noted at 150 mg/m^3. All the findings were considered treatment-related. A NOAEL of 10 mg/m^3 was established for local effects based on the concentration-related lesions in larynx, trachea and lung observed in rats (REACH 2013). No adverse systemic effects were reported. A NOAEL for systemic effects could not be established in this study.

Repeated inhalation exposure of dogs, guinea pigs and rats to 66 to 102 ppm (160 to 255 mg/m^3) ethanolamine for 24 to 90 days induced behavioural effects and degenerative changes in different organs, especially cloudy swelling in the liver and in the tubular epithelium of the kidneys (Weeks et al. 1960). The animals also displayed pronounced clinical signs of skin and respiratory irritation, which progressed with time to hair loss, severe skin lesions, moist rales and fever in dogs and breathing difficulties in rats and guinea pigs. There was a decrease in the albumin-globulin ratio and a decrease in haemoglobin and haematocrit values in dogs exposed to 102 ppm ethanolamine. A NOAEL could not be established in this study as the effects were seen at all doses tested.

Repeated inhalation of low doses of 30 mg/m^3 ethanolamine for 90 days caused behavioural effects in dogs, such as progressive stages of excitation followed by depression (Gillner et al. 1993).

Rats exposed to 5 ppm (13 mg/m^3) ethanolamine also exhibited skin irritation and lethargy after 2 to 3 weeks exposure (Weeks et al. 1960). The EU Scientific Expert Group on Occupational Exposure Limits for Ethanolamine considered this LOAEL (5 ppm or 13 mg/m^3) as the best available basis for proposing occupational exposure limits (SCOEL 1996). Based on the observations in the above studies, a NOAEL of 10 mg/m^3 was established for local effects being just below the LOAEL derived by the EU Scientific Expert group.

A NOAEL for systemic effects due to repeated inhalation of ethanolamine could not be established in any of the available studies.

14.5.5.4 Observations in humans

Occupational asthma and skin sensitisation following ethanolamine exposure have been reported (EC 1992). Data for the establishment of Soviet Maximum Admissible Workplace Concentrations for ethanolamine reported that workers exposed to concentrations of 1 mg/m^3 (0.4 ppm) showed increased incidence of liver and gall bladder disease and chronic bronchitis. No details about the number of subjects or duration of exposure were given and the primary source of the data was not cited (EC 1992). Chronic hepatitis was also found in one subject following accidental high exposure to ethanolamine (EC 1992).

The general population may be exposed by dermal contact to ethanolamine in cosmetic formulations. The effects on humans are related to the primarily irritant local action of ethanolamine. A concentration of 5.9% is irritating to human skin (EC 1992). There have also been reports of occupational asthma and skin sensitisation following ethanolamine exposure (EC 1992).

Paustovskaya et al. (1977) reported that out of a group of 454 workers, some of whom worked with ethanolamine in metal corrosion inhibition, 11.6% were diagnosed as having

chronic hepatitis or hepatocholecystitis compared to a prevalence of 4.9% for a non-exposed control group.

14.5.6 *Genotoxicity*

Ethanolamine lacked mutagenic potential in the Ames bacterial mutagenicity test when tested in the presence or absence of a metabolic activation system with a variety of *Salmonella typhimurium* tester strains, namely TA 1535, TA 1537, TA 1538, TA 98, and TA 100 (JETOC 1996). The highest ineffective dose tested in any *Salmonella typhimurium* strain was 10 000 mg/plate (Mortelmans et al. 1986).

Ethanolamine also failed to cause mutations in a test organism sensitive to oxidative-type mutagens (*Escherichia coli*) (REACH 2013). Assays of the potential of ethanolamine to damage DNA in *Bacillus subtilis* and to cause chromosomal damage in yeast cells (*Saccharomyces cerevisiae* gene conversion assay) were negative (REACH 2013).

Ethanolamine did not induce chromosome damage in rat liver epithelial-type cells or transformation of Chinese hamster cells (Chen et al. 1984). It did not induce a mutagenic response in the mouse lymphoma forward mutation assay in the absence or presence of metabolic activation (REACH 2013).

In the only *in vivo* chromosomal aberration study, the Mammalian Erythrocyte Micronucleus Test, in which mice were fed 375, 750 and 1500 mg/kg ethanolamine dissolved in water, there were no biologically relevant, significant differences in the frequency of erythrocytes containing micronuclei between the solvent control and the three dose groups. The study concluded that, under the experimental conditions chosen, ethanolamine has no chromosome-damaging (clastogenic) effect, nor does it lead to any impairment of chromosome distribution in the course of mitosis (REACH 2013).

Based on the observations, it is concluded that ethanolamine is not genotoxic.

14.5.7 *Carcinogenicity*

No data on the carcinogenicity of ethanolamine are available.

14.5.8 *Reproductive toxicity*

14.5.8.1 Fertility

In a reliable two-generation reproductive study, Crl:WI rats (25 animals per sex per dose) were administered 0, 100, 300 or 1000 mg/kg bw/day ethanolamine in normal diet daily for the period of the study (REACH 2013). Pairs of rats were housed in cages (one male and one female rat in each cage) until mating occurred, after which each pregnant female was caged individually.

At 100 and 300 mg/kg bw/day no test substance-related findings were observed. Oestrous cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning, as well as sperm parameters, sexual organ weights and gross and histopathological findings of these organs (including differential ovarian follicle counts in the F1 females) were comparable between all test groups.

At 1000 mg/kg bw/day, absolute and relative weights of epididymides and cauda epididymidis were decreased and, in the F0 generation only, the number of homogenisation resistant caudal epididymal sperm was slightly, but significantly, reduced. However, histomorphological correlates for these findings were not reported.

At 1000 mg/kg bw/day in F0 and F1 generation females, decreased numbers of implants and increased resorption rates resulted in significantly smaller litters, providing evidence of an adverse effect of the test compound on fertility and / or reproductive performance. At 1000 mg/kg bw/day, systemic toxicity was also observed in these females, such as reduced food consumption and / or body weight gain during gestation/lactation.

Based on the observations in this two-generation reproduction toxicity study, a NOAEL for fertility, reproductive performance and systemic toxicity in parental F0 and F1 rats is 300 mg/kg bw/day.

This study shows that ethanolamine may affect fertility in rats at very high concentrations (1000 mg bw/day), at which maternal toxicity is also observed.

14.5.8.2 Developmental toxicity

In the study discussed above, all data recorded during gestation and lactation in terms of embryonal/fetal and pup development gave no indications of any developmental toxicity in the F1 and F2 offspring up to a dose level of 1000 mg/kg bw/day. The test substance did not adversely influence pup viability, body weight, sex ratio and sexual maturation. The NOAEL for pre-and postnatal developmental toxicity was established as 1000 mg/kg bw/day.

In a reproductive/development toxicity study reported earlier (Hellwig and Liberacki 1997), pregnant rats were administered 0, 40, 120 and 450 mg/kg bw/day ethanolamine by gavage. Evidence of maternal toxicity such as reduced food consumption, lower mean body weights and impaired body weight gain were reported at 450 mg/kg/day. No effects on development of the pups were reported.

In another developmental toxicity study, pregnant rats (10 per dose group) were administered 0, 50, 150, 300 and 500 mg/kg bw ethanolamine by gavage daily on gestation days 6 to 15.

The animals showed no abnormal clinical signs during the whole study period. There were no mortalities. The mean body weights at 500 mg/kg bw/day were statistically significantly lower on days 10, 13 and 15 post-conception, when compared with the control group. Body weight gain at 500 mg/kg/day was reduced on days 6 to 15.

There were no substance-related significant differences between the control and test animals in the mean number of corpora lutea and implantation sites or in the values calculated for the pre- and post-implantation losses, the number of resorptions and viable fetuses. Fetus weights were not significantly different from those of the control rats. External examination of the fetuses revealed no malformation and variation in any test group.

At 500 mg/kg bw/day signs of maternal toxicity were reported such as impairments in food consumption and body weight gain, reductions of total protein and albumin and substance-induced reactions of the forestomach wall. No adverse effects on the fetuses occurred. NOAELs of 300 mg/kg bw/d for maternal toxicity and 500 mg/kg bw/day for developmental effects were established in this study (REACH 2013).

Based on the study observations, ethanolamine is not considered a developmental toxin in rats.

14.6 Health hazard summary

14.6.1 *Critical health effects*

In summary for this chapter, ethanolamine has moderate acute oral and inhalational toxicity and low acute toxicity by the dermal route. The oral and dermal LD50values in rats are 1089 mg/kg bw and 2504 mg/kg bw, respectively and the inhalation LC50 is >1.3 mg/L. Ethanolamine is corrosive to the skin and eyes. Information on respiratory irritation activity is not available, however based on a repeated dose inhalation study, signs of irritation were reported in the trachea and lungs indicating that it is respiratory irritant. Ethanolamine is not considered to be a skin sensitiser.

The most appropriate NOAEL for human health risk assessment purposes is 320 mg/kg bw/day, determined in an oral repeat dose study in rats based on increase in liver and kidney weights. Repeat dose dermal studies for ethanolamine are not available.

Ethanolamine is not genotoxic or a carcinogen based on available data.

Effects on fertility were observed at a high dose of 1000 mg/kg bw/day at which dose maternal toxicity was also observed. No developmental toxicity effects were noted in rats.

Skin and eye irritation is the critical effect for human health risk assessment. Ethanolamine is also harmful by oral and inhalation routes. The oral NOAEL will be used for risk assessment for repeated exposure.

14.6.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004).

The equivalent classification and labelling under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) is shown in Table A14.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A14.3 Recommended hazard classification

	GHS* classification
Acute toxicity	Harmful if swallowed – Cat. 4 (H302) Harmful in contact with skin – Cat. 4 (H312) Harmful if inhaled (H332)
Irritation / Corrosivity	Causes severe skin burns and eye damage – Cat. 1B (H314) May cause respiratory irritation - Specific target organ toxicity, single exposure – Cat. 3 (H335) Affected organs: Respiratory tract Route of exposure: Inhalation

** Globally Harmonised System (UNECE 2009)*

14.7 References

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A15 Sintered bauxite

CAS No.	CAS Name
144588-68-1	Bauxite ($Al_2O_3.xH_2O$), sintered

15.1 Chemical identity

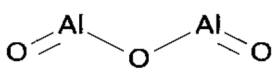
The chemical under assessment, bauxite ($Al_2O_3.xH_2O$), sintered, was incorrectly identified in the industry survey as having the CAS No. 1318-16-7. This CAS No. is assigned to bauxite, which is not an equivalent substance.

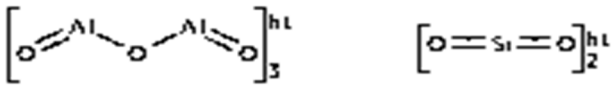
Bauxite (CAS No. 1318-16-7) is a naturally occurring and complex heterogeneous material composed of aluminium hydroxides, including gibbsite (γ-$Al(OH)_3$, CAS No 14762-49-3), and the oxyhydroxides boehmite [α-Al_2O_3• H_2O or α-AlO(OH)] and diaspore [β- Al_2O_3 • H_2O or β-AlO(OH)] (Pearson 1992). It also contains various amounts of clay (kaolinite), silica, iron and titania impurities (Leigh 1997).

Bauxite ($Al_2O_3.xH_2O$), sintered (CAS No. 144588-68-1), also known as '*sintered bauxite*', is produced by crushing bauxite to a powder and then fusing it into spherical beads at very high temperature (typically 1 500-2 000°C) (USITC 1989; Hellman et al. 2014; Maczura 1992). The sintering process increases the physical strength of the alumina crystals and the hardness of the beads. Heating also removes the intrinsic moisture and increases the alumina content by converting the tri-hydrate and mono-hydrate forms (gibbsite and boehmite, respectively) into corundum (α-Al_2O_3, CAS No. 1302-74-5), a natural form of aluminium oxide, by expulsion of water of crystallisation (Australian Bauxite Limited 2014). The kaolinite clay (i.e. the silica and alumina bearing minerals) present in the bauxite are transformed into mullite ($Al_6O_5(SiO_4)_2$) (aluminosilicate, mullite CAS No. 1302-93-8) (Leigh 1997).

The information on the identity of sintered bauxite was obtained from Safety Data Sheets (SDS) published by companies for products used specifically as proppants in coal seam gas extraction (Saint-Gobain Proppants 2011; CarboCeramics 2007). Peer-reviewed data available describing the chemical constituents of sintered bauxite were limited to a report by the United States International Trade Commission (USITC) (1989), and the chemical structures obtained from ChemID*plus* (2012). Details are provided in Table A15.1.

Table A15.1 Chemical identity and constituents of sintered bauxite

	Sintered bauxite
Synonyms	Ceramic proppant
Appearance and odour	Greyish-brown to dark green to black spheres or free flowing granules, no odour
Chemical constituents (typical)	65 to 85% Corundum [Corundum (Al2O3), CAS No. 1302-74-5, MW = 101.961, Al2O3]  15-35% Mullite [Aluminosilicate, mullite CAS No. 1302-93-8, MW = 426.051,

	Sintered bauxite
	3Al2O3.2SiO2] 

15.2 Physical properties

The information on the physical properties of sintered bauxite and chemical constituents was obtained from the USITC (1989), O'Neill et al. (2013), Krewski et al. (2007), the European Commission (2000), REACH (2014a, 2014b) and CarboCeramics (2007) and is provided in Table A15.2.

Table A15.2 Physical properties of sintered bauxite and chemical constituents

Property	**Sintered bauxite**	**Corundum**	**Mullite**
Melting point	2200 °C (est.)	2015 °C	1860-1880 °C
Boiling point	No data	2980 °C	No data
Density (kg/m^3 at 20°C)	3150-3740	3990-4100	3110-3260
Vapour pressure	negligible	negligible	negligible
Water solubility	insoluble	insoluble	insoluble
Partition coefficient n-octanol/water (log Kow)	Not applicable	Not applicable	Not applicable

15.3 Current regulatory controls

15.3.1 *Hazard classification for occupational health and safety*

Sintered bauxite and its constituents are not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

15.3.2 *Occupational exposure standards*

15.3.2.1 Australia

Time weighted average occupational exposure standards of 10 mg/m^3 for emery (dust) (aluminium oxide, CAS No 1302-74-5) and α-alumina (Al2O3)(aluminium oxide, CAS No 1344-28-1) are recommended in Australia. Emery is defined as an impure form of corundum which may contain small amounts of iron, magnesium and silica (CDC 2011).The value of 10 mg/m^3 is for inspirable dust containing no asbestos and <1% crystalline silica.

15.3.2.2 International

The following exposure standards (Galleria Chemica 2013) were identified for emery but also apply to aluminium oxide.

Time Weighted Average (TWA):

- 10 mg/m^3 (total inhalable dust) [Belgium, Canada, Czech Republic, Ireland, Korea, Mexico, New Zealand, Portugal, Spain, United Kingdom, US-ACGIH]
- 15 mg/m^3 (total inhalable dust) [US-OSHA]
- 3 to 4 mg/m^3 (respirable dust) [Ireland, Korea, Switzerland, United Kingdom]
- 5 mg/m^3 (respirable dust) [US-OSHA]

Short-Term Exposure Limit (STEL):

- 20 mg/m^3 [Canada, Mexico].

These exposure standards were identified for aluminium and oxide (as Al):

- Level Limit Value (LLV): 5 mg/m^3 (total dust) [Sweden]
- LLV: 2 mg/m^3 (respirable dust) [Sweden].

15.3.3 *Australian food standards*

Silicates, including calcium aluminium silicate and sodium aluminosilicate, are listed in the Australia New Zealand Food Standards Code – Standard 1.3.3 - Processing Aids – as generally permitted processing aids that may be used in the course of manufacture of any food at a level necessary to achieve a function in the processing of that food (Food Standards Australia New Zealand 2013).

15.3.4 *Australian drinking water guidelines*

An aesthetic guidance value of 0.2 mg/L was identified for aluminium (acid-soluble) in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

15.3.5 *Additional controls*

15.3.5.1 Australia

The chemical or its chemical constituents are not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

15.3.5.2 International

No international restrictions were identified.

15.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

15.5 Health hazard characterisation

In this report, the term '*aluminium*' is used to represent the ionic species (i.e. aluminium oxide contains aluminium ions) and does not refer to the metal, unless otherwise specified the information on health hazards is obtained from the following comprehensive reviews:

- toxicological profiles for metallic aluminium and compounds (ATSDR 2008; WHO 1997, 2012)

- a human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide (Krewski et al. 2007)
- REACH dossiers on aluminium oxide (REACH 2014a) and mullite (REACH 2014b).

Unless otherwise noted, references to individual studies below are taken from these reviews.

There were no toxicity data available for sintered bauxite, however limited data were available for the major constituent, corundum (CAS No. 1302-74-5), which is the alpha crystalline form of aluminium oxide (CAS No. 1344-28-1). As the toxicity of corundum is driven predominantly by aluminium ion, the information available for this polymorph of aluminium oxide is supplemented in this assessment with a wider range of toxicity studies conducted for the gamma form and other minor transitional, lower temperature polymorphs of aluminium oxide (χ-, κ-, δ-, θ-Al2O3) that are also grouped under the CAS No. 1344-28-1. In addition, limited toxicity data were available for mullite (CAS No. 1302-93-8), the minor constituent of sintered bauxite.

Sintered bauxite is insoluble and data available for the insoluble aluminium compound, aluminium oxide, are being used to read across to the endpoints for sintered bauxite. In addition, the sintered bauxite assessment will draw on available data for corundum and mullite. Data available for soluble aluminium compounds are not considered to be relevant for sintered bauxite. The information available for corundum, aluminium oxide and mullite is presented in Table A15.3.

Table A15.3 Summary of available toxicity endpoint data

Hazard	**Sintered bauxite (CAS No. 144588-68-1)**	**Corundum (CAS No. 1302-74-5)**	**Aluminium oxide (CAS No. 1344-28-1)**	**Mullite (CAS No. 1302-93-8)**
Acute oral toxicity	×	×	✓	×
Acute dermal toxicity	×	×	×	×
Acute inhalation toxicity	×	×	✓	✓
Skin irritation	×	✓	✓	✓
Eye irritation	×	✓	✓	✓
Respiratory irritation	×	×	✓	×
Skin sensitisation	×	×	✓	✓
Respiratory sensitisation	×	×	✓	×
Repeat dose toxicity (oral)	×	×	✓[1]	×
Repeat dose toxicity (dermal)	×	×	×	×
Repeat dose toxicity (inhalation)	×	✓	✓	✓
Genotoxicity *in vitro*	×	×	✓	✓
Genotoxicity *in vivo*	×	×	✓	×
Carcinogenicity	×	✓	✓	×
Reproductive toxicity	×	×	✓[1,2]	×

✓ Existing data point; × Missing data point; [1] 'Aluminium chloride basic' that consisted of 17.0% aluminium oxide, 9.0% aluminium and 19.9% aluminium chloride; [2] Study for insoluble aluminium hydroxide also included

15.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

No data were available for sintered bauxite or corundum.

Although studies on the absorption of the gamma- and transitional forms of aluminium oxide are available, in contrast to the alpha form, these polymorphs can readily take up water and dissolve in acids. Therefore, estimates of uptake based on data from these studies are likely to represent conservative assumptions.

15.5.1.1 Oral absorption

In a rat study, conducted in accordance with OECD Test Guideline (TG) 417, the uptake of 26Al in the bloodstream was measured following gavage administration of 12 radio-labelled aluminium compounds, including an aluminium oxide suspension (form unreported) (REACH 2014a). The absorption of the aluminium oxide was determined to be 0.018% and the more soluble compounds up to 10-fold higher. These values are broadly consistent with reports of oral aluminium ion bioavailability in humans from the diet of 0.1 to 0.3% based on daily aluminium intake and urinary elimination (Krewski et al. 2007). More recent data reviewed by the World Health Organisation (WHO 2012), indicated that absorption of aluminium ions following the ingestion of various aluminium compounds by rats is generally in the region of 0.01 to 0.3% and support the assumption that the more water-soluble aluminium compounds are generally more bioavailable. Absorption of aluminium ions in human volunteers was within the same range as that in rats.

In a non-guideline, *in vitro* study of gastrointestinal effects, using a standard method for determination of absorption of pollutants from soils in accordance with DIN 19738, the uptake of white fused mullite (measured as aluminium) was 0.008% or 0.3% in the absence or presence of lactate, respectively (REACH 2014b).

Based on rounding and statistical variation within data available for aluminium oxide, for human risk assessment purposes an oral absorption of 0.02% is assumed for sintered bauxite.

15.5.1.2 Dermal absorption

Aluminium oxide or mullite absorption via the skin in animals has not been studied. There is no direct evidence that aluminium is absorbed through the intact skin of humans (WHO 1997).

For the purposes of risk assessment, 0% dermal absorption in humans is therefore assumed for sintered bauxite.

15.5.1.3 Inhalation absorption

Owing to the chemical properties of aluminium, the absorption of its compounds by the respiratory system depends on the aluminium species inhaled and the biological environment in the tissue compartment where they are deposited. There is evidence from a number of

reports that even aluminium compounds that are almost insoluble in water are bioavailable in the respiratory system (WHO 1997).

Priest (2004) estimated the ^{26}Al absorption from inhalation of ^{26}Aluminium oxide particles (mean aerodynamic diameter of 1.2 µm) by two male volunteers was 1.9%. The aluminium oxide polymorphs assessed in this study were transitional forms and contained little of the alpha form.

Other data were available from occupational inhalation exposure studies. The absorption of aluminium from the lung was estimated from 12 aluminium welders exposed to welding fumes containing 39% aluminium (as aluminium oxide) based on daily lung burden of 4.2 mg and daily urinary aluminium excretion of 0.1 mg (Sjögren et al. 1997). This would suggest absorption of approximately 2.4% of the aluminium. Results from a group of production workers exposed to 0.2 to 0.5 mg soluble aluminium/m^3 in the air (particle size not described) suggest approximately 2% absorption (Pierre et al. 1995).

In a bioaccessibility assay using inhalation of white fused mullite, an uptake value of 0.005% was calculated based on the highest measured aluminium concentration (REACH 2014b).

For the purposes of risk assessment, 2% inhalation absorption in humans is therefore assumed for sintered bauxite.

15.5.1.4 Distribution

In humans, plasma aluminium is predominantly associated with transferrin with a normal concentration of 1 to 2 µg/L (Krewski et al. 2007). Approximately 60, 25, 10, 3 and 1% of the aluminium body burden is in the bone, lung (due to particle entrapment), muscle, liver and brain, respectively.

15.5.1.5 Metabolism

Because aluminium has a very high affinity for proteins, polynucleotides, and glycosaminoglycans, much of the aluminium in the body exists as bound macromolecular complexes with these substances. These complexes are so stable that they are essentially irreversible; e.g. the nucleus and chromatin are often sites of aluminium binding in cells. Aluminium may also form low-molecular-weight complexes with organic acids, amino acids, nucleotides, phosphates, and carbohydrates, and these are more metabolically active than the macromolecular complexes (ATSDR 2008).

15.5.1.6 Excretion

Urinary excretion is the primary route of elimination of absorbed aluminium after inhalation exposure in humans. Elevated levels of aluminium in urine have been detected in aluminium welders and aluminium flake workers, with the suggestion that the urinary excretion is biphasic (Pierre et al. 1995; Sjögren et al. 1985, 1988). No studies were located regarding excretion in animals after inhalation exposure to aluminium or its compounds.

Following ingestion in animals and humans, absorbed aluminium from the blood is eliminated in the kidney and excreted in the urine, and the unabsorbed aluminium is excreted primarily in the faeces (ATSDR 2008).

15.5.2 *Acute toxicity*

15.5.2.1 Oral

No data were available for sintered bauxite, corundum or mullite.

In two separate studies, administration of a dose of 10 000 mg/kg bw 33% aqueous aluminium oxide suspension by gavage to Wistar rats reported no mortality (REACH 2014a).

Similarly, administration of doses of up to 15 900 mg/kg bw fumed alumina (aluminium oxide) by gavage to Sprague-Dawley rats reported no mortality (REACH 2014a). Clinical signs of depression, laboured respiration, and piloerection (males) were noted immediately after administration of the compound, and a hunched appearance was noted at 24 hours post-administration. Animals appeared normal by day eight.

Because mullite is poorly absorbed after gastrointestinal administration, it is predicted that it will have a low acute toxicity when administered by this route.

Sintered bauxite is expected to have low acute oral toxicity based on data available for aluminium oxide.

15.5.2.2 Dermal

No data were available for sintered bauxite or its constituents. Because aluminium oxide is poorly absorbed after dermal administration, it is expected that it will have low acute dermal toxicity. Similarly, sintered bauxite is expected to have low acute dermal toxicity.

15.5.2.3 Inhalation

No data were available for sintered bauxite or corundum.

Rats were exposed (whole body) to aerosol of Alon-C fumed alumina (a high surface area fumed alumina, predominantly gamma-aluminium oxide) in a non-guideline study at concentrations of 0, 5.06, 5.88, 6.28 and 8.22 mg/L for 1 hour (REACH 2014a). The acute inhalation median concentration (LC50) was estimated to be 7.6 mg/L, with decedent animals found to have a white gel in their trachea and stomachs. The investigators suggest that the deaths were likely due to suffocation from blockage of air passages by the gel formed from the test substance. Discolouration and slight increase in the number of lesions on the lungs of the test animals was also reported.

Rats were exposed (whole body) to aerosol of fumed alumina (unspecified forms of aluminium oxide) at a concentration of 2.3 mg/L for four hours (REACH 2014a). No mortality was observed during this study, with minor clinical signs in only one animal showing lung abnormalities on necropsy. No deaths were reported following an acute four hour exposure to up to 1000 mg aluminium/m^3 as aluminium oxide in groups of male Fischer 344 rats (Thomson et al. 1986).

In a four-hour inhalation study in rats, conducted in accordance with OECD TG 403, white fused mullite did not produce signs of toxicity at the maximal technically feasible concentration of 2190 mg/m^3 (REACH 2014b).

Sintered bauxite is expected to have low acute inhalation toxicity based on data available for aluminium oxide and mullite.

15.5.2.4 Observation in humans

No data were available for sintered bauxite, corundum, aluminium oxide or mullite.

15.5.3 *Irritation / Corrosivity*

15.5.3.1 Skin irritation

No data were available for sintered bauxite. Corundum is extensively used as an abrasive and polisher in sandpaper, emery, etc. and can cause abrasion of the skin or any other tissue against which it is rubbed. Aluminium salts can produce dermal irritation that is aluminium species-dependent (Krewski et al. 2007).

The application of 0.5 g of aluminium oxide to rabbit skin elicited slight erythema in 2/12 animals after a 24-hour semi-occluded exposure, while the application of a 0.5 mg/mL suspension of Alon-C to rabbit skin elicited slight erythema to abraded skin only (REACH 2014a). Aluminium oxide was not irritating to rabbit skin in a test conducted in accordance with OECD TG 404 (European Commission (EC) 2000).

White fused mullite was negative in a Reconstructed Human Epidermis (RhE) test for skin irritation conducted in accordance with OECD TG 439 (REACH 2014b).

Sintered bauxite is not expected to be a skin irritant based on the results of the data available for the two constituents and aluminium oxide.

15.5.3.2 Eye irritation

No data were available for sintered bauxite. Corundum is used as an abrasive and can cause physical abrasion of the eyes (Krewski et al. 2007).

In a Draize test, 0.1 g of solid aluminium oxide was applied to rabbit eyes (REACH 2014a). The effects observed included slight conjunctival redness (grade 1) and slight chemosis (grade 1). Similarly, slight erythema was observed in rabbit eyes after instillation of powdered Alon-C. Aluminium oxide was not irritating to rabbit eyes in a test conducted in accordance with OECD TG 405 (EC 2000).

An *in vitro* study assessed the irritating potential of white fused mullite using the hen's egg test on the chorio-allantoic membrane (HET-CAM). The chemical was not irritating in this test, as validated by the expected results for negative and positive controls (REACH 2014b).

Sintered bauxite is not expected to be an eye irritant based on the results of tests available for the two constituents.

15.5.3.3 Respiratory irritation

No data were available for sintered bauxite, corundum or mullite.

In guinea pigs, inhalation of aluminium oxide particles (form not reported), of 0.2 µm mean size and maximum size of 1 µm, at doses of 0.38 or 0.58 mg/L for 30 minutes caused a constriction of pulmonary air flow (Robillard & Alarie 1963a). In contrast, inhalation of the chemical at a concentration of 0.38 mg/L by rats for up to 15 minutes produced a time-dependent lung dilatory effect, the opposite to that seen in the guinea pig, dog and cat (Robillard & Alarie 1963b). No further details were provided.

Rats given a single intratracheal instillation of a 5 mg saline suspension of virginal (primary) aluminium oxide showed changes at the pulmonary surface and in lung tissue. There was also an eight-fold increase in the number of polymorphonuclear leukocytes in the lung, which was interpreted by the investigators as a response to a nuisance dust (White et al. 1987).

Overall, it is expected that sintered bauxite may have the potential to cause respiratory irritation, since aluminium oxide is the main constituent of the substance.

15.5.3.4 Observation in humans

No acute irritation data were available for sintered bauxite, corundum, aluminium oxide or mullite.

15.5.4 *Sensitisation*

15.5.4.1 Skin sensitisation

No data were available for sintered bauxite or corundum.

No evidence of skin sensitisation was observed for two batches of aluminium oxide (form not reported) tested as a 33% aqueous suspension in a guinea pig study using the Landsteiner/Draize method (REACH 2014a).

A Local Lymph Node Assay (LLNA) conducted in accordance with OECD TG 429, reported that concentrations up to 25% white fused mullite in acetone/olive oil (4:1) was negative for skin sensitisation (REACH 2013b).

Sintered bauxite is not expected to be a skin sensitiser based on the data available for aluminium oxide and mullite.

15.5.4.2 Respiratory sensitisation

No data were available for sintered bauxite, corundum or mullite.

Four intratracheal instillations of an aluminium oxide particle suspension (form not reported) did not produce allergic inflammatory effects (including elevated cellular infiltration, chemokines and interleukins) in the lungs of mice (Ichinose et al. 2008; REACH 2014a).

The potential for sintered bauxite to cause respiratory sensitisation is likely to be low based on the animal data available for aluminium oxide.

15.5.4.3 Observation in humans

No data were available for sintered bauxite, corundum or mullite.

Asthma-like effects have been seen in workers chronically exposed to airborne aluminium and compounds, including oxides (ATSDR 2008). Exposure to aluminium fumes and dust occurs in potrooms (where hot aluminium metal is recovered from ore) in foundries and welding operations. Because these workers were also exposed to a number of other irritant chemicals, including sulfur dioxide, polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, hydrogen fluoride, and chlorine, it is difficult to ascribe the respiratory effects to aluminium. Wheezing, dyspnea, and / or impaired lung function have been observed in potroom workers (Bast-Pettersen et al. 1994; Radon et al. 1999), foundry workers (Al-Masalkhi and Walton 1994; Burge et al. 2000; Halatek et al. 2005; Halatek et al. 2006), and welders (Abbate et al. 2003; Herbert et al. 1982; Hull and Abraham 2002; Vandenplas et al. 1998), although other studies have not found a significant effect (Musk et al. 2000).

Case reports provide suggestive evidence that chronic exposure to aluminium may cause occupational asthma, although aluminium oxide has not been identified as the causative agent. An atopic individual who had intermittently welded aluminium for four years developed

symptoms of asthma one to four hours after ceasing welding (Vandenplas et al. 1998). Although skin tests with soluble aluminium compounds did not show an immediate reactivity, the worker exhibited a large decrease in Forced Expiratory Volume (FEV1) following aluminium welding. Asthmatic symptoms in this subject appeared after welding and concomitant exposure to fumes of aluminium oxides in the absence of detectable fluorides.

15.5.5 *Repeat dose toxicity*

15.5.5.1 Oral

No data were available for the sintered bauxite, corundum or mullite.

Although no oral repeated dose studies were located for aluminium oxide alone, one study used a test substance described as '*aluminium chloride basic*' that consisted of 17.0% aluminium oxide, 9.0% aluminium and 19.9% aluminium chloride in aqueous solution (Beekhuijzen 2007 cited by WHO 2012). In this combined repeated-dose toxicity study using reproduction and developmental toxicity screening, in accordance with OECD TG 422, Wistar rats were administered aluminium chloride basic at 0, 40, 200, or 1000 mg/kg bw/day (0, 3.6, 18 and 90 mg/kg bw/day, expressed as aluminium) by gavage. Males were dosed for 28 days and females were dosed for 37 to 53 days during pre-mating, mating, gestation and early lactation periods. At the top dose, a transient decrease in body weight and feed intake was reported in females. At autopsy, there were signs of local irritation in the stomach in both sexes at the top dose, together with mild to moderate inflammation of the glandular stomach. No treatment-related changes to reproductive parameters were reported. A NOAEL of 200 mg/kg bw/day was established for local irritation in the absence of significant systemic effects.

15.5.5.2 Dermal

No data were available for the sintered bauxite, corundum, aluminium oxide or mullite.

15.5.5.3 Inhalation

No data were available for the sintered bauxite.

In a study of the pulmonary effects of fine metallic aluminium powders, aluminium oxide dust was included as a '*non-fibrogenic*' control substance (Gross et al. 1973). Rats and guinea pigs were exposed to 30 mg/m³ of aluminium oxide dust (mean diameter 0.8 µm) for one year and rats and hamsters exposed to 75 mg/m³ for six months. In rats exposed to aluminium oxide at the top dose, small foci (consisting of clustered alveoli with swollen macrophages engorged with particles) were observed, concentrated in respiratory bronchioles and alveolar ducts. No observations for the low dose group were reported. In contrast to animals dosed with flaked and spherical aluminium powders, in the aluminium oxide treated animals there was no thickening of alveolar walls evident and no evidence of alveolar proteinosis or pneumonitis. A NOAEC was not established for systemic effects.

Brief reports of non-guideline inhalation studies of aluminium oxide polymorphs were available but were not considered adequate to set a reliable NOAEC. The γ transitional form was believed to be the most biologically active. Mice and rats were exposed to 33 mg/m^3 γ-aluminium oxide by inhalation five hours/day for 285 days (Klosterkötter 1960). Increased mortality was noted together with limited connective tissue thickening in the alveolar walls and bronchioles with mild collagenous fibrosis. These effects were interpreted as alveolar proteinosis, a non-specific response to pulmonary dust exposure (Dinman 1988).

Rats and hamsters inhaled a powder (20% aluminium, 80% aluminium oxide) hourly, eight hours per day for 3 to 19 months (Christie et al. 1963). Increased exposure duration produced enlarged lungs covered by slightly thickened pleura, with sub-pleural plaques that progressed to consolidated areas surrounding the small bronchioles. Microscopic examination revealed diverse pulmonary effects (including cellular infiltration) considered to be a lipid pneumonia.

Rats and guinea pigs were exposed to arc-produced fumes of pure aluminium oxide (alumina) for 18.3 hours daily for six months (MacFarland and Hornstein 1949). Six months after completion of exposure, their lungs contained 1 to 11% of fume material and exhibited nodule-like collections of endothelial cells, fibroblasts and mononuclear leucocytes.

Inhalation of 40 to 120 mg/m³ of boehmite (gamma form of aluminium oxide) or 21 to 33 mg/m³ aluminium oxide (considered to be gibbsite, the hydrated alpha form), by guinea pigs 8 hr/day, 6 day/wk for 14 months did not produce adverse pulmonary alterations (Gardner et al. 1944).

Dinman (1988) reviewed the experimental studies of the toxicity of aluminium oxide in the lung and concluded that the low temperature forms of aluminium oxide can produce irreversible fibronodular changes, but only after intratracheal instillation. There was a positive correlation between the surface area of the aluminium oxide particles and the fibronodular response.

The ability of seven aluminium oxide samples to produce lung cytotoxicity, as measured by biomarkers in bronchoalveolar lavage fluid, was tested in rats by the intratracheal instillation of a total of 50 mg of aluminium oxide given in five instillations over two weeks (Ess et al. 1993). The samples were smelter grade aluminas, a chemical grade and a laboratory produced aluminium oxide with surface areas of 0.5 to 43 m^2/g, 100 m^2/g and 100 m^2/g, respectively. The α-aluminium oxide content of the samples was 8 to 79%, 0% and 0%, respectively. Increased lung cytotoxicity was seen as surface area increased and α-aluminium oxide content decreased.

In summary, studies of aluminium oxide have reported pulmonary effects. These lung effects, noted more with the gamma form of the compound than the alpha form, include increases in alveolar macrophages, alveolar thickening and epithelialisation, granulomatous lesions, and inflammatory cellular infiltration. The effects observed are suggestive of dust overload. Evidence presented suggests that fibronodular and cytotoxic effects seen after intratracheal injection are artefactual. NOAELs were not established for local or systemic effects.

In a briefly reported study, rats were exposed nose-only to mullite dust at 0, 0.5, 2, and 10 mg/m^3 over a period of 13 weeks (Hotchkiss 2006). Localised effects (dose not reported) included a reversible and transient, dose-dependent, mucous cell hypertrophy in the nasal airways together with cellular inflammation and increased alveolar cells (10 mg/m^3 only) in the lungs. No systemic effects were reported and a NOAEC could not be derived based on the upper and lower respiratory tract effects at undisclosed dose levels.

In a 28-day study, Fischer 344 rats were exposed nose-only to mullite (acicular form) aerosol at 0, 10, and 60 mg/m^3 for 6 hrs/day, 5 days/wk (REACH 2014b). Statistically decreased mean bodyweights for treated animals were accompanied by an increase in food consumption at most time-points, although values were not reported. There were slight changes noted in white blood cell counts in both treatment groups, which were regarded as not toxicologically significant. A dose-dependent irritant response was observed within the upper respiratory tract, characterised by mucous cell hyperplasia and hypertrophy in the respiratory epithelium lining, anterior nasal airways and the nasopharynx. These morphologic changes were reversed during the 10-week post-exposure recovery period. Pulmonary

inflammation was noted in the centriacinar region of the lung, together with an increase in particle-laden macrophages and neutrophils, and a slight, diffuse, multifocal influx of mononuclear cells within alveolar ducts. The investigators concluded that the pulmonary response to inhaled mullite is similar to that observed following exposure to other inert, but irritating, inorganic particulates (e.g. amorphous silica). In conclusion, local effects (respiratory tract irritation and pulmonary changes) were seen at 10 mg/m^3 and above. As no significant systemic effects were reported at the highest concentration of 60 mg/m^3 (equivalent to a dose of 12.6 mg/kg bw/day), a NOAEL could not established.

Overall, repeated dose inhalation studies of aluminium oxide and mullite in animals, with exposure ranging in duration from two weeks to 19 months have shown reversible respiratory irritancy and pulmonary changes, including epithelialisation, mucous cell hypertrophy and inflammatory cell infiltration. Based on the absence of adverse systemic effects observed in these studies, for the purposes of quantifying the health risk, the highest dose tested (12.6 mg/kg bw/day) in the critical study for mullite (REACH 2014b) will be taken through to the risk assessment of sintered bauxite.

15.5.5.4 Observation in humans

No data were available for sintered bauxite or mullite.

Occupational exposure to aluminium oxide occurs during the refining of the primary metal and in secondary industries that use aluminium products. Pulmonary fibrosis is the most commonly reported respiratory effect observed in workers exposed to fine aluminium dust, alumina (aluminium oxide), or bauxite, however there is disagreement on the fibrogenic potential of aluminium (ATSDR 2008). In some of the cases, the fibrosis was attributed to concomitant exposure to other chemicals. For example, Shaver and Riddell (1947) described a lung disease seen in 23 furnace operators, who had worked for 23 months to 15 years in a facility manufacturing corundum. These workers were exposed to fumes containing considerable amounts of very fine aluminium oxide, as well as silica and smaller quantities of many other substances. The disease was characterised by dyspnoea, extreme breathlessness, pneumothorax, and diffuse shadows on X-rays progressing to a non-nodular fibrosis. This became known as Shaver's disease, a pulmonary fibrosis seen in workers in bauxite refining or exposed to finely divided aluminium powders. The fumes were shown to contain 30% silicon dioxide and 55% aluminium oxide; the silicon particle size (0.02 to 0.5 µm) was smaller than that associated with classical silicosis. Wyatt and Riddell (1949) reported that the initial lesion was intracellular oedema with fibroblastic proliferation, followed by inflammatory cell infiltration within the thickened alveolar walls and then by collagen deposition. They hypothesised that intense exposure to amorphous aluminium dust may play a role in this disorder. Other examples include pulmonary fibrosis observed in a number of bauxite workers or potroom workers where it is very likely that there was simultaneous exposure to silica, and this was the causative agent rather than the aluminium (ATSDR 2008). Case reports of fibrosis in workers exposed to aluminium oxide fumes have also been reported (Vallyathan et al. 1982; Al-Masalkhi and Walton 1994), however other studies have not found any radiological evidence of pulmonary fibrosis in workers exposed to alumina or fine aluminium powder. It is possible that the conflicting study results are due to differences in the lubricant used to retard surface oxidation during milling (Dinman 1987).

No effect of cumulative bauxite exposure was observed on respiratory symptoms or lung function respiratory health in a cross-sectional survey of 651 employees from three bauxite mines conducted during 1995 and 1996 (Beach et al. 2001).

In an epidemiological study, Friesen et al. (2009) investigated the associations between alumina and bauxite dust exposure and disease mortality in a cohort of 5770 workers from four bauxite mines and three alumina refineries in Western Australia. Cumulative exposure to

inhalable bauxite and alumina were estimated using job histories and historical air monitoring data. The study cohort had a mean duration of employment of 14.1 years. The relative risk of death from non-malignant respiratory disease (chronic obstructive pulmonary disease, asbestosis, unspecified bronchopneumonia and interstitial pulmonary disease with fibrosis) showed a significant trend (seven deaths; $p<0.01$) with cumulative bauxite exposure with adjustment for age, calendar year and smoking. Cumulative alumina exposures also showed a marginally significant trend with mortality from cerebrovascular disease (10 deaths; $p = 0.04$). It was noted that the analyses in this study were based on only a few cases accrued during a relatively short follow-up, and adjustment for smoking was done using only a crude categorical variable.

In reviewing the clinical reports on aluminium oxide, Dinman (1988) suggested that enhanced bioreactivity occurs as particle surface area increases, contributing to pulmonary fibrogenicity, and that the low temperature transitional forms have higher pulmonary bioreactivity than the high temperature, low surface area alpha form. In their review of evidence for a relationship between work in the aluminium industry and lung disease, Abramson et al. (1989) concluded that pulmonary fibrosis had not been shown to be a significant problem, especially in view of the extensive industrial use of the metal and its compounds.

There is also some evidence suggesting aluminium-induced pneumoconiosis (Hull and Abraham 2002; Korogiannos et al. 1998; Kraus et al. 2000), pulmonary alveolar proteinosis (Miller et al. 1984b), interstitial pneumonia (Herbert et al. 1982), and granulomas (Cai et al. 2007; Chen et al. 1978; De Vuyst et al. 1987); however, these reports are based on a small number of cases, which limits their interpretation (ATSDR 2008).

Overall, respiratory effects, in particular impaired lung function and fibrosis, have been observed in a variety of workers exposed to aluminium and oxide dust or fumes; however, this has not been consistently observed across studies and it is possible that co-exposure to other compounds (such as silica) contributed to observed effects. Interpretation of the human data is also complicated by the lack of proper exposure assessment.

15.5.6 *Genotoxicity*

No data were available for sintered bauxite or corundum.

Negative results for mutagenicity of aluminium oxide were reported in an Ames test in *Salmonella typhimurium* strains (with and without metabolic activation) and a *Bacillus subtilis* recombination assay (EC 2000). In *in vivo* studies in rats with aluminium oxide administered by gavage as a suspension at up to 2000 mg/kg bw, negative results were obtained in a chromosomal aberration test (REACH 2014a), a comet assay and a micronucleus test (Balasubramanyam et al. 2009).

In an Ames test with white fused mullite, conducted in accordance with OECD TG 471, the *Salmonella typhimurium* strains TA 97a, TA 98, TA 100, TA 102 and TA 1535 showed negative responses with and without metabolic activation (REACH 2014b).

Based on the available constituent studies, sintered bauxite is not considered likely to be a genotoxicant.

15.5.7 *Carcinogenicity*

No data were available for the sintered bauxite or mullite.

In a non-guideline study, tumours (blood and localised) were seen in rats given intra-peritoneal doses of corundum at 225 mg/kg intermittently over a one week period (RTECS 2014). No further details were available.

An increase in pulmonary or other tumours was not observed in Wistar rats exposed via whole-body inhalation to atmospheres containing alumina fibers (approximately 96% aluminum oxide) at up to 2.45 mg/m^3 for 86 weeks (Pigott et al. 1981).

15.5.7.1 Observation in humans

Edling et al. (1987) found no significant increase in cancer morbidity or mortality in 521 workers exposed to aluminium oxide in Swedish abrasive-manufacturing plant with the cohort followed up between 1958 and 1983.

In an epidemiological study (discussed in section A15.5.5.4), Friesen et al. (2009) investigated the associations between alumina and bauxite dust exposure and cancer incidence in a cohort of 5770 workers from four bauxite mines and three alumina refineries in Western Australia. No notable associations or trends were observed for cancer outcomes.

Several epidemiological studies have reported an increased risk of developing lung cancer or bladder cancer for workers in the aluminium industry, however, in all of these studies the risk has been attributed to the exposure to the polycyclic aromatic hydrocarbons (PAHs) generated during aluminium production rather than from exposure to aluminium compounds (Krewski et al. 2007).

The American Conference of Governmental Industrial Hygienists (ACGIH) listed aluminium oxide as not classifiable as a human carcinogen (A4) (ACGIH 2005).

Sintered bauxite is not considered to be carcinogenic based on the animal and human data available for the different forms of aluminium oxide.

15.5.8 *Reproductive toxicity*

15.5.8.1 Fertility

No data were available for sintered bauxite, corundum or mullite. Although there were no studies for the reproductive effects of aluminium oxide alone, a combined repeated-dose study using reproduction and developmental toxicity screening (described in the section A15.5.5.1) tested a substance described as '*aluminium chloride basic*' that consisted of 17.0% aluminium oxide, 9.0% aluminium and 19.9% aluminium chloride in aqueous solution. No treatment-related changes to reproductive parameters were reported in Wistar rats administered aluminium chloride basic at up to 1000 mg/kg bw/day by gavage for 28 to 53 days (Beekhuijzen 2007 as cited by WHO 2012).

15.5.8.2 Developmental toxicity

Although no data were available for sintered bauxite, corundum, aluminium oxide or mullite, information was available for another insoluble aluminium compound, aluminium hydroxide, which is poorly absorbed after oral administration (Colomina et al. 1994; Domingo et al. 1991).

Several studies investigated the possible association between the oral exposure to aluminium hydroxide and developmental toxicity. Two of these studies investigated administration of aluminium hydroxide alone to mice (Domingo et al. 1989) and rats (Gómez et al. 1990), and neither reported any effects. The former study evaluated the impact of exposures to the chemical on gestation days 6 to 15 at doses as high as

266 mg/kg bw/day, and the latter evaluated the impact of exposures up to 768 mg/kg bw/day on gestation days 6 to 15.

Similarly, in mouse studies involving the concurrent administration of aluminium hydroxide with lactate and ascorbate, no adverse effects were seen in dams or offspring to the chemical alone at doses of 166 mg/kg bw/day (Colomina et al. 1992) or 300 mg/kg bw/day (Colomina et al. 1994).

Aluminium oxide is unlikely to be a developmental toxicant based on the supporting data available for aluminium hydroxide. Similarly, sintered bauxite is not expected to show adverse developmental effects, noting that no data were available for mullite, which is a minor constituent of sintered bauxite.

15.5.9 *Other health effects*

15.5.9.1 Neurotoxicity

A number of studies have investigated the neurotoxic potential in workers chronically exposed to aluminium and aluminium oxide by the inhalation route. With the exception of isolated cases (for example, McLaughlin et al. 1962), none of these studies reported overt signs of neurotoxicity in workers exposed to aluminium dust (smelter workers) (Bast-Pettersen et al. 1994; Dick et al. 1997; Hosovski et al. 1990; Sim et al. 1997; White et al. 1992), in aluminium welders (Hänninen et al. 1994; Kiesswetter et al. 2007, 2009; Sjögren et al. 1996), or in miners exposed to McIntyre powder (finely ground aluminium and aluminium oxide) (Rifat et al. 1990). Higher incidences of subjective neurological symptoms (e.g., incoordination, problems concentrating, headaches, depression, fatigue) were reported in aluminium smelter workers (Iregren et al. 2001; Sim et al. 1997; Sińczuk-Walczak et al. 2003; White et al. 1992) and in aluminium welders (Bast-Pettersen et al. 2000; Riihimäki et al. 2000; Sjögren et al. 1990). Among the studies examining the potential association between neurological symptoms and aluminium exposure estimates (urinary and / or blood aluminium levels), some found a significant association (Riihimäki et al. 2000; Sińczuk-Walczak et al. 2003) and others did not (Bast-Pettersen et al. 2000; Iregren et al. 2001; Kiesswetter et al. 2007, 2009).

Although subclinical effects have been reported in various types of aluminium workers, findings have been inconsistent. Significant alterations in performance tests assessing reaction time, eye-hand coordination, memory, and / or motor skills were found in aluminium welders and miners exposed to McIntyre powder in some studies but not in others. In general, the available occupational exposure studies poorly characterise aluminium exposure. The lack of adequate exposure monitoring data, potential exposure to other neurotoxicants, and the different types of aluminium exposure make it difficult to draw conclusions regarding the neurotoxic potential of inhaled aluminium in workers (ATSDR 2008).

15.6 Health hazard summary

15.6.1 *Critical health effects*

No information is available for sintered bauxite. For the purpose of hazard assessment, it is assumed that the effects observed with its two constituents, corundum (a specific form of aluminium oxide) and mullite (an aluminosilicate), demonstrate the likely toxicological profile of the substance.

In summary for this chapter, sintered bauxite has low acute oral and inhalation toxicity based on the data available for aluminium oxide (in its general form) and both constituents

respectively. Other data available for both constituents indicate the substance is not irritating to the skin or eye but is a respiratory irritant. Aluminium oxide is not a respiratory sensitiser and aluminium oxide and mullite are not skin sensitisers; it is therefore likely that sintered bauxite is neither a respiratory sensitiser nor a skin sensitiser.

Repeated dose inhalation studies of aluminium oxide and mullite in animals have reported localised irritant effects and pulmonary changes, including inflammation and influx of mononuclear cells in a mullite study at 10 mg/m^3 (2.1 mg/kg bw/day). No systemic effects were reported at any of the doses. Based on the absence of adverse systemic effects observed in these repeat dose toxicity studies, for the purposes of quantifying the health risk, the highest dose tested in the critical 28-day inhalation study of mullite (REACH 2014b) of 12.6 mg/kg bw/day will be taken through to the risk assessment of sintered bauxite.

Sintered bauxite is not genotoxic based on data available for aluminium oxide and mullite, and is not carcinogenic or toxic to fertility based on data available for aluminium oxide.

15.6.2 *Hazard classification*

Sintered bauxite is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) and under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A15.4. These NICNAS recommendations do not consider physical or environmental hazards.

Table A15.4 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation/ corrosivity	Irritating to the respiratory system (X_i; R37)	May cause respiratory irritation – Specific target organ toxicity, single exposure-Cat. 3 (H335)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

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A16 Cristobalite, Quartz, Tridymite, Calcined silica

CAS No.	CAS Name
14808-60-7	Quartz (SiO_2)
14464-46-1	Cristobalite (SiO_2)
15468-32-3	Tridymite (SiO_2)
91053-39-3	Diatomite, calcined

16.1 Justification for group assessment

The silicon dioxide group represents a polymorphic category containing a large number of forms identical in composition but with different atomic arrangements. There are two sub-categories within this group: crystalline silica and amorphous silica. Quartz, cristobalite and tridymite are the three most common polymorphs of crystalline silica. They are metastable under ambient conditions - in a state of apparent equilibrium although capable of changing to a more stable state - and can be converted into other polymorphs upon heating. Quartz heated at 870 °C converts to trimydite, which when heated to 1470 °C, converts to cristobalite (IARC 1997).

Diatomite, calcined (CAS No. 91053-39-3), also known as calcined silica or calcined diatomaceous earth, is produced when naturally occurring amorphous silica (diatomaceous earth) is subjected to high temperature calcination at 800-1000 °C. Calcined silica belongs to the amorphous silica group, however, it is not available in a pure amorphous form; rather, it can contain up to 25% crystalline silica, mostly cristobalite, formed during the calcination process. Small amounts of quartz and tridymite and other impurities (alumina, ferric oxide and sodium, potassium and calcium oxides) have also been reported (OECD 2004).

Group assessment of the three forms of crystalline silica is justified based on the similarities in chemical composition, physico-chemical properties and human health hazards. Calcined silica, though amorphous in nature, has been assessed along with the crystalline forms as it contains substantial amounts of crystalline silicas as impurities, which are believed to influence the health effects of calcined silica.

16.2 Chemical identity

The following chemical identity information was obtained from National Institute of Occupational Safety and Health (NIOSH) (1997a, 1997b) and Health Canada (2011). Table A16.1 provides details of the chemical identity.

Table A16.1 Chemical identity

	Quartz	Cristobalite	Tridymite	Calcined silica
Synonyms	Crystalline silica Fibrous glass Crystalite	Sibelite Belcron	Christensenite	Kieselguhr, calcined Diatomaceous earth, calcined Diatomite, calcined
Structural formula	O = Si = O	O = Si = O	O = Si = O	O = Si = O
Molecular formula	SiO2	SiO2	SiO2	SiO2
Molecular weight	60.08	60.08	60.08	60.08
Appearance and odour	Colourless or white crystals. Many colored varieties are semiprecious stones	Colourless or white crystals	Colourless or white crystals	Pink or yellowish to dark brown powder or granules, odourless
SMILES notation	O=[Si]=O	O=[Si]=O	O=[Si]=O	O=[Si]=O

16.3 Physical properties

The following information on the physical properties was obtained from NIOSH (1997a, 1997b) and Health Canada (2011). The physical properties of the four forms of silica are presented in Table A16.2.

Table A16.2 Physical properties of the three crystalline silicas and the amporphous calcined silica

Property	Quartz	Cristobalite	Tridymite	Calcined silica
Melting point	1610 °C	1713 °C	1703 °C	No data
Boiling point	2230 °C	2230 °C	2230 °C	No data
Density	2.6 x 10^3 kg/m^3 at 20 °C	2.32 x 10^3 kg/m^3 at room temp.	2.28 x 10^3 kg/m^3 at room temp.	2.25 g/cc
Water solubility	Insoluble (temp. not indicated)	Insoluble (temp. not indicated)	Insoluble (temp. not indicated)	Negligible
Partition coefficient (log K_{ow})	Not relevant	Not relevant	Not relevant	Not relevant
Vapour pressure	Negligible	Negligible	Negligible	Negligible

16.4 Current regulatory controls

16.4.1 *Hazard classification for occupational health and safety*

Quartz, cristobalite and tridymite are listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2014a) as hazardous substances. Calcined silica is not listed in the HSIS.

The listing in the HSIS is due to exposure standards being assigned to these substances.

16.4.2 *Occupational exposure standards*

16.4.2.1 Australia

Time Weighted Average (TWA) occupational exposure standard of 0.1 mg/m³ for quartz, cristobalite and tridymite are recommended in Australia (Safework Australia 2013).

A Short-Term Exposure Limit (STEL) is not recommended for any of the compounds.

16.4.2.2 International

Occupational exposure limits for quartz, cristobalite and tridymite recommended by other countries are provided in Table A16.3 (Galleria Chemica 2013 and NIOSH (1997a, 1997b)).

Table A16.3 International operational exposure limits

Country	Exposure value	Exposure metric
Canada	0.025 mg/m³	TWA
France	0.05 mg/m^3	TWA
Japan	0.03 mg/m³	TWA
Sweden	0.05 mg/m^3	TWA
US (ACGIH)*	0.025 mg/m^3	Threshold limit value - TWA
US (NIOSH)**	0.05 mg/m^3	Recommended Exposure Limit - TWA
US (OSHA)***	0.1 mg/m^3	Permissible exposure Limit - TWA

**American Conference of Governmental Industrial Hygienists (ACGIH) **National Institute of Occupational Safety and Health ***Occupation Safety and Health Administration*

The US Department of Energy has designated the following Temporary Emergency Exposure Limits (TEEL) for the calcined silica (Galleria Chemica 2013), shown in Table A16.4.

Table A16.4 Temporary Emergency Exposure Limits (TEEL)

Substance	TEEL-0	TEEL-1	TEEL-2	TEEL-3	Units
Diatomaceous silica, calcined	0.3	0.9	1.5	500	mg/m^3

No other countries have exposure limits specifically for calcined silica.

16.4.3 *Australian food standards*

No Australian food standards have been identified for crystalline silica (quartz, cristobalite or tridymite).

16.4.4 *Australian drinking water guidelines*

The Australian Drinking Water Guidelines state: '*To minimise an undesirable scale build up on surfaces, silica (SiO_2) within drinking water should not exceed 80 mg/L*' (National Health and Medical Research Council (NHMRC) 2001).

16.4.5 *Additional controls*

16.4.5.1 Australia

In Australia crystalline silica is included in Schedule 10 (Restricted Hazardous Chemicals) and Schedule 14 (Hazardous Chemicals (other than lead) Requiring Health Monitoring) of the Safework Australia's Model Work Health and Safety Regulations (Safework Australia 2014b).

SafeWork Australia has also prepared guidelines for health monitoring of persons working with crystalline silica (Safework Australia 2013).

16.4.5.2 International

In Canada crystalline silica is included in the '*Designated Substances*' list under Regulation 845 of the Occupational Health and Safety Act, Canada (CCOHS 2014). The Canadian Workplace Hazardous Material Information System (WHMIS) has classified quartz as D2A - Very Toxic (Carcinogenicity).

16.5 Use

The use of these chemicals in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of Chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

16.6 Health hazard characterisation

The information on health hazards is obtained from the following comprehensive reviews of crystalline silica: IARC Monograph (1997, 2012), World Health Organisation (WHO) (2000), US Environmental Protection Agency (EPA) (1996), and Health Canada (2011). Unless otherwise noted, references to individual studies below are taken from these reviews.

16.6.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

16.6.1.1 Oral absorption

No data were available. Since silica is insoluble in water and particulate in nature, its absorption in the gastrointestinal tract is unlikely. Based on the physico-chemical properties of crystalline and calcined silica, a 0% oral absorption for the two forms of silica will be assumed for human health risk assessment.

16.6.1.2 Dermal absorption

Data on dermal absorption of crystalline silica or calcined silica are not available. Consistent with the oral absorption, based on the physico-chemical properties of the two forms of silica, a 0% dermal absorption will be assumed for human health risk assessment.

16.6.1.3 Inhalation absorption

Respirable size particles of silica (aerodynamic diameter of <5 µm) predominantly deposit and accumulate in the alveolar region of the lung and distribute throughout the lung and associated lymph tissue. Particles larger than 5 µm may be deposited in the tracheobronchial airways and cleared by ciliary movement of the epithelial cells lining the airways and thus do not reach the alveolar region (WHO 2000).

In an inhalation study in rats with silica of aerodynamic diameter 3.7 µm, more than 80% of the particles that deposited peripherally were found on the alveolar ducts and on the distal terminal bronchioles (IARC 2012). Particles deposited in the alveoli are engulfed by macrophages and then transported to the bronchioli or to the interstitial tissues and the lymphatic vessels (US EPA 1996).

Based on the above information, 100% absorption of silica by the inhalation route will be assumed for human health risk assessment.

16.6.1.4 Distribution

Following deposition of quartz in the mammalian lung, there is either rapid mucociliary clearance, if deposition is in the upper airways, or phagocytosis by alveolar macrophages and slower clearance if deposition is in the lung periphery. Silica particles, after deposition in the lung, can also penetrate the interstitium for phagocytosis by interstitial macrophages and be translocated to the lymph nodes of the lungs (IARC 2012).

Lungs of silicotic patients may contain up to one hundred times more crystalline silica than normal lungs. After a post-exposure period of about two to three months, most of the deposited silica aggregates in the proximal alveolar ducts and in the distal portion of the acini. Crystalline forms of silica are not distributed readily in other organs of the body. However, secondary evidence in humans indicates that some silica is transported to the kidneys of silicotic patients (US EPA 1996). Increased kidney weights and higher silicon deposits have been observed in the kidneys of these patients, up to eight times more in some patients compared to normal persons (US EPA 1996). No information is available on the distribution of silica to organ systems other than the kidneys.

16.6.1.5 Metabolism

Crystalline silica is poorly soluble and biopersistent. Silica itself is not metabolised in the body of an organism. Quartz is very slightly soluble in body fluids, forming silicic acid. Crystalline silica polymorphs also generate reactive oxygen species in the lungs that could be taken up by epithelial cells (WHO 2000).

16.6.1.6 Excretion

Data regarding the excretion of silica in laboratory animals and humans are limited. Silicic acid formed from quartz is readily excreted via the kidneys (King and McGeorge 1938). After respiratory exposure to silica particles, total silicon measured in urine can be attributed to particles dissolved either in the lung or in the gastrointestinal tract. The level of silicon in urine either after clearance from the lung or after ingestion has been shown to be influenced by the diet (IARC 1997). Some rodent ingestion studies found that 95% of silica is not

absorbed and is excreted in the faeces unmetabolised; 4% is excreted in urine, and 1% remains in tissues (FASEB 1979).

16.6.2 *Acute toxicity*

16.6.2.1 Oral, dermal and inhalation

No adequate acute oral, dermal or inhalation exposure studies are available for quartz, cristobalite or tridymite in experimental animals. Most acute toxicity studies for quartz or cristobalite were conducted using intratracheal instillation.

There is no specific human or animal information available on the acute or short-term effects of calcined diatomaceous earth. In general, exposure to high concentrations of dust may cause coughing and mild, temporary irritation (CCOHS 2001).

16.6.2.2 Intratracheal

Single intratracheal instillation of quartz caused inflammatory effects and formation of discrete silicotic nodules in rats, mice and hamsters (IARC 2012; WHO 2000). Other effects like oxidative stress, cellular proliferation and increases in water, protein, and phospholipid content of rat lungs, apoptosis (programmed cell death) and lung cancer were also noted.

In an acute dose study, rats were dosed once with 0, 0.75, 1.5, 3.0, 6.0 or 12 mg/kg bw quartz by intratracheal instillation (Seiler et al., 2001). Microscopically, increased fibrogenic structural changes in lung tissues and changes in surfactant phospholipid ratio in bronchoalveolar lavage fluid were observed at all concentrations 90 days after instillation.

In another study (Clouter et al. 2001), inflammatory response in rat lungs was observed at 0.75 mg/kg bw of quartz, examined three and 14 days after single intratracheal instillation of 0, 0.75 and 3 mg/kg bw quartz. No mortalities were noted in any of the studies for up to 12 mg/kg bw quartz (Health Canada 2011). The Lowest Observed Adverse Effect Level (LOAEL) of 0.75 mg/kg bw was derived from these studies.

Two other similar studies of single intratracheal instillation of quartz reported higher LOAELs in rats (3 and 40 m/kg bw) based on inflammation and fibrosis (Saffiotti et al. 1996).

16.6.2.3 Observations in humans

No data were available.

16.6.3 *Irritation / Corrosivity*

16.6.3.1 Skin and eye irritation

Studies on skin and eye irritation of crystalline silica are limited. The European Association of Silica Producers (EUROSIL) conducted studies on the skin and eye irritation potential of quartz and cristobalite (EUROSIL 2008). These studies were performed in compliance with United Kingdom Good Laboratory Practice (GLP) standards and were designed to meet the OECD Test Guideline (TG) 404 (Acute Dermal Irritation/Corrosion) and TG 405 (Acute Eye Irritation/Corrosion).

In these studies, quartz (coarse sand and flour) and cristobalite (coarse sand and flour) products found in the European Union (EU) market were tested. A single four-hour, semi-occluded application of the test material to the intact rabbit skin or instillation in the eyes of rabbits did not produce any signs of irritation (mean Draize scores were 0 for both

erythema and oedema formation in the skin test; and 0, 0, 0.3 and 0.1 for cornea opacity, iris lesion, redness and chemosis, respectively).

The study concluded that '*for the skin and eye irritation aspects, quartz and cristobalite do not meet the criteria for classification as dangerous substances according to EU Directive 67/548/EEC*' (EUROSIL 2008).

There is no human or animal information available of the skin and eye irritation potential of calcined diatomaceous earth. In general, the dust would probably be irritating as a '*foreign substance*', rather than through a chemical action. Some tearing, blinking and mild, temporary pain may occur as the solid material is rinsed from the eye by tears (CCOHS 2001).

16.6.3.2 Observations in humans

No acute, oral, dermal or inhalation effects of crystalline silica or calcined diatomaceous earth have been documented in humans.

16.6.4 *Sensitisation*

Information on skin sensitisation effects of crystalline silica (quartz, cristobalite or tridymite) or calcined diatomaceous earth is not available. However, based on the structure and physico-chemical properties, the three forms of crystalline silica or the calcined diatomaceous silica are not expected to cause skin sensitisation.

Acute toxicity data for quartz, cristobalite or tridymite are not available. These substances are not skin or eye irritants, although acute inhalation of dust may cause discomfort and stress as well as signs of local irritation to nasal, bronchiolar and ocular mucous membranes (OSHA 2013). Data on the skin sensitisation potential of these chemicals are not available. Based on the structure and physico-chemical properties, the three forms of crystalline silica are not expected to cause skin sensitisation. Information on the acute toxicity of calcined silica is not available.

16.6.5 *Repeat dose toxicity*

16.6.5.1 Oral

No data were available.

16.6.5.2 Dermal

No data were available.

16.6.5.3 Inhalation

Repeated inhalation exposure to crystalline silica is known to cause adverse effects.

Silicosis has been identified as the main non-cancer effect of silica exposure, although available epidemiologic data as well as animal data provide evidence for several other effects associated with silica exposure, such as silicotuberculosis, enlargement of the heart (cor pulmonale), interference with the body's immune system and damage to the kidneys (Health Canada 2011). The most frequently reported autoimmune diseases in crystalline silica exposed workers are scleroderma, rheumatoid arthritis, polyarthritis, mixed connective tissue disease, systemic lupus erythematosus, autoimmune haemolytic anaemia, and dermatopolymyositis.

All the short or long term repeated dose studies identified for quartz and cristobalite were conducted either by inhalation exposure or by intratracheal instillation.

Tridymite is rarely found in nature and rarely reported in the workplace (OSHA 2013).

The following key rodent data (Table A16.5) on repeat dose inhalation toxicity of crystalline silica (quartz and cristobalite) were summarised from Health Canada (2011) and IARC (2012).

Table A16.5 Repeat dose inhalation toxicity studies with crystalline silica

Test substance	Method	NOAEC/LOAEC	Remarks	Reference
Cristobalite, 0, 10 or 100 mg/m^3	CD rats; 6 h/d for 3 days	LOAEC = 10 mg/m^3	Elevated levels of granulocytes (approx 34%, mainly neutrophils) and elevated markers of cytotoxicity in lung lavage fluid at both doses. Effects were observed three months after exposure.	Warheit et al. 1995
Quartz, 100 mg/m^3	Rats; 6 h/d for 3 days	not established (only one dose)	Lesions in lungs were observed within one month. Two months after exposure, the lesions had progressed and developed into a multifocal, granulomatous-type pneumonitis.	Warheit and Hartsky 1997
Cristobalite 10 and 43 mg/m^3	C3HHeN mice; 9 days	LOAEC = 10 mg/m^3	Minimal degree of interstitial thickening, accumulations of mononuclear cells and slight lymphoid tissue hypertrophy at both doses.	Davis et al. 1998
Cristobalite 0, 0.1. 1.0 or 10 mg/m^3	Rats; 4 weeks	LOAEL= 1 mg/m^3 NOAEC= 0.1 mg/m^3	Elevated levels of granulocytes and cytotoxicity markers (LDH and β-glucuronidase) were observed at 1 mg/m^3 and higher.	Henderson et al. 1995
Quartz 5 mg/m^3	Female Balb/c mice; 6 h/d, 5 days/week for 3 and 9 weeks	Not established (only one dose used)	No treatment related effects in mice exposed to approximately 5 mg/m^3 of Min-U-Sil 5 (quartz).	Burns et al. 1980
Cristobalite 3 mg/m^3	Rats; 6 h/d, 5 days/week, 13 weeks	Not established (only one dose used)	Inflammation of the lung and changes in bronchoalveolar lavage fluid markers of lung injury were noted. Oxidative DNA damage in lung tissue.	Johnston et al. 2000
Quartz 5 mg/m^3	Female Balb/c mice; 6 h/d, 5 days/week for 15 and 27 weeks	Not established (only one dose used)	Increased spleen weight and an increased response to *E. coli* (i.e. formation of plaque forming cells in the spleen).	Burns et al. 1980

Test substance	Method	NOAEC/LOAEC	Remarks	Reference
Quartz 0, 2, 10, and 20 mg/m^3	F344 rats; 6 h/d, 5 days/week for 6 months	LOAEC= 2 mg/m^3	Virtually all lung functional parameters were significantly affected by silica, tissue proliferation and fibrogenesis and lipoproteinosis.	Drew and Kutzman 1984
Quartz 0, 3 mg/m^3	Syrian hamsters; 6 h/d, 5 days/week for 78 weeks	LOAEC= 3 mg/m^3	Increased relative lung weight, chronic pulmonary inflammation and slight interstitial fibrosis, changes in the lung associated lymph nodes.	Muhle et al. 1998
Quartz 0-1 mg/m^3	F344 rats; 6 h/d, 5 days/week for 24 months	LOAEC= 0.74 mg/m^3	Lipoproteinosis, multifocal fibrosis, inflammatory cell infiltrate and alveolar hyperplasia.	Muhle et al. 1991

A number of animal studies have found that cristobalite is more toxic to the lung than quartz, and more tumorigenic (e.g., King et al. 1953; Wagner et al. 1980). However, several other authors concluded that this is not the case (Bolsaitis and Wallace 1996; Guthrie and Heaney 1995). OSHA (2013) has examined evidence on the comparative toxicity of the silica polymorphs (quartz, cristobalite, and tridymite) and found no difference in toxicity effects between cristobalite and quartz. Furthermore, no difference in toxicity between cristobalite and quartz has been observed in epidemiologic studies (NIOSH 2002). No studies on tridymite have been reported.

There is no information on the repeat dose oral, inhalation or dermal effect of calcined silica. However, since calcined diatomaceous earth contains varying amounts of crystalline silica in the form of cristobalite, and may also contain small amounts of quartz and tridymite, it is expected that any long-term health hazards associated with diatomaceous earth would mainly be due to the effects of crystalline silica.

16.6.5.4 Observations in humans

Silica-related health effects are most commonly detected among active or retired workers in industries such as (USEPA 1996):

- brick, tile and clay production
- cement production
- quarrying and tunnelling
- abrasives and blasting
- sandblasting diatomaceous earth calcining; foundry work
- glass making
- metal ore mining and milling
- and synthetic mineral fibers production.

The most prevalent effect identified from long term exposure in these occupational settings is silicosis, a diffused nodular pulmonary fibrosis (US EPA 1996).

Chronic silicosis is the most common fibrotic lung disease arising after 10 or more years' employment at low dust concentrations (US EPA 1996). Acute silicosis, a highly fatal disease, results from intense and significant overexposure to respirable-sized, high silica-content dust over a short time. Actute silicosis is the reaction of the lung to acute dust injury, resulting in the filling of air spaces with fluid containing lipid-rich protein debris from fractured cells in the respiratory tract. Clinically, the condition is similar to pulmonary edema and includes shortness of breath, with fluid accumulations in the upper and middle areas of the lungs (US EPA 1996). Table A16.6 provides some key studies in workers exposed to silica in the mining industry (adapted from Health Canada 2011).

Table A16.6 Silicosis in workers exposed to silica in the mining industry

Study description	LOAEC	Reference
Cross sectional study to investigate the prevalence of silicosis in mine workers. Chest photographs of 520 miners in South African goldmines were taken. The mean length of service of the subjects was 22 years. The mean intensity of respirable quartz exposure was 0.053 mg/m^3. The prevalence of silicosis among the miners was 18.3 to 19.9%. Silicosis prevalence increased significantly with increasing length of service.	0.053 mg/m^3	Churchyard et al. (2004)
Cohort study of 3330 United States. gold miners with an average exposure to underground silica for nine years. Silicosis was identified through death certificates or chest X-rays taken during two cross-sectional surveys in 1960 and 1976. Silica content in the respirable dust in the mine was estimated at 13%. The median crystalline silica exposure was 0.05 mg/m^3, and 170 cases of silicosis were identified.	0.05 mg/m^3	Steenland and Brown (1995)
Community population-based random sample survey of 134 males. Group included previous mining workers (100) and people who never worked in mining (34, used as an internal control group). Silicosis was defined as subjects with a median radiologic profusion of small opacities with profusion of ≥1/0. Average silica exposure was estimated at 0.064 mg/ m3. Prevalence of silicosis was 32%. Threre were no abnormal chest radiographs in the control group (34 people with no dust exposure). Silicosis prevalence rate has a strong positive correlation with cumulative silica exposure, mean silica exposure, duration of exposure and the time since last silica exposure.	0.064 mg/m^3	Kreiss and Zhen (1996)

Several epidemiologic studies conducted on silica-exposed workers reported statistically significant increases in cases of emphysema, bronchitis, autoimmune diseases and renal failure compared to the general population (OSHA 2013). Chronic renal disease observed in workers exposed to crystalline silica is believed to be due to adverse effects on the immune system following silica exposure (Steenland and Brown 1995).

The US EPA (1994) calculated the human equivalent concentrations (HECs) for LOAELs for non-cancer effects obtained in subchronic (3 months) and chronic inhalation studies in rats and mice. The results varied widely - from 0.18 mg/m^3 (based on rat study) to 0.90 mg/m^3 (based on mouse study). These calculations are based on a series of empirical equations that estimate fractional deposition of relatively insoluble particles and adjust for dosimetric differences between species by incorporating normalising factors such as body weight or surface area (US EPA 1994).

Exposure–response models based on cumulative exposure data were developed that could provide predictions of silicosis risk for exposure to silica over a period of time. Using data from various cross-sectional epidemiological studies, the models predicted the occurrence of at least two cases of radiographic silicosis per 100 workers (silicosis prevalence varied between 2 to 90%) at cumulative respirable quartz dust exposures of 0.05 or 0.10 mg/m^3 over a 45-year working lifetime (WHO 2000).

Based on the above information and the data from human studies (Table A16.6), a LOAEC of 0.05 mg/m^3 for silicosis will be used for human risk assessment for non-carcinogenic effects of crystalline silica.

Information on the short-term exposure effect of calcined silica in humans is not available. However, as mentioned earlier, since calcined diatomaceous earth contains varying amounts of crystalline silica, it is expected that any long-term health hazard associated with diatomaceous earth would mainly be due to the effects of crystalline silica.

A number of studies have observed X-ray evidence of scarring of the lungs (silicosis/progressive fibrosis) in employees in the diatomaceous earth mining and processing industry, who were exposed to both calcined and uncalcined diatomaceous earth. However, these effects were generally attributed to the cristobalite content of the dust, which can be present at up to 25% concentration in diatomaceous earth silica, and which is confirmed to elicit these effects (CCOHS 2001).

Other cases of advanced silicosis and silicosis with tuberculosis have been observed in workers occupationally exposed to airborne dust containing 80% calcined diatomaceous earth (in the manufacturing of filter candles) for more than one year (CCOHS 2001). The long-term health hazard associated with diatomaceous earth is mainly dependent on its cristobalite content.

16.6.6 *Genotoxicity*

There have been mixed results with mutagenicity studies with quartz, cristobalite and tridymite. In many *in vitro* and *in vivo* tests, quartz, cristobalite and tridymite tested positive for mutagenicity, while in other tests, especially the standard bacterial mutagenecity and chromosomal aberration (aneuploidy and polyploidy) assays, these three crystalline silicas tested negative (IARC 1997). Chromosomal changes, including DNA damage, have been observed in experimental systems, both *in vitro* and *in vivo*. Although the results of some studies demonstrated that quartz caused damage to isolated DNA (strand breakage) in acellular systems, the relevance of these assays to assess quartz-related genetic effects *in vivo* was '*questionable*' (IARC 1997). Uncertainties were expressed because the non-physiological experimental conditions did not apply to intracellular silica exposure and because very high doses of silica were used in the DNA breakage assays (IARC 1997).

Liu et al. (1996) applied experimental conditions (Chinese hamster lung fibroblasts challenged with dusts pre-treated with a phospholipid surfactant) to simulate the condition of particles immediately after deposition on the pulmonary alveolar surface. Results of the experiments showed that untreated Min-U-Sil 5 and Min-U-Sil 10 induced micronucleus formation in a dose-dependent manner, but surfactant pre-treatment suppressed that activity (Liu et al. 1996).

Tridymite (87.9% of particles with diameter <1 µm) was reported to significantly increase the number of sister chromatid exchanges in co-cultures of human lymphocytes and monocytes, while results were less reproducible for quartz (IARC 1997).

A study of DNA strand breakage with quartz, cristobalite and tridymite samples showed the following gradient of toxicity when using a similar surface area of particles: quartz >cristobalite >tridymite (IARC 1997). DNA damage was affected by the presence of oxygen and was accelerated by sulfur-oxide dismutase and hydrogen peroxide. DNA damage was blocked by catalase and by free-radical-scavenging agents (dimethyl sulfoxide and sodium benzoate), supporting the viewpoint that it is the presence of radicals generated in response to quartz and cristobalite that causes the DNA damage, and not quartz or cristobalite themselves.

Similarly, hypoxanthine-guanine phosphoribosyl transferase (HPRT) mutation assays both *in vitro* and *in vivo* were positive in response to quartz (Driscoll et al. 1997). The positive results *in vivo* were seen only in the presence of significant inflammatory responses in the treated animals. In *in vitro* assays, addition of catalase (an enzyme which inactivates H_2O_2) before incubation inhibited the increase in HPRT mutation.

Some studies have demonstrated the ability of quartz to induce micronuclei in pulmonary alveolar macrophages of male Wistar rats in a time (Leigh et al. 1998) and dose-dependent manner (Wang et al. 1997). However, in other *in vitro* studies no chromosomal aberration (Oshimura et al. 1984) or HPRT gene mutation (Driscoll et al. 1997) were observed.

Pairon et al. (1990) tested quartz particles for their ability to induce a significant number of sister chromatid exchanges in cultures of human lymphocytes plus monocytes, or of human purified lymphocytes. The results were not '*clear cut'* for any of the three doses tested (i.e. 0.5, 5.0, and 50 µg/cm2) (Pairon et al. 1990).

In summary, conflicting results have been reported in genotoxicity studies with crystalline quartz or cristobalite, and a direct genotoxic effect for crystalline silica has not been confirmed or ruled out. Studies on genotoxicity of calcined diatomaceous silica are not available.

Based on these observations, it is concluded that further studies are required for crystalline silica to be classified as genotoxic.

16.6.7 *Carcinogenicity*

There is extensive data on the carcinogenic effects of crystalline silica, both from animal and human epidemiological studies investigating the link between crystalline silica exposure and cancer. The International Agency for Research on Cancer (IARC) identified more than 50 epidemiological studies on lung cancer from occupational exposure to dust containing respirable crystalline silica (IARC 1997, 2012).

The strongest evidence supporting the carcinogenicity of crystalline silica in the lung comes from pooled and meta-analyses of available data. Such analyses, despite their reliance on different studies, not only confirmed an overall effect of crystalline silica dust exposure in lung cancer but also demonstrated a clear exposure–response relationship (IARC 2012). The IARC concluded that crystalline silica is a confirmed human carcinogen based largely on nine studies of cohorts in four industry sectors that were considered to be least influenced by confounding factors. Sectors included (IARC 2012):

- gold mining, quarries and granite works
- ceramic/pottery/refractory brick industries
- the diatomaceous earth industry.

From analyses of numerous epidemiology studies, it was noted that lung cancer tended to increase with the following parameters (Health Canada 2011):

- cumulative exposure
- duration of exposure
- peak intensity of exposure
- presence of silicosis.

The United States Occupational Safety and Health Administration (OSHA) conducted an independent review of the epidemiological literature on exposure to respirable crystalline silica and lung cancer, covering more than 30 occupational groups (OSHA 2013). Approximately 60 primary epidemiological studies were reviewed, which also included a large national death certificate study, two national cancer registry studies, six meta-analyses and a pooled case-control study. Based on its review, OSHA (2013) concluded that the human data provided ample evidence that exposure to respirable crystalline silica increases the risk of lung cancer among workers. The strongest evidence, according to OHSA, came from the worldwide cohort and case-control studies reporting excess lung cancer mortality among workers exposed to respirable crystalline silica dust in various industrial sectors. These included the granite/stone quarrying and processing, industrial sand, mining, and pottery and ceramic industries. Other studies, including a clinic-based pooled case-control analysis of seven European countries by Cassidy et al. (2007), and two national death certificate registry studies in Finland (Pukkala et al. 2005) and the United States (Calvert et al. 2003), also support the findings from the cohort and case-control analysis (OSHA 2013).

OSHA (2013) also concluded that the available data do not support the hypothesis that the development of silicosis is necessary for silica exposure to cause lung cancer. Early steps in the proposed mechanistic pathways that lead to silicosis and lung cancer seem to share some common features resulting in the suggestion that silicosis is a prerequisite to lung cancer. It was also suggested that the increased lung cancer risk associated with silica maybe a consequence of the inflammation (and concomitant oxidative stress) and increased epithelial cell proliferation associated with the development of silicosis. However, other researchers have noted that other key factors and proposed mechanisms, such as direct damage to DNA by silica, inhibition of tumour suppressor protein p53, loss of cell cycle regulation, stimulation of growth factors, and production of oncogenes, may also be involved in carcinogenesis induced by silica (OSHA 2013). Other studies have found increased lung cancer risk among exposed workers who had no radiological evidence of silicosis (Checkoway et al. 1999). Checkoway and Franzblau (2000), in reviewing the international literature, found all epidemiological studies conducted to that date were insufficient to conclusively determine the role of silicosis in the etiology of lung cancer.

Kurihara and Wada (2004) studied the link between silica, silicosis and lung cancer. Over 50 epidemiology studies carried out between 1966 and 2001 were selected and pooled according to the type of study and the parameter being linked to lung cancer (i.e. silica exposure, presence of silicosis in subjects). Meta-analysis of the studies has indicated pooled risk ratios of 1.32 for crystalline silica exposure, 2.37 for individuals determined to have silicosis, and 0.96 for individuals with no evidence of silicosis even after exposure to silica. These results highlight the fact that silicosis has a stronger temporal relationship with crystalline silica exposure and support the hypothesis that this could be a preliminary stage in the development of cancer.

A more recent case-control study of nearly 6000 individuals investigated exposure–response relationships for lung cancer in relation to silica exposure, adjusted for smoking and occupational confounders (Cassidy et al. 2007). The results clearly showed trends of increasing risk of lung cancer with increasing cumulative exposure to silica, and with duration of exposure. The results are consistent with a causal interpretation of the association

between exposure to silica and lung cancer. However, the authors could not draw any conclusions on the role of silicosis in this causal pathway.

According to the Scientific Committee on Occupational Exposure Limits (SCOEL) there is evidence that the incidence of lung cancer increases with increasing cumulative exposure to respirable crystalline silica dust and that the relative lung cancer risk is increased for persons with silicosis. The studies differ with respect to exposure levels and durations, with respect to the type of crystalline silica and also the occupational cofounders (SCOEL 2003).

The positive results from human data were also supported by studies conducted in experimental animal models where clear and consistent increases in lung tumours have been noted after chronic inhalation exposure (Health Canada 2011). Studies of the carcinogenicity of crystalline silica have shown quartz dust to be a lung carcinogen in rats following inhalation, but not in mice or hamsters (Mauderly 1996). Rats are known to be more sensitive than mice or hamsters to induction of lung tumours (Mauderly et al. 1994).

In inhalation studies with treatment-related tumours, crystalline silica (quartz or cristobalite) doses ranged from 1 to 50 mg/m^3 and duration of exposure ranged from 29 days to two years (Health Canada 2011). For the intratracheal instillation studies, doses ranged from 4 to 57 mg/kg bw. Exposure regimes were diverse and included single instillation to weekly instillation for 10 weeks, with observation for up to two years post-exposure. The most common tumours reported across the long term rat studies were adenocarcinomas. Squamous-cell carcinoma, alveolar carcinoma and bronchiole-alveolar adenoma were also reported in some studies, and all animals that developed tumours also showed some degree of fibrosis

In a low dose exposure study, groups of 50 rats per sex were exposed six hours/day, five days/week for 24 months to filtered air or 1 mg/m^3 of quartz through whole-body exposure (Muhle et al. 1989). In the exposed group, 18 animals developed tumours (12 females, six males). The majority (10/18) of the tumours observed were adenocarcinomas. The mean mass of particle at the end of the exposure period was 0.91 mg/lung. In a group of 50 animals exposed to 5 mg/m^3 of titanium dioxide as positive controls, only three exhibited tumours.

Although most carcinogenicity studies are from inhalation exposure, quartz-induced lymphoma incidence was also increased in several experiments in rats following intrapleural administration, and in one study in mice after subcutaneous administration (IARC 2012). Cristobalite-induced lymphomas were observed in one experiment.

In a carcinogenicity study, rats received a single intratracheal instillation of 12 or 20 mg quartz and 12 mg of cristobalite, suspended in saline (Saffiotti et al. 1992). Rat lungs showed a clear progression of effects starting with an initial inflammatory response leading to a marked hyperplasia and hypertrophy of alveolar cells after one month. At six months hyperplasia was evident and at 11 months after instillation lung tumours were observed with a 17% and 42% incidence in males and females, respectively. Seventeen months after instillation, incidences of lung tumour were 32% in male rats and 59% in females. No lung tumours were found in ferric oxide treated rats (negative controls).

In a carcinogenicity study with three different strains of mice, 10 mg/mL tridymite, instilled intratracheally failed to produce any treatment-related tumours (IARC 1997). However, in another study, a single intra-thoracic injection of 10 mg/animal tridymite in saline in Marsh mice produced lesions considered as *'lymph node reactive hyperplasia simulating malignancy*'. The differences between the tridymite-treated and saline-only treated mice were highly statistically significant (Bryson et al. 1974).

IARC (2012) concluded that there is sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources. There is sufficient evidence in experimental animals for the carcinogenicity of quartz and cristobalite.

The IARC has also concluded that inhaled crystalline silica in the form of cristobalite or quartz from occupational sources is carcinogenic to humans (Group 1) (IARC 2012). There is limited evidence in experimental animals for the carcinogenicity of tridymite.

The United States National Toxicology Program classified crystalline silica of respirable size as 'known to be a human carcinogen' (NTP 2011). The basis for this classification is sufficient evidence from human studies indicating a causal relationship between exposure to respirable crystalline silica in the workplace, and increased lung cancer rates in workers. While the mode of induction of lung tumours is not fully elucidated, sufficient data exists to demonstrate that a threshold approach to risk characterisation is appropriate (NTP 2011).

16.6.7.1 Conclusion

In summary of the previous discussion, evaluation of the available data on carcinogenic effects of crystalline silica indicates that crystalline silica induces tumours in lungs. Several epidemiological studies provide evidence for an association between occupational exposure to crystalline silica and lung cancer. Most of the studies that have been able to quantify exposure also provide evidence for an exposure–response relationship between crystalline silica and lung cancer. Steenland et al. (2001) have demonstrated strong evidence for an exposure–response relationship between crystalline silica and lung cancer risk in a pooled analysis of 10 cohort studies of occupationally exposed workers. The Cassidy et al. 2007 study not only demonstrated an overall positive association, but also strong evidence for an exposure–response relationship. Based on these observations it is concluded that there is sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources.

Information on the carcinogenic effects of pure calcined diatomaceous earth is not available. However, since calcined diatomaceous earth contains varying amounts of crystalline silica in the form of cristobalite and quartz, risk of carcinogenicity exists from exposure to calcined diatomaceous earth.

16.6.8 *Reproductive and developmental toxicity*

Data on the reproductive and developmental effects of quartz, cristobalite or tridymite in laboratory animals are not available. Due to their practically low solubility it is unlikely that the three forms of silica would be bioavailable to cause any specific effects at the reproductive and developmental level.

No developmental toxicity studies are available for calcined silica.

16.6.9 *Other health effects*

No data were available.

16.7 Health hazard summary

16.7.1 *Critical health effects*

In summary for this chapter, acute oral, dermal and inhalation toxicity data for quartz, cristobalite, tridymite or calcined diatomaceous earth are not available. The substances are

not skin or eye irritants, although acute inhalation of dust may cause discomfort and stress as well as signs of local irritation to nasal, bronchiolar and ocular mucous membranes. Data on the skin sensitisation potential of these chemicals are not available. Based on the structure and physico-chemical properties, the three forms of crystalline silica or the calcined diatomaceous earth are not expected to cause skin sensitisation.

Data on oral and dermal repeat dose toxicity of silica are not available. In experimental animals repeated inhalation and intratracheal exposure to crystalline silica induced inflammation, elevated levels of granulocytes and cytotoxicity of lung tissue. In humans the main critical non-neoplastic effects of crystalline silica are silicosis, silicotuberculosis, enlargement of the heart (cor pulmonale), interference with the body's immune system and damage to the kidneys. The most frequently reported autoimmune diseases in crystalline silica exposed workers are scleroderma, rheumatoid arthritis, polyarthritis, mixed connective tissue disease, systemic lupus erythematosus, autoimmune haemolytic anaemia, and dermatopolymyositis. A LOAEC of 0.05 mg/m^3 for crystalline silica was established in humans based the incidence of silicosis in mine workers exposed to crystalline silica.

Results of genotoxicity studies on crystalline silica conflict and a direct genotoxic effect for crystalline silica has not been confirmed or ruled out. Data on reproductive and developmental parameters are not available.

There is extensive data on the carcinogenic effects of crystalline silica, both from animal and human epidemiological studies investigating the link between crystalline silica exposure and cancer. The International Agency for Research on Cancer (IARC) identified more than 50 epidemiological studies on lung cancer from occupational exposure to dust containing respirable crystalline silica.

Based on the evaluation of the epidemiological data it is concluded that inhalation exposure to crystalline silica results in lung cancer. This conclusion is also supported by animal studies in which inhalation and intratracheal exposure to crystalline silica resulted in lung tumours. The most common types of lung tumour observed in rats were lung adenocarcinomas.

16.7.2 *Hazard classification*

Crystalline silica in the form of quartz and cristobalite is recommended by NICNAS to Safe Work Australia for classification and labelling under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) and adopted *Globally Harmonised System* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A16.7. There is insufficient data for tridymite and calcined silica for classification. These NICNAS recommendations do not consider physical or environmental hazards.

Table A16.7 Hazard classification recommended by NICNAS to Safe Work Australia for quartz and cristobalite

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Repeat dose toxicity	Danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)	Causes damage to organs through prolonged or repeated exposure [inhalation] Cat. 1 (H372)
Carcinogenicity	May cause cancer by inhalation, Cat. 1 (T; R49)	May cause cancer by inhalation, Cat. 1A (H350)

[a] *Approved Criteria for Classifying Hazardous Substances (NOHSC 2004);* [b] *Globally Harmonised System (UNECE 2009)*

Mixtures containing the chemical are classified as hazardous based on the concentration (Conc) of the chemical in the mixtures. The NICNAS recommended risk phrases for mixtures containing the chemical are:

- Safe work Australia (2013) Approved Criteria:
  - Conc ≥0.1%: T; R49 (Toxic: May cause cancer by inhalation)
  - 1% ≤Conc <10%: T; R49, R48/20 (Toxic: May cause cancer by inhalation, danger of serious damage to health by prolonged exposure through inhalation)
  - Conc ≥10%: T; R49, R48/23; (Toxic: May cause cancer by inhalation, danger of serious damage to health by prolonged exposure through inhalation).
- GHS (2009) classification:
  - Conc ≥0.1%: H350 (May cause cancer by inhalation (Cat. 1A))
  - 1% ≤Conc <10%: H350, H373; (May cause cancer by inhalation (Cat. 1A), may cause damage to organs through prolonged or repeated exposure (inhalation) (Cat. 2))
  - Conc ≥10%: H350, H372 (May cause cancer by inhalation (Cat. 1A), causes damage to organs through prolonged or repeated exposure (inhalation) (Cat. 1)).

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A17 MEA polyborate

CAS No.	CAS Name
26038-87-9	Boric acid (H_3BO_3), compd. with 2-aminoethanol (1:?)

17.1 Chemical identity

The following chemical identity information was obtained from ChemID*plus* (2012) and Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH 2013a). Table A17.1 provides details of the chemical identity.

Boric acid, 2-aminoethanol is considered to be a substance of Unknown or Variable composition, Complex reaction products or Biological materials (UVCB). As boric acid can form mono-, di- and tri-esters and / or mono-, di- and tri-amides ($C_2H_7NO.BH_3O_3$ and $C_2H_7NO.2BH_3O_3$, and $C_2H_7NO.3BH_3O_3$), all three may be present in the product. In addition, boric acid readily forms oligomers in solution, hence the use of the term polyborate. The substance represents a range of compositions, all broadly similar, but with varying ratios of monoethanolamine (MEA) to boric acid in the salt (Alkanolamine Borates Consortium 2013).

Table A17.1 Chemical identity

	MEA polyborate
Synonyms	MEA polyborate Boric acid, 2-aminoethanol salt; Monoethanolamine, boric acid salt
Structural formula	
Molecular formula	$C_2H_7NO.xBH_3O_3$
Molecular weight	123 (MEA-polyborate 1:1 molar ratio)
Appearance and odour	Clear, colourless liquid
SMILES notation	OB(O)O.NCCO

The molar ratio of boric acid to ethanolamine in the substance is unknown (US EPA 2013). Moreover, boric acid – MEA mixtures are often prepared by industry to suit their needs and therefore may not have the same composition as that which is available commercially.

When boric acid is dissolved in an alcohol at neutral or alkaline pH, rather than the formation of simple amine salts of boric acid, borate esters of the type $(HO)_2BOR$, $HOB(OR)_2$, and $B(OR)_3$ are formed, where R is an alcohol, alcoholamine etc. These are well-characterised compounds that are manufactured as commercial products and exist as a significant fraction of the MEA-borate systems. Moreover, the depiction of MEA polyborate as a salt of the borate mono-anion is also inaccurate since this borate does not exist alone in solution but is always present together with the well-known tetraborate and pentaborate anions (Alkanolamine Borates Consortium 2013).

The chemical is referred to as MEA polyborate in the report.

17.2 Physical properties

The information on the physical properties of MEA polyborate in Table A17.2 was obtained from REACH (2013a).

Table A17.2 Physical properties

Property	Value
Boiling point	>200 °C
Density	1.35 kg/m^3 at 20 °C
Vapour pressure	Not available
Water solubility	Miscible with water
Partition coefficient n-octanol/water (log K_{ow})	Not available (not possible due to complex nature of polyborate mixture)

17.3 Current regulatory controls

17.3.1 *Hazard classification for occupational health and safety*

MEA polyborate is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

17.3.2 *Occupational exposure standards*

No exposure standards have been established for MEA polyborate in Australia or other countries.

17.3.3 *Australian food standards*

No Australian food standards were identified (Food Standards Australia New Zealand 2013).

17.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values exist specifically for MEA polyborate. However, the guidelines note that boron in the environment is likely to be predominantly in the form of boric acid and that based on health considerations, the concentration of boron in drinking water should not exceed 4 mg/L (National Health and Medical Research Council (NHMRC) 2011).

17.3.5 *Additional controls*

17.3.5.1 Australia

MEA polyborate is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

17.3.5.2 International

According to the European Commission Cosmetics Directive Annex III (List of Restricted Substances), restrictions exist for boric acid, borates and tetraborates for certain types of cosmetic products in the European Community (European Commission 2013).

- The maximum concentration for boric acid, borates and tetraborates in talc cosmetic products is 5% (as boric acid). These are not to be used in products for children under three years of age and not to be used on peeling or irritated skin if the concentration of free soluble borates exceeds 1.5% (as boric acid).
- For oral cosmetic products, the maximum concentration is 0.1% (as boric acid). These are not to be used in products for children under three years of age.
- For other cosmetic products, the maximum concentration is 3% (as boric acid). These are not to be used in products for children under three years of age and not to be used on peeling or irritated skin if the concentration of free soluble borates exceeds 1.5% (as boric acid).

17.4 Use

The use of MEA polyborate in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

17.5 Health hazard characterisation

The information on health hazards is obtained from REACH dossiers on the chemical (REACH 2013a). Unless otherwise noted, references to individual studies below are taken from these sources.

Limited toxicity data exist for MEA polyborates. The toxicity studies available for MEA polyborate were conducted with either 1:1 or 1:3 MEA-polyborates). Both the 1:1 and 1:3 MEA-polyborates and ratios in between are complex mixtures of ethanolamine ($HO(CH_2)2NH_3^+$) salts borate esters, structures where the free electrons of the NH_2 amino moiety take part in cyclisation and various polyborates (Table A17.3). The various components of the mixture exist in rapid equilibrium (Alkanolamine Borates Consortium 2013).

Table A17.3 MEA polyborate composition

Ratio	MEA (%)	Borate (%)	Water (%)	pH
1:1	35	35	30	10.7
1:3	20	60	20	8.0

Source: Caleb Management Services Ltd (2013), pers comm. 24 October

For endpoints with no data for MEA polyborates data were read across from '*boric acid reaction products with ethanolamine and triethanolamine (CAS No. 68512-53-8)*' as this compound, like MEA-polyborate, is a reaction product of boric acid with alcoholamines (monoethanolamine and triethanolamine) and is expected to have similar toxicological properties. In addition, some amount of MEA polyborate may also be present in this reaction product due to the reaction between boric acid and monoethanolamine.

Moreover, since MEA polyborate is likely to break down in the body at physiological pH into boric acid and monoethanolamine, according to the following equilibrium equation, toxicity studies of boric acid and ethanolamine were also considered (Belien et al. 2009).

The equilibrium equation is:

$$H_3BO_3(aq) + MEA + H_2O \leftrightarrow [B(OH)_4]^- [H_3NCH_2CH_2OH]^+$$

Accordingly, the data gaps for the MEA polyborate are read across from the data of '*boric acid reaction products with ethanolamine and triethanolamine (CAS No. 68512-53-8)*', ethanolamine and boric acid. Information available for the selected chemicals is presented in Table A17.4.

Table A17.4 Summary of available toxicity endpoint data

	MEA Polyborate (CAS No. 26038-87-9)	**Boric acid reaction products with ethanolamine and triethanolamine (CAS No. 68512-53-8))**	**Ethanolamine (CAS No. 141-43-5)**	**Boric acid (CAS No. 10043-35-3)**
Acute oral toxicity	✓	×	✓	✓
Acute dermal toxicity	×	✓	✓	✓
Acute inhalation toxicity	×	×	✓	✓
Skin irritation	✓	×	✓	✓
Eye irritation	✓	×	✓	✓
Respiratory irritation	×	×	✓	✓
Skin sensitisation	×	✓	✓	✓
Respiratory sensitisation	×	×	×	×
Repeat dose toxicity (oral)	×	✓	×	✓
Repeat dose toxicity (dermal)	×	×	×	×
Repeat dose toxicity (inhalation)	×	×	✓	×
Genotoxicity	✓	✓	✓	✓
Carcinogenicity	×	×	✓	✓
Reproductive toxicity	×	×	✓	✓

✓Existing data point; × Missing data point

17.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

17.5.1.1 Oral, dermal and inhalation absorption

Information on oral, dermal and inhalation absorption of MEA polyborate is not available.

In the absence of available data, 100% absorption is taken for each route of exposure.

17.5.1.2 Distribution

No information available.

17.5.1.3 Metabolism

Information on MEA polyborate metabolism is not available. As mentioned above, MEA polyborate is likely to break down in the body into boric acid and monoethanolamine.

Boric acid is not metabolised in either animals or humans due to the high energy level required to cleave the B-O bond (Emsley 1989). Studies of inhalation and oral exposures of animals and humans to borates have consistently only reported recovery of the parent borate in the blood, tissues, and urine (Culver et al. 1994).

The main metabolic pathway for ethanolamine in rats involves its incorporation into phospholipids, presumably via exchange with serine in phosphatidylserine, resulting in the formation of phosphatidylethanolamine. It has been suggested that the incorporation of ethanolamine into phospholipids occurs via the CDP-ethanolamine pathway or by a base-exchange reaction (Massarelli et al. 1986).

17.5.1.4 Excretion

Information on the excretion of MEA polyborate is not available. Boric acid is excreted unchanged in the urine. The major route of elimination of ethanolamine is through urine. Forty per cent of ^{15}N-labeled ethanolamine administered to rabbits was excreted as urea within 24 hours, suggesting that ethanolamine is deaminated in the body (ACGIH 2005).

17.5.2 *Acute toxicity*

17.5.2.1 Oral

In an acute oral toxicity study conducted in rats according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 420, 300 mg/kg bw and 2000 mg/kg bw MEA polyborate were administered to Sprague-Dawley rats by gavage (REACH 2013a). The rats were observed for 14 days. The chemical was practically non-toxic to the animals. The median lethal dose (LD50) was determined to be above 2000 mg/kg bw.

Based on the available research, MEA polyborate has low acute oral toxicity.

17.5.2.2 Dermal

Acute dermal toxicity studies with MEA polyborate are not available.

In one dermal toxicity study, a structurally related compound, Boric acid (H_3BO_3) reaction product with ethanolamine and triethanolamine (CAS No. 68512-53-8), was applied to male and female rats at a dose of 2000 mg/kg bw (application details not available) (REACH 2013b). The rats were observed for two weeks. No deaths occurred during the observation period. Based on the results obtained in this study the dermal LD50for male and female rats was greater than 2000 mg/kg bw. Boric acid and ethanolamine have low acute dermal toxicity (see Sections A1.6.2.2 and A14.5.2.2).

Based on available research, MEA polyborate is considered to have low acute dermal toxicity.

17.5.2.3 Inhalation

No information available. Boric acid and ethanolamine have low acute inhalation toxicity (see Sections A1.6.2.3 and A14.5.2.3).

17.5.2.4 Observation in humans

No information is available.

17.5.3 *Irritation / Corrosivity*

17.5.3.1 Skin irritation

In a skin irritation study conducted according to European Economic Community (EEC) Annex V guidelines, a 0.5 aliquot of MEA polyborate was applied over a clipped area on the dorsal skin of each of three albino rabbits (REACH 2013a). The test substance was held in contact with the skin, under a semi-occlusive patch assembly, for four hours. The patches were then removed and skin reaction assessed after 1, 24, 48 and 72 hours.

The treated site on two of the three rabbits remained free from apparent irritation throughout the 72 hour observation period. A barely perceptible erythema was noted at the treated site on the third animal, 1 and 24 hours after patch removal but was no longer apparent at the 48 and 72 hour examinations.

MEA polyborate was considered to be non-irritating to skin.

17.5.3.2 Eye irritation

The eye irritation effect of MEA polyborate was studied by the Bovine Corneal Opacity and Permeability test (BCOP) method (REACH 2013a). Freshly isolated bovine corneas were mounted on cornea holders and the initial opacity was determined. After equilibration, 750 µL of the test substance preparations were topically administered to the epithelial surface. Ten minutes after application the final opacity of the corneas was measured.

The mean *in vitro* irritancy score of the positive control (10% (w/v) Benzalkonium Chloride) was 144 and was within the historical positive control data range, indicating that the test conditions were adequate and that the test system functioned properly.

MEA polyborate did not induce ocular irritation resulting in a mean *in vitro* irritancy score of 0.8 after 10 minutes of treatment. It was concluded that MEA polyborate is not an eye irritant in the BCOP test.

In a second study, 0.1 mL of the test substance was placed by syringe into the conjunctival sac of one eye of New Zealand White rabbits while the other eye served as a control (REACH 2013a). The treated eye of each rabbit was examined for irritation of the cornea, iris and conjunctiva at 1, 24, 48 and 72 hours post dose. Ocular reactions were graded according to the numerical Draize technique. There was no corneal opacity or iritis noted at any observation period. Conjunctival irritation, noted in 3/3 eyes, cleared by 48 hours. There were no abnormal physical signs noted during the observation period.

MEA polyborate was concluded to be non-irritating to the eyes.

17.5.3.3 Respiratory irritation

Animal studies for the respiratory tract irritation potential of MEA polyborate are not available.

17.5.3.4 Observation in humans

No data were available.

17.5.4 *Sensitisation*

17.5.4.1 Skin sensitisation

No data were available for MEA polyborate.

Results of the closely related compound, reaction product of boric acid with monoethanolamine and triethanolamine (CAS No. 68512-53-8), indicate that MEA polyborate is non-sensitising to skin (REACH 2013b). A skin sensitisation test was performed in female guinea pigs. Dermal induction and challenge treatment were performed using the pure substance. The control group was exposed to deionised water only. No sensitisation effects were seen in any of the test animals. Validity of the test system was confirmed by periodically conducting positive control tests using alpha-hexyl cinnamic aldehyde for the Buehler test. The test substance was considered non-sensitising to skin according to the classification criteria of Directive 93/2 1EEC (REACH 2013b).

17.5.4.2 Respiratory sensitisation

Respiratory sensitisation data in experimental animals are not available.

17.5.4.3 Observation in humans

No information is available.

Based on available studies, MEA polyborate has low acute oral toxicity. Information on acute inhalation toxicity is not available. MEA polyborate is not a skin or eye irritant. Results from acute dermal and sensitisation studies using a closely related compound (boric acid reaction products with momoethanolamine and triethanolamine) indicate that MEA polyborate has low acute dermal toxicity and is not likely to be a skin sensitiser.

Information on the acute toxicity of MEA polyborate in humans is not available.

17.5.5 *Repeat dose toxicity*

17.5.5.1 Oral

Information on the oral repeated dose toxicity of MEA polyborate is not available.

A single oral toxicity study, described below, with the related compound, boric acid reaction products with ethanolamine and triethanolamine (CAS No. 68512-53-8) is available and the data has been used to read across to MEA polyborate.

Groups of male and female rats were given the compound by oral gavage at dose levels of 0, 62.5, 250 or 1000 mg/kg bw/day for a period of 28 days (REACH 2013b). No treatment-related clinical signs were observed in any of the animals. There were no substance-related adverse findings, either in haematological examinations, clinical chemistry or urine analyses throughout the study period. Slightly lower total bilirubin, cholesterol and triglycerides were observed in the high dose group rats (1000 mg/kg bw/day) when compared to controls at the

end of the study period. These changes were at the lower range of the historical control data for this rat strain and age and hence were not considered to be of toxicological significance. No changes in organ weights were observed and the test substance did not affect any of the neuro-toxicological parameters. Necropsy at terminal sacrifice revealed no gross pathology findings in experimental animals of all the groups.

In conclusion, repeated administration of the test substance, CAS No. 68512-53-8, at dose levels of up to 1000 mg/kg bw/day did not cause any adverse substance-related alterations. A No Observed Adverse Effect Level (NOAEL) could not be established in this study.

As mentioned earlier, MEA polyborate breaks down in body fluids into boric acid and monoethanolamine, according to the following equilibrium equation (Belien et al. 2009):

$$H_3BO_3(aq) + MEA + H_2O \leftrightarrow [B(OH)_4]^- [H_3NCH_2CH_2OH]^+$$

Ethanolamine has low oral repeat dose toxicity. In a 90-day sub-chronic oral study, rats were fed 320, 640 or 1280 mg/kg/day ethanolamine mixed in food (Smyth et al. 1951). No effects were observed in rats at 320 mg/kg bw/day ethanolamine. At 640 mg/kg/day, liver and kidney weights were altered and at the highest dose of 1280 mg/kg/day, death occurred. No further details of the study were available. The results indicated an oral NOAEL of 320 mg/kg/day.

Repeated oral exposure to boric acid resulted in toxic effects in rats. In a 13-week oral study, rats were fed boric acid in diets at doses equivalent to 0, 2.6, 8.8, 26, 88 and 260 mg boron/kg bw/day (Weir 1962). Bodyweight reduction and clinical signs of toxicity and testicular atrophy were noted at doses 88 mg boron/kg bw/day and above. At 26 mg boron/kg bw/day partial testicular atrophy was noted in one animal. Based on this effect, a NOAEL of 8.8 mg boron/kg bw/day was established in this study.

In an oral chronic study, rats were given boric acid at doses equivalent to 0, 5.9, 17.5, 58.5, mg boron/kg bw/day for two years. Reduction in body weights, red cell volume and haemoglobin and testicular atrophy were noted in rats at and above 58.5 mg boron/kg bw/day. A NOAEL of 17.5 mg boron/kg bw/day was established in this study (RIVM 2013; Weir 1996).

Overall, a NOAEL for effects on the testes and the blood system of 17.5 mg boron/kg bw/day (LOAEL of 58.5 mg boron/kg bw/day) was derived from a two year study with boric acid in rats (RIVM 2013; Weir 1996). The NOAEL was the equivalent of 100 mg boric acid/kg bw/day. Assuming a 1:1 MEA:borate complex (1:1 molar ratio, both compounds have molecular weights of 61), a NOAEL of 200 mg/kg bw/day can be derived for MEA polyborate.

The NOAEL of 200 mg/kg bw/day will be used for human risk assessment.

17.5.5.2 Dermal

No data were available.

17.5.5.3 Inhalation

No data were available.

17.5.5.4 Observation in humans

No data were available.

17.5.6 *Genotoxicity*

In two separate *in vitro* mammalian chromosome aberration tests, MEA polyborate did not show any clastogenic effects in human lymphocytes.

In one of the tests, statistically significant increases in the number of cells with chromosome aberrations were observed in cultures treated with MEA polyborate (REACH 2013a). The pH of the test solution in this test ranged between 8.42–9.14, whereas the pH of the negative control was 8.0. Since high pH of the test solution is known to induce significant increases in chromosome aberrations, an additional third cytogenetic assay was performed in which the pH of the cultures treated with MEA polyborate was adjusted to the pH of the solvent control (pH 8.0). In this assay, MEA polyborate did not induce any significant increase in the number of cells with chromosome aberrations in the absence and presence of S9-mix. Based on the results of this study, it was concluded that MEA polyborate is not clastogenic in human cells.

Two gene mutation studies were performed with the closely related chemical, '*boric acid products with monoethanolamine and triethanolamine (CAS No. 68512-53-8)*'. The first study was the bacterial reverse mutation assay (Ames test) using *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 (REACH 2013b). The test substance did not result in significant increases in the number of revertants in any of the bacterial strains, in the presence or absence of the metabolic activation system.

In the second study, the potential of CAS No. 68512-53-8 to induce gene mutations in V 79 cells of the Chinese hamster lung *in vitro* was investigated (REACH 2013b). The test compound was dissolved in cell culture medium and tested at 10, 50, 100, 250, 1000, 2500 and 5000 µg/mL with and without S9 –mix. The test compound did not induce any relevant or reproducible increase in mutant colony numbers up to the highest investigated dose. It was concluded that CAS No. 68512-53-8 is not mutagenic.

Based on all four studies, MEA polyborate is not considered to be mutagenic.

17.5.7 *Carcinogenicity*

Carcinogenicity data were not available for MEA polyborate or its components ethanolamine and boric acid. In a chronic two-year study in rats, boric acid did not produce any tumors in rats (Weir 1996).

17.5.8 *Reproductive toxicity*

Information on the effects of MEA polyborate on fertility or development in animals is not available. As mentioned above, MEA polyborate breaks down in body fluids into monoethanolamine and boric acid.

In a two-generation reproductive study, 0, 100, 300 or 1000 mg/kg bw/day ethanolamine were administered to Crl:WI rats (25 animals per sex per dose) in normal diet daily for the period of the study (REACH 2013c). Decreased numbers of implants and increased resorption rates resulted in significantly smaller litters noted in F0 and F1 generation females at the highest dose (1000 mg/kg bw/day) , providing evidence of an adverse effect of the test compound on fertility and / or reproductive performance. At 1000 mg/kg bw/day, systemic toxicity was also observed in these females, such as reduced food consumption and / or body weight gain during gestation/lactation.

Reproductive toxicity studies with boric acid are not available, however repeat dose oral studies with boric acid in rodents indicated that boric acid (boron) impaired fertility through effects on the testes. The following key rodent data (Table A17.5) on fertility and

developmental toxicity of boric acid were summarised from WHO (1998), ECHA (2009) and RIVM (2013).

Table A17.5 Reproductive toxicity studies with boric acid

Test substance	Method	Results	Remarks	References
Boric acid	Mouse 13 weeks, diet. Doses: equivalent to 0, 34, 71, 142, 284, 568 mg boron/kg bw/day (males); 0, 47, 98, 196, 392, 784 mg boron/kg bw/day (females)	LOAEL = 142 mg boron)/kg bw/day (males) NOAEL = 71 mg boron/kg bw/day (males)	Degeneration and atrophy of seminiferous tubules at ≥142 mg boron/kg bw/day. No treatment-related adverse systemic effects were observed in females.	NTP (1987)
Boric acid	Rat 2 year, diet. Doses: equivalent to 0, 5.9, 17.5, 58.5 mg boron/kg bw/day.	LOAEL = 58.5 mg boron/kg bw/day NOAEL = 17.5 mg boron/kg bw/day	Testicular atrophy at 58.5 mg boron/kg bw/day	Weir (1966)
Boric acid	Rat prenatal developmental toxicity study (compliant with OECD TG 414) Doses 0, 18, 37, 55, 74, or 148 mg/kg bw/day boric acid in feed equivalent to 0, 3.2, 6.4, 9.6, 12.8 and 25.6 mg boron/kg bw/day	Dams: NOAEL = 25 mg boron/kg bw/day. Foetuses: NOAEL = 9.6 mg boron/kg bw/day.	Dams: no toxicity. Foetuses: at 13.3 mg boron/kg bw d, reduced bodyweight, short 13th rib, wavy rib; not seen postnatally.	Price (1996a)
Boric acid	Rabbit prenatal developmental toxicity study (compliant with OECD TG 414) Doses 0, 62.5, 125, or 250 mg/kg/day boric acid in feed equivalent to 0, 11, 22, 44 mg boron/kg bw/day.	Dams: NOAEL = 22 mg boron/kg bw/day. Foetuses: NOAEL = 22 mg boron/kg bw/day.	Dams: at 43.5 mg boron/kg bw/day, reduced bodyweight and food intake with abortions and resorptions. Foetuses: at 43.5 mg boron/kg bw/day, resorptions and cardiovascular malformations.	Price (1996b)

Based on data from the two year feeding studies with boric acid in rats, in which testicular atrophy was noted, the NOAEL for fertility was established at 17.5 mg boron/kg bw/day (equivalent to 100 mg boric acid/kg bw/day) (Weir 1966). Assuming a 1:1 MEA borate complex, a NOAEL of 200 mg/kg bw/day can be derived for MEA polyborate.

Developmental toxicity (malformations) of boric acid was observed in studies in mice, rats and rabbits (Table 82). The rat was the most sensitive species. There was no information to suggest that developmental effects were secondary to other toxic effects or to exposures via lactation. The NOAEL for developmental effects was 9.6 mg boron/kg bw/day (equivalent to 55 mg boric acid/kg bw/day (Price 1996a). Assuming a 1:1 MEA borate complex, a NOAEL of 110 mg/kg bw/day can be derived for MEA polyborate.

Fertility studies with ethanolamine showed that ethanolamine affects fertility in rats at very high concentrations (1000 mg bw/day), at which systemic maternal toxicity is also observed (REACH 2013c). Ethanolamine did not have any adverse effects on development in rat fetus.

Based on the effects of boric acid on fertility and development in experimental animals, repeated exposure to MEA polyborate is likely to have adverse effects on fertility and development. The compound is therefore considered to be a fertility and developmental toxicant.

17.5.9 *Other health effects*

No data were available.

17.6 Health hazard summary

17.6.1 *Critical health effects*

In summary for this chapter, MEA polyborate has low acute oral toxicity. Information on acute inhalation toxicity is not available. MEA polyborate is not a skin or eye irritant. Results from acute dermal and sensitisation studies using a closely related compound (boric acid reaction products with momoethanolamine and triethanolamine) indicate that MEA polyborate is likely to have low acute dermal toxicity and is not likely to be a skin sensitiser.

No repeat dose toxicity studies were available for MEA polyborate. An appropriate NOAEL for repeat dose toxicity by any exposure route could not be established in animal studies conducted with closely related compounds such as '*boric acid reaction products with momoethanolamine and triethanolamine*'.

However, since MEA polyborate is likely to hydrolyse into boric acid and monoethanolamine under physiological conditions, critical effects related to these two chemicals are relevant.

Ethanolamine has low repeat dose oral and inhalational toxicity. Repeated exposure to boric acid induced effects on fertility (testes) and development. The NOAEL for effects on fertility was 17.5 mg boron/kg bw/day. This NOAEL was equivalent to 100 mg boric acid/kg bw/day and 200 mg MEA polyborate/kg bw/day. The most sensitive endpoint for boric acid was its effect on development with a NOAEL of 9.6 mg boron/kg bw/day. This NOAEL was equivalent to 55 mg boric acid/kg bw/day and 110 mg MEA polyborate/kg bw/day.

MEA polyborate or its related compound is not considered to be genotoxic. Carcinogenicity data were not available for MEA polyborate or its components ethanolamine and boric acid. In a chronic two-year study in rats, boric acid did not produce any tumours in rats.

17.6.2 *Hazard classification*

There is insufficient toxicological data on MEA polyborate to classify it under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) or under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009). However, given that in physiological conditions the compound can

hydrolyse into ethanolamine and boric acid, the toxic effects of boric acid and ethanolamine in the physiological environment (short and long-term oral and inhalation exposure) are relevant to MEA polyborate. It is therefore considered appropriate to assign classification and risk phrases to MEA polyborate that are relevant to boric acid and ethanolamine.

MEA polyborate is recommended by NICNAS to Safe Work Australia for classification and labelling under the Approved Criteria for Classifying Hazardous Substances and adopted GHS as shown in Table A17.6. These NICNAS recommendations do not consider physical or environmental hazards.

Table A17.6 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Reproductive toxicity	Repr. Cat. 2; May impair fertility (T; R60) Repr. Cat. 2; May cause harm to the unborn child (T; R61)	May damage fertility.May damage the unborn child - Cat. 1B (H360FD)

a Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); b Globally Harmonised System (UNECE 2009)

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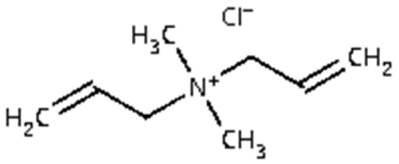
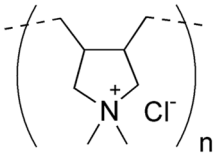
A18 Polydimethyldiallylammonium chloride

CAS No.	CAS Name
26062-79-3	2-Propen-1-aminium, N,N-dimethyl-N-2-propen-1-yl-, chloride (1:1), homopolymer

18.1 Chemical identity

2-Propen-1-aminium, N,N-dimethyl-N-2-propenyl-, chloride, homopolymer, referred to in this report as PolyDADMAC, is a homopolymer of diallyldimethylammonium chloride (DADMAC). The identity information was obtained from ChemID*plus* (2012). A description of the chemical identity is provided in Table A18.1.

Table A18.1 Chemical identity

	Polydimethyldiallylammonium chloride
Synonyms	Polydimethyldiallylammonium chloride Polydiallyldimethylammonium chloride (PolyDADMAC) Polymer, dimethyldiallylammonium chloride Polyquaternium 6
Appearance and odour	Granular white solid with a slight odour
Structural formula	 (monomer)  (polymer)
Molecular formula	(C8H16N.Cl)n
Molecular weight	Typical molecular weight of a polyDADMAC polymer is 2-3 million (Nozaic et al. 2001).
SMILES notation	Not applicable

18.2 Physical properties

Limited information is available on the physical properties of polyDADMAC. The information on physical properties, obtained from Galleria Chemica (2013), is provided in Table A18.2.

Table A18.2 Physical properties

Property	Value
Melting point	Not available
Boiling point	Not available
Density – kg/m^3	1.09 (20 °C)
Vapour pressure	Not available
Water solubility (g/L)	Soluble
Partition coefficient (log K_{ow})	Not applicable

18.3 Current regulatory controls

18.3.1 *Hazard classification for occupational health and safety*

The substance is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

18.3.2 *Occupational exposure standards*

18.3.2.1 Australia

No exposure standards are available for polyDADMAC.

18.3.2.2 International

Occupational exposure limits for polyDADMAC identified internationally are provided below (Galleria Chemica 2013):

- US Department of Energy Temporary Emergency Exposure Limits (TEELs):
  - TEEL-0=12.5 mg/m^3, TEEL-1=35 mg/m^3, TEEL-2=250 mg/m^3, TEEL- 3=500 mg/m^3.

No other occupational exposure limit exists internationally for polyDADMAC.

18.3.3 *Australian food standards*

No Australian food standards were identified (Food Standards Australia New Zealand 2013).

18.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for polyDADMAC in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

18.3.5 *Additional controls*

18.3.5.1 Australia

PolyDADMAC is listed in Appendix B (Substances Considered Not To Require Control By Scheduling) of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

The reason given for listing in Appendix B is '*Low Toxicity*' and the area of use of the chemical is '*Water treatment*'.

18.3.5.2 International

No additional controls were identified.

18.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

18.5 Health hazard characterisation

18.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

PolyDADMAC is synthesised by the polymerisation of the diallyldimethyl ammonium chloride (DADMAC) monomer (CAS No. 7398-69-8). The monomer content in the preparation can range from 1 to 5% (John 2008). Toxicity data on polyDADMAC are limited. Since the polymer preparation contains up to 5% monomer residue, data gaps for some endpoints for commercial polyDADMAC can be filled by reading across from DADMAC studies (refer to Table A18.3).

Table A18.3 Summary of available toxicity endpoint data

	PolyDADMAC	DADMAC
Acute oral toxicity	×	✓
Acute dermal toxicity	×	×
Acute inhalation toxicity	×	×
Skin irritation	×	✓
Eye irritation	×	✓
Respiratory irritation	×	×
Skin sensitisation	×	×
Respiratory sensitisation	×	×
Repeat dose toxicity (oral)	×	✓
Repeat dose toxicity (dermal)	×	×
Repeat dose toxicity (inhalation)	×	×
Genotoxicity	×	✓
Carcinogenicity	×	×
Reproductive toxicity	✓	×

✓ Existing data point; × Missing data point

In addition, Quantitative Structure-Activity Relationship (QSAR) modelling was conducted for skin sensitisation and genotoxicity endpoints on the monomer using the predictive modelling tool OASIS-TIMES.

18.5.1.1 Oral absorption

No data were available for oral absorption. PolyDADMAC is a large molecule. Stability studies indicate that it is very stable and does not break down into smaller molecules except under extreme temperature and pH conditions (John 2008). Moreover, its monomer (DADMAC) has been shown to be poorly absorbed in the intestine (Easterday 1965). For the purposes of human risk assessment, 0% oral absorption is assumed.

18.5.1.2 Dermal absorption

No data were available. Absorption across intact skin is expected to be limited due to the large molecular size of the polymer (Basketter et al. 2012). Therefore 0% dermal absorption is assumed.

18.5.1.3 Inhalation absorption

No data were available. For the purpose of risk assessment, 100% inhalation absorption is therefore assumed.

18.5.1.4 Distribution

No data were available.

18.5.1.5 Metabolism

No data were available.

18.5.1.6 Excretion

No data were available.

18.5.2 *Acute toxicity*

18.5.2.1 Oral

No data available. Due to its large size, the polyDADMAC molecule is not expected to be absorbed from the gastrointestinal tract and as a result, oral toxicity is not likely. The monomer, DADMAC, has very low oral acute toxicity (LD50 of 3030 mg/kg bw) (US EPA 2004). Hence the polymer is regarded as not being acutely toxic by the oral route.

18.5.2.2 Dermal

No data were available. Absorption, and therefore toxicity through the skin is not likely.

18.5.2.3 Inhalation

No data were available.

18.5.2.4 Observation in humans

No data were available.

18.5.3 *Irritation / Corrosivity*

18.5.3.1 Skin irritation

No information is available for polyDADMAC. Skin irritation studies with DADMAC monomer indicate that it is not a skin irritant (REACH 2013). However some authors have speculated that the quaternary ammonium chloride moiety in the polymer could cause skin irritation (John 2008; Nozaic et al. 2001). Based on information collected from various manufacturing companies, John and Trollip (2009) concluded that exposure to polyDADMAC may cause skin irritation.

18.5.3.2 Eye irritation

No information is available for this endpoint. Eye irritation studies with DADMAC monomer indicate that it is not an eye irritant (REACH 2013). However some authors have speculated that the quaternary ammonium chloride moiety in the polymer may irritate the eyes (John 2008; Nozaic et al. 2001). Based on information collected from various manufacturing companies, John and Trollip (2009) concluded that exposure to polyDADMAC may cause eye irritation.

18.5.3.3 Respiratory irritation

No data available. Based on information collected from various manufacturing companies, John and Trollip (2009) concluded that inhalation exposure to polyDADMAC may result in irritation of the upper respiratory tract.

18.5.3.4 Observation in humans

No data were available.

18.5.3.5 Summary of Irritation / Corrosivity

In summary of the above discussion, information on skin, eye and respiratory tract irritation is not available for polyDADMAC. Skin and eye irritation studies with the DADMAC monomer indicate that these chemicals are not irritants. The presence of the quaternary ammonium chloride moiety in the molecule may result in skin and eye irritation. However, in the absence of experimental data, polyDADMAC cannot be classified as skin or eye irritant.

18.5.4 *Sensitisation*

18.5.4.1 Skin sensitisation

No data available. QSAR modelling using OASIS-TIMES predicted negative results for skin sensitisation.

18.5.4.2 Respiratory sensitisation

No data were available.

18.5.4.3 Observation in humans

No data were available.

18.5.5 *Repeat dose toxicity*

18.5.5.1 Oral

No data available. Due to its large size, the polyDADMAC molecule is not expected to be absorbed from the gastrointestinal tract, and as a result oral toxicity is not likely.

In a 13-week repeat oral dose study in dogs with the monomer DADMAC, full details of which are not available, there was a decrease in body weight gain at 800 mg/kg/day (per cent decrease in body weight not provided) (Tegeris 1976). No other treatment-related effects were observed. The NOAEL in this study was 200 mg/kg bw/day based on reduced body weight gain. However, this NOAEL is not considered appropriate for human health risk assessment as sufficient study details are not available to determine if the reduced bodyweight gain can be considered as an adverse effect.

18.5.5.2 Dermal

No data were available. Absorption through the skin and consequent toxicity is not likely.

18.5.5.3 Inhalation

No data were available.

18.5.5.4 Observation in humans

No data were available.

18.5.6 *Genotoxicity*

No data were available. *In vivo* and *in vitro* studies with the DADMAC monomer did not reveal any genotoxic effects (REACH 2013). QSAR modelling using OASIS-TIMES predicted negative results for *in vitro* and *in vivo* genotoxicity.

18.5.7 *Carcinogenicity*

No experimental studies on the carcinogenic potential of polyDADMAC are available.

18.5.8 *Reproductive toxicity*

18.5.8.1 Fertility

In a multi-generation reproduction study (Adamik 1979) Sprague-Dawley rats (10 per sex per dose group) were given 0, 0.375, 12.5 or 125 mg/kg bw polyDADMAC by gavage. F0 animals (male and female) were treated from the day of mating to weaning of the F1 pups. At weaning, 10 male and 20 female F1 rats were randomly selected from each group and continued with the same dose from 21 days of age through to weaning of the F2 generation. The F2 litters were weaned at 21 days post-partum and killed.

The following reproductive parameters were assessed during the study:

- duration of gestation
- evidence of difficult or prolonged labour
- maternal neglect and agalactia
- total offsprings at birth

- number and sex of dead at birth
- number and sex of abnormal offspring at birth
- viable offspring at days 4,7,14 and 21 (F1 and F2)
- live weight of litters.

In addition, one male and one female from each litter was subjected to gross pathology, and reproductive organs from 10 rats per sex from control and high dose groups were examined for microscopic pathology.

There were no effects on maternal body weights, litter size, mating index, fecundity index, male and female fertility indices or incidence of parturition. There were also no compound-related effects on F1 and F2 generations - no effects on the number of live births, total litter size, pup body weights or any effect on maternal instinct and raising of the pups were observed. No remarkable pathology was noted amongst F1 and F2 animals.

PolyDADMAC was considered to be not toxic to fertility in rats.

18.5.8.2 Developmental toxicity

In a developmental study female Sprague-Dawley rats (24/dose group) were given 0, 50, 150, 450, or 600 mg/kg bw polyDADMAC by gavage daily from gestational day six to 15 (Palmer 1991). Food consumption and maternal body weights were noted daily, and at scheduled sacrifice, dams were evaluated for gravid uterus weight, and the numbers of corpora lutea, live and dead foetuses were determined. Foetuses were analysed for skeletal abnormalities and malformations.

There was no compound-related effect on body weight or body weight gain. Food consumption was significantly suppressed on days 6 through 11, but all measured maternal parameters were normal. Foetus weights and sex were similar to the control and no compound-related malformations or anomalies were observed. A NOAEL was not established in this study.

PolyDADMAC was not considered to be toxic to development.

18.6 Health hazard summary

18.6.1 *Critical health effects*

In summary of this chapter, very limited toxicological data were available for polyDADMAC. Being a large molecule (molecular weight ~2 to 3 million), absorption and consequent acute or repeated dose toxicity by oral and dermal routes is not expected. PolyDADMAC may have eye, skin and respiratory irritation effects by virtue of the quaternary ammonium chloride moiety in the molecule. However no experimental data is available. Multigenerational reproductive studies with polyDADMAC did not show any effects on fertility parameters or development. No critical health effects are known.

The monomer DADMAC had low acute and repeat dose toxicity and was not genotoxic. In a developmental study, doses of up to 600 mg/kg bw polyDADMAC did not have any adverse effect on the foetuses in Sprague-Dawley rats. In the absence of an appropriate No Observed Adverse Effect Level (NOAEL) the highest tested concentration will be used for human health risk assessment.

18.6.2 *Hazard classification*

Although it has been speculated that pure polyDADMAC may cause skin, eye and respiratory tract irritation, data were insufficient to be able to classify for these endpoints. No other adverse effects were noted in studies with polyDADMAC or its monomer, DADMAC. PolyDADMAC is therefore not recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) and under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) for human health effects.

18.7 References

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A19 Methylchloroisothiazolinone, Methylisothiazolone

CAS No.	CAS Name
26172-55-4	3(2H)-Isothiazolone, 5-chloro-2methyl-
2682-20-4	3(2H)-Isothiazolone, 2-methyl-

19.1 Justification for group assessment of isothiazolones

The isothiazolone category assessed in this report consists of the above two chemicals and the mixture of the two. The justification for inclusion of members within the isothiazolone category is supported by common features which include:

- similarity of chemical structure and functional groups – a five-membered heterocyclic ring (consisting of three carbon atoms, one nitrogen atom, and one sulfur atom) directly connected by a double bond to an oxygen atom, and the nitrogen in the heterocyclic ring is connected to an organic or inorganic constituent
- similarity of physico-chemical properties – molecular weight, melting point, density, vapour pressure, water solubility
- similarity of mammalian toxicity although in varying severity for some endpoints – acute toxicity, Irritation / Corrosivity, skin sensitisation, genotoxicity
- similarity of mode of action (MOA) – conjugation of the thiol group with proteins by breaking the sulfur-nitrogen bond (S-N) in the isothiazolone ring. The chloro compound also undergoes an additional conjugation reaction with proteins.

Toxicity data exist for 3(2H)-Isothiazolone, 2-methyl- (CAS No. 2682-20-4, more commonly known as 3-Isothiazolone, 2-methyl-) for most health endpoints, and for the 3:1 mixture of 3(2H)-Isothiazolone, 5-chloro-2methyl- (CAS No. 26172-55-4) and 3-Isothiazolone, 2-methyl-. Information specific for the chloro compound is very limited. Although the chloro compound is available for purchase as an individual chemical, the Scientific Committee on Consumer Safety (SCCS) (2009) indicated that 3(2H)-Isothiazolone, 5-chloro-2methyl- (chloro compound) is currently formulated by an integrated production process in combination with 3-Isothiazolone, 2-methyl- (hydro compound) at a 3:1 ratio. The NICNAS coal seam gas Industry Survey showed that in a formulation, the concentration ratio of the two chemicals in the mixture is approximately 3:1 (NICNAS 2017a).

The available data show that the toxicity of the 3:1 mixture of chloro to hydro compound is greater than the toxicity of the 3-Isothiazolone, 2-methyl. As the chloro compound undergoes another conjugation reaction with proteins, it has the potential for a greater potency.

In this report, the hazards of 3-Isothiazolone, 2-methyl- are evaluated as the health effects of the individual chemical and where data were not available read across from the data on the mixture is carried out.

Also in this report, data available for the mixture are used to assess the health effects of combined 3-Isothiazolone, 2-methyl- and 3(2H)-Isothiazolone, 5-chloro-2-methyl. Based on available information, the hazard of the mixture is not expected to be significantly different

from the hazard of the chloro compound based on the 3:1 ratio of this chemical with the hydro compound. Hazard evaluations by international regulatory agencies were also conducted on the mixture.

Information available for the chemicals is presented in Table A19.1. Accordingly, the data gaps for the chloro compound are read across from the data of the 3:1 mixture of the chloro and hydro compounds. The data gaps for the hydro compound are also read across from the data of the 3:1 mixture of the chloro and hydro compounds, noting that the potency could be lower for the hydro compound.

Table A19.1 Summary of available toxicity endpoint data

	3-Isothiazolone, 2-methyl- (CAS No. 2682-20-4)	**3(2H)-Isothiazolone, 5-chloro-2methyl- (CAS No. 26172-55-4)**	**3:1 Mixture of 3(2H)-Isothiazolone, 5-chloro-2methyl- (CAS No. 26172-55-4) and 3-Isothiazolone, 2-methyl- (CAS No. 2682-20-4)**
Acute oral toxicity	✓	×	✓
Acute dermal toxicity	✓	×	✓
Acute inhalation toxicity	×	×	✓
Skin irritation	✓	×	✓
Eye irritation	✓	×	✓
Respiratory irritation	×	×	✓
Skin sensitisation	✓	✓	✓
Respiratory sensitisation	×	×	✓
Repeat dose toxicity (oral)	✓	×	✓
Repeat dose toxicity (dermal)	×	×	✓
Repeat dose toxicity (inhalation)	×	×	✓
Genotoxicity	✓	×	✓
Carcinogenicity	×	×	✓
Reproductive toxicity	×	×	✓

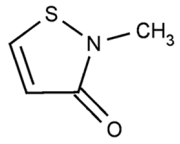
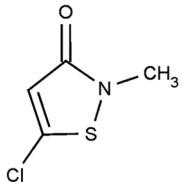
✓Existing data point; × Missing data point

19.2 Chemical identity

The information on chemical identity was obtained from ChemID*plus* (2012), the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) (2004), and the SCCS (2009). Details are provided in Table A19.2.

Table A19.2 Chemical identity

	Methylisothiazolone	**Methylchloroisothiazolinone**

Synonyms	2-Methyl-3-isothiazolone Methylisothiazolone	5-Chloro-2-methyl-3-isothiazolone Methylchloroisothiazolinone
Structural formula	 CAS No. 2682-20-4	 CAS No. 26172-55-4
Molecular formula	C_4H_5NOS	C_4H_4ClNOS
Molecular weight	115.16	149.45
Appearance and odour	Off-white to light brown solid at room temperature	Clear, light amber liquid (in a 3:1 mixture with CAS No. 2682-20-4)
SMILES Notation	C1(=O)C=CSN1C	C1(=O)C=C(Cl)SN1C

19.3 Physical properties

The physical properties of the chemicals are presented in Table A19.3. The information was obtained from SCCNFP (2004) and SCCS (2009). Physical properties specific for 3(2H)-Isothiazolone, 5-chloro-2methyl-are obtained from suppliers (Chemical Book 2013) and SCCS (2009).

Table A19.3 Physical properties

Property	**3-Isothiazolone, 2-methyl- (CAS No. 2682-20-4)**	**3(2H)-Isothiazolone, 5-chloro-2methyl- (CAS No. 26172-55-4)**	**3:1 Mixture of 3(2H)-Isothiazolone, 5-chloro-2methyl- (CAS No. 26172-55-4) and 3-Isothiazolone, 2-methyl- (CAS No. 2682-20-4)**
Melting point	46.7-48.3 °C	42-45 °C	22.3-50.3 °C
Boiling point	155 °C (thermal decomposition)	-	100-106.5 °C
Density	1350 kg/m^3 at 25 °C	1250 at unspecified temperature	1256 kg/m^3 at 20 °C; 1296 kg/m^3 at 25 °C
Vapour pressure	7.3 x 10^{-4} kPa at 20 °C	-	1.08 x 10^{-4} kPa at 20 °C
Water solubility	>1000 g/L at 20 °C and pH=5	706-751 g/L at 20 °C	≥1000 g/L at 20 °C
Partition coefficient n-octanol/water (log K_{ow})	-0.486 at 24 °C	-	0.75 at 27 °C

19.4 Current regulatory controls

The document from here on refers to the chemicals 3-Isothiazolone, 2-methyl- (CAS No. 2682-20-4) and 3(2H)-Isothiazolone, 5-chloro-2methyl- (CAS No. 26172-55-4) as 'methylisothiazolone' and 'methylchloroisothiazolinone', respectively. These are synonyms of the two chemicals. The 3:1 mixture of methylchloroisothiazolinone and methylisothiazolone will be referred to as 'MCI/MI'.

19.4.1 *Hazard classification for occupational health and safety*

Methylisothiazolone is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

The 3:1 mixture of methylchloroisothiazolinone and methylisothiazolone is classified as hazardous for human health in the HSIS (Safe Work Australia 2013) with the following risk phrases:

- T (Toxic); R23/24/25
- C (Corrosive); R34, R43.

Mixtures containing MCI/MI are classified as hazardous with the following risk phrases based on the concentration of MCI/MI in the mixtures. The risk phrases for different concentration (Conc) ranges are:

- Conc ≥25%: T: R23/24/25 (Toxic by inhalation, in contact with skin, and if swallowed); R34 (Causes burns); R43 (May cause sensitisation by skin contact)
- 3% ≤Conc <25%: C: R34, R20/21/22 (Harmful by inhalation, in contact with skin, and if swallowed), R43
- 0.6% ≤Conc <3%: C: R34, R43
- 0.06% ≤Conc <0.6%: X_i (Irritant): R36/38 (Irritating to eyes and skin), R43
- 0.0015% ≤Conc <0.06%: X_i: R43.

19.4.2 *Occupational exposure standards*

19.4.2.1 Australia

No specific exposure standards were available in Australia.

19.4.2.2 International

No specific exposure standards were available.

19.4.3 *Australian food standards*

No Australian food standards were identified.

19.4.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

19.4.5 *Additional controls*

19.4.5.1 Australia

The chemicals are not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (TGA 2014).

19.4.5.2 International

Methylisothiazolone is currently regulated in the European Union (EU) Cosmetic Directive 76/768/EEC in Annex VI, Part 1 with the maximum authorised concentration of 0.01%. The 3:1 MCI/MI mixture is also currently regulated in the same Directive with a maximum authorised mixture concentration of 0.0015% (EC 2010).

Methylisothiazolone is currently permitted at concentrations ≤0.01% for use as a preservative, and MCI/MI is currently permitted at levels ≤0.0015% in rinse-off products and ≤0.00075% in leave-on products (Health Canada 2011). The Expert Panel of the Cosmetic Ingredient Review (CIR) recommended a concentration of 15 ppm MCI/MI for cosmetic rinse-off products and ≤7.5 ppm in cosmetic leave-on products (CIR 1992).

19.5 Use

The use of these chemicals in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports*;* the Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

19.6 Health hazard characterisation

The available European scientific opinions for methylisothiazolone (SCCNFP 2003 and 2004) and MCI/MI (SCCS 2009) are the main sources of information for the chemicals. Note that the SCCS and the SCCNFP are the same non-food scientific committee of the European Commission. Unless otherwise noted, references to individual studies below are taken from these reviews.

19.6.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

19.6.1.1 Oral absorption

No data were available. Based on the effects reported in acute and repeat dose oral toxicity studies (Sections A19.6.2 and A19.6.5), the chemicals are likely to be absorbed via the oral route.

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

19.6.1.2 Dermal absorption

Radiolabelled MCI/MI was applied by 24-hour occlusion to the skin of Sprague-Dawley Charles River rats at a dose of 2000 ppm. The range of total recovery of ^{14}C-labelled MCI/MI was 74 to 91% of the applied dose. At 24 hours, the systemic bioavailability of methylchloroisothiazolinone and methylisothiazolone were estimated to be 15 and 24%, respectively (Rohm and Haas 1982c).

In a study conducted in accordance with the Organisation for Economic Co-operation and Development Test Guideline (OECD TG) 417, a mixture of 11% methylchloroisothiazolinone and 3.5% methylisothiazolone was tested in Crl:CD BR rat skin at doses of 25 or 2500 ppm. Methylisothiazolone was absorbed across the skin to a larger extent than methylchloroisothiazolinone but there was no determination if the chemicals bound to the skin were systemically available (Rohm and Haas 1989a).

In vitro human skin absorption studies on MCI/MI conducted in accordance with OECD TG 428 reported maximum potential systemic availability for methylchloroisothiazolinone as 84.5% (Rohm and Haas 2005b) and 58.7% (Rohm and Haas 2005c) of the applied doses.

In an *in vitro* human skin absorption study conducted in accordance with OECD TG 428, aqueous solutions of products containing methylisothiazolone were applied by occlusion for 24 hours at doses of 52.2, 104.3 or 313 µg/mL. Potential systemic bioavailability was estimated at a maximum of 75.5% of the applied dose (Rohm and Haas 2005a).

For the purposes of risk assessment, 100% dermal absorption in humans is therefore assumed.

19.6.1.3 Inhalation absorption

No data were available. Based on the effects reported in acute and repeat dose toxicity studies (Sections A19.6.2 and A19.6.5), the chemicals are likely to be absorbed via the inhalation route.

For the purposes of risk assessment, 100% inhalation absorption in humans is therefore assumed.

19.6.1.4 Distribution

Aqueous ^{14}C-methylisothiazolone was administered orally to CD-1 mice at a single dose of 100 mg/kg bw and ^{14}C-methylisothiazolone was determined in blood, plasma, liver, bone marrow, and femur bones. High levels of radioactivity were detected in all the tissues at the 1 and 3 hour sampling point. The concentrations decreased progressively with the partitioning of radioactivity observed from plasma into the tissues after 24 hours (Rohm and Haas 2000c).

No data were available for MCI/MI.

19.6.1.5 Metabolism

A ringed-opened metabolite, N-methyl-malonamic acid (NMMA), was reported as the major metabolite of both methylisothiazolone and methylchloroisothiazolinone. Other metabolites of the isothiazolones included Phase I reductive and oxidative cleavage metabolites. Phase II metabolites comprised of glutathione-derived conjugates of Phase I metabolites (Rohm and Haas 1997). No other details were provided.

A biocide supplier of preservatives containing methylisothiazolone and methylchloroisothiazolinone indicated that the mode of action of the chemicals involves protein conjugation by cleavage of the S-N bond in the isothiazolone ring and a similar mechanism can be expected in humans (Sigma-Aldrich 2009). This additional conjugation reaction with proteins could provide greater potency of the methylchloroisothiazolinone from the possible further activation of the metabolites.

19.6.1.6 Excretion

No data were available for methylisothiazolone.

In the previously described study of Rohm and Haas (1982c) (refer to Section A19.6.1.2 Dermal Absorption), the absorbed radioactive MCI/MI was excreted mostly in the urine of Sprague-Dawley Charles River rats within 72 to 96 hours (Rohm and Haas 1982c).

19.6.2 *Acute toxicity*

19.6.2.1 Oral

Animal data on acute oral toxicity of methylisothiazolone and MCI/MI are summarised from SCCNFP (2003) and SCCS (2009), and presented in Table A19.4. The acute oral median lethal doses (LD50s), as equivalent doses based on the concentration of the chemicals, are indicated.

Table A19.4 Acute oral toxicity studies with methylisothiazolone and MCI/MI

Substance	Species Doses	LD50 (mg/kg bw)	Reference
Methylisothiazolone	Crl:CD BR rats 75, 150, 180, 225, or 300 mg/kg bw	235 in males 183 in females	Rohm and Haas (1999d)
9.7% Methylisothiazolone	Crl:CD BR rats 193.8, 242.3, 290.7, or 484.5 mg/kg bw (males); 96.9, 145.4, or 193.8 mg/kg bw (females)	274.6 in males 105.7 in females	Rohm and Haas (2000a)
1.5% MCI/MI	Rats (strain not specified) Doses not specified	>75 in males 49.6 in females	Rohm and Haas (1999d)
14% MCI/MI	Rats (strain not specified) Doses not specified	69 combined – Bliss' method 66 combined – Litchfield and Wilcoxon's method	Rohm and Haas (2000a)
14% MCI/MI	Rats (strain not specified) Doses not specified	69 in males 59 in females	Rohm and Haas (2000b)
1.5% MCI/MI	Rats (strain not specified) Doses not specified	Between 500 and 5000 in females	Rohm and Haas (2000h)

Similar effects were observed following oral administration of methylisothiazolone in Crl:CD BR rats. Varying degrees of intoxication exhibited as respiratory noises, salivation, passiveness, ataxia, scant or no faeces, mucus in faeces, yellow or brown stained anogenital area, red-stained muzzle and / or lacrimation were reported. Necropsy of decedents showed reddened intestines and / or stomach mucosa, reddened glandular portion of the stomach, and distended stomachs (Rohm and Haas 1999d; Rohm and Haas 2000a).

The effects in the acute oral studies with MCI/MI were not specified.

The studies show that methylisothiazolone has moderate acute oral toxicity, and MCI/MI has high acute oral toxicity. Based on a read across of the data available for MCI/MI methylchloroisothiazolinone is also considered to have high acute oral toxicity.

19.6.2.2 Dermal

A preservative containing 9.7% methylisothiazolone was applied with occlusion to shaved intact skin of Crl:CD BR rats for 24 hours at 2000, 3500, or 5000 mg/kg bw. Minimal effects were seen which included scant faeces in the higher dose groups. Skin effects observed included pocketing oedema, erythema, blanching, desiccation, darkened or reddened areas, scabs, eschar, and / or sloughing. The acute dermal LD50 of the applied solution was determined as >5000 mg/kg bw, equivalent to 485 mg/kg bw methylisothiazolone for both sexes (Rohm and Haas 2000b).

The acute dermal LD50s for MCI/MI were reported to be >5000 mg for a 15% solution/kg bw (>75 mg/kg bw MCI/MI) in rabbits (Rohm and Haas 1999b) and 1008 mg of 14% solution/kg bw (141 mg/kg bw MCI/MI) in rats (Pharmakon Europe 1994a). The rabbit and rat strains, doses, and effects were not specified.

The studies show that methylisothiazolone has moderate acute dermal toxicity, and MCI/MI has high acute dermal toxicity. Based on reading across from data available for MCI/MI methylchloroisothiazolinone is considered to have high acute dermal toxicity.

19.6.2.3 Inhalation

No data were available for methylisothiazolone.

In a four hour aerosol exposure to a formulation containing 13.9% MCI/MI in rats (strain not specified), an acute inhalation median lethal concentration (LC50) of 2.36 mg/L (equivalent to 0.33 mg/L MCI/MI) was reported (Rohm and Haas 1991). No other details were provided.

The study shows that MCI/MI has high acute inhalation toxicity and reading across from this data, methylisothiazolone and methylchloroisothiazolinone are considered to have high acute inhalation toxicity.

19.6.2.4 Observation in humans

No data were available.

19.6.3 *Irritation / Corrosivity*

19.6.3.1 Skin irritation

New Zealand White rabbits were observed for signs of irritation 14 days after patch removal following a single semi-occluded application of 0.5 mL undiluted (presumably melted) methylisothiazolone to shaved intact skin of the animals. The rabbits were grouped with varying contact periods of three minutes, one hour, and four hours. Skin irritation indicative of corrosivity was observed on day 14 and 7 on the four- and one-hour sites, respectively (Rohm and Haas 2000c). No other details were specified.

MCI/MI was found to be corrosive in rabbit skin at concentrations of 1.5% (Rohm and Haas 1999c) and 14.2% (Pharmakon Europe 1994b). No other details were specified.

Based on a read across of the data available for MCI/MI, methylisothiazolone and methylchloroisothiazolinone are corrosive to rabbit skin.

19.6.3.2 Eye irritation

A 100 ppm aqueous solution of 9.5% methylisothiazolone was applied to the conjunctival sac of New Zealand White rabbits and eye irritation was evaluated using the Draize criteria at 1, 24, 48, and 72 hours. There were no corneal, conjunctival or iridial effects observed during the study (Rohm and Haas 2000d).

MCI/MI was found to be non-irritating to rabbit eyes at 0.01% (Rohm and Haas 1975c) and severely irritating at 1.5% (Rohm and Haas 1999a). MCI/MI was assessed as a non-irritant at concentrations of 0.0015%, 0.015%, and 0.15% and a mild irritant at a concentration of 1.5% from an *in vitro* bovine cornea opacity permeability (BCOP) test (Thor Specialities 2002). No other details of these studies were specified.

Methylisothiazolone is not an eye irritant, while MCI/MI is a severe eye irritant. Based on a read across of the data available for MCI/MI, methylchloroisothiazolinone is a severe eye irritant.

19.6.3.3 Respiratory irritation

No data were available for methylisothiazolone.

The RD50 (exposure concentration producing a 50% respiratory rate decrease) of 1.5% MCI/MI was determined as 69 µg/L in rats (Rohm and Haas 1993).

19.6.3.4 Observation in humans

A modified Human Repeat Insult Patch Test (HRIPT) was conducted with human volunteers to determine the cumulative irritation potential of methylisothiazolone. The chemical was applied to the back under occlusive patches for 23 hours daily for 21 consecutive days at doses up to 1000 ppm. A challenge test was conducted after 10 to 14 days resting period. At the induction phase, a number of irritant reactions were observed but these were mostly transient in nature. One individual from the 1000 ppm introduction group showed cumulative irritation (Rohm and Haas 1994b).

No data were available for MCI/MI.

19.6.4 *Sensitisation*

19.6.4.1 Skin sensitisation

Animal data on the skin sensitisation effects of methylisothiazolone and MCI/MI are summarised from SCCNFP (2003) and SCCS (2009), and presented in Table A19.5.

Table A19.5 Skin sensitisation studies with methylisothiazolone, methylchloroisothiazolinone, and MCI/MI

Substance	Method, Species	Results	Reference
Methylisothiazolone	Buehler (OECD TG 406), Guinea pig	EC50 ≥5000 ppm (induction); EC50 ≥15 000 ppm (challenge)	Rohm and Haas (1989b)
14% MCI/MI	Buehler, Guinea pig	Sensitiser (7 studies)	SCCS (2009)
1.5% MCI/MI	GPMT, Guinea pig	Non-sensitiser at 56 ppm	Rohm and Haas (1977)

Substance	Method, Species	Results	Reference
14% MCI/MI	GPMT, Guinea pig	Non-sensitiser at 30 and 50 ppm	Rohm and Haas (2000k)
MCI/MI (unspecified concentration)	GPMT, Guinea pig	Sensitiser	Huntingdon Research Centre (2000)
14% MCI/MI (2.5:1 ratio)	GPMT, Guinea pig	Sensitiser at 0.025-10% (v/v); Non-sensitiser at 0.0025% (v/v)	TRC Ltd (2000)
14% MCI/MI	LLNA, Mouse	Sensitiser, EC3 = 30 ppm	Rohm and Haas (2000l)
14% MCI/MI	LLNA, Mouse	Sensitiser, EC3 = 70 ppm	Rohm and Haas (2000m)
Methylchloroisothiazolinone*	LLNA, Mouse	Sensitiser, EC3 = 81 ppm	Potter and Hazelton (1991)
Methylisothiazolone	LLNA, Mouse	Sensitiser, EC3 = 25 150 ppm	Rohm and Haas (1982d)
Methylchloroisothiazolinone*	LLNA, Mouse	EC3 = 2 µg/cm2	Potter and Hazelton (1995)
Methylisothiazolone	LLNA, Mouse	EC3 = 200 µg/cm2	Potter and Hazelton (1995)

** Not indicated whether methylchloroisothiazolinone was tested individually or as part of a mixture; EC50 – effective concentration to induce and elicit a response in 50% of the animals; GPMT – guinea pig maximisation test; LLNA – local lymph node assay; EC3 – effective concentration required to produce a three-fold increase in stimulation index*

Methylisothiazolone is a skin sensitiser and methylchloroisothiazolinone is a strong sensitiser in animals.

19.6.4.2 Respiratory sensitisation

No data were available for methylisothiazolone.

In a pulmonary hypersensitivity study, Dunkin Hartley guinea pigs were exposed to aerosolised MCI/MI at an induction concentration of 4.8 mg/m^3 for 80 minutes/day for five days. Challenge concentrations of 0.17, 0.35, and 0.72 mg/m^3 MCI/MI were given at 14 and 28 days after final induction. There were no immediate or delayed pulmonary hypersensitivity responses in the animals (Rohm and Haas 1995).

The study shows that MCI/MI is not a respiratory sensitiser. Based on a read across from the data available for MCI/MI, methylisothiazolone and methylchloroisothiazolinone are not respiratory sensitisers.

19.6.4.3 Observation in humans

In the modified HRIPT study of Rohm and Haas (1994b) previously described (refer to Section 19.6.2.2 Acute Dermal Toxicity), one individual from the 500 ppm induction group reacted on challenge and two individuals from the 1000 ppm induction group were considered to be sensitised. The authors concluded that the threshold for skin sensitisation was approximately 1000 ppm methylisothiazolone. In other similarly-designed HRIPT studies, aqueous solutions of methylisothiazolone were applied by occlusive patches to adult volunteers for a contact period of 24 hours/day, three times a week for three weeks. Under the conditions of the test, the chemical did not induce skin sensitisation at 100 ppm (Rohm and Haas 2000j), 200 ppm (Rohm and Haas 2000e), and 300 ppm (Rohm and Haas 2000f).

Contact allergy clinical data were available for MCI/MI. Patch testing results from 6958 patients from nine UK dermatology centres in 2004 to 2005 showed a mean positivity rate of 2% (Jong et al. 2007). In an allergy screening program for 9320 children (7 and 16 years old), 12.6% reported chronic/recurrent eczema symptoms. A sample (n = 229) of the children with eczema symptoms were patch tested, with 6.3% and 0.8% of the 7- and 16-year-old children, respectively, having MCI/MI contact allergy (Czarnobilska et al. 2009). Clinical and patch test information in 2005/2006 of 19 793 patients from 10 European countries (part of the European Surveillance System on Contact Allergies (ESSCA)) showed that MCI/MI contact allergy rates were 4.1% in Southern Europe and 2.1 to 2.7% in the other European regions (Uter et al. 2009).

19.6.5 *Repeat dose toxicity*

19.6.5.1 Oral

The key animal data on repeated dose oral toxicity of methylisothiazolone and MCI/MI are summarised from SCCNFP (2003) and SCCS (2009), and presented in Table A19.6. The Lowest-Observed-Adverse-Effect-Levels (LOAELs) and No-Observed-Adverse-Effect-Levels (NOAELs) for the active ingredients in the test substances are indicated for each study. The concentrations of MCI/MI and the ratio of methylchloroisothiazolinone and methylisothiazolone are also indicated, where available.

Table A19.6 Repeat oral toxicity studies with methylisothiazolone and MCI/MI

Substance **Doses**	**Species** **Test Method**	**LOAEL / NOAEL**	**Remarks**	**Reference**
Methylisothiazolone 0, 75, 250, or 1000 ppm	Crl:CD rats 90-day drinking water study	1000/250 ppm equivalent to 65.7/19.0 mg/kg bw/day in males 93.5/24.6 mg/kg bw/day in females	Decreased bodyweight gain (both sexes), decreased food consumption (males), and decreased water consumption (females) at the top dose. The magnitude of the changes was not specified. No mortality or other treatment-related effects.	Rohm and Haas (2000h)

Substance **Doses**	**Species** **Test Method**	**LOAEL / NOAEL**	**Remarks**	**Reference**
MCI/MI 0, 40-80, 132-260, 400-800 ppm	Charles River CD rats 90-day dietary study	No LOAEL or NOAEL could be established	No treatment-related effects observed at all doses.	Rohm and Haas (1975a)
15.1% MCI/MI 0, 2.38, 6.28, or 16.3 mg/kg bw/day (males) 0, 4.06, 10.8, or 24.7 mg/kg bw/day (females)	COBS CD (SD) rats 90-day drinking water study	16.3/6.28 mg/kg bw/day in males 24.7/10.8 mg/kg bw/day in females	At the top dose, effects were decreased bodyweight (males), increased liver weight (males), increased kidney weight (females), decreased total protein, and local irritation of the glandular mucosa of stomach (both sexes).	Rohm and Haas (1982b)
14.2% MCI/MI (2.6:1 ratio) 0, 2.0, 6.6, or 17.2 mg/kg bw/day (males) 0, 3.1, 9.8, or 25.7 mg/kg bw/day (females) Control group water with magnesium salt	Charles River Crl:CD BR rats 2-year drinking water study (OECD TG 453)	LOAEL and NOAEL based on local effects only 6.6/2.0 mg/kg bw/day in males 9.8/3.1 mg/kg bw/day in females	Dose-dependent decrease in water consumption reported at all doses but were attributed to unpalatability since water consumption in the control group was comparable to salt control group; Slight to moderate forestomach hyperplasia seen at the mid- and top dose groups.	Rohm and Haas (1983)
73–75% MCI/MI 0, 2.7, 8.9, 26.9 mg/kg bw/day (both sexes)	Beagle dogs Dietary study of unspecified duration	No LOAEL or NOAEL could be established	No treatment-related effects observed at all doses.	Rohm and Haas (1975b)
14% MCI/MI (2.7:1 ratio) 0, 150, 500, or 750 mg/kg diet (nominal doses for both sexes)	Beagle dogs 90-day dietary study (OECD TG 409)	No LOAEL or NOAEL could be established	Decreased bodyweight gain correlated with decreased food consumption at the top dose but attributed to unpalatability of the diet; No treatment-related effects observed at all doses.	Covance Laboratories (1998)

The only repeated oral dose toxicity study available for methylisothiazolone is the study of Rohm and Haas (2000h), with a NOAEL of 19 mg/kg bw/day based on decreased bodyweight and food and water consumption at the LOAEL of 65.7 mg/kg bw/day.

A NOAEL could not be established for systemic effects in the repeated dose toxicity studies for MCI/MI. Repeated oral exposure to MCI/MI was associated with local irritant effects on the stomach. The critical study for determining the effects of repeated exposures to MCI/MI is the study by Rohm and Haas (1983) as this study was of a longer duration and conducted in accordance with OECD guidelines. The LOAEL and NOAEL in this study were 2.0 and 6.6 mg/kg bw/day, respectively.

19.6.5.2 Dermal

No data were available for methylisothiazolone.

A formulation containing 14.2% MCI/MI (2.55:1 ratio) was applied by semi-occlusive dressing for six hours to intact skin of Sprague-Dawley rats. The application was conducted once daily for 91 days at doses of 0, 0.75, 3.75, or 18.75 mg/kg bw/day. Treatment-related skin reactions at all doses included slight to moderate erythema and desquamation, slight oedema and atonia, and eschar formation. Microscopic findings revealed treatment-related lesions such as inflammation, parakeratosis, and acanthosis at the treated sites. The LOAEL and NOAEL identified for local effects in this study, reported as the MCI/MI equivalent of the doses, were ≥0.104 and <0.104 mg/kg bw/day MCI/MI, respectively (Hazelton Europe 1994).

In another study, a formulation containing 14.6% MCI/MI was applied once daily for 65 days to New Zealand White rabbit skin at doses of 0, 100, 200, or 400 ppm. At the low, mid- and top doses, deaths were reported as 50%, 83%, and 67%, respectively. Ocular and nasal discharge was seen in the treated rabbits. There were no observed dose-related changes to body weight, food consumption, haematology, biochemistry and urinalysis. The authors concluded that the mortalities were due to an aggravation of an endemic pulmonary disease induced by dermal irritation and not necessarily a direct toxic effect of MCI/MI (Rohm and Haas 1982a).

19.6.5.3 Inhalation

No data were available for methylisothiazolone.

In a study conducted in accordance with OECD TG 413, Charles River Crl: CD(SD) BR rats were exposed to an aerosol product containing 14% MCI/MI for 13 weeks at six hours/day, five days/week. The doses were 0, 0.34, 1.15, or 2.64 mg/m^3 MCI/MI. At the top dose, effects included decreased bodyweight gain and signs consistent with sensory irritation such as chromorhinorrhoea, rhinorrhoea, eye squint, bradypnoea, and dyspnoea. Slight to moderate eosinophilic droplets in the anterior mucosa of the nasal turbinates and slight rhinitis in the lining of the nasal cavity were also reported at the top dose. At the mid-dose, slight incidence of rhinitis was observed. The study authors noted that eosinophilic droplets in the nasal turbinates and rhinitis were possibly reversible responses to upper respiratory tract inflammation. The LOAEC and NOAEC for this study were 2.64 mg/m^3 and 1.15 mg/m^3, respectively (Rohm and Haas 1984).

19.6.5.4 Observation in humans

No data were available.

19.6.6 *Genotoxicity*

In vitro and *in vivo* data on genotoxicity of methylisothiazolone and MCI/MI are summarised from SCCNFP (2003, 2004) and SCCS (2009), and presented in Table A19.7 and Table A19.8.

Table A19.7 In vitro genotoxicity studies with methylisothiazolone and MCI/MI

Substance	Test	Results	Reference
Methylisothiazolone	Reverse mutation test in *Salmonella typhimurium* (OECD TG 471)	Negative with and without activation	Rohm and Haas (1999f)
Methylisothiazolone	Gene mutation test in CHO cells (OECD TG 476)	Negative with and without activation up to 50 µg/mL	Rohm and Haas (1999e)
Methylisothiazolone	Chromosome aberration test in CHO cells (OECD TG 473)	Positive with and without activation up to 16.9 µg/mL	Rohm and Haas (2000i)
CMI/MI	4 Reverse mutation tests in *S. typhimurium*	Positive only in strain TA100 without activation	SCCS (2009)
CMI/MI	Reverse mutation test in *S. typhimurium*	Positive in strains TA100/102 with activation and positive in TA98/100/102/1535/1537 without activation	SCCS (2009)
CMI/MI	2 Gene mutation tests in mouse lymphoma cells	Positive	SCCS (2009)
CMI/MI	*In vitro* UDS assay in primary rat hepatocytes	Negative	SCCS (2009)
CMI/MI	Chromosome aberration test in CHO cells	Negative	SCCS (2009)

CHO – Chinese hamster ovary; UDS – unscheduled deoxyribonucleic acid (DNA) synthesis

Table A19.8 In vivo genotoxicity studies with methylisothiazolone and MCI/MI

Substance	Test	Results	Reference
Methylisothiazolone	Crl:CD-1 mice micronucleus test in bone marrow cells (OECD TG 474) from gavage administration at doses of 10, 50, or 100 mg/kg bw	Negative	Rohm and Haas (2000g)
Methylisothiazolone	Crl:CD-1 mice UDS by gavage at doses of 100, 200, or 300 mg/kg bw	Negative	Rohm and Haas (2000n)
CMI/MI	1 Rat chromosome aberration test in bone marrow cells from single gavage or feed administration at doses up to 28 mg active ingredient/kg	Negative	SCCS (2009)
CMI/MI	3 Mouse chromosome aberration tests in bone marrow cells from single gavage administration at doses up to 30 mg active ingredient/kg	Negative	SCCS (2009)
CMI/MI	2 Mouse micronucleus assay tests from gavage administration at doses up to 50 mg active ingredient/kg	Negative	SCCS (2009)
CMI/MI	1 Mouse micronucleus assay test from gavage	Negative	SCCS (2009)

Substance	Test	Results	Reference
	administration at doses up to 4.17 mg active ingredient/kg		
CMI/MI	2 UDS tests in rats by gavage at doses up to 500 mg active ingredient/kg	Negative	SCCS (2009)

Methylisothiazolone was positive in an *in vitro* chromosome aberration test (Rohm and Haas 2000i) but this was not confirmed by the negative results in the *in vivo* micronucleus test (Rohm and Haas 2000g) and UDS assay (Rohm and Haas 2000n).

The positive results for MCI/MI in *in vitro* gene mutation assays in bacteria and mammalian cells (SCCS 2009) were not corroborated by the negative results in the *in vitro* and *in vivo* UDS assays (SCCS 2009). *In vivo* chromosome aberration and micronucleus tests were also negative for the mixture (SCCS 2009).

Based on available data, methylisothiazolone and MCI/MI are not genotoxic. On this basis methylchloroisothiazolinone is also not genotoxic.

19.6.7 *Carcinogenicity*

No data were available for methylisothiazolone.

In the study by Rohm and Haas (1983) in Charles River Crl:CD BR rats described earlier (refer to Table A19.6), there were no treatment-related effects in the type or incidence of neoplasms at up to the highest dose tested, 300 ppm, equivalent to 17.2 mg/kg bw/day MCI/MI in males and 25.7 mg/kg bw/day MCI/MI in females.

The study shows that MCI/MI is not carcinogenic and based on reading across from the available data, methylisothiazolone and methylchloroisothiazolinone are not carcinogenic.

19.6.8 *Reproductive toxicity*

19.6.8.1 Fertility

No data were available for methylisothiazolone.

In the study by Rohm and Haas (1982b) described earlier (refer to Table A19.6), there were no adverse effects observed on the reproductive capability of male and female COBS CD rats up to and including the highest dose tested of 16.3 mg/kg bw/day MCI/MI in males and 24.7 mg/kg bw/day MCI/MI in females.

Methylisothiazolone and methylchloroisothiazolinone are not considered to be toxic to fertility based on available data for MCI/MI.

19.6.8.2 Developmental toxicity

No data were available for methylisothiazolone.

In a two-generation reproductive toxicity study conducted in accordance with OECD TG 416, a formulation containing 14.76% MCI/MI was administered to Crl:CD BR rats via drinking water at doses of 0, 0 (salt control), 30, 100, or 300 ppm. The formulation was given to the males and females (P1) and second parent (P2) generations. Treatment-related histopathological changes in the stomach, such as erosion of glandular mucosa, oedema and inflammation in the submucosa of the glandular and non-glandular stomach, were observed for P1 and P2 generations at the 100 and 300 ppm dose groups. There were no

developmental effects observed in the pups of both generations (Rohm and Haas 1998). The parental NOAEL for local effects was 30 ppm, equivalent to 2.8 to 4.4 mg/kg bw/day MCI/MI in the P1 generation and 4.3 to 5.5 mg/kg bw/day MCI/MI in the P2 generation, based on stomach irritation. A NOAEL for developmental effects could not be established in the study.

Methylisothiazolone and methylchloroisothiazolinone are not considered to be developmental toxicants based on reading across from data available for MCI/MI.

19.6.9 *Other health effects*

No data were available.

19.7 Health hazard summary

19.7.1 *Critical health effects*

Methylisothiazolone has moderate acute oral and dermal toxicity and high acute inhalation toxicity, is corrosive to the skin, and is a skin sensitiser. Based on a read across from data for MCI/MI, methylchloroisothiazolinone has high acute oral, dermal, and inhalation toxicity, and is corrosive to the skin. Methylchloroisothiazolinone is also a strong skin sensitiser.

The critical health effect of the chemicals is skin sensitisation. In high concentrations, the chemicals are also corrosive.

For methylisothiazolone, the most appropriate NOAEL is 19 mg/kg bw/day based on decreased bodyweight and food and water consumption from the 90-day oral study of Rohm and Haas (2000h). For methylchloroisothiazolinone, no adverse systemic effects were observed at the highest dose of 17.2 mg/kg bw/day from the two-year oral study of Rohm and Haas (1983) on MCI/MI.

Methylisothiazolone is not genotoxic. Methylchloroisothiazolinone, based on a read across data available for MCI/MI, is not genotoxic. Methylisothiazolone and methylchloroisothiazolinone are neither carcinogenic nor reproductive toxicants based on read across from data available for MCI/MI.

19.7.2 *Hazard classification*

Methylisothiazolone is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (ACCHS) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A19.9. These NICNAS recommendations do not consider physical or environmental hazards.

Table A19.9 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Toxic by inhalation (T; R23), Conc. ≥25% Harmful by inhalation (X_n; R20), 3% ≤Conc. <25% Toxic if swallowed (T; R25), Conc. ≥25% Harmful if swallowed (X_n; R22), 3% ≤Conc. <25%	Toxic if inhaled – Cat. 3 (H331), Conc. ≥25% Harmful if inhaled – Cat. 4 (H332), 3% ≤Conc. <25% Toxic if swallowed – Cat. 3 (H301), Conc. ≥25% Harmful if swallowed – Cat. 4 (H302), 3% ≤Conc. <25%

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
	Harmful in contact with skin (X_n; R21), Conc. ≥25%	Harmful in contact with skin – Cat. 4 (H312), Conc. ≥25%
Irritation / Corrosivity	Causes burns (C; R34), Conc. ≥0.6% Irritating to skin (X_i; R38), 0.06% ≤Conc. <0.6%	Causes severe skin burns and eye damage – Cat. 1B (H314), Conc. ≥0.6% Causes serious eye irritation – Cat. 2 (H319), 0.06% ≤Conc. <0.6% Causes skin irritation – Cat. 2 (H315), 0.06% ≤Conc. <0.6%
Sensitisation	May cause sensitisation by skin contact (X_i; R43), Conc. ≥0.01%	May cause an allergic skin reaction – Cat. 1B (H317), Conc. ≥0.01%

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System(UNECE 2009)

Methylchloroisothiazolinone is recommended by NICNAS to Safe Work Australia for classification and labelling under the current ACCHS and the GHS as shown in Table A19.10. These NICNAS recommendations do not consider physical or environmental hazards.

Table A19.10 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Toxic by inhalation (T; R23), Conc. ≥25% Toxic in contact with skin (T; R24), Conc. ≥25% Toxic if swallowed (T; R25), Conc. ≥25% Harmful by inhalation (X_n; R20), 3% ≤Conc. <25% Harmful in contact with skin (X_n; R21), 3% ≤Conc. <25% Harmful if swallowed (X_n; R22), 3% ≤Conc. <25%	Toxic if inhaled – Cat. 3 (H331), ≥25% Toxic in contact with skin – Cat. 3 (H311), Conc. ≥25% Toxic if swallowed – Cat. 3 (H301), Conc. ≥25% Harmful if inhaled – Cat. 4 (H332), 3% ≤C <25% Harmful in contact with skin – Cat. 4 (H312), 3% ≤C <25% Harmful if swallowed – Cat. 4 (H302), 3% ≤C <25%
Irritation / Corrosivity	Causes burns (C; R34), Conc. ≥0.6% Irritating to eyes (X_i; R36), 0.06% ≤Conc. <0.6% Irritating to skin (X_i; R38), 0.06% ≤Conc. <0.6%	Causes severe skin burns and eye damage – Cat. 1B (H314), Conc. ≥0.6% Causes serious eye irritation – Cat. 2 (H319), 0.06% ≤C <0.6% Causes skin irritation – Cat. 2 (H315), 0.06% ≤C <0.6%
Sensitisation	May cause sensitisation by skin contact (X_i; R43)	May cause an allergic skin reaction – Cat. 1A (H317)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

The hazard assessment for MCI/MI confirms the existing hazard classification under the ACCHS (NOHSC 2004).

The equivalent classification and labelling under the adopted GHS is shown in Table A19.11. These NICNAS recommendations do not consider physical or environmental hazards.

Table A19.11 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Acute toxicity	Toxic if inhaled – Cat. 3 (H331), Conc. ≥25% Toxic in contact with skin – Cat. 3 (H311), Conc. ≥25% Toxic if swallowed – Cat. 3 (H301), Conc. ≥25% Harmful if inhaled – Cat. 4 (H332), 3% ≤C <25% Harmful in contact with skin – Cat. 4 (H312), 3% ≤C <25% Harmful if swallowed – Cat. 4 (H302), 3% ≤C <25%
Irritation / Corrosivity	Causes severe skin burns and eye damage – Cat. 1B (H314), Conc. ≥0.6% Causes serious eye irritation – Cat. 2 (H319), 0.06% ≤C <0.6% Causes skin irritation – Cat. 2 (H315), 0.06% ≤C <0.6%
Sensitisation	May cause an allergic skin reaction – Cat. 1 (H317), 0.0015% ≤C <0.06%

** Globally Harmonised System (UNECE 2009)*

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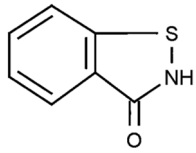
A20 Benzisothiazolinone

CAS No.	CAS Name
2634-33-5	1,2-Benzisothiazol-3(2H)-one

20.1 Chemical identity

Information on chemical identity was obtained from ChemID*plus* (2012) and SCCS (2012). Details are provided in Table A20.1.

Table A20.1 Chemical identity

	Benzisothiazolinone
Synonyms	1,2-Benzisothiazolin-3-one Benzisothiazolinone
Structural formula	
Molecular formula	C_7H_5NOS
Molecular weight	151.19
Appearance and odour	Off-white to yellowish solid
SMILES Notation	C1(=O)c2c(cccc2)SN1

20.2 Physical properties

The physical properties of the chemical are presented in Table A20.2. The information was obtained from SCCS (2012).

Table A20.2 Physical properties

Property	**Value**
Melting point	156.6 °C
Boiling point	327.6 °C
Density	1483 kg/m^3 at 20 °C
Vapour pressure	3.7 x 10^{-7} kPa at 25 °C
Water solubility	1.1 g/L at 20 °C
Partition coefficient n-octanol/water (log K_{ow})	0.4 at 20 °C

20.3 Current regulatory controls

The document from here on refers to 1,2-Benzisothiazol-3(2H)-one (CAS No. 2634-33-5) as 'benzisothiazolinone', one of the synonyms of the chemical.

20.3.1 *Hazard classification for occupational health and safety*

The chemical is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) with the following risk phrases:

- X_n (Harmful); R22
- X_i (Irritant); R38, R41, R43

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration of the chemicals in the mixtures. The risk phrases for different concentration (Conc) ranges are:

- Conc ≥25%: X_n, N: R22 (Harmful if swallowed), R38 (Irritating to skin), R41 (Risk of serious eye damage), R43 (May cause sensitisation by skin contact)
- 20% ≤Conc <25%: X_i: R38, R41, R43
- 10% ≤Conc <20%: X_i: R41, R43
- 5% ≤Conc <10%: X_i: R36 (Irritating to eyes), R43
- 0.05% ≤Conc <5%: X_i: R43.

20.3.2 *Occupational exposure standards*

20.3.2.1 Australia

No specific exposure standards were available.

20.3.2.2 International

No specific exposure standards were available.

20.3.3 *Australian food standards*

No Australian food standards were identified.

20.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian drinking water guidelines (National Health and Medical Research Council (NHMRC) 2011).

20.3.5 *Additional controls*

20.3.5.1 Australia

The chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

20.3.5.2 International

No international restrictions were identified.

20.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

20.5 Health hazard characterisation

The information on health hazards is obtained from the following comprehensive reviews of benzisothiazolinone: SCCNFP (2004) and SCCS (2012). The review by the Scientific Committee on Consumer Safety (SCCS) is an updated version of the previous review by the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP). Unless otherwise noted, references to individual studies below are taken from this review.

20.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

20.5.1.1 Oral absorption

No data were available. The SCCS (2012) assumed a 50% oral absorption but did not provide details of how this value was obtained. Based on the uptake of the chemical from the animal studies summarised below, the chemical is absorbed through the oral route.

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

20.5.1.2 Dermal absorption

In an *in vitro* human skin absorption study conducted to Organisation of Economic Co-operation and Development Technical Guideline (OECD TG) 428, 0.01% w/v aqueous benzisothiazolinone was applied to human dermatomed skin. The absorbed dose of the chemical was 25.63% and the total dislodgeable dose was 42.05% of the applied dose (Charles River Laboratories 2008). The SCCS (2012) concluded that the applicable dermal absorption was 61.9% of the applied dose (1.29 µg/cm2) when 0.01% benzisothiazolinone aqueous was applied.

For the purposes of risk assessment, 100% dermal absorption in humans is therefore assumed.

20.5.1.3 Inhalation absorption

No data were available.

For the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

20.5.1.4 Distribution

No data were available.

20.5.1.5 Metabolism

No data were available.

20.5.1.6 Excretion

No data were available.

20.5.2 *Acute toxicity*

20.5.2.1 Oral

Sprague-Dawley rats were administered 82.3% benzisothiazolinone by gavage at doses of 823, 1646, or 4115 mg/kg bw. This study was conducted according to the United States Environmental Protection Agency Office of Pesticide Programs (EPA OPP) 81–1. The effects observed at any of the doses were not specified. The reported acute oral median lethal dose (LD50), calculated using Probit Analysis, was 2100 mg/kg bw for males. The reported acute oral LD50 for females, estimated graphically, was 1050 mg/kg bw (Product Safety Labs 1996a).

The study shows that benzisothiazolinone has low to moderate acute toxicity by the oral route in rats.

20.5.2.2 Dermal

Topical application of a single dose of 4115 mg/kg bw of 82.3% benzisothiazolinone to Sprague-Dawley rats showed no gross toxicity, adverse effects, or abnormal behaviour (details not provided). This study was conducted in accordance with EPA OPP 81–2. The acute dermal LD50 was >4115 mg/kg bw (Product Safety Labs 1996d).

The study shows that benzisothiazolinone has low acute toxicity by the dermal route in rats.

20.5.2.3 Inhalation

No data were available.

20.5.2.4 Observation in humans

No data were available.

20.5.3 *Irritation / Corrosivity*

20.5.3.1 Skin irritation

In a skin irritation test in New Zealand albino rabbits conducted in accordance with EPA OPP 81-5, 82.3% benzisothiazolinone was applied by semi-occlusion. Well-defined moderate erythema and oedema were observed at all treated sites one hour after patch removal. The chemical was found to be a skin irritant based on the conditions of the test (Product Safety Labs 1996c).

The effects observed in this test demonstrate that benzisothiazolinone is a skin irritant in animals.

20.5.3.2 Eye irritation

In an eye irritation test in New Zealand albino rabbits conducted in accordance with EPA OPP 81-4, 82.3% benzisothiazolinone was instilled undiluted to the eyes. All of the treated eyes showed severe to maximal irritation with corneal opacity, iritis and conjunctivitis from 1 to 48 hours with the severity of irritation increasing with time. The chemical was found to be severely irritating to the rabbit eye (Product Safety Labs 1996b).

An *in vitro* assessment of the eye irritancy potential of benzisothiazolinone using the bovine corneal opacity and permeability assay is available. Bovine eyes were exposed to up to 7500 ppm aqueous solution of the chemical and corneal opacity and permeability were determined to give an *in vitro* score. The chemical was considered to be non-irritating to the eyes at all dose levels under the conditions of the test (Thor Specialities UK Limited 2003). The SCCS (2012) noted that the method used in this test is non-validated.

The effects observed in the *in vivo* test demonstrate the severe eye irritation potential of benzisothiazolinone.

20.5.3.3 Respiratory irritation

No data were available.

20.5.3.4 Observation in humans

A randomised double blind open epicutaneous application study, aimed to compare the effects of a cream with and without a preservative (containing 2.5% benzisothiazolinone and 2.5% methylisothiazolinone), was conducted (Sequani Consumer Limited 2002a). Subjects with determined sensitivity to isothiazolinones were excluded from the study. The treatment regime included twice daily application of 1.5 mL of test cream and control for four weeks, assessing the skin reactions at two and four weeks after application. Irritant effects such as redness or itching, tingling or stinging sensation were reported on application but disappeared after product absorption. Under the conditions of the test, the cream was found to be tolerated by the individuals treated (Sequani Consumer Limited 2002a).

These studies demonstrate that benzisothiazolinone is a skin irritant in humans.

20.5.4 *Sensitisation*

20.5.4.1 Skin sensitisation

In a guinea pig maximisation test (GPMT) (OECD TG 406), benzisothiazolinone at 79.8% was found to be a moderate contact sensitiser (Quintiles England Limited 1997). In a Buehler test in accordance with EPA OPP 81-6 in Hartley albino guinea pigs, the chemical (at 82.3%) was not a sensitiser based on the test conditions (Product Safety Labs 1996e).

An EC3 (the effective concentration required to produce a three-fold increase in stimulation index)of 2.3% was identified for benzisothiazolinone in a local lymph node assay (LLNA) dataset review; however, the experimental details were not provided (Roberts et al. 2007).

These studies show benzisothiazolinone causes skin sensitisation in animals.

20.5.4.2 Respiratory sensitisation

No data were available.

20.5.4.3 Observation in humans

Volunteers with identified sensitivity to isothiazolinones were included in a randomised double blind open epicutaneous application study aimed to compare the effects of a cream with and without a preservative containing 0.15% w/w benzisothiazolinone. The application regime was similar to the study of Sequani Consumer Limited (2002a). A flare of eczema was noticed in some of the individuals who were later withdrawn from the study (Sequani Consumer Limited 2002b). SCCS (2012) noted that limited conclusions can be drawn from this study.

Occupational dermatitis has been reported in water-based solutions containing benzisothiazolinone from cutting fluids, paint manufacture, pottery mould-makers, acrylic emulsions manufacture, printer, and paper makers (Burden et al. 1994; Dias et al. 1992; Greig 1991; Sanz-Gallen et al. 1992; Geier et al. 2004; Walker et al. 2004). The chemical has also been used as a slimicide in disposable powder-free polyvinyl chloride (PVC) glove manufacture. Allergic contact dermatitis was reported in individuals wearing such gloves with a concentration of 20 ppm benzisothiazolinone causing sensitisation (Aalto-Korte et al. 2007).

These studies demonstrate that benzisothiazolinone may cause skin sensitisation in humans.

20.5.5 *Repeat dose toxicity*

20.5.5.1 Oral

Benzisothiazolinone at 84.29% was administered by gavage to Wistar rats for 28 days (OECD TG 407) at doses of 12.63, 37.89, or 113.67 mg/kg bw/day. There were no adverse effects observed at the lowest dose (Toxicology Department Rallis Research Centre 2002a). Histopathological lesions were observed in the non-glandular stomach only at the 37.89 mg/kg bw/day dose. At the highest dose significant decrease in bodyweight gain in males (no details reported) and slight salivation, in all males and two females, were observed. Based on the histopathological lesions found in the non-glandular stomach, the No-Observed-Adverse-Effect-Level (NOAEL) for this study was determined to be 12.63 mg/kg bw/day. The SCCS (2012) concluded that the adverse effects reported in this study were most likely due to the irritant property of the chemical.

Wistar rats were administered 84.9% benzisothiazolinone by gavage at doses of 8.42, 25.26, or 63.15 mg/kg bw/day for 90 days (OECD TG 408) (Toxicology Department Rallis Research Centre 2002b). There were no treatment-related clinical signs, neurological effects or adverse effects on growth reported in all dose groups. At the 25.26 mg/kg bw/day group, treatment-related effects observed included macroscopic and histological changes in the non-glandular stomach region such as increased incidence of lesions (hyperkeratosis, epithelial hyperplasia, and ulceration) in males and females. The effects were reversible in the recovery group and are likely to be due to the irritant property of the chemical. At the 63.15 mg/kg bw/day group, treatment-related salivation was seen in both sexes. Bodyweight gain was significantly reduced in the males. In both sexes, increased incidences of histopathological lesions in the non-glandular stomach (hyperkeratosis, epithelial hyperplasia, ulceration, and keratin cysts) were observed. This review confirms the SCCS (2012) findings that the histopathological lesions reported at the mid-dose was due to the irritant property of the chemical and the NOAEL for systemic effects is 25.26 mg/kg bw/day.

Repeated oral exposure to benzisothiazolinone in rats was consistently associated with increased incidence of histopathological lesions on the non-glandular stomach such as hyperkeratosis, epithelial hyperplasia, ulceration, and keratin cysts. These effects are attributed to local irritant effects of the chemical. A NOAEL of 25.26 mg/kg bw/day was

established from the 90-day study based on systemic effects at the Lowest-Observed-Adverse-Effect-Level (LOAEL) of 63.15 mg/kg bw/day (Toxicology Department Rallis Research Centre 2002b).

20.5.5.2 Dermal

No data were available.

20.5.5.3 Inhalation

No data were available.

20.5.5.4 Observation in humans

No data were available.

20.5.6 *Genotoxicity*

An *in vitro* mammalian cell gene mutation test (OECD TG 476) showed that benzisothiazolinone was not mutagenic up to 5.2 µg/mL with and without metabolic activation (Toxicology Department Rallis Research Centre 2002e). The chemical was not clastogenic to Chinese hamster ovary (CHO) cells with and without metabolic activation in an *in vitro* mammalian chromosome aberration test conducted to OECD TG 473 at levels up to 6.4 µg/mL (Toxicology Department Rallis Research Centre 2002c).

Benzisothiazolinone was not clastogenic in Swiss albino mice in an *in vivo* mammalian erythrocyte micronucleus test conducted to OECD TG 474 at doses up to 210.5 mg/kg (Toxicology Department Rallis Research Centre 2002d). In an unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo* conducted to OECD TG 486, the chemical did not induce UDS in Wistar rat hepatocytes at concentrations up to 750 mg/kg (RCC Cytotest Cell Research 2002).

Benzisothiazolinone is not considered to be genotoxic.

20.5.7 *Carcinogenicity*

No data were available.

20.5.8 *Reproductive toxicity*

20.5.8.1 Fertility

In a two-generation reproductive toxicity study (EPA OPPTS 870.3800), Crl:W1 rats were fed benzisothiazolinone in the diet at concentrations of 250, 500, or 1000 ppm (24, 50, 100 mg/kg bw/day) (Covance 2003). The same doses were administered to the parent (P) and first filial (F1) generation. Parents received the chemical for 10 weeks before being paired for up to two weeks. Dosing continued during the pairing period, and throughout the resulting pregnancies. The treatment of the F1 generation was continued during maturation, mating, and weaning of the second (F2) generation offspring. For the P generation, there were no treatment-related effects observed on bodyweight, clinical chemistry, and fertility in all dose groups. At the 1000 ppm group, the effects observed were increased mean liver weight in males, decreased mean testes weight, and presence of limiting ridge hyperplasia in the stomach. No details of the changes were provided. Pup weights in the high dose group were slightly low up to two weeks post-partum but returned to normal later. In the F1 generation, effects observed at the 1000 ppm group were slightly lower (magnitude not specified) F2 pup survival and F2 mean pup weight gain. At the 500 and 1000 ppm groups,

limiting ridge hyperplasia in the stomach was reported, more prominently for the females at the high dose group with squamous cell hyperplasia, fore stomach gastritis, hyperkeratosis, and erosion/ulcer. There were no adverse effects at the lowest dose of benzisothiazolinone tested. The NOAEL for parental local effect is 50 mg/kg bw/day. No fertility effects have been observed in the absence of parental toxicity.

This study shows that dietary exposure to benzisothiazolinone in rats showed no fertility effects. The NOAEL for local effect of the parent generation is 50 mg/kg bw/day.

20.5.8.2 Developmental toxicity

No data were available.

20.5.9 *Other health effects*

No data were available.

20.6 Health hazard summary

20.6.1.1 Critical health effects

Benzisothiazolinone demonstrates acute oral toxicity effects, irritation of the skin, corrosive effects in the eyes, and skin sensitisation.

Repeated oral exposure caused increased incidence of histopathological lesions on the non-glandular stomach which are attributed to the local irritant effects of the chemical. These effects are consistent with the two-generation reproductive toxicity study by Covance (2003), with the most appropriate NOAEL for risk assessment purposes of 25.26 mg/kg bw/day based on decrease in bodyweight gain and salivation at the LOAEL of 63.15 mg/kg bw/day.

The chemical is not genotoxic. Benzisothiazolinone shows no fertility effects.

20.6.1.2 Hazard classification

The hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A20.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A20.3 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* Classification
Acute toxicity	Harmful if swallowed – Cat. 4 (H302)
Irritation	Causes skin irritation – Cat. 2 (H315) Causes serious eye damage – Cat. 1 (H318)
Sensitisation	May cause an allergic skin reaction – Cat. 1 (H317)

** Globally Harmonised System (UNECE 2009)*

20.7 References

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Product Safety Labs (1996c) Study No. 3861 Primary skin irritation. Sponsor: Hüls America Inc., joint ownership: Prom Chem Ltd and Thor GmbH, 24-01-1996.

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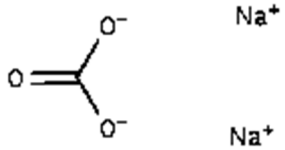
A21 Soda ash

CAS No.	CAS Name
497-19-8	Carbonic acid sodium salt (1:2)

21.1 Chemical identity

The following chemical identity information was obtained from Organisation for Economic Cooperation and Development (OECD) (OECD 2002) and other resources identified in brackets. Table A21.1 provides details of the chemical identity. The chemical is more commonly known as sodium carbonate.

Table A21.1 Chemical identity

	Soda ash
Synonyms	Carbonic acid disodium salt Disodium carbonate Calcined soda (Clayton and Clayton 1993) Soda ash
Structural formula (ChemID*plus* 2012)	
Molecular formula	Na_2CO_3
Molecular weight	106
Appearance and odour	Sodium carbonate is a white, crystalline, hygroscopic powder with purity >98%. Sodium carbonate is available as light soda and dense soda (OECD 2002).
SMILES notation	C(=O)([O-])[O-].[Na+].[Na+] (eChemPortal 2013)

21.2 Physical properties

The following information on the physical properties was obtained from OECD (2002) and other resources identified in brackets. The physical properties of sodium carbonate are presented in Table A21.2.

Table A21.2 Physical properties

Property	Value
Melting point	851 °C
Boiling point	Decomposes at higher temperatures

Property	Value
Density	2.52 kg/m^3
Vapour pressure	Negligible at 20 °C
Water solubility	215 g/L at 25 °C
Partition coefficient n-octanol/water (log K_{ow})	Not relevant

21.3 Current regulatory controls

21.3.1 *Hazard classification for occupational health and safety*

Sodium carbonate is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) with the following risk phrase:

- Xi; R36 (Irritant; irritating to eyes).

Mixtures containing the chemical are classified as hazardous based on the concentration (Conc) of the chemical in the mixtures with the following risk phrase:

- Conc ≥20%: Xi; R36 (Irritating to eyes).

21.3.2 *Occupational exposure standards*

21.3.2.1 Australia

The occupational exposure standards for sodium carbonate (Safe Work Australia 2013) are:

- Time Weighted Average (TWA) of 7.5 mg/m^3 (5 ppm)
- Short-Term Exposure Limit (STEL) of 15 mg/m^3 (10ppm).

21.3.2.2 International

Occupational exposure limits for sodium carbonate identified internationally are provided below (Galleria Chemica 2013).

US Department of Energy Temporary Emergency Exposure Limits (TEELs):

- TEEL-0 = 10 mg/m^3
- TEEL-1 = 30 mg/m^3
- TEEL-2 = 50 mg/m^3
- TEEL-3 = 500 mg/m^3.

No other occupational exposure limit exists internationally specifically for sodium carbonate; however, many countries have assigned a generic TWA exposure limit of 10 mg/m^3 (inhalable dust) and 3 mg/m^3 (respirable dust) for Particles Not Otherwise Classified (PNOC).

21.3.3 *Australian food standards*

Sodium carbonate is permitted in Australia for use as an acidity regulator (Food Standards Australia New Zealand 2013).

Sodium carbonate is allotted an International Numbering System of food additives number: INS 500.

21.3.4 *Australian drinking water guidelines*

Sodium carbonate was endorsed by the National Health and Medical Research Council (NHMRC) for use as a drinking water treatment chemical in 1983 (NHMRC 2011). In water treatment, sodium carbonate is used mainly as a source of alkalinity and pH adjustment. Typical sodium carbonate concentrations used can vary from 5 to more than 500 mg/L, and the appropriate concentration is determined by laboratory trials.

21.3.5 *Additional controls*

21.3.5.1 Australia

Sodium carbonate is included in Schedule 5, Schedule 6 and Appendix C of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

- Schedule 5: ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination for non-domestic use in:

  (a) solid orthodontic device cleaning preparations, the pH of which as an “in-use”‖ aqueous solution is more than 11.5

  (b) solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solution or mixture is more than 11.5 but less than or equal to 12.5

  (c) other solid preparations, the pH of which in a 10 g/L aqueous solution is more than 11.5 or

  (d) liquid or semi-solid preparations, the pH of which is more than 11.5, unless:

  b. (i) food additive preparations for domestic use or

  c. (ii) automatic dish washing preparations for domestic use with a pH of more than 12.5, except when separately specified in these Schedules.

- Schedule 6: ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination for non-domestic use in:

  (a) solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solution or mixture is more than 12.5 or

  (b) liquid or semi-solid automatic dishwashing preparations, the pH of which is more than 12.5.

- Appendix C: ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination for domestic use in:

  (a) liquid or semi-solid food additive preparations, the pH of which is more than 11.5

  (b) solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solution or mixture is more than 12.5 or

  (c) liquid or semi-solid automatic dishwashing preparations, the pH of which is more than 12.5.

The SUSMP also recommends appropriate '*Warning Statements*' and '*Safety Directions*' for sodium carbonate when used in consumer products.

Sodium carbonate is not included in the Australian Dangerous Goods Code Edition 7(ADG7) (National Transport Commission 2007). However, corrosive inorganic basic (alkali) liquids are included in Class 8 and packaging groups I and II of the ADG7.

21.3.5.2 International

No international restrictions were identified.

21.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

21.5 Health hazard characterisation

The information on health hazards is obtained from the SID Initial Assessment Report (SIAR) on Sodium carbonate (OECD 2002). Unless otherwise noted, references to individual studies below are taken from this review.

Where toxicity data for sodium carbonate were unavailable, data were read across from sodium bicarbonate. Dissociation of sodium carbonate in water gives rise to carbonate and bicarbonate ions.

21.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

Human blood and cytosol have a pH of 7.4. Irreversible damage to tissue occurs if the pH falls below 7.0 or rises above 7.8. The bicarbonate buffer system is the major extracellular buffer in the blood and interstitial fluid of vertebrates that maintains the pH and is described by the following equation:

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

When sodium carbonate comes into contact with liquids, including body fluids, it dissociates into sodium and carbonate ions. These are normal physiological constituents in humans. The carbonate ion could potentially increase the pH of the blood. Compensatory mechanisms for acid-base disturbances function to alter the ratio of HCO_3- to PCO_2 in order to return the pH of the blood to normal (OECD 2002).

21.5.1.1 Oral absorption

Information on the rate of oral absorption of sodium carbonate is not available. Oral uptake of sodium carbonate results in its dissociation into sodium and carbonate ions. Sodium ion is readily absorbed throughout the small intestine and is subject to rapid exchange by the large majority of cells in the body. Carbonate ions are neutralised in the stomach by the gastric acids. Significant amounts of gastric acids are present in the stomach (pH about 2) which will result in a formation of bicarbonate and / or carbon dioxide.

A 100% absorption rate for sodium carbonate is assumed by the oral route.

21.5.1.2 Dermal absorption

No data were available on dermal absorption of sodium carbonate. Absorption of ionic salts by the skin is essentially negligible (Schaefer and Redelmeier 1996). Sodium carbonate is not expected to be absorbed from the skin and be systemically available.

21.5.1.3 Inhalation absorption

Information on inhalation absorption of sodium carbonate is not available. However, based on adverse effects noted in a rat repeated inhalation dose study (Reshetyuk and Shevchenko 1966; OECD 2002), 100% inhalation absorption is assumed for human health risk assessment.

21.5.1.4 Distribution and metabolism

The main regulation of the concentration of sodium ions in the body takes place in the kidney. However, the uptake of sodium ions, via exposure to sodium carbonate, is considered much less than the uptake of sodium ions via food.

Any change in the physiological concentration of carbonate ions as a result of increased exposure/absorption of carbonate is regulated physiologically by the bicarbonate buffer system in the body (Johnson and Swanson 1987).

21.5.1.5 Excretion

Carbonate ions are neutralised to carbon dioxide in the body. The CO_2 from the tissues diffuses rapidly into red blood cells, where it is hydrated with water to form carbonic acid. This reaction is accelerated by carbonic anhydrase, an enzyme present in high concentrations in red blood cells. The carbonic acid formed dissociates into bicarbonate and hydrogen ions. Most of the bicarbonate ions diffuse into the plasma and are excreted as respiratory CO_2 (Hazardous Substances Data Bank, HSDB 2013). Sodium ions are excreted by the kidneys through the sodium-potassium pump.

21.5.2 *Acute toxicity*

21.5.2.1 Oral

In an acute oral toxicity study (OECD 2002), Wistar strain rats were dosed with a 20% w/v sodium carbonate solution in water by intubation. Five male and five female rats were tested for each of the five dose levels of 1300, 1800, 2600, 3600, and 5000 mg/kg bw. The majority of the animals that died showed oral or nasal discharge, lesions in the liver, mottled lungs, mottled or pale kidneys and a red or partly gas-filled gastrointestinal tract. Several of the surviving animals also had mottled livers. A median lethal dose (LD50) of 2800 mg/kg bw was established from this study.

21.5.2.2 Dermal

In an acute dermal toxicity study, six New Zealand White rabbits were exposed dermally to an aqueous slurry of 1000 mg/mL sodium carbonate monohydrate; three animals had abraded skin and three had non-abraded skin (REACH 2013). The slurry was administered on 30% of the body surface area of the animals at a dose of 2000 mg/kg bw (details of application not provided). After 24 hours of occluded exposure, the test area was wiped clean. No mortality occurred in either group of animals. It was concluded that the LD50 was greater than 2000 mg/kg bw.

21.5.2.3 Inhalation

A series of whole-body inhalation exposures of male rats (Sprague-Dawley and Wistar strains), male mice (Swiss-Webster) and male guinea pigs (Hartley-albino) to aerosols of sodium combustion products of varying concentrations was performed (OECD 2002). The major constituent of these aerosols was shown to be sodium carbonate (91% Na_2CO_3 in rat study, dose range 800 to 4600 mg/m^3, 95% Na_2CO_3 in mice study, dose range 600 to 3000 mg/m^3 and 95% Na_2CO_3 in guinea pigs study, dose range 500 to 3000 mg/m^3).The animals exhibited respiratory impairment when exposed for two hours to the aerosols. Clinical signs included dyspnoea, wheezing, excessive salivation and distension of abdomen. Mortality occurred mainly in two periods; during exposure and within 1 to 2 hours afterwards or beginning at one day after exposure peaking at 5 to 7 days and continuing to 9 to 10 days after exposure. In animals that died during or shortly after exposure, lesions were found in the posterior pharynx and larynx along with accumulation of mucus, vesiculation and mucosal oedema. Other lesions included oedema and vesiculation of the anterior trachea, haemorrhage in the lungs, and severe gastric tympany. For animals that survived, lesions in the respiratory tract were limited to the laryngeal mucosa. The median lethal concentration (LC50) for guinea pigs, mice and rats was calculated to be 800, 1200 and 2300 mg/m^3, respectively.

21.5.2.4 Observation in humans

No cases of acute oral poisoning have been found in the published literature. The low oral toxicity of sodium carbonate is likely to be due to the neutralisation mechanism of sodium carbonate in the stomach (OECD 2012).

21.5.3 *Irritation / Corrosivity*

21.5.3.1 Skin irritation

In a reliable skin irritation study conducted by a method comparable to OECD test guideline (TG) 404, 0.5 g sodium carbonate was applied to intact and abraded skin (6.25 sq cm) of six New Zealand White rabbits. The area was covered with an occlusive bandage for four hours after which the skin was washed. Animals were observed every hour for up to 72 hours. No signs of erythema or oedema were observed (Rinehardt 1978a).

In another reliable study (Chibanguza 1985) whose method was comparable to OECD guideline 404, 0.5 g sodium carbonate was applied to intact and abraded skin (6.25 cm^2) of six New Zealand White rabbits. The area of application was covered with an occlusive bandage for four hours. After this period the skin was washed. Thirty minutes, 1, 24, 48 and 72 hours after exposure no signs of erythema or oedema were observed. The study concluded that sodium carbonate is not a skin irritant (Chibanguza 1985).

In a skin irritation test not well documented, an aqueous solution of sodium carbonate (50% w/v) was applied to the intact and abraded skin of six rabbits and six guinea pigs for four hours (Nixon et al. 1975). The animals were examined at 4, 24 and 48 hours after application of the solution for erythema and oedema. The abraded skin of the rabbits had slight erythema and oedema, and that of the guinea pigs was negligibly affected. There were no signs of erythema or oedema of the intact skin.

In other studies in rabbits (details of which are not provided) a 50% sodium carbonate solution was slightly irritating to abraded skin only (OECD 2002).

It was concluded from these studies that sodium carbonate is not a skin irritant (OECD 2002).

21.5.3.2 Eye irritation

In a study comparable to OECD TG 405, ocular irritancy of sodium carbonate was tested by instilling 0.1 g of the compound into the left eye (conjunctival sac) of New Zealand White rabbits while the right eye served as the untreated control. After 1, 24, 48 and 72 hours the eyes were examined for effects on conjunctivae, cornea and iris. Ocular irritation was scored according to the Draize scale. The mean Draize intensity scores for conjunctival redness, conjunctival chemosis and the iris were 1.67, 1.38 and 0.25 (Chibanguza 1985 reported in OECD 2002). The study concluded that sodium carbonate was not an eye irritant. However, in this study the powdered form of the compound of unknown purity was used.

In another reliable eye irritation study, 0.1 mL sodium carbonate (concentration not provided) was instilled in one eye of each of the nine New Zealand rabbits (Rinehart 1978b). After approximately four seconds the treated eyes of three rabbits were rinsed with 30ml distilled water, while the remaining rabbits' eyes were not irrigated during the 14 days observation period.

Among the animals with unwashed eyes, two suffered ruptured eyes and the remaining four still had signs of irritation at the termination of the study (Rinehart 1978b). One of the animals with washed eyes had signs of irritation at the termination of the study, while the exposed eye appeared normal in the remaining two animals from day two and 14, respectively. According to the scoring system that complied with the EPA 16 CFR 1500.42 guideline the responses were either positive or negative. Six of six animals with unwashed eyes had a positive cornea score, iris score, and conjunctivitis (redness and chemosis) score. One out of three animals with washed eyes had a positive cornea score, iris score and conjunctivitis (redness and chemosis) score. Based on these results sodium carbonate was considered irritating to the eyes (OECD 2002).

Ocular irritation of sodium carbonate was also evaluated in two groups of six New Zealand White rabbits (male and female) based on Draize method comparable to OECD TG 405 (Murphy et al. 1982). Sodium carbonate (0.1 mL, concentration not provided) was administered to the right eye, the left eye served as the untreated control. Thirty seconds after instillation, the eyes of the first group of rabbits were rinsed for two minutes, (rinsed eyes), while the eyes of the second group were not rinsed (unrinsed eyes). Control and treated eyes were scored at one hour and 1, 2, 3 and 7 days after exposure according to the Draize scale. Corneal opacities were observed in unrinsed eyes within one hour after exposure to sodium carbonate and the severest effect was noted by day three (mean Draize intensity score 3.8), the severity was maintained through to day seven. In rinsed eyes, corneal opacities were observed on day two (mean Draize intensity score 0.8) and had disappeared by day seven. Iritis was observed in unrinsed eyes at one hour after exposure to sodium carbonate and a mean Draize score of two was reported on days 1, 2, 3 and 7. In rinsed eyes, iritis was observed at one hour after exposure (mean Draize intensity score 1.0) and had disappeared by day three. Sodium carbonate produced conjunctivitis which lasted through day day in all animals tested. It also produced pannus in 6/12 unrinsed eyes and keratoconus in 2/12 unrinsed eyes. Based on the results of the test, sodium carbonate was considered highly irritating to eyes (Murphy et al. 1982).

Dry, powdered sodium carbonate, as 25% to 75% of a mixture with dry sodium sulfate (sodium sulfate is only slightly irritating to eyes (OECD 2005)), applied to eyes of rabbits and monkeys in a systemic study was judged 'corrosive' or 'harmful' to both species, whether or not followed by irrigation at two minutes after application. However, most monkey eyes exposed to 50% mixture showed little or no persistent injury 21 days after exposure (Grant 1986).

Based on the overall results sodium carbonate is considered a severe eye irritant.

21.5.3.3 Respiratory irritation

Animal studies for the respiratory tract irritation effect of sodium carbonate are not available. However, aqueous solutions are strongly alkaline; concentrated solutions tend to produce local necrosis of mucous membranes as observed in the acute inhalation studies. Dusts of vapours of sodium carbonate may cause irritation of mucous membranes with subsequent coughing and shortness of breath (US EPA 2006).

Based on the effects seen in acute inhalation toxicity studies, sodium carbonate is considered irritating to the respiratory system.

21.5.3.4 Observation in humans

A human patch (skin irritation) test with 98% sodium carbonate was performed using 26 human volunteers exposed for 15, 30 or 60 minutes through to 2, 3 and 4 hours (York et al. 1996). The patch test involved the application of 0.2 g on to a plain Hill Top Chamber and treated sites were assessed 24, 48 and 72 hours after patch removal. The results showed no reactivity among the volunteers and therefore these solutions of sodium carbonate were not classified as irritant based on the human patch test.

An aqueous solution of sodium carbonate (50% w/v) was applied to the skin (intact and abraded) of six human volunteers for four hours (Nixon et al. 1975). The volunteers were examined at 4, 24 and 48 hours after application of the solution for erythema and oedema. Categorisation of irritancy to human skin was based on the Primary Irritation Index (PII). The abraded skin had erythema and oedema (mean score >2) with two subjects having a maximum grade greater than 4. There were no signs of erythema or oedema in the intact skin (mean PII >1.0).

These studies indicate that sodium carbonate has no or a low skin irritation potential in humans (OECD 2002).

Twenty-seven army inductees assigned to dish washing immersed their bare hands for four to eight hours in hot water containing a strong detergent blend of sodium carbonate. All developed irritation of the exposed surfaces. Six developed vesicles and giant bullae within 10 to 12 hours after exposure. Three also had subligual purpura. Secondary infections were noted in several individuals (Clayton and Clayton 1994).

Acute exposures to dusts or vapours of sodium carbonate may cause irritation of mucous membranes with subsequent coughing and shortness of breath (Clayton and Clayton 1994).

Sodium carbonate is alkaline enough to injure corneal epithelium. Reported instances of permanent corneal opacification were caused not by pure chemical but by splash of molten chemical at 820°C and by a mixture containing calcium hydroxide (Grant 1986).

21.5.4 *Sensitisation*

21.5.4.1 Skin sensitisation

Animal studies for skin sensitisation effect of sodium carbonate are not available.

21.5.4.2 Respiratory sensitisation

Animal studies for respiratory tract sensitisation effect of sodium carbonate are not available.

21.5.4.3 Observation in humans

Skin sensitisation has not been reported in workers exposed to sodium carbonate during handling of sodium carbonate at worksites. Sodium carbonate is not considered a skin sensitiser (HERA 2005).

21.5.5 *Repeat dose toxicity*

21.5.5.1 Oral

No animal data were available on repeated dose toxicity studies by the oral route for sodium carbonate or sodium bicarbonate.

21.5.5.2 Dermal

No animal data were available on repeated dose toxicity studies by the dermal route for sodium carbonate or sodium bicarbonate.

21.5.5.3 Inhalation

In a 1966 repeated dose inhalation study (Reshetyuk and Shevchenko 1966; OECD 2002), male rats were exposed to an aerosol of 2% aqueous sodium carbonate for four hours/day, five days/week for 3.5 months. The final concentration of sodium carbonate was calculated to be 70 mg/m^3.

When compared to controls, there were no changes in body weight gain, organ weights or any blood parameters although pulmonary ascorbic acid levels were decreased. Physiological changes in lungs were found in controls as well as exposed animals but only exposed animals displayed hyperplasia and desquamation of bronchiolar epithelium, and perivascular oedema.

Other pulmonary changes included thickening of alveolar walls, hyperaemia and lymphoid infiltration but these changes were also observed in about 50% of the controls. The histopathological changes observed in the lungs were due to the alkaline nature of the solution (0.1 M (ca. 1%), pH = 11.6).

The upper respiratory tract was not examined. However, in view of the histopathological lesions observed in the upper respiratory tract (pharynx and larynx) in rabbits exposed to sodium carbonate aerosol for a single two hour period in a separate study (Busch et al. 1983), it was concluded that changes in the upper respiratory tract would have been more severe than those observed at the pulmonary level in the above described study of 3.5 months (OECD 2002).

The histopathological changes of the respiratory tract and the lungs observed following repeated inhalation exposure to sodium carbonate (70 mg/m^3 at pH 11.6) were considered local responses to the high alkalinity of this group of chemicals (OECD 2002; REACH 2013). A No Observed Adverse Effect Concentration (NOAEC) of 70 mg/m^3 for sodium carbonate was established in this study for the absence of any effect on the dose tested. This NOAEC will be taken forward for human health risk assessment.

21.5.6 *Genotoxicity*

Sodium carbonate was examined for its potential to induce primary DNA damage in the *Escherichia coli* Chromotest (Olivier and Marzin 1987). Concentrations of 0.11 to 11 000 µg/mL were incubated with samples of an exponentially growing culture of *Escherichia coli* PQ37 for two hours without metabolic activation. Toxicity was observed at

1100 µg/mL. It was concluded that sodium carbonate did not induce primary DNA damage in *Escherichia coli* Chromotest without metabolic activation.

Data on the structural analogue, potassium carbonate, do not show any genotoxic activity in the Ames assay with *Salmonella typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537 at concentrations up to 10 mg/plate with and without metabolic activation and in a cytogenetic assay in Chinese hamster fibroblasts up to 1 mg/mL without metabolic activation (Olivier and Marzin 1987).

From the available information it is concluded that sodium carbonate is not genotoxic.

21.5.7 *Carcinogenicity*

Carcinogenicity studies with sodium carbonate are not available. Sodium carbonate is not systemically available and therefore a carcinogenic effect is unlikely (HERA 2005).

A carcinogenicity study with a related substance (sodium bicarbonate, $NaHCO_3$) has been reported by Fukushima et al. (1989). In this study, male Fischer 344 rats were fed with 0.64% $NaHCO_3$ in the diet for 104 weeks. After gross examination, the liver, kidney and bladder were removed for histological examination. Although survival was not decreased, the final body weight of the exposed male rats was lower compared to the control. No difference in the incidence of tumour formation in the control and $NaHCO_3$ exposed animals was noted. Papillary or nodular hyperplasia and papilloma incidence did not differ from the control group incidence. $NaHCO_3$ was considered to be non-carcinogenic.

Based on the available information, sodium carbonate is not considered to be a carcinogen.

21.5.8 *Reproductive toxicity*

21.5.9 *Fertility*

No fertility studies in animals were available for sodium carbonate.

21.5.9.1 Developmental toxicity

In a developmental study, aqueous solutions of sodium carbonate were administered daily via oral intubation to pregnant mice at doses ranging from 3.4 to 340 mg/kg bw during days 6 to 15 of gestation. The test substance affected neither implantation nor the survival of dams and foetuses. Soft and skeletal tissue anomalies were noted in the experimental group, but the incidence of these findings did not differ from that of controls (FDA 1974).

Similar negative results were reported for rats and rabbits with daily doses from 2.45 to 245 mg/kg bw and 1.79 to 179 mg/kg bw sodium carbonate, respectively. This study confirms in three species that sodium carbonate does not produce developmental toxicity (OECD 2002).

21.5.10 *Other health effects*

No data were available.

21.6 Health hazard summary

21.6.1 *Critical health effects*

In summary for this chapter, sodium carbonate has low acute oral, dermal and inhalation toxicity. The acute oral LD50 in rats is 2 800 mg/kg bw, while the dermal LD50 in rats is

>2 000 mg/kg bw. The LC50 in guinea pig, mice and rat are 800, 1 200 and 2 300 mg/m^3 respectively. Sodium carbonate has low skin irritation potential. It is a severe eye and respiratory irritant.

Information on repeated dose toxicity by the oral and dermal routes is not available. Given that the constituent ions are normal components of the body that are subject to homeostatic controls, systemic effects from repeated doses are not expected. In rats, inhalation exposure to 2% sodium carbonate aerosol (70 mg/mg^3) for over three months did not have any adverse effect. Histopathological changes of the respiratory tract and lungs seen following repeated inhalation exposure were considered local responses to the high alkalinity of this group of chemicals.

A No Observed Adverse Effect concentration (NOAEC) of 70 mg/m^3 for sodium carbonate was established in this study for local reversible effects. In the absence of a more suitable NOAEL, this NOAEC will be taken forward for risk assessment.

Sodium carbonate was not genotoxic or carcinogenic. Reproductive toxicity studies are not available; however, no effects on reproductive organs were noted when rats were exposed to sodium carbonate aerosol. Developmental studies with rats did not show any toxicity.

Eye irritation is the only critical effect for risk assessment.

21.6.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria (NOHSC 2004) and adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A21.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A21.3 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Irritation / Corrosivity	Causes serious eye damage – Cat. 1 (H318) May cause respiratory irritation - Specific target organ toxicity, single exposure - Cat. 3 (H335)

** Globally Harmonised System (UNECE 2009)*

21.7 References

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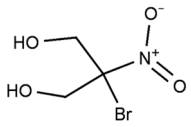
A22 Bronopol

CAS No.	CAS Name
52-51-7	1,3-Propanediol, 2-bromo-2-nitro-

22.1 Chemical identity

The information on chemical identity was obtained from ChemID*plus* (2012) and IPCS (2012). Details are provided in Table A22.1.

Table A22.1 Chemical identity

	Bronopol
Synonyms	2-Bromo-2-nitropropane-1,3-diol Bronopol BE 6
Structural formula	
Molecular formula	$C_3H_6BrNO_4$
Molecular feight	199.99
Appearance and odour	White crystalline powder with a faint odour
SMILES Notation	C(Br)(CO)(CO)N(=O)=O

22.2 Physical properties

The physical properties of the chemical are presented in Table A22.2. The information was obtained from US EPA (1995) and IPCS (2012).

Table A22.2 Physical properties

Property	**Value**
Melting point	120–122 °C
Boiling point	300.57 °C
Density	1100 kg/m^3
Vapour pressure	1.7 x 10^{-6} kPa at 20 °C
Water solubility	250 g/L at 22 °C
Partition coefficient n-octanol/water (log K_{ow})	0.18

22.3 Current regulatory controls

The document from here on refers to 1,3-Propanediol, 2-bromo-2-nitro- (CAS No. 52-51-7) as 'bronopol', one of the synonyms of the chemical.

22.3.1 *Hazard classification for occupational health and safety*

Bronopol is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) with the following risk phrases (Safe Work Australia 2013):

- X_n (Harmful); R21/R22
- X_i (Irritant); R37/38, R41

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration of the chemical in the mixtures. The risk phrases for different concentration (Conc) ranges are:

- Conc ≥25%: X_n, N: R21/22 (Harmful in contact with skin and if swallowed), R37/38 (Irritating to respiratory system and skin), R41 (risk of serious eye damage)
- 20% ≤Conc <25%: X_i: R37/38, R41
- 10% ≤Conc <20%: X_i: R41
- 5% ≤Conc <10%: X_i: R36 (Irritating to eyes).

22.3.2 *Occupational exposure standards*

22.3.2.1 Australia

No specific exposure standards were available.

22.3.2.2 International

No specific exposure standards were available.

22.3.3 *Australian food standards*

No Australian food standards were identified.

22.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian drinking water guidelines (National Health and Medical Research Council (NHMRC) 2011).

22.3.5 *Additional controls*

22.3.5.1 Australia

The chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

22.3.5.2 International

Bronopol is currently regulated in the EU Cosmetic Directive 76/768/EEC in Annex VI, Part 1 with a maximum authorised concentration of 0.1% (EC 2010).

The chemical is not to be included in specific product types in the European market as regulated in the European Commission Decision of 2008 to Directive 98/8/EC. Bronopol is prohibited in the following product types: human hygiene biocidal products, veterinary hygiene biocidal products, food and feed area disinfectants, and metalworking fluid preservatives (EC 2008).

Formaldehyde may be released when bronopol decomposes in aqueous solutions but the release is not related to the biocidal mechanism of action due to the chemical's slow decomposition (US EPA 1995). An Opinion of the European Commission's Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) includes the maximum authorised concentrations of certain formaldehyde releasers in cosmetic products (SCCNFP 2002). The Opinion has not proposed a maximum authorised concentration for bronopol.

22.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

22.5 Health hazard characterisation

The information on health hazards was obtained from the US EPA reregistration eligibility decision for bronopol (US EPA 1995). Bronopol was tested at concentrations of ≥98.8 to 99.7% in most of the studies. Unless otherwise noted, references to individual studies below are taken from this review.

22.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

22.5.1.1 Oral absorption

No data were available. The metabolism studies, conducted on Sprague-Dawley rats dosed with bronopol by gavage, evaluated by the US EPA (1995) reported rapid absorption of bronopol. The International Chemical Safety Card (ICSC) for bronopol indicated that the substance can be absorbed into the body by ingestion (IPCS 2012).

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

22.5.1.2 Dermal absorption

No data were available. The absence of dermal absorption data may be due to the irritant properties of bronopol as reported in the studies by Inolex Chemical Company (1976), Smithson (1984), and Davies et al. (1973). The ICSC for bronopol indicated that the substance can be absorbed into the body through the skin (IPCS 2012).

For the purposes of risk assessment, 100% dermal absorption in humans is therefore assumed.

22.5.1.3 Inhalation absorption

No data were available. The ICSC for bronopol indicated that the substance can be absorbed into the body by aerosol inhalation (IPCS 2012). Acute inhalation toxicity studies demonstrated that bronopol is absorbed by the inhalation route (Section A22.5.2.3).

For the purposes of risk assessment, 100% inhalation absorption in humans is therefore assumed.

22.5.1.4 Distribution

No data were available. However, oral repeat dose toxicity studies in rats reported treatment-related effects in numerous organs, suggesting wide distribution of the chemical (Section A22.5.5.1).

22.5.1.5 Metabolism

The US EPA (1995) evaluated four separate metabolism studies of Sprague-Dawley rats administered bronopol by gavage (doses up to 50 mg/kg bw). The only metabolite found in urine, at levels of 45 to 50%, was 2-nitropropane-1,3-diol.

22.5.1.6 Excretion

Four metabolism studies indicated that 64 to 78% of the chemical was excreted in 24 hours and 68 to 83% in seven days with urine being the major route of excretion.

22.5.2 *Acute toxicity*

22.5.2.1 Oral

Rats administered bronopol orally (doses not specified) exhibited clinical signs of sedation, nasal exudate, gasping, wheezing, cyanosis, and convulsions. The study reported acute oral median lethal doses (LD50s) of 307 and 342 mg/kg bw for males and females, respectively (Inolex Chemical Company 1976).

The study shows that bronopol has moderate acute toxicity by the oral route in rats.

22.5.2.2 Dermal

Bronopol applied to rat skin at dose levels of 0, 64, 160, 400, or 1000 mg/kg bw produced oedema, haemorrhage, laboured breathing, prostration, and lung congestion. The study reported an acute dermal LD50 of 64 to 160 mg/kg bw (Inolex Chemical Company 1976; Smithson 1984). No details of the study were provided.

The study shows that bronopol has moderate to high acute toxicity by the dermal route in rats.

22.5.2.3 Inhalation

An inhalation study in rats exposed to bronopol (particle size 1.3 to 6.7 µm) (doses not specified) reported diffuse red lungs, sore eyelids, and severe dermatitis and ulceration on the head at 0.588 mg/L. The effects observed at 0.089 mg/L dose included piloerection, hunched posture, and hydronephrosis. The acute inhalation median lethal concentration (LC50) for this study was identified by the author as >0.588 mg/L (Collins 1986).

In another study, clinical signs observed in rats exposed to 0, 0.05, 0.5, or 5 mg/L bronopol (particle sizes 1 to 5 µm and 1 to 15 µm) included eye irritation, dyspnoea, profuse mucus

production and lethargy. Chronic pneumonitis was also observed after the test duration. The acute inhalation LC50 was >5 mg/L (Binns et al. 1971).

These studies show that bronopol has low to moderate acute toxicity by the inhalation route in rats.

22.5.2.4 Observation in humans

No data were available.

22.5.3 *Irritation / Corrosivity*

22.5.3.1 Skin irritation

Application of 0, 0.5, 2, or 5% bronopol solution in aqueous methylcellulose to the skin of rats produced slight to moderate erythema and slight to severe oedema after six hours of exposure (Inolex Chemical Company 1976). The US EPA (1995) classified the chemical as a severe skin irritant.

The effects observed in this test at the low concentrations demonstrate the strong skin irritation potential of bronopol.

22.5.3.2 Eye irritation

Instillation of a 5% bronopol solution with polyethylene glycol in rabbit eyes produced redness and swelling of the conjunctiva with moderate discharge one hour after dosing. The effects subsided in most of the animals after seven days (Liggett and Parcell 1984). The US EPA (1995) classified the chemical as corrosive to the eyes. No details of the study were provided.

The effects observed in this test at low bronopol concentrations demonstrate the corrosive potential of the chemical to the eyes.

22.5.3.3 Respiratory irritation

No data were available. Acute oral, dermal, and inhalation toxicity studies indicate respiratory irritation following bronopol exposure.

22.5.3.4 Observation in humans

No data were available.

22.5.4 *Sensitisation*

22.5.4.1 Skin sensitisation

Bronopol at 1% concentration in acetone was determined as not sensitising to the skin following dermal applications (three induction and one challenge treatments) in guinea pigs (Maibach 1977; Smithson 1984).

Bronopol is not a skin sensitiser in guinea pigs.

22.5.4.2 Respiratory sensitisation

No data were available.

22.5.4.3 Observation in humans

Patch testing of 8149 individuals with bronopol was conducted in seven European contact clinics. The results reported low reactivity with 0.12% irritant and 0.47% allergic reactions. The study concluded that the sensitisation rate to bronopol in Europe is quite low (Frosch et al. 1990).

Contact allergy to bronopol in six individuals included four cases of lower leg stasis dermatitis, wherein the cause of sensitisation was attributed to bronopol-containing ointments (Frosch and Weickel 1987).

The studies demonstrate that bronopol is not a skin sensitiser in humans.

22.5.5 *Repeat dose toxicity*

22.5.5.1 Oral

Male and female SPF rats were given bronopol by gavage for 13 weeks at doses of 0, 20, 80, or 160 mg/kg bw/day (Hunter et al. 1973a). At the 20 mg/kg bw/day group, one female died in week 10 and dilated tubules in the kidneys were observed in two males. At the 80 mg/kg bw/day group, mortality was 35% in males and 45% in females. The effects observed at this dose were respiratory distress such as gasping and wheezing, decreased bodyweight gain (7 to 20% in males and 12 to 16% in females), and dilated tubules in the kidney of one male. At the 160 mg/kg bw/day group, the study reported high mortality but the number of animals that died was not specified. The effects observed at the highest dose included decreased bodyweight gain (29 and 13% less compared to controls for males and females, respectively), severe respiratory distress, and gaseous or fluid distension of the gastrointestinal (GI) tract in most of the rats. GI lesions such as superficial ulceration with underlying inflammation, epithelial hyperplasia and hyperkeratosis were also observed in the animals. The effects on the kidneys (dilated tubules) observed at the lowest and mid-dose groups were not dose-related since it was not reported at the highest dose tested. The No-Observed-Adverse-Effect-Level (NOAEL) was 20 mg/kg bw/day based on systemic effects at the Lowest-Observed-Adverse-Effect-Level (LOAEL) of 80 mg/kg bw/day.

Beagle dogs were administered bronopol by gavage for 13 weeks at doses of 0, 4, 8, or 20 mg/kg bw/day. The NOAEL identified was 8 mg/kg bw/day based on increased liver (15%) and spleen (39%) weights at the LOAEL of 20 mg/kg bw/day (Rivett et al. 1973).

In a chronic feeding/carcinogenic study, Sprague-Dawley rats were administered bronopol in drinking water for 104 weeks with actual intake doses of 0, 10.4, 40.7, or 158.4 mg/kg bw/day for females and 0, 10.5, 40.2, or 152.2 mg/kg bw/day for males (Hunter et al. 1973b; Hunter et al. 1976) . Dose-related reduced water intake was observed in all the animals. At the 40 mg/kg bw/day group, treatment-related effects included reduction in bodyweight gain (20 to 52%), and squamous metaplasia, inflammation or atrophic acini in the salivary glands (48% in males and 13% in females). At the 160 mg/kg bw/day group, treatment-related effects included reduced grooming activity, high mortality (80% in males and 67% in females), decreased bodyweight gain (13 to 84% in males and 11 to 53% in females), increased relative weight of organs (i.e. adrenals, brain, kidneys, liver, and lungs – proportions were not reported in the study), decreased absolute weight of organs (i.e. 29% in heart, 35% in liver, 12% in lungs, 47% in seminal vesicles, 20% in testes, and 26% in thyroid), stomach lesions (37% in males and 29% in females), and squamous metaplasia, dilatation of the ducts, acinar atrophy and / or inflammation of the salivary glands in 92% of the males and 55% of the females. The NOAEL was 10.4 mg/kg bw/day for both sexes based on the systemic effects at the LOAEL of 40 mg/kg bw/day.

Repeated oral exposure to bronopol in rats was associated with adverse effects on the respiratory system (gasping and wheezing), kidney (dilated tubules), GI tract (gaseous or fluid distension, superficial ulceration with inflammation), and salivary gland (inflammation or atrophic acini). A NOAEL of 10.4 mg/kg bw/day was established from the 104-week chronic feeding/carcinogenicity studies of Hunter et al. (1973b, 1976) based on systemic effects at the LOAEL of 40 mg/kg bw/day.

22.5.5.2 Dermal

Bronopol suspended in aqueous methyl cellulose was applied to New Zealand White rabbit skin at doses of 0, 0.2, or 0.5% (w/v) for three weeks. Effects observed at the highest dose included moderate erythema and oedema, thickening, hardening, and sloughing at the site of application. No systemic effects were observed. The NOAEL established in this study for local effects was 0.2% (w/v) bronopol, equivalent to 2 mg/kg bw/day, based on dermal irritation at the highest dose (Davies et al. 1973).

In another study (Hunter et al. 1975)., bronopol was applied on the skin of CFLP mice three days a week for 80 weeks at doses of 0, 20, or 50 mg/kg bw/day. At the highest dose, the only treatment-related effects observed were hair loss at the periphery of the shaved area in some mice (numbers not reported) and reduced bodyweight gain (percentages not reported) (Hunter et al. 1975).

22.5.5.3 Inhalation

No data were available.

22.5.5.4 Observation in humans

No data were available.

22.5.6 *Genotoxicity*

Bronopol was negative for mutagenicity in an Ames test (up to 125 µg/plate concentration) (Everest and Williams 1986a) and in a cell mutation assay (Chinese hamster lung fibroblasts at up to 8 µg/mL concentration) (Everest and O'Donovan 1986). In a mammalian cell (human lymphocyte) culture, the chemical was found to be clastogenic without metabolic activation at 30 µg/mL, and not clastogenic with metabolic activation at doses up to 20 µg/mL (Everest and Williams 1986b). In an *in vivo* micronucleus assay in mice, the chemical was negative at up to the maximum tolerated dose of 160 mg/kg bw/day (Everest and Williams 1986c).

A growth inhibition study of *Escherichia coli* exposed to bronopol reported inhibited bacterial growth followed by growth at an inhibited rate (Shepherd et al. 1988). The cytotoxic effects of JMAC TD, bronopol, CA 24, and Euxyl K100, all preservative agents in cosmetics, were investigated. The study found that bronopol exhibited the highest cytotoxic effect on the proliferation of V79 and VH10 fibroblasts (Jantova et al. 2001).

Bronopol is not considered to be genotoxic based on the available data.

22.5.7 *Carcinogenicity*

In the previously described chronic feeding/carcinogenicity study by Hunter et al. (1973b and 1976), the tumours most frequently observed in Sprague-Dawley rats were pituitary adenoma in males (23, 32, 17, and 5% at the 0, 10, 40, and 160 mg/kg bw/day group, respectively) and females (45, 47, 55, and 37% at the 0, 10, 40, and 160 mg/kg bw/day

group, respectively), and fibroadenoma in the females (79, 80, 71, and 50% at the 0, 10, 40, and 160 mg/kg bw/day group, respectively).

In the previously described dermal study by Hunter et al. (1975) on CFLP mice, the tumour incidences were 48, 42, and 46% (in males) and 49, 36, and 45% (in females) at 0, 20, and 50 mg/kg bw/day dose groups, respectively. The tumours most frequently observed were lymphoma and lung tumours. The authors indicated that the tumour incidences observed in mice of both sexes were not statistically significant as compared to controls.

The US EPA (1995) indicated that bronopol was classified as a Group E carcinogen (evidence of non-carcinogenicity in humans) based on a lack of carcinogenicity evidence from acceptable studies in rat and mouse. The dose levels utilised in the tests were considered satisfactory for carcinogenicity evaluation. The conclusion was based on increased mortality, stomach lesions and reduction in bodyweight gain in rats, and no statistically significant increases in tumour incidences in the dose groups.

22.5.8 *Reproductive toxicity*

22.5.8.1 Fertility

In a reproductive study, bronopol was administered to Charles River COBS CD rats in drinking water during the pre-mating, mating, gestation and lactation periods (US EPA 1995). The doses tested were 0, 25, 70, and 200 mg/kg bw/day. There were no treatment-related effects observed at the 25 mg/kg bw/day group. At the 70 mg/kg bw/day group, effects observed were increased kidney weight (14.5% in parent females), decreased liver weight (11% males and 11% females of the first generation), and increased incidence of nephropathy of the parents (both sexes). At the 200 mg/kg bw/day group, the effects observed included decreased bodyweights of the first generation males (11 to 22%), increased organ weights (22% in adrenals of parent females, 36% in kidney of parent females, 14% in kidney of first generation males, 26% in thyroid/parathyroid of first generation males), and increased incidence of nephropathy of the parents (both sexes). At the highest dose, a 12.5% decrease in the female fertility index during mating was also reported. The NOAELs for systemic and fertility effects were 25 and 70 mg/kg bw/day, respectively. The LOAELs for systemic and fertility effects were 70 and 200 mg/kg bw/day, respectively (as cited in US EPA 1995).

This study shows that bronopol may affect fertility in rats (decrease in female fertility index) at 200 mg/kg bw/day and above.

22.5.8.2 Developmental toxicity

In a developmental toxicity study, bronopol was administered to Sprague-Dawley rats by gavage in doses of 0, 10, 28, or 80 mg/kg bw/day from gestation day six to fifteen. There were no dose-related clinical signs observed in the animals and no developmental effects observed in the pups. No maternal toxicity was noted apart from a 1% decrease in bodyweight gain. The NOAEL for both maternal and developmental toxicity was >80 mg/kg bw/day (Palmer 1995; Steele 1994).

In a developmental toxicity study, New Zealand White rabbits were administered the chemical by gavage at doses of 5, 20, 40, or 80 mg/kg bw/day (Irvine 1992a; Irvine 1992b). Maternal effects observed were a 13% decrease in bodyweight gain and 38% decrease in food consumption at the highest dose. Developmental effects observed only at the highest dose were 10% decrease in foetal bodyweight in both sexes, 6.9% increase in foetuses with major external/visceral and skeletal abnormalities, 19.3% increase in foetuses with minor skeletal abnormalities, and increased incidence of foetuses with skeletal variants

(8% unossified forelimb and 16% hindlimb epiphyses). There were no developmental effects observed in the absence of maternal toxicity. The NOAEL for both maternal and developmental toxicity was 40 mg/kg bw/day based on the effects noted above, the LOAEL for both maternal and developmental toxicity was 80 mg/kg bw/day.

These studies demonstrate that bronopol causes developmental effects (increase in foetuses with skeletal abnormalities and increase in incidence of foetuses with skeletal variants). The effects were not observed in the absence of maternal toxicity.

22.5.9 *Other health effects*

No data were available.

22.6 Health hazard summary

22.6.1 *Critical health effects*

Bronopol has moderate acute dermal and oral toxicity, is irritant to the skin and respiratory system, and corrosive to the eyes. The chemical is not a skin sensitiser in animals and humans.

The most appropriate NOAEL for risk assessment purposes, determined from the well-documented 104-week rat chronic feeding/carcinogenicity studies of Hunter et al. (1973b, 1976), is 10.4 mg/kg bw/day based on systemic effects.

The chemical is not genotoxic or a carcinogen based on available data. The NOAEL for fertility effects was 70 mg/kg bw/day, respectively. Developmental effects of the chemical were not observed in the absence of maternal toxicity.

22.6.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification under the current Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) for acute oral toxicity and Irritation / Corrosivity. The existing hazard classification for acute dermal toxicity is recommended for amendment from ‘R21 Harmful in contact with skin’ to ‘R24 Toxic in contact with skin’ (Table A22.3).

The equivalent classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) is shown inTable A22.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A22.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful if swallowed (X_n; R22)* Toxic in contact with skin (T; R24)[†]	Harmful if swallowed – Cat. 4 (H302) Fatal in contact with skin – Cat. 2 (H310)
Irritation/ Corrosivity	Irritating to respiratory system and skin (X_i; R37/38)* Risk of serious eye damage (X_i; R41)*	Causes skin irritation – Cat. 2 (H315) May cause respiratory irritation – Specific target organ toxicity, single exposure - Cat. 3 (H335) Causes serious eye damage – Cat. 1

		(H318)

*[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009); * Existing hazard classification. No change recommended by NICNAS to Safe Work Australia for this classification; [†] NICNAS recommended amendment to existing hazard classification.*

22.7 References

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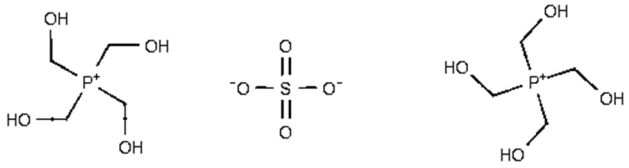
A23 THPS

CAS No.	CAS Name
55566-30-8	Phosphonium, tetrakis(hydroxymethyl)-, sulfate salt (2:1)

23.1 Chemical identity

The information on chemical identity was obtained from ChemID*plus* (2012) and the International Programme on Chemical Safety (IPCS) (IPCS 2000). Details are provided in Table A23.1.

Table A23.1 Chemical identity

	THPS
Synonyms	Tetrakis(hydroxymethyl)phosphonium sulfate THPS Magnacide 575 Tolcide
Structural formula	
Molecular formula	$C_8H_{24}O_{12}P_2S$
Molecular feight	406.28
Appearance and odour	Light coloured liquid (75% THPS); Soft waxy solid (100% THPS)
SMILES Notation	C(O)P{+}(CO)(CO)(CO).O{-}S(=O)(=O)O{-}.P{+}(CO)(CO)(CO)CO

23.2 Physical properties

The physical properties of the chemical are presented in Table A23.2. The information was obtained from IPCS (2000).

Table A23.2 Physical properties

Property	Value
Melting point	54.2–81.5 °C
Boiling point	108.5 °C for 75% THPS
Density	1390-1530 kg/m^3 at unspecified temperature
Vapour pressure	<2.6 x 10^{-4} kPa at 20 °C
Water solubility	Completely soluble

Property	Value
Partition coefficient n-octanol/water (log K_{ow})	-9.8 (calculated)
Conversion factor	1 ppm = 16.61 mg/m^3 1 mg/m^3 = 0.0602 ppm

23.3 Current regulatory controls

The document from here on refers to Phosphonium, tetrakis(hydroxymethyl)-, sulfate salt (2:1) (CAS No. 55566-30-8) as 'THPS', one of the synonyms of the chemical.

23.3.1 *Hazard classification for occupational health and safety*

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

23.3.2 *Occupational exposure standards*

23.3.2.1 Australia

No specific exposure standards were available.

23.3.2.2 International

No specific exposure standards were available.

23.3.3 *Australian food standards*

No Australian food standards were identified.

23.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian drinking water guidelines (National Health and Medical Research Council (NHMRC) 2011).

23.3.5 *Additional controls*

23.3.5.1 Australia

The chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

23.3.5.2 International

THPS is classified as a hazardous substance, acutely toxic and a contact sensitiser, under the Hazardous Substances and New Organisms (HSNO) Act of the Environmental Protection Authority New Zealand (EPA NZ) (2012).

23.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

23.5 Health hazard characterisation

23.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

23.5.1.1 Oral absorption

No data were available. Effects observed in acute and repeat oral toxicity studies indicate that THPS is absorbed in the gastrointestinal tract (Sections A23.5.2.1 and A23.5.5.1).

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

23.5.1.2 Dermal absorption

No data were available. Effects observed in the repeat dermal toxicity study indicate that THPS is absorbed through the skin (Section A23.5.5.2).

For the purposes of risk assessment, 100% dermal absorption in humans is therefore assumed.

23.5.1.3 Inhalation absorption

No data were available.

In the absence of data, for the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

23.5.1.4 Distribution

No data were available.

23.5.1.5 Metabolism

No data were available. The IPCS (2000) reported three metabolites (trihydroxymethyl phosphine oxide, bishydroxymethylphosphonic acid, and one other possible formaldehyde adduct of the trihydroxy compound) in rat urine, but did not provide supporting information.

23.5.1.6 Excretion

No data were available.

23.5.2 *Acute toxicity*

23.5.2.1 Oral

The acute oral median lethal dose (LD50) reported for an aqueous solution containing 72% THPS was 200 mg/kg bw in female mice (Tuffnell 1991).

In gavage studies conducted by the United States National Toxicology Program (US NTP), F344/N rats and B6C3F1 mice were administered 100, 200, 400, 800, or 1600 mg/kg bw of an aqueous solution of 72% THPS. The acute oral LD50s were 333 and 248 mg/kg bw in male and female rats, respectively. No LD50 was established for the mice (US NTP 1987). The effects observed from these studies were not provided.

The studies show that 72% THPS has moderate acute toxicity by the oral route in rodents.

23.5.2.2 Dermal

There were no deaths observed following application of 2000 mg/kg bw THPS to the skin of rats (Liggett and Allen 1989). No other details were provided.

The study shows that THPS has low acute toxicity by the dermal route in rats.

23.5.2.3 Inhalation

The four-hour acute median lethal concentration (LC50) was 5.5 mg/L in a nose-only exposure of rats to aerosolised THPS (McDonald and Anderson 1989). The effects observed from this study were not provided.

The study shows that THPS has moderate acute toxicity by the inhalation route in rats.

23.5.2.4 Observation in humans

No data were available.

23.5.3 *Irritation / Corrosivity*

23.5.3.1 Skin irritation

No dermal irritation was observed in New Zealand White rabbit skin when 0.5 mL of THPS was applied for four hours (Liggett 1989a). In another study, the 75% aqueous solution of the chemical was applied to shaved Charles River-derived CD rat neck skin at 25, 250, or 500 mg/kg bw/day. The dosing had to be terminated due to the severity of the skin reactions after 6 days (Hill 1989). No other details were available for these studies.

The skin irritation potential of THPS cannot be sufficiently determined from the inadequate reporting of the studies.

23.5.3.2 Eye irritation

In an eye irritation test conducted in accordance with the Organisation for Economic Co-operation and Development Test Guideline (OECD TG) 405, application of 0.1 mL of 75% THPS to New Zealand White rabbit eyes resulted in opacity, red coloration of the conjunctiva and considerable swelling. Although the Draize score was not reported in this study, on the basis of the observed effects, THPS was considered a severe eye irritant (Liggett 1989b).

The chemical is an eye irritant in rabbits.

23.5.3.3 Respiratory irritation

No data were available.

23.5.3.4 Observation in humans

No data were available.

23.5.4 *Sensitisation*

23.5.4.1 Skin sensitisation

In a Magnusson and Kligman maximisation test conducted in accordance with OECD TG 406, 14/20 animals challenged with 75% THPS were sensitised (Guest 1994). No other details were provided.

The study shows that THPS is a skin sensitiser in guinea pigs.

23.5.4.2 Respiratory sensitisation

No data were available.

23.5.4.3 Observation in humans

No data were available.

23.5.5 *Repeat dose toxicity*

23.5.5.1 Oral

The key animal data on repeat dose oral toxicity of THPS are summarised from the US NTP (1987) and IPCS (2000), and presented in Table A23.3. The Lowest Observed Adverse Effect Levels (LOAELs) and No Observed Adverse Effect Levels (NOAELs) are indicated for each study. Note that the LOAELs and NOAELs are reported as the equivalent THPS dose.

Table A23.3 Repeat oral toxicity studies with THPS in rodents

Species	Method, study duration and doses	Results	Remarks	Reference
F344/N rats	Gavage, 14 days 0, 12.5, 25, 50, 100, or 200 mg/kg bw/day (72% THPS)	LOAEL = 18 mg/kg bw/day NOAEL = 9 mg/kg bw/day	At 100 and 200 mg/kg bw/day, effects before mortality were tremors and partial loss of hind leg movement; 100% mortality at top 2 doses; Decreased bodyweight gain at 25 and 50 mg/kg bw/day.	US NTP (1987)
Charles River CD rats	Gavage, 28 days 6, 30, or 60 mg/kg bw/day (75% THPS)	LOAEL = 22.5 mg/kg bw/day NOAEL = 4.5 mg/kg bw/day	Mortality (males only) at the top dose; Post-dose salivation, emaciation, hypoactivity, hunched posture, noisy breathing, urogenital staining and ptosis at the top dose; Severe weight loss (74% in females and 52% in males) at mid-dose.	Hill (1989)
F344/N rats	Gavage, 13 weeks 0, 5, 10, 20, 40, or 60 mg/kg bw/day (72% THPS)	LOAEL = 7.2 mg/kg bw/day NOAEL = 3.6 mg/kg bw/day	Mortality at 60 mg/kg bw/day; Vacuolar degeneration in the liver at 10 mg/kg bw/day and higher; Lymphoid depletion in the spleen at 60 mg/kg bw/day (males only); Bone marrow hyperplasia at 60 mg/kg bw/day (both sexes).	US NTP (1987)
Charles River	Gavage, 13 weeks	LOAEL = 3.75 mg/kg bw/day	Mortality at the mid- and top dose groups; Increased mean plasma alanine aminotransferase (ALT) and	Hill and Newman

Species	Method, study duration and doses	Results	Remarks	Reference
CD rats	0, 1, 5, or 10 mg/kg bw/day (75% THPS)	NOAEL = 0.75 mg/kg bw/day	aspartate aminotransferase (AST) at the top dose; Cytoplasmic vacuolisation of periportal hepatocytes at the top dose.	(1990)
F344/N rats	Gavage, 104 weeks 0, 5, or 10 mg/kg bw/day (72% THPS)	LOAEL = 3.6 mg/kg bw/day NOAEL not established	Decreased survival of males at low dose (after week 102) and high dose (after week 67); Dose-related increased incidence of hepatocellular cytoplasmic vacuolisation in both sexes.	US NTP (1987)
B6C3F1 mice	Gavage, 14 days 0, 12.5, 25, 50, 100, or 200 mg/kg bw/day (72% THPS)	LOAEL = 18 mg/kg bw/day NOAEL = 9 mg/kg bw/day	At 100 and 200 mg/kg bw/day, increased mortality, laboured breathing, rough coat, and loss of movement in female hind legs; Decreased bodyweight gain at all doses except 12.5 mg/kg bw/day.	US NTP (1987)
B6C3F1 mice	Gavage, 13 weeks 0, 5, 10, 20, 40, or 60 mg/kg bw/day (72% THPS)	LOAEL = 14.4 mg/kg bw/day NOAEL = 7.2 mg/kg bw/day	Mortality at 40 and 60 mg/kg bw/day; Periportal vacuolar degeneration at 20 (males only), 40 mg/kg bw/day and above in both sexes; Reduced bodyweight gain at 20, 40, and 60 mg/kg bw/day (both sexes).	US NTP (1987)
B6C3F1 mice	Gavage, 104 weeks 0, 5, or 10 mg/kg bw/day (72% THPS)	LOAEL = 7.2 mg/kg bw/day NOAEL = 3.6 mg/kg bw/day	Increased incidence of hepatocellular cytoplasmic vacuolisation in males only	US NTP (1987)

The critical study for determining the effects of repeated exposures to the chemical is the 13-week gavage study by the US NTP (1987) in rats as this study was conducted in accordance with national guidelines. The NOAEL is 3.6 mg/kg bw/day based on systemic effects at the LOAEL of 7.2 mg/kg bw/day.

23.5.5.2 Dermal

THPS was applied daily to depilated back skin of male ICR mice for 14 days at doses of 125, 350, 700, or 1000 mg/kg bw/day. The effects observed were decreased bodyweight (dose group not specified), paralysed back muscles at 700 and 1000 mg/kg bw/day, and superficial necrosis at all doses (Connor et al. 1980). No other details were provided.

23.5.5.3 Inhalation

No data were available.

23.5.5.4 Observation in humans

No data were available.

23.5.6 *Genotoxicity*

In vitro and *in vivo* data on genotoxicity of THPS are summarised from IPCS (2000) and US NTP (1987), and presented in Table A23.4 and Table A23.5.

Table A23.4 In vitro genotoxicity studies with THPS

Test	Results	Reference
Reverse mutation test in *Salmonella typhimurium*	Negative with and without activation	Dillon and Riach (1990)
Reverse mutation test in *S. typhimurium*	Negative with and without activation	Ballentyne (1996)
Gene mutation test in mouse lymphoma cells	Positive with and without activation	Riach (1996)
Gene mutation test in mouse lymphoma cells	Positive without activation	US NTP (1987)
Chromosome aberration test in CHO* cells	Positive with and without activation	Leddy (1990)
Chromosome aberration test in CHO cells	Positive (activation not specified)	Coutino (1979)
In vitro UDS[#] assay in primary rat hepatocytes	Negative	Downey et al. (1990); Riach (1994)

** CHO – Chinese hamster ovary; [#] UDS – unscheduled deoxyribonucleic acid (DNA) synthesis*

Table A23.5 In vivo genotoxicity studies with THPS

Test	Results	Reference
Dominant lethal assay in male rats dosed at 5, 10 or 15 mg/kg bw/day for 10 weeks	Negative	Clode (1996)
Swiss ICR mice micronucleus test in bone marrow cells treated with 125, 350, 700, or 1000 mg/kg bw/day by gavage	Negative	Connor et al. (1980)
Swiss ICR male mice micronucleus test in bone marrow cells from dermal contact of 2500 mg untreated fabric per kg diet for 5 days.	Negative	Connor et al. (1980)
Swiss ICR male mice chromosome aberration test from dermal contact of 2500 mg untreated fabric per kg diet for 5 days.	Negative	Connor et al. (1980)

From the available data, no mutagenic activity of THPS was observed in bacteria, but there is evidence of genotoxicity in mouse lymphoma cells and CHO cells. However, in *in vivo* assays the chemical did not induce increases in bone marrow micronuclei or chromosome aberrations.

THPS is not considered to be genotoxic.

23.5.7 *Carcinogenicity*

In the 104-week gavage studies by the US NTP (1987), F344/N rats and B6C3F1 mice were administered 72% THPS solution at doses of 0, 5 or 10 mg/kg bw/day. In male rats, increased incidence of mononuclear cell leukaemia was observed at the low dose compared to controls; and in male mice, increased incidence of malignant lymphomas was observed at the low dose compared to controls. The US NTP reported the incidences of the tumours as marginal and established that the effects were not considered biologically related to chemical exposure since no dose-response relationship was observed and the incidence of the lesions were highly variable in the control group. The US NTP concluded that there was no evidence of carcinogenicity in the rodents administered THPS (US NTP 1987).

The International Agency for Research on Cancer (IARC) evaluated the US NTP carcinogenicity studies in rodents and the *in vitro* and *in vivo* mutagenicity studies of tetrakis (hydroxymethyl) phosphonium salts. The IARC concluded that tetrakis (hydroxymethyl) phosphonium salts belong to Group 3 (Not classifiable as to their carcinogenicity to humans) (IARC 1990; IARC 1999).

23.5.8 *Reproductive toxicity*

23.5.8.1 Fertility

No data were available.

23.5.8.2 Developmental toxicity

In a study conducted in accordance with OECD TG 414, New Zealand White rabbits were administered 75% THPS solution by gavage at 0, 6, 18, or 60 mg/kg bw/day from gestation day (GD) 7 to 19 (Barker 1991a). At the top dose, decreased bodyweight gain of the dams was reported. Increased incidence of foetus eye malformations (42/120) and some with additional, hydrocephaly, or limb/phalangeal reduction defects were observed at the top dose. No adverse effects were observed at the other doses. No other study details were provided to reliably determine whether the developmental effects observed can be directly attributed to the chemical. The LOAEL and NOAEL for maternal toxicity are 45 and 13.5 mg/kg bw/day THPS, respectively. No foetal effects were observed in the absence of maternal toxicity. The LOAEL and NOAEL for developmental toxicity cannot be established due to the limited information provided.

In another study, Charles River CD rats were administered 75% THPS solution, by gavage, at doses of 0, 15, 30, or 60 mg/kg bw/day from GD 6 to 15 (Barker 1991b). At the top dose, decreased bodyweight gain of the dams was observed from GD 12 until the end of treatment. Incidence of foetuses with extra thoracic and / or lumbar rib was increased at the top dose. The LOAEL and NOAEL for maternal toxicity are 45 and 22.5 mg/kg bw/day THPS. No foetal effects were observed in the absence of maternal toxicity.

Based on the limited reporting of the studies, whether the developmental effects are attributable to the direct effect of the chemical or secondary to maternal toxicity cannot be reliably determined.

THPS is not considered a developmental toxicant.

23.5.9 *Other health effects*

No data were available.

23.6 Health hazard summary

23.6.1 *Critical health effects*

THPS has moderate acute oral and inhalation toxicity, low acute dermal toxicity, and is an eye irritant and a skin sensitiser.

The most appropriate NOAEL for risk assessment purposes, determined from the 13-week gavage study in rats by the US NTP (1987) is 3.6 mg/kg bw/day.

The chemical is neither genotoxic nor a carcinogen. THPS is not considered a developmental toxicant.

23.6.2 *Hazard classification*

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A23.6. These NICNAS recommendations do not consider physical or environmental hazards.

Table A23.6 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Toxic if swallowed (T; R25)	Toxic if swallowed – Cat. 3 (H301)
Irritation / Corrosivity	Risk of serious eye damage (X_i; R41)	Causes serious eye damage – Cat. 1 (H318)
Sensitisation	May cause sensitisation by skin contact (X_i; R43)	May cause an allergic skin reaction – Cat. 1 (H317)
Repeated dose toxicity	Danger of serious damage to health by prolonged exposure if swallowed (T; R48/22)	May cause damage to organs through prolonged or repeated exposure via the oral route – Cat. 2 (H373)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

23.7 References

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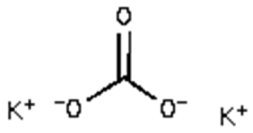
A24 Potassium carbonate

CAS No.	CAS Name
584-08-7	Carbonic acid, potassium salt (1:2)

24.1 Chemical identity

The following chemical identity information was obtained from ChemID*plus* (2012) and the Registration, Evaluation, Authorisation and Restriction of Chemicals dossiers on Carbonic acid, potassium salt (1:2) (REACH 2013). Table A24.1 provides details of the chemical identity. The substance is more commonly known as potassium carbonate.

Table A24.1 Chemical identity

	Potassium carbonate
Synonyms	Potassium carbonate Carbonic acid dipotassium salt Dipotassium carbonate Carbonate of Potash
Structural formula	
Molecular formula	K_2CO_3
Molecular weight	138
Appearance and odour	Hygroscopic white powder or as hygroscopic colourless crystals.
SMILES Notation	C(=O)([O-])[O-].[K+].[K+]

24.2 Physical properties

The following information on the physical properties was obtained from Haynes (2011). The physical properties of potassium carbonate are presented in Table A24.2.

Table A24.2 Physical properties

Property	**Value**
Melting point	899 °C
Boiling point	Decomposes at higher temperatures
Density	2.29 kg/m^3 at 20 °C
Vapour pressure	Negligible at 20 °C

Property	Value
Water solubility	1110 g/L at 25 °C
Partition coefficient n-octanol/water (log K_{ow})	Not relevant

24.3 Current regulatory controls

24.3.1 *Hazard classification for occupational health and safety*

Potassium carbonate is not listed on the Hazardous Substances Information System (HSIS) (Safework Australia 2013).

24.3.2 *Occupational exposure standards*

24.3.2.1 Australia

No specific exposure standards were available.

24.3.2.2 International

Occupational exposure limits for potassium carbonate identified internationally are provided below (Galleria Chemica 2013):

- 5 mg/m^3 Time Weighted Average (TWA) (US - Michigan Exposure Limits for Air Contaminants).

No other occupational exposure limit exists internationally specifically for potassium carbonate; however, many countries have assigned a generic TWA exposure limit of 10 mg/m^3 (inhalable dust) and 3 to 5 mg/m^3 (respirable dust) for Particles Not Otherwise Classified (PNOC).

24.3.3 *Australian food standards*

Potassium carbonate is permitted in Australia for use as an acidity regulator (Food Standards Australia New Zealand 2013).

Potassium carbonate is allotted an International Numbering System of Food Additives number: INS 501.

24.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

24.3.5 *Additional controls*

24.3.5.1 Australia

Potassium carbonate, as an alkaline salt, is included in Schedule 5, Schedule 6 and Appendix C of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

- Schedule 5: ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination for non-domestic use in:

(a) solid orthodontic device cleaning preparations, the pH of which as an "in-use" aqueous solution is more than 11.5

(b) solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solution or mixture is more than 11.5 but less than or equal to 12.5

(c) other solid preparations, the pH of which in a 10 g/L aqueous solution is more than 11.5 or

(d) liquid or semi-solid preparations, the pH of which is more than 11.5, unless:

d. (i) food additive preparations for domestic use or

e. (ii) automatic dish washing preparations for domestic use with a pH of more than 12.5, except when separately specified in these Schedules.

- Schedule 6: ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination for non-domestic use in:

  (a) solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solution or mixture is more than 12.5 or

  (b) liquid or semi-solid automatic dishwashing preparations, the pH of which is more than 12.5.

- Appendix C: ALKALINE SALTS, being the carbonate, silicate or phosphate salts of sodium or potassium alone or in any combination for domestic use in:

  (a) liquid or semi-solid food additive preparations, the pH of which is more than 11.5

  (b) solid automatic dishwashing preparations, the pH of which in a 500 g/L aqueous solution or mixture is more than 12.5 or

  (c) liquid or semi-solid automatic dishwashing preparations, the pH of which is more than 12.5.

The SUSMP also recommends appropriate '*Warning Statements'* and '*Safety Directions'* for sodium carbonate when used in consumer products.

Potassium carbonate is not included in the Australian Dangerous Goods Code Edition 7(ADG7) (National Transport Commission 2007). However, corrosive inorganic basic (alkali) liquids are included in Class 8 and packaging groups I and II of the ADG7.

24.3.5.2 International

No international restrictions were identified.

24.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

24.5 Health hazard characterisation

The information on health hazards is obtained from the REACH dossiers (REACH 2013). Unless otherwise noted, references to individual studies below are taken from these sources.

Data were read across from potassium bicarbonate for the carcinogenic endpoint because of similarities in structural formula and physical properties between these chemicals.

24.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

When potassium carbonate comes into contact with liquids, including body fluids, it dissociates into potassium and carbonate ions. The carbonate ion can potentially increase the pH of the blood. Compensatory mechanisms for acid-base disturbances function to alter the ratio of HCO_3^- to PCO_2 in order to return the pH of the blood to normal (OECD 2002). Human blood and cytosol have a pH of 7.4. Irreversible damage to tissue occurs if the pH falls below 7.0 or rises above 7.8. The bicarbonate buffer system is the major extracellular buffer in the blood and interstitial fluid of vertebrates that maintains the pH and is described by the following equation:

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

24.5.1.1 Oral absorption

After ingestion, potassium carbonate rapidly dissociates in the gastric juice to yield carbonate ions (CO_3^{2-}) and potassium ions (K^+).

Ninety per cent of the dietary potassium (K^+) is absorbed in the intestines, the vast majority of absorption occurring in the small intestine (Agarwal et al. 1994). Carbonate ions are neutralised in the stomach by the gastric acids present in significant amounts in the stomach (pH about 2) resulting in the formation of bicarbonate ion and / or carbon dioxide.

For human risk assessment purposes, an oral absorption of 100% is therefore assumed.

24.5.1.2 Dermal absorption

No data were available on dermal absorption of potassium carbonate. Absorption of ionic salts by the skin is essentially negligible (Schaefer and Redelmeier 1996). A report by the United States Environmental Protection Agency (US EPA) Design for the Environment (DfE), investigating cleaner technology substitutes, concluded that absorption of potassium carbonate is expected to be nil through the skin (US EPA 1997).

24.5.1.3 Inhalation absorption

Information on the inhalation absorption of potassium carbonate is not available. However, based on adverse effects noted in a rat repeated inhalation dose study, 100% inhalation absorption is assumed for human health risk assessment.

24.5.1.4 Distribution and metabolism

Potassium is the most abundant cation in the human body, and regulates intracellular enzyme function and neuromuscular tissue excitability. It is one of the main positive electrolytes found within the cells, where 98% of the 120 g of potassium contained in the body is found. Serum potassium is normally maintained within the narrow range of 3.5 to 5.5 mEq/L (Osorio and Lewis 1999). Because only a small portion of potassium is extracellular, neuromuscular tissue excitability is markedly affected by small changes in extracellular potassium. The human body has developed elaborate regulatory mechanisms to maintain potassium homeostasis. Long-term potassium balance is maintained by renal excretion of ingested potassium.

On an average diet, 77 mEq of potassium are ingested, and 7 mEq excreted in the faeces (Spencer 1959). The daily absorption amounts to 2.2% of exchangeable potassium. Potassium is transported in both directions across the intestinal mucosa.

Any change in the physiological concentration of carbonate ions as a result of increased exposure/absorption of carbonate is regulated physiologically by the bicarbonate buffer system in the body (Johnson and Swanson 1987).

24.5.1.5 Excretion

The kidneys are the chief regulators of body potassium, keeping the blood levels steady even with wide variation in intake. The adrenal hormone, aldosterone, stimulates elimination of potassium by the kidneys.

Most excess potassium is eliminated in the urine; some is eliminated in the sweat. Potassium is also lost with vomiting and diarrhoea. In contrast to sodium, which is effectively conserved by the body, there is no effective method for potassium conservation (Haas 2011).

Carbonate ions are neutralised to carbon dioxide in the body. The CO_2 from the tissues diffuses rapidly into red blood cells, where it is hydrated to form carbonic acid. This reaction is accelerated by carbonic anhydrase, an enzyme present in high concentrations in red blood cells. The carbonic acid formed dissociates into bicarbonate and hydrogen ions. Most of the bicarbonate ions diffuse into the plasma and are excreted as respiratory CO_2 (HSDB 2013).

24.5.2 *Acute toxicity*

24.5.2.1 Oral

In an acute oral toxicity study conducted according to OECD Test Guideline (TG) 401, five male and five female fasted Sprague-Dawley rats were administered a single oral dose of 2000 mg/kg bw potassium carbonate by gavage. The rats were observed for 14 days. There were no treatment-related clinical signs, necropsy findings or changes in body weight. Piloerection was observed in all animals during the first 30 minutes after administration. No mortality occurred. A median lethal dose (LD50) of >2000 mg/kg bw was established from this study (REACH 2013).

In two other acute oral studies in rats, carried out according to OECD guidelines, following administration of 2000 mg/kg bw of potassium carbonate no effects were observed in the animals. The LD50 of >2000 mg/kg bw was confirmed by these studies (REACH 2013).

24.5.2.2 Dermal

In an acute dermal toxicity study performed according to the US EPA Pesticide Assessment Guidelines, five male and five female New Zealand White rabbits were exposed dermally to the test article ‘Biocide #5654, Potassium Carbonate’ moistened in distilled water at a dose of 2000 mg/kg bw/day (application details not provided) (REACH 2013). The substance was wiped from the skin 24 hours after the start of exposure. Animals were observed for 14 days. All animals survived. No significant clinical signs, effects on body weight or gross pathological findings were observed apart from dermal irritation at the application site of all animals. It was concluded that the dermal LD50 was greater than 2000 mg/kg bw/day. This is not unexpected, because dermal absorption of potassium carbonate in animals is negligible.

24.5.2.3 Inhalation

No data were available.

24.5.2.4 Observation in humans

No cases of acute oral or dermal poisoning from potassium carbonate have been found in the published literature. The low oral toxicity of potassium carbonate is likely to be due to the neutralisation mechanism of carbonate ions in the stomach and the fact that potassium ions are not conserved by the body.

24.5.3 *Irritation / Corrosivity*

24.5.3.1 Skin irritation

In a primary dermal irritation study conducted according to United States Food and Drug Administration (US FDA) guidelines – '*Appraisal of the safety of chemicals in food, drugs and cosmetics*' – six New Zealand White rabbits were dermally exposed to 500 mg potassium carbonate (REACH 2013). The test substance 'potash-calc' was moistened with physiological saline and applied to one abraded and one intact test site per animal and covered with a 2.5 x 2.5 cm gauze patch. After 24 hours, the coverings were removed and remaining test substance was wiped off. Animals were examined for signs of erythema and oedema one to two hours, and 48 hours, after patch removal. Irritant effects were scored by the method of Draize for erythema and oedema.The intact skin
sites were free of erythema and oedema at both readings, i.e. 24 and 72 hours after substance application (i.e. one and 48 hours after patch removal). At the abraded skin sites, a dark brown discoloration with moderate red edges (score 4) was observed at the 24 and 72 hour readings in all animals. These findings were interpreted by the study authors as necrosis, and slight oedema (score 2) at the 24 hour reading.

In another dermal irritation study, conducted according to US EPA Pesticide Assessment Guidelines, six New Zealand White rabbits were clipped free of hair from the scapular to the lumbar region (REACH 2013). One 6 cm^2 intact site on each rabbit was treated with 0.5 g of the test substance 'Biocide #5654' (potassium carbonate). The sites were covered with a semi-occlusive dressing for approximately four hours, at which time the patches were removed and the sites were wiped clean. Animals were observed for further 72 hours. The sites were scored by the Draize method for erythema and oedema at 1, 24, 48 and 72 hours after patch removal. One hour after patch removal, all animals exhibited very slight to well-defined erythema and two rabbits had very slight to slight oedema. The incidence and severity of irritation decreased with time. Very slight erythema and oedema was noted at only one site at 24 hours. By 72 hours all treated sites were free from any dermal irritation. All animals appeared active and healthy. Apart from skin irritation, there were no signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour. The authors concluded that potassium carbonate is not a dermal irritant.

Based on the two studies, it is concluded that potassium carbonate is not a skin irritant. Although in the first study erythema was observed, this effect was noted only in abraded skin and not in intact skin. According to OECD TG 404 (Acute dermal irritation/corrosion), care needs to be taken when shaving the skin areas so as not to abrade the skin and only intact skin should be treated with the test substance. Therefore, the observed effects on abraded skin cannot be considered as an irritant reaction.

This conclusion is further supported by the fact that dermal irritation tests with a structurally related compound, sodium carbonate, were negative (Section A21.5.3.1).

24.5.3.2 Eye irritation

In a study conducted according to US FDA guidelines, ocular irritancy of potassium carbonate was tested by instilling the moistened test substance 'potash-calc' into the

conjunctival sac of the left eyes of six male New Zealand White rabbits (REACH 2013) . The right eyes served as the untreated controls. The eyes were not rinsed after substance application. Animals were observed for 1 hour, 1, 2, 3, 4 and 7 days after instillation of test substance. Irritation was scored by the Draize method. One hour after application of the test material, clear irritation of the eyes was observed. All animals showed conjunctival redness (mean score 3) and chemosis (mean score 4), accompanied by moderate secretion (score 2) and corneal opacity (2.2). Iritis was observed in all the animals. The mean scores decreased within the observation period of seven days for all observed effects. At day 7, all animals still showed slight to moderate conjunctival redness and slight to distinct chemosis accompanied by secretion. Corneal pannus formation was present in 2/6 animals. Five of the six animals had opacity of the cornea of different magnitudes (score 1 to 3). The iritis was completely reversible in 3/6 animals and had decreased in the other three animals to score 1 by day 7. According to the test protocol, no observations were carried out beyond seven days. It is therefore not clear whether or not the observed effects were reversible after 21 days of application.

A second study reported the eye irritation effects of potassium carbonate using the OECD TG 437 (REACH 2013). Freshly isolated bovine corneas were mounted in cornea holders and the initial opacity was determined. After equilibration, 750 µL of the test substance preparations (various concentrations of potassium carbonate) were topically administered to the epithelial surface. Four hours after application the final opacity of the corneas was measured. In each experiment, two groups of three corneas each served as positive and negative controls. The opacity and mean permeability values were corrected for background opacity and the negative control permeability values. A 3.0% potassium carbonate solution gave an *in vitro* irritation score of 72.1 indicating that it is a severe eye irritant.

Based on the overall results potassium carbonate is considered a severe eye irritant.

24.5.3.3 Respiratory irritation

No data were available.

24.5.3.4 Observation in humans

Data regarding specific human toxicity following potassium carbonate exposure is not available. The HSDB (2013) speculates that ingestion of dilute aqueous solution of potassium carbonate may result in irritation and burns of the oropharynx, oesophagus or stomach. Concentrated solutions of potassium carbonate may cause deep burns and necrosis of the gastrointestinal mucosa including oesophageal and gastric perforations and gastrointestinal bleeding.

Ocular exposure could lead to severe conjunctival irritation and chemosis, corneal epithelial defects, limbal ischaemia, permanent visual loss and in severe cases perforation.

24.5.4 *Sensitisation*

24.5.4.1 Skin sensitisation

In a dermal sensitisation study using the Buehler method, young adult Hartley guinea pigs (10 test and five control animals) were tested with Potassium Carbonate (Biocide #5654). To enhance skin contact, the substance was moistened with water (95% w/w) for induction and challenge exposure.

No irritation was noted at any of the test or negative control sites during the induction phase. After challenge exposure, no skin reactions were observed in test or control animals at any observation time. Sensitisation rate was therefore considered to be 0%.

Dinitrochlorobenzene (sensitisation rate of 80%) was used as a positive control substance and tested on equal numbers of animals (10 test and five controls) in the same study.

It was concluded that potassium carbonate is not a skin sensitiser.

24.5.4.2 Respiratory sensitisation

No data were available.

24.5.4.3 Observation in humans

Skin sensitisation has not been reported in workers exposed to potassium carbonate during handling of potassium carbonate at worksites.

In summary, potassium carbonate has low acute oral and dermal toxicity. Information on inhalation toxicity is not available. It is not a skin irritant but a severe eye irritant and is expected to be a moderate respiratory irritant based on repeat dose inhalation effects. Tests with guinea pigs indicated that potassium carbonate is not a skin sensitiser.

24.5.5 *Repeat dose toxicity*

24.5.5.1 Oral

No data were available on repeated dose toxicity by the oral route for potassium carbonate. No data were available for related compounds, sodium carbonate or sodium bicarbonate.

24.5.5.2 Dermal

No data were available on repeated dose toxicity by the dermal route for potassium carbonate. No data were available for related compounds, sodium carbonate or sodium bicarbonate.

24.5.5.3 Inhalation

In the only available sub-acute inhalation toxicity study conducted to OECD TG 412, 30 Sprague Dawley rats per sex per dose group were exposed to aerosols of different concentrations of a potassium carbonate-based scrubbing solution, ‘Catacarb’ (main active ingredient 30.8% potassium carbonate) (Bui et al. 1998). Animals were exposed to the aerosols as whole body exposure at concentrations of 0, 0.1, 0.2 and 0.4 mg/L Catacarb for 6 hrs/day, 7 days/wk for a total of 21 consecutive days. Respirable-range aerosols of the liquid generated by stainless-steel atomisers were piped into the exposure chamber where the target concentrations of 0.1, 0.2, or 0.4 mg/L scrubbing solution were achieved by dilution with the chamber ventilation air flow.

No apparent adverse effects were noted at any exposure level as determined by clinical observations, haematology, serum chemistry, ophthalmologic observations, and gross pathology. There were no significant changes in any organ weights. Histopathological findings restricted to the respiratory tract were characterised by minimal to moderate epithelial hyperplasia, epithelial necrosis, and cytoplasmic vacuolation at levels I and II of the nasal cavities. Lung bronchiolisation and alveolar macrophage infiltration were also observed. The histopathological respiratory tract findings were fully reversible in all dose groups, except for the 0.4 mg/L exposure group, in which bronchiolisation and alveolar

macrophage infiltration were not fully reversible. The respiratory-tract findings were considered a local response to the high alkalinity of the test material (pH approximately 9.9) as substantiated by the return to normal upon cessation of exposure.

No treatment-related findings were seen in organs and tissues further examined, including the reproductive organs (ovaries, mammary glands, uterus, vagina, testes, prostate, and seminal vesicles).

A functional observational battery (FOB) and locomotor activity tests were also conducted on 10 rats per sex per group at prestudy, one hour following the completion of the first exposure, 18 hours after the first exposure, following completion of the last exposure (day 21) and at the end of the 14-day recovery period. The scrubbing solution had no adverse effect on FOB endpoints and locomotor activity evaluations, brain weight and size, and neuro-histopathologic examinations.

The authors concluded that whole body exposure of up to 0.4 mg/L of a scrubbing solution aerosol, at pH 9.9, containing 30.8% potassium carbonate, for six hours/day for 21 consecutive days did not result in any persistent systemic toxicity or neurotoxicity in either male or female rats. Reversible histopathological changes noted in levels I and II of the nasal cavities and in the lungs of the treated animals were indicative of a local response to the alkalinity of the test material as substantiated by the return to normal upon cessation of exposure.

A No Observed Adverse Effect Concentration (NOAEC) of 0.4 mg/L for the product ‘Catacarb’ and 0.12 mg/L for potassium carbonate (calculated based on its content in the test item) were established in this study for local reversible effects. This NOAEC will be taken forward for human health risk assessment.

24.5.5.4 Observation in humans

No data were available.

24.5.6 *Genotoxicity*

In two separate reverse gene mutation assays in bacteria (Ames method), *S. typhimurium* strains TA 92, TA 94, TA 97, TA 98, TA 100, TA 102, TA 1535 and TA 1537 were exposed to anhydrous potassium carbonate at concentrations of 100, 500, 1000, 5000 and 10 000 µg/plate in the presence and absence of mammalian metabolic activation using the pre-incubation method (Ishidate et al. 1984). There was no evidence of induced mutant colonies over background in any of the tested *S. typhimurium* strains up to and including the highest dose tested. Anhydrous potassium carbonate was tested beyond the limit concentration of 5000 µg/plate. Cytotoxicity was not reported in these studies. Potassium carbonate was considered to be negative with and without metabolic activation in this study.

In a mammalian cell cytogenetics assay, similar to OECD TG 473, Chinese hamster fibroblast CHL cell cultures were exposed to potassium carbonate (purity 99.8%) at three concentrations (concentrations not specified) including the highest non-cytotoxic concentration of 1000 µg/mL without metabolic activation (Ishidate et al. 1984). Only 2% polyploid cells and 3% cells with structural chromosomal aberrations were detected. The incidence of chromosomal aberrations was <4.9%, indicating a negative result and therefore the test result was considered to be negative. There was no evidence of chromosome aberration induced over background when anhydrous potassium carbonate was exposed to Chinese hamster fibroblast without metabolic activation.

From the above information it is concluded that potassium carbonate is not genotoxic.

24.5.7 *Carcinogenicity*

Carcinogenicity studies with potassium carbonate are not available. Potassium carbonate rapidly dissociates into its constituent ions and will not be systemically available in the body. As a consequence, potassium carbonate is not expected to cause systemic toxicity in any organs. A carcinogenic effect of potassium carbonate is unlikely.

A carcinogenicity study with a related substance, potassium bicarbonate, has been reported by Lina et al. (1994). In this study, Wistar rats were fed 0, 1299 and 2861 mg/kg bw/day potassium bicarbonate (male rats) and 0, 1686 and 3566 mg/kg bw/d potassium bicarbonate (female rats) in the diet for 78 weeks.

No treatment-related adverse effects were observed in the rats. In the urinary bladder, significant pre-neoplastic epithelial alterations developed, which are common findings in rats after long term high dose alkali intakes. It is widely accepted that these high dose effects are specific to the rat and are of no relevance to humans (IARC 1999).

Potassium bicarbonate did not affect the type, incidence or multiplicity of tumours, nor the time of tumour appearance and the ratio of benign-malignant tumours.

Based on the available information, potassium carbonate is not considered to be a carcinogen.

24.5.8 *Reproductive toxicity*

24.5.8.1 Fertility

No data were available.

24.5.8.2 Developmental toxicity

In a developmental toxicity study similar to OECD TG 414, potassium carbonate was administered to female Wistar rats (22 to 25 rats/dose group) by gavage at 0, 1.8, 8.4, 38.8 or 180 mg/kg bw/day from days 6 through 15 of gestation (REACH 2013). On day 20, all dams were subjected to Caesarian section, and the sex, numbers of corpora lutea, implantation sites, resorption sites, and live and dead foetuses, as well as the body weights of live pups, were recorded. The urogenital tract of each dam was examined in detail for anatomical normality. All foetuses were examined grossly for the presence of external congenital abnormalities. One-third of the foetuses of each litter underwent detailed visceral examination, the remaining two-thirds were examined for skeletal defects.

There were no effects on mortality, body weight gain and the urogenital tracts of dams. There were no effects on numbers of corpora lutea, live litters, implantations, resorptions, live and dead foetuses, sex ratio of the foetuses or the average foetus weight. Soft tissue and skeletal anomalies noted in the experimental group did not differ from anomalies occurring in sham-treated controls.

There were no treatment-related maternal or developmental toxic effects observed in this study when potassium carbonate was administrated up to and including the highest tested dose of 180 mg/kg bw/day. A NOAEL could not be established in this study.

It was concluded from the study that potassium carbonate does not have developmental toxicity.

24.5.9 *Other health effects*

No data were available.

24.6 Health hazard summary

24.6.1 *Critical health effects*

Potassium carbonate has low acute oral, dermal and inhalation toxicity. The acute oral as well as dermal LD50 in rats is 2000 mg/kg bw. An LC50 for potassium carbonate has not been established. Potassium carbonate has low skin irritation potential. It is a severe eye irritant and is expected to be a moderate respiratory irritant based on repeat dose inhalation effects.

Information on repeated dose toxicity by the oral and dermal routes is not available. In rats, whole body exposure of up to 0.4 mg/L of a scrubbing solution aerosol, at pH 9.9, containing 30.8% potassium carbonate, for 6 hrs/day for 21 consecutive days did not result in any persistent systemic toxicity or neurotoxicity in either male or female rats. Reversible histopathological changes noted in nasal cavities and the lungs of the treated animals were considered to be a local response to the alkalinity of the test material as substantiated by the return to normal upon cessation of exposure.

Given the constituent ions of potassium carbonate are normal physiological components of the body that are subject to tight homeostatic control, systemic effects from repeated exposure to potassium carbonate are not expected.

A No Observed Adverse Effect concentration (NOAEC) of 0.4 mg/L for the product 'Catacarb' and 0.12 mg/L for potassium carbonate (calculated based on its content in the test item) were established in this study for local reversible effects. In the absence of a more suitable NOAEL, this NOAEC will be taken forward for risk assessment.

Potassium carbonate was not genotoxic or carcinogenic. Reproductive toxicity studies are not available; however, no effects on reproductive organs were noted when rats were exposed to potassium carbonate aerosols. Developmental studies with rats did not show any toxicity.

Eye irritation is the critical effect for risk assessment.

24.6.2 *Hazard classification*

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria (NOHSC 2004) and adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A24.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A24.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved criteria	**GHS* classification**
Irritation / Corrosivity	Risk of serious damage to eyes (X_i; R41) Irritating to respiratory system (X_i; R37)	Causes serious eye damage – Cat. 1 (H318) May cause respiratory irritation - Specific target organ toxicity, single exposure - Cat. 3; (H335)

** Globally Harmonised System (UNECE 2009)*

NICNAS has recommended that Safe Work Australia should classify mixtures containing potassium carbonate as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures:

- Conc ≥10%: Xi; R41 (Risk of serious damage to eyes)
- 5% ≤Conc <10%: Xi; R36 (Irritant; irritating to eyes)
- Conc ≥20%: Xi; R37 (Irritating to respiratory system).

24.7 References

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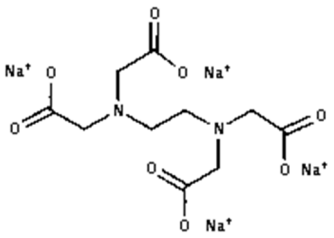
A25 Tetrasodium EDTA

CAS No.	CAS Name
64-02-8	Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, sodium salt (1:4)

25.1 Chemical identity

The identity information was obtained from ChemID*plus* (2012) and the European Chemicals Bureau (ECB) (2005). A description of the chemical identity is provided in Table A25.1.

Table A25.1 Chemical identity

	Tetrasodium EDTA
Synonyms	Ethylenediaminetetraacetic acid, tetrasodium salt Edetate sodium EDTA tetrasodium Tetrasodium edetate Tetrasodium ethylene diamine tetraacetate Acetic acid, (ethylenedinitrilo)tetra-, tetrasodium salt Trilon B
Appearance	White powder
Structural formula	
Molecular formula	$C_{10}H_{16}N_2O_8.4Na$
Molecular weight	380.171
SMILES Notation	N(CCN(CC(=O)[O])CC(=O)[O])(CC(=O)[O])CC(=O)[O].[Na+].[Na+].[Na+].[Na+]

25.2 Physical properties

The following information on physical properties was obtained from the ECB (2005) and the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH 2013), and is provided in Table A25.2.

Table A25.2 Physical Properties

Property	Value
Melting point	>300 °C
Density – kg/m^3	1.67 x 10^{-3} (20 °C)
Vapour pressure	2 x 10^{-13} (25 °C) (calculated)
Water solubility	500 g/L (20 °C)
Partition coefficient (log K_{ow})	-13.17 (calculated)

25.3 Current regulatory controls

Hereinafter the document refers to glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, sodium salt (1:4) as tetrasodium EDTA, one of the synonyms of the chemical.

25.3.1 *Hazard Classification for occupational health and safety*

Tetrasodium EDTA is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) with the following risk phrases (Safe Work Australia 2013):

- Xn (harmful); R22 (Harmful if swallowed)
- X_i (irritant); R41 (Risk of serious eye damage).

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures. The risk phrases for this chemical are:

- Conc ≥25%: Xn: R22, R41
- 10% ≤Conc <25%: Xi: R41
- 5% ≤Conc <10%: Xi: R36 (Irritating to the eyes).

25.3.2 *Occupational exposure standards*

25.3.2.1 Australia

No specific exposure standards were available.

25.3.2.2 International

No specific exposure standards were available.

25.3.3 *Australian food standards*

Tetrasodium EDTA is listed in the Australia New Zealand Food Standards Code – Standard 1.3.3 - Processing Aids – Permitted processing aids used in packaged water and in water used as an ingredient in other foods (Food Standards Australia New Zealand 2013).

25.3.4 *Australian drinking water guidelines*

No Australian drinking water guideline exists specifically for tetrasodium EDTA. However tetrasodium EDTA will dissociate in water to an equilibrium mixture of various EDTA ions and unionised EDTA; the latter is called the EDTA free acid. The guidelines note that the concentration of EDTA (measured as the free acid) in drinking water should not exceed 0.25 mg/L based on health considerations (National Health and Medical Research Council (NHMRC) 2011).

25.3.5 *Additional controls*

25.3.5.1 Australia

The chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

25.3.5.2 International

Tetrasodium EDTA is listed by the US FDA under 21 CFR 178.1010 as acceptable for use in food contact surface sanitising solutions (US FDA 2013).

The chemical is classified as a hazardous substance, acutely toxic (oral) and irritating to the eye under the Hazardous Substances and New Organisms (HSNO) Act of the Environmental Protection Authority New Zealand (EPA NZ) (EPA NZ 2012).

25.4 Use

The use of this chemical in coal seam gas extraction processes is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

25.5 Health hazard characterisation

The information on health hazards was sourced primarily from the REACH dossier for tetrasodium EDTA (REACH 2013), a European Union Risk Assessment Report for tetrasodium EDTA (ECB 2005), a science assessment for EDTA chemicals (US EPA 2006) and an Organisation for Economic Co-operation and Development (OECD) Screening Information Dataset Initial Assessment Profile (SIAP) for aminocarboxylic acid-based chelants (OECD 2012).

Only limited toxicity data were available for tetrasodium EDTA. Reliable data for disodium EDTA (CAS No. 139-33-3) and trisodium EDTA (CAS No. 150-38-9), both analogues of the tetrasodium compound, were available for the majority of the toxicity endpoints. All compounds have a similar chemical structure and functional groups. The ethylenediamine backbone structure has four acetic acid groups which are in the form of the carboxylate anion, in which two or more hydrogens have been neutralised to a sodium salt. The molecular weight range for the three edetate sodium salts is 336 to 380 g/mol. The presence of the multiple carboxylic acid groups at the opposite ends of the amine backbone provide the three chemicals with the molecular structure which enables a metal ion chelating or sequestering property. This common property is largely responsible for the indirect mammalian toxicity of the compounds. However, some subtle differences in the toxicity between the sodium salts may occur in endpoints such as acute toxicity, skin and eye irritation, sensitisation and genetic toxicity. In these cases, the effects are a consequence of pH, which can influence local irritation potential and to some extent acute toxicity (OECD 2012). For systemic studies, EDTA and its sodium salts are considered to be

equivalent as they are dissociated under physiological conditions (pH 7 to 9) into sodium cations and the respective anionic species of edetic acid depending on the pH dependent dissociation equlilibria of edetic acid (ECB 2005). For the salts, as the sodium counter-ions are normal constituents of the blood and are regulated by excretion into the urine, they are not considered to significantly contribute to the toxicity. Thus, the use of data for the disodium and trisodium salts, as analogues for tetrasodium EDTA, are appropriate to read across for the endpoints where no data were available for the tetrasodium salt (Table A25.3).

Table A25.3 Summary of available toxicity endpoint data

	Tetrasodium EDTA (CAS No. 64-02-8)	**Trisodium EDTA (CAS No. 150-38-9)**	**Disodium EDTA (CAS No. 139-33-3)**
Acute oral toxicity	✓	✓	✓
Acute dermal toxicity	×	×	×
Acute inhalation toxicity	✓	×	✓
Skin irritation	✓	✓	✓
Eye irritation	✓	✓	✓
Respiratory irritation	×	×	✓
Skin sensitisation	×	✓	✓
Respiratory sensitisation	×	×	×
Repeat dose toxicity (oral)	×	✓	✓
Repeat dose toxicity (dermal)	×	×	×
Repeat dose toxicity (inhalation)	×	×	✓
Genotoxicity *in vitro*	✓	✓	✓
Genotoxicity *in vivo*	×	✓	✓
Carcinogenicity	×	✓	×
Reproductive toxicity (fertility)	×	×	✓
Reproductive toxicity (development)	✓	✓	✓

✓Existing data point; × Missing data point

Additional sources of hazard information for the chemical include published reports by peer reviewed committees such as the Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE) (CSTEE 2003) and the Cosmetic Ingredient Review (CIR) (CIR 2002). Unless noted, references to individual studies below are taken from these reviews.

25.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

25.5.1.1 Oral absorption

No data were available for tetrasodium EDTA.

A study in a single rat using 95 mg disodium EDTA indicated that this compound is poorly absorbed after oral administration with approximately 93% recovered in the colon and 6% in the urine within 32 hours (Yang and Chan 1964 as cited in CIR 2002). Similar findings were reported when rats were dosed with 95 mg/day for seven days. In rats fed the compound at dietary levels of 0.5, 1 and 5%, the faeces contained 99.4, 98.2, and 97.5% of the excreted material and the urine contained 0.6%, 1.8%, and 2.5% of the material for the respective doses (Yang and Chan 1964 as cited in CIR 2002).

Following oral administration of [^{14}C]-EDTA ($CaNa_2EDTA$, 50 mg/kg bw) to rats, only 2 to 4% of the dose was absorbed within 48 hours (Foreman et al. 1953 as cited in World Health Organization-WHO 1974).

In a human study, oral doses of [^{14}C]-EDTA administered to two patients passed through the intestine and 95% to 100% of the dose was recovered in the stool within 2 to 5 days and urinary excretion less than 8%. Additionally, blood samples taken from 1 hour to 3 days after oral administration of the [^{14}C]-EDTA did not have any ^{14}C activity (Stevens et al. 1962 as cited in CIR 2002).

Foreman and Trujillo (1954) studied the oral uptake of [^{14}C]-EDTA ($CaNa_2EDTA$, 2 mg) in healthy males. They concluded that EDTA is poorly absorbed from the gastrointestinal tract with a maximum of 5% of the dose detected in the urine within 24 hours. In similar human studies, only 2.5% of a 3 g dose of the compound was found to be excreted in the urine (Srbova and Teisinger 1957 as cited in WHO 1974).

In general, studies with EDTA and its salts indicate that these chelants are poorly absorbed in mammals after oral administration with a systemic availability of no more than 5% within 24 to 48 hours.

For the purposes of risk assessment, 5% oral absorption in humans is therefore assumed.

25.5.1.2 Dermal absorption

No data were available for tetrasodium EDTA.

Negligible amounts of radioactivity were found in the tissues of rats at 24 hours after application to the intact skin of [^{14}C]-labelled, disodium EDTA (Furlani and Vertua 1970).

In a skin absorption study in healthy males, 2 mg of a ‘sodium salt’ of [^{14}C]-labelled EDTA and 1 g of unlabelled ‘sodium salt’ of EDTA was applied in a water-soluble base over an area of 100cm^2. Radioactivity in the urine accounted for only 0.001% of the administered dose (Foreman and Trujillo 1954).

For the purposes of risk assessment, 0.001% dermal absorption in humans is assumed.

25.5.1.3 Inhalation absorption

No data were available. For the purposes of risk assessment, 100% inhalation absorption in humans is therefore assumed.

25.5.1.4 Distribution

No data were available for tetrasodium EDTA.

The tissue distribution of radioactivity after application to the skin of [^{14}C]-labelled, disodium EDTA was compared in the rat with that found after intraperitoneal (i.p.) administration. At 24 hours after i.p. administration, radioactivity was mainly found in the liver, small intestine, large intestine and concentrated in the kidney. While radioactivity was found in the same tissues at 24 hours after application on normal skin, it was only present at trace levels and was not concentrated in the kidney (Furlani and Vertua 1970).

25.5.1.5 Metabolism

No data were available for tetrasodium EDTA.

After oral intake, disodium EDTA is at most scarcely metabolised and is excreted as a chelated complex in the urine (WHO 1974; ECB 2005).

25.5.1.6 Excretion

No data were available for the tetrasodium compound.

Rats fed disodium EDTA at 300, 600, and 3000 mg/kg bw/day for 12 weeks excreted 99.4, 98.2 and 97.5% of the dose in the faeces and 0.6, 1.8, and 2.5% in the urine respectively (Yang and Chan 1964). In a second study, rats were given single doses of 47.5, 95.0, and 142.5 mg disodium EDTA (corresponding to 238, 475, and 713 mg/kg bw assuming a body weight of 200 g) (Yang and Chan 1964). For all groups, urinary excretion peaked at four hours after ingestion with the amount of EDTA recovered directly proportional to the dose. The linear relationship suggested that EDTA was absorbed from the gastrointestinal tract by a process of diffusion.

In a human study, after oral doses of [^{14}C]-EDTA were administered to two patients the kidneys were the major route of excretion. At the end of 24 hours, 90% to 100% of the absorbed dose was excreted in the urine (Stevens et al. 1962 as cited in CIR 2002).

25.5.2 *Acute toxicity*

25.5.2.1 Oral

Acute oral toxicity data for tetrasodium EDTA are summarised from ECB (2005) and OECD (2012).

In two studies, acute oral median lethal dose (LD50) values of 2700 mg/kg bw (BASF AG 1970) and 3200 mg/kg bw (BASF AG 1978b) were reported, while in three other tests the LD50 values ranged from 1658 mg/kg bw (BASF AG 1982), 1700 mg/kg bw (BASF AG 1978a) to 1780 to 1913 mg/kg bw (BASF AG 1983). The most prominent clinical signs were dyspnoea, ataxia, staggering gait, tremor and piloerection. At necropsy there was evidence of redness and / or bloody ulceration of the glandular stomach, redness of the mucous membranes of the intestine and general hyperaemia.

Supporting oral toxicity data were available for the other sodium salts, with studies reporting LD50 values in rats of 2000 mg/kg bw for disodium EDTA and 2150 mg/kg bw for the trisodium EDTA (US EPA 2006).

Tetrasodium EDTA has moderate acute toxicity by the oral route.

25.5.2.2 Dermal

No data were available for tetrasodium EDTA or suitable analogues.

25.5.2.3 Inhalation

Acute inhalation toxicity data were available for tetrasodium EDTA (as cited in ECB 2005). There were no deaths when rats were exposed for eight hours at 20ºC to an atmosphere enriched with the dust of the compound at an undisclosed concentration (BASF AG 1978a). Similarly, no mortality occurred when rats were exposed to a dust atmosphere (of unknown concentration) that was either heated to 20ºC or 80ºC (BASF AG 1970).

Data were also available for the disodium analogue. No deaths were reported when rats were exposed for seven hours at 20ºC to an atmosphere enriched with the dust of disodium EDTA at a concentration of 1.13 mg/L (Pinkerton and Schwebel 1976). Exposure of male rats for six hours to respirable dust aerosols of disodium EDTA at concentrations of 33.3, 320 and 1103 mg/m^3 resulted in significant mortality (6/20 rats) at the top dose (BASF SE 2010 as cited in REACH 2013). Histological examination of the lung of the dead rats revealed congestion, oedema, multifocal haemorrhages and inflammatory cell infiltrates.

Tetrasodium EDTA is toxic by the inhalation route based on recent unpublished data available for the disodium analogue.

25.5.2.4 Observation in humans

No data were available.

25.5.3 *Irritation / Corrosivity*

25.5.3.1 Skin irritation

The application of a 40% aqueous solution of tetrasodium EDTA (pH 11) elicited mild redness on the back and ear of a rabbit after a 20-hour exposure period. No effects were observed after exposure periods of 15 minutes or less (BASF AG 1978b). An 80% solution of the substance tested under the same conditions produced no irritation after exposure periods of 15 minutes and less while, for an exposure time of 20 hours, severe erythema and mild scales were observed on the back, and mild redness and mild scales were observed on the ear. No oedema was noted (BASF AG 1970).

In a study in rabbits, conducted in accordance with OECD Test Guideline (TG) 404, 0.5 g of an 80% aqueous preparation of Trilon B powder (tetrasodium EDTA, 75% pure) was applied for an occlusive exposure period of four hours. Erythema was observed with mean scores after 24, 48, and 72 hours of 1.0, 0, and 0.3 reported which resolved within eight days. No other dermal effects were noted (BASF AG 1982b).

In another test, conducted in accordance with OECD TG 404, a four-hour occlusive application of 0.5 mL of a 40% aqueous solution of tetrasodium EDTA to the skin of three rabbits elicited no dermal reactions (ASTA-Werke AG 1984a).

Either no irritation or slight irritation to intact rabbit skin was reported for neat and / or aqueous solutions of both disodium and trisodium EDTA salts (CIR 2002).

Tetrasodium EDTA is slightly irritating to rabbit skin at 80% but is not irritating at 40%.

25.5.3.2 Eye irritation

In a non-guideline eye irritation test in rabbits, 50 mg of a tetrasodium EDTA powder was instilled to the eyes with no washout after one hour. Strong irritation, extreme oedema and mild opacity were seen from 1 to 24 hours with pus formation that was reversible within eight days (BASF AG 1970). In another test under the same conditions, instillation of 50 mg

substance to the eyes produced mild redness, mild-strong oedema and mild opacity from 1 to 24 hours with the redness and oedema still present after eight days. A grease-like layer was observed on the eyes at all observation times (BASF AG 1978a).

Instillation of a 40% aqueous solution of tetrasodium EDTA to the eye of one rabbit resulted in mild redness, mild oedema and secretion after one hour with the redness persisting for at least eight days (BASF AG 1978b).

In one study, a 40% aqueous dilution of the chemical was applied in rabbit eyes. The effects observed included corneal opacity (grade 1), iritis (grade 1), conjunctival redness (grade 3), and chemosis (grade 2 to 3) (ASTA-Werke 1984b).

Either no irritation or slight irritation to rabbit eyes was reported for disodium EDTA (OECD 2012; CIR 2002). It was concluded that the difference in the pH of the chemicals, rather than the EDTA structure itself, is most likely to influence the eye irritancy of the EDTA salts (OECD 2012).

Tetrasodium EDTA is severely irritating to rabbit eyes under the conditions of the tests.

25.5.3.3 Respiratory irritation

The respiratory irritation potential of tetrasodium EDTA has not been assessed.

Inhalation exposure of rats to disodium EDTA at a concentrations of 30 mg/m^3 and above for six hours/day for five days (BASF SE 2010 cited in REACH 2013) caused concentration dependent lesions in the larynx and lungs that were fully reversible within 14 days (seeSection A25.5.5.3).

The results of this analogue study suggest that it is likely that the chemical is irritating to the respiratory mucosa. Tetrasodium EDTA is therefore likely to be a respiratory irritant.

25.5.3.4 Observation in humans

No data were available for tetrasodium EDTA. The irritancy potential of disodium EDTA was investigated in 26 volunteers using a fourhour patch test (Basketter et al. 1997 as cited in CIR 2002). None of the 26 volunteers treated with disodium EDTA had irritation, compared to 21 of the 26 volunteers treated with 20% sodium dodecyl sulfate as positive control.

25.5.4 *Sensitisation*

25.5.4.1 Skin sensitisation

No data were available for tetrasodium EDTA, however sensitisation tests with disodium EDTA and trisodium EDTA were used to read across to the tetrasodium salt for this endpoint.

In a guinea pig maximisation test, conducted in accordance with OECD TG 406, an initial challenge with 30% disodium EDTA (Trilon BD, purity 99%) resulted in 30% (3/10) and 0% (0/10) of test animals with a discrete patchy erythema at 24 hours and 48 hours after patch removal, respectively. At a second challenge conducted seven days later, 10% (1/10) of test animals demonstrated a positive reaction after 24 hours, but not after 48 hours (BASF AG 2000a). The authors concluded that although erythema was observed after the first challenge in 3/10 animals (the criterion for a positive test), it was not due to delayed contact hypersensitivity since it was mild and transient in nature and was observed only in 1/10 animals after the second challenge. There was no evidence of an allergic reaction in guinea pigs in a Draize test using disodium EDTA (Yang and Chan 1964)

No evidence of skin sensitisation was observed for 10% trisodium EDTA in a repeat insult patch test in guinea pigs (Henck et al. 1980).

The disodium and trisodium salts of EDTA are not skin sensitisers based on studies in guinea pigs and therefore it is unlikely that tetrasodium EDTA would be a skin sensitiser.

25.5.4.2 Respiratory sensitisation

No data were available for tetrasodium EDTA.

In a 5-minute inhalation challenge, 6% aerosolised disodium EDTA elicited bronchoconstriction in Basenji-Greyhound dogs with hyperreactive airways (Downes and Hirshman 1983). In a study to elucidate the mechanism of chelator induced airway constriction it was concluded that calcium chelators such as disodium EDTA can produce airway constriction via a non-immunological mechanism such as stimulating release of bronchoconstricting prostanoids in dogs with airway hyperresponsiveness (Lindeman et al. 1993).

25.5.4.3 Observation in humans

Human data on skin sensitisation of EDTA salts are summarised from CIR (2002) and presented below.

A 78-year-old female with recurrent leg ulcers yielded a positive patch test on two occasions to a 1% aqueous solution of tetrasodium EDTA (de Groot 1986).

Repeat-insult patch tests were conducted on 100 subjects to assess the skin sensitisation potential of cosmetic products with disodium EDTA as an ingredient (CTFA 1998). No sensitisation was observed in occlusive tests with 25 different products containing from 0.02% to 0.2% disodium EDTA.

It was reported that no positive reactions were observed when EDTA was included in the North American Contact Dermatitis Group's screening tray for several years (Fisher 1979). Although the exact identity of the test substance was not disclosed it is likely that it was a sodium salt.

The sensitivity to 'EDTA' (2%, chemical not specified) was investigated in 465 individuals who suffered from eczema (Meynadier et al. 1982). EDTA caused one positive patch test reaction.

Based on limited experimental data and the lack of reports of skin and respiratory sensitisation during widespread industrial use of tetrasodium EDTA, the CSTEE (2003) concluded that the chemical does not cause sensitisation by skin contact or by inhalation.

25.5.5 *Repeat dose toxicity*

25.5.5.1 Oral

No data were available for tetrasodium EDTA. Under physiologically relevant conditions (pH 2 to 7), salts of EDTA are expected to ionise based on the dissociation of EDTA, and therefore all such salts will chelate metal ions *in vivo* (ECB 2005). On this basis, repeated dose studies with disodium EDTA and trisodium EDTA were used to read across to the tetrasodium salt for this endpoint.

Animal data on oral repeat dose toxicity of disodium EDTA and trisodium EDTA are summarised from the European Commission –EC (2000), ECB (2005) and US EPA (2006)

and are presented in Table A25.4. The Lowest-Observed-Adverse-Effect-Levels (LOAELs), No-Observed-Adverse-Effect-Levels (NOAELs) and Klimisch scores (Klimisch et al. 1997) (1 = reliable without restrictions; 2 = reliable with restrictions; 3 = invalid; 4 = not assignable) are indicated for each study.

Table A25.4 Repeat oral toxicity studies with disodium EDTA and trisodium EDTA

Substance	Species, treatment and doses	Results	Remarks	Reference
Disodium EDTA	Rats, females only Diet, 1 month 0, 0.3, 1, or 3% (est. 0, 237, 839, or 2007 mg/kg bw/day)	LOAEL = 839 mg/kg bw/day NOAEL = 237 mg/kg bw/day	At the top dose, reduced bodyweight gain and decreased food consumption. At the mid dose, reduced bodyweight gain.	McCollister (1955) Klimisch = 4
Disodium EDTA	Rats Diet, 1 month 0, 1, 2.25, or 5% (est. 0, 500, 1125, or 2500 mg/kg bw/day)	LOAEL = 2500 mg/kg bw/day NOAEL = 1125 mg/kg bw/day	At the top dose, mortality, reduced bodyweight gain, haematological and clinical chemistry effects including reduced leucocytes and lymphocytes and decreased serum Ca^{2+} levels. Decreased organ weights (liver, spleen and thymus). Parakeratosis in the oesophagus and forestomach.	Kawamata et al. (1980) Klimisch = 4
Disodium EDTA	Holtzmann rats, males only. Limited biochemistry. Diet, 13 week 0, 1, 5, or 10% (est. 0, 692, 4206, or 8466 mg/kg bw/day)	LOAEL = 4206 mg/kg bw/day NOAEL = 692 mg/kg bw/day	At the top dose, increased mortality, reduced bodyweight gain, diarrhoea and emaciation. Transient decrease of hematocrit and hemoglobin levels. Pale livers. At the mid dose, increased mortality, reduced bodyweight gain, diarrhoea and emaciation.	Wynn et al. (1970) Klimisch = 2
Disodium EDTA	Albino rats Diet, 2 years 0, 0.5, 1, or 5% (est. 0, 300, 600 or 3000 mg/kg bw/day)	No LOAEL or NOAEL could be established.	At the top dose, transient reduced food consumption and diarrhoea.	Yang and Chan (1964) Klimisch = 3
Trisodium EDTA	Fisher 344 rats Diet, 2 years 0, 3750, or 7500 ppm (est. 0, 248, or 495 mg/kg bw/day)	No LOAEL or NOAEL could be established.	No treatment-related effects were observed.	NTP (1977) Klimisch = 2
Trisodium EDTA	$B6C3F_1$ mice Diet, 2 years	No LOAEL or NOAEL could be	No treatment-related effects were observed.	NTP (1977) Klimisch =

Substance	Species, treatment and doses	Results	Remarks	Reference
	0, 3750, or 7500 ppm (est. 0, 469, or 938 mg/kg bw/day)	established.		2

Tetrasodium EDTA has not been tested for its oral repeated dose toxicity and therefore toxicity data for disodium EDTA and trisodium EDTA were used for evaluation of this endpoint.

Based on a reliable two year dietary exposure study in rats (NTP 1977) with a top dose of approximately 495 mg/kg bw/day, a NOAEL could not be derived for trisodium EDTA. This result is broadly supported by a 13-week, non-guideline study (Wynn et al. 1970) for disodium EDTA where a NOAEL of 692 mg/kg bw/day was established based on increased mortality, reduced bodyweight gain, diarrhoea and emaciation at a LOAEL of 4206 mg/kg bw/day. A shorter term study at higher dose levels (Kawamata et al. 1980) showed similar effects at a LOAEL of 2500 mg/kg bw/day in addition to haematological and serum metal ion changes attributable to chelation of critical metal species, most notably calcium and zinc (OECD 2012).

These results are judged to be sufficiently representative for the assessment of tetrasodium EDTA and overall it can be concluded that the chemical has a low potential for toxicity after repeated oral administration.

25.5.5.2 Dermal

No data were available.

25.5.5.3 Inhalation

No repeat dose inhalation studies are available for tetrasodium EDTA.

In a study, conducted in accordance with OECD TG 412 apart from a shortened dosing schedule, inhalation exposures in male rats at 33.3, 320, or 1103 mg/m^3 (0.03, 0.32, or 1.1 mg/L) disodium EDTA for six hours/day for up to five days produced adverse effects at all doses (BASF SE 2010 as cited in REACH 2013). After a single exposure at the high dose, 6/20 rats died with observed lung changes including congestion, oedema, multifocal haemorrhages and inflammatory cell infiltrates. Inhalation exposure for five days caused concentration dependent lesions in the larynx and lungs that were fully reversible within 14 days. A LOAEC of 30 mg/m^3 was determined due to histopathological changes at the lowest dose that included epithelial necrosis (multifocal) and inflammatory cell infiltration at the base of the epiglottis, regenerative hyperplasia of the bronchiolar epithelium, mucous cell hyperplasia in large bronchi and interstitial infiltration of eosinophylic granulocytic cells.

This result appears to be sufficiently representative also for the assessment of tetrasodium EDTA.

25.5.5.4 Observation in humans

No data were available for tetrasodium EDTA. Large doses of EDTA (or one of its salts) have been used to treat heavy metal poisoning. The EDTA preferentially binds with the heavy metal present and the resultant complex is then excreted from the body (US EPA 2006). Disodium EDTA was administered intravenously in five-day courses over a 15-month period

to four patients with noncalcific acrosclerosis. Each patient received 37 mg/kg bw/day with the total dose ranging from 132 to 212 g. Side effects were minimal and did not require discontinuation of therapy (Keech et al. 1966 as cited in CIR 2002).

25.5.6 *Genotoxicity*

Tetrasodium EDTA has been studied in *in vitro* mutagenicity assays. Supporting data were available from both *in vitro* and *in vivo* studies performed with the disodium and trisodium EDTA salts as summarised in Table A25.5 from ECB (2005), CIR (2002) and OECD (2012).

Table A25.5 Mutagenicity tests with tetrasodium EDTA, trisodium EDTA and disodium EDTA

Test	Chemical	Type*	Results	Reference
In vitro: bacterial	Disodium EDTA	Ames/ *S.typhimurium* (*S. typh*.)	Negative TA98, TA100, TA1535, TA1537, TA1538 (±S9)	DeFlora (1981)
	Disodium EDTA	Ames/*S. typh*.	Negative strains not reported (±S9)	Dunkel et al. (1999)
	Trisodium EDTA	Ames/*S.typh.*	Negative TA98, TA100, TA1535, TA1537, TA1538, *E. coli* WP2 uvrA (±S9)	Dunkel et al. (1985)
	Trisodium EDTA	Ames/*S.typh*.	Negative TA97, TA98, TA100, TA1535 TA97, TA102 (±S9)	Zeiger et al. (1988)
In vitro: non-bacterial	Tetrasodium EDTA	*S. cerevisiae*	Negative	LeBoeuf et al. (1990)
	Tetrasodium EDTA	CA/CHO cells	Negative	Thomson et al. (1990)
	Disodium EDTA	CT/SHE cells	Negative	LeBoeuf et al. (1990)
	Disodium EDTA	Mouse lymphoma L5178Y/TK+/-	Negative	Dunkel et al. (1999)
	Disodium EDTA	Mouse lymphoma L5178Y/TK+/-	Negative	Whittaker et al. (2001)
	Trisodium EDTA	CT/SHE cells	Negative	Fukuda (1987)
	Trisodium EDTA	CT/BALBc-3T3 cells	Negative	Matthews et al. (1993)
	Trisodium EDTA	Mouse lymphoma L5178Y/TK+/-	Negative	McGregor et al. (1988)
	Trisodium EDTA	CA/CHO cells	Negative	Martinez et al. (2000)
In vivo	Disodium	MN/Mouse BM	Negative	BASF AG (2000b)

Test	Chemical	Type*	Results	Reference
	EDTA			
	Disodium EDTA	MN/Mouse BM	Negative	Russo and Levis(1992)
	Disodium EDTA	MN/Mouse spermatids	Positive	Russo and Levis(1992)
	Disodium EDTA	CA/Mouse spermatogonia	Negative	Russo and Levis(1992)
	Disodium EDTA	MN/Mouse BM	Positive	Muraldihara and Narasimhamurthy (1991)
	Disodium EDTA	Cytogenicity/ Mouse germ cells	Negative	Zordan et al. (1990)
	Disodium EDTA	Dominant Lethal/Mouse	Negative	Muraldihara and Narasimhamurthy (1991)

** CA chromosome aberration, CHO Chinese Hamster Ovary, SHE Syrian Hamster Embryo CT cell transformation MN micronucleus, BM bone marrow*

Tetrasodium EDTA tested negative (with and without metabolic activation) in a bacterial reverse mutation assay (OECD TG 471) with *Salmonella typhimurium* (LeBoeuf et al. 1990). It also did not induce chromosomal aberrations in Chinese Hamster Ovary cells (OECD TG 473) (Thomson et al. 1990).

Supporting data were available for disodium and trisodium EDTA. Reliable negative results were obtained in several Ames tests, non-bacterial *in vitro* gene mutation assays, *in vitro* cell transformation tests, chromosome aberration assays and *in vivo* cytogenetic tests. Two positive results were noted for disodium EDTA in micronuclei tests in mouse spermatids (Russo and Levis 1992) and mouse bone marrow cells (Muraldihara and Narasimhamurthy 1991). In the former study, the increased incidence of micronuclei was observed at very high dose levels while the latter study was judged to be of poor reliability.

Overall, it is concluded that tetrasodium EDTA is unlikely to be genotoxic.

25.5.7 *Carcinogenicity*

No data were available for tetrasodium EDTA and therefore toxicity data for trisodium EDTA were used for the evaluation of this endpoint.

The potential carcinogenicity of trisodium EDTA (trihydrate) has been examined in a chronic oral study where Fischer 344 rats and B6C3F1 mice were exposed to the chemical in the diet at 3750 and 7500 ppm (equivalent to approximately 248 and 495 mg/kg bw/day for rats and 469 and 938 mg/kg bw/day for mice) for 103 weeks (NTP 1977). No treatment-related signs of clinical toxicity were noted. A variety of tumours observed in the reproductive, haematopoietic and endocrine systems in addition to the lungs and liver occurred in both treated and control groups of both species, but the two groups were not statistically significantly different. In conclusion, trisodium EDTA was not carcinogenic to rats or mice under the conditions of the study.

Based on the negative results of this carcinogenicity study as well as the low mutagenic potential for the three sodium EDTA salts, it is considered unlikely that tetrasodium EDTA is a carcinogen.

25.5.8 *Reproductive toxicity*

25.5.8.1 Fertility

No information was available for tetrasodium EDTA but data were available from studies for disodium EDTA and trisodium EDTA.

In a poorly reported oral study, male and female rats were given 0, 0.5, 1.0 or 5.0% disodium EDTA in the diet (Yang and Chan 1964). The rats were mated after 100 days, and mating was repeated 10 days after weaning the first litters. Parental rats of the 0.5% and 1.0% groups had normal first and second litters, while the high dose group failed to produce any litters, even after a two month mating period.

In the previously described two year carcinogenicity study in rats and mice with trisodium EDTA in the diet (NTP 1977), doses of 7500 ppm had no effect on the reproductive systems of either species.

A non-guideline, oral study in male mice with disodium EDTA was reported by Muralidhara and Narasimhamurthy (1991). Doses of 5, 10, and 15 mg/kg bw for five days had no effect on sex organs, sperm counts or sperm morphology. Additionally, treatment of male mice with the chemical at 10 mg/kg bw for five days induced no increase in the incidence of post-implantation embryonic deaths over a mating period of eight weeks. No LOAEL or NOAEL could be established for paternal or fertility effects.

Overall, tetrasodium EDTA is not likely to be toxic to fertility based on limited data available for the other sodium salts.

25.5.8.2 Developmental toxicity

One prenatal developmental toxicity study, conducted according to OECD TG 414, was available for tetrasodium EDTA (Schardein et al. 1981). Groups of female rats were treated at equimolar concentrations of EDTA in comparison with disodium, trisodium, tetrasodium and calcium disodium EDTA. The four salts, at equimolar EDTA doses of 1000 mg EDTA/kg bw/day (buffered to pH values ranging from 3.9 to 9.2), were administered in two split doses by gavage during gestation day (g.d.) 7 to 14. For the dams significant effects including diarrhoea, decreased food intake, and reduced bodyweight gain were reported in all groups and 3/20 animals died during treatment with disodium EDTA. EDTA, disodium EDTA, and tetrasodium EDTA had the greatest effects on bodyweight gain. None of the test compounds significantly affected litter size, foetal mortality, foetal bodyweight, or rate of malformations. No LOAEL or NOAEL could be established as the study was restricted to a single dose equivalent to 1374 mg tetrasodium EDTA/kg bw/day.

The effect of route of administration on developmental toxicity of disodium EDTA was reported by Kimmel (1977). Pregnant rats were given (g.d. 7 to 14) 954, 1250 (or 1500) or 375 mg/kg bw/day disodium EDTA in the diet, by gastric intubation or by subcutaneous injection, respectively. All of these dosing regimens produced maternal toxicity as evidenced by decreased food consumption, diarrhoea and reduced bodyweight gain. Disodium EDTA administered in the diet (954 mg/kg/day) produced maternal toxicity and foetal death and malformations in 71% of the offspring. Rats given 1250 mg/kg or 1500 mg/kg by gavage exhibited greater maternal toxicity than the diet group (as evidenced by lethality in 36% and 88% of dams) but produced only 21% malformations in the offspring at the lower dose. The

subcutaneously administration of 375 mg/kg was also maternally toxic, but did not result in malformations in the offspring. The maternal LOAEL for systemic oral toxicity was 954 mg/kg/day based on diarrhoea and reduced bodyweight gain. The developmental toxicity LOAEL was 954 mg/kg/day based on foetal deaths and malformations. The US EPA (2006) concluded that the differences in maternal and developmental toxicity are probably related to absorption differences and interaction with metal ions. Of particular note is that the dams in the study were maintained on deionised water and possibly became zinc deficient, thus causing toxicity in the offspring.

Pregnant Sprague-Dawley rats were exposed during gestation to purified diets containing 2% or 3% disodium EDTA (approximately 1000 mg/kg/day or 1500 mg/kg/day) supplemented with either 100 or 1000 ppm zinc (Swenerton and Hurley 1971). All dams fed EDTA had moderate to severe diarrhoea. Complete reproductive failure occurred with the 3% disodium EDTA/100 ppm zinc diet fed during g.d. 0 to 21, with the 2% disodium EDTA/100 ppm zinc diet reproductive outcome was essentially comparable to that of controls, however with lower bodyweight of the pups and with 7% malformed of the full-term foetuses. Exposure to the 3% disodium EDTA/100 ppm zinc diet during the period of g.d. 6 to 14, and 6 to 21 resulted in respectively 40% and 54% dead or absorbed foetuses, reduced number of dams with live pups, reduced foetal bodyweight and ratios of respectively 87% and 100% malformed living offspring. The reported developmental effects were similar to those from earlier experiments with zinc deficient diets administered to pregnant rats for various periods of during gestation (Hurley and Swenerton 1966; Hurley et al. 1971). In contrast, the live offspring of dams fed 3% disodium EDTA/1000 ppm zinc from g.d. 6 to 21 did not exhibit any malformations, and the number of live pups/litter and the foetal body weight were comparable to those of controls. The maternal LOAEL was 1000 mg/kg/day based on diarrhoea. The developmental toxicity LOAEL was 1000 mg/kg/day based on reduced foetal bodyweights and malformations however no NOAEL or LOAEL were established when the zinc concentration in the diet was adjusted to 1000 ppm (but not from 100 ppm). The CSTEE (2003) concluded that the developmental toxicity observed was most likely due to zinc depletion by the very high doses of disodium EDTA. This conclusion was supported by zinc analyses of foetuses (Hurley and Swenerton 1966), where lower zinc contents were found in foetuses from deficient mothers in comparison to those from zinc supplemented dams, indicating that the reported effects on foetal development occur because of a direct lack of zinc in foetal tissues than from indirect effects of maternal metabolism.

Overall, in the only developmental toxicity study available for the chemical, tetrasodium EDTA at a high dose level was not a developmental toxicant. The developmental toxicity seen in studies for the disodium salt was a high dose effect that could be prevented with adequate dietary zinc supplementation.

25.5.9 *Other health effects*

No additional health effects were identified.

25.6 Health hazard summary

25.6.1 *Critical health effects*

Tetrasodium EDTA is harmful by the oral route. This potential for acute toxicity was also demonstrated by the inhalation route based on data available for disodium EDTA. The chemical is not irritating to the skin but is a severe eye irritant in animals. Limited data for disodium EDTA suggest exposure to aerosols may cause adverse effects with a LOAEC of 30 mg/m^3 established for laryngeal necrosis and regenerative hyperplasia of bronchi at the

lowest dose. It is therefore likely that tetrasodium EDTA is a respiratory irritant. Based on data available for disodium EDTA, tetrasodium EDTA is not a skin sensitiser.

Tetrasodium EDTA has not been tested for its repeated dose toxicity however supporting data available for the other sodium salts indicate a low potential for toxicity after repeated oral administration. Specifically, toxicity data for disodium EDTA were used for evaluation of the critical (most sensitive) health effect for repeated exposures to the chemical. In a 13-week dietary study in rats, disodium EDTA was associated with systemic effects involving increased mortality, reduced bodyweight gain, diarrhoea and emaciation. The No-Observed-Adverse-Effect Level (NOAEL) established for these effects (692 mg/kg bw/day) is taken through to the risk assessment for tetrasodium EDTA.

It should be noted, however, that this NOAEL may be conservative (unnecessarily low) as the next dose in the study, which was identified as the Lowest-Observed-Adverse-Effect Level (LOAEL) for these systemic effects, was approximately six times that of the NOAEL, namely 4206 mg/kg bw/day. This gap between the two dosing levels is unusually large, and had intermediate doses been tested, a higher (less conservative) NOAEL than 692 mg/kg bw/day may have been identified.

The chemical is not genotoxic or a developmental toxicant and, based on data for trisodium and disodium EDTA respectively, is not a carcinogen or toxic to fertility.

The critical health effect of tetrasodium EDTA for risk characterisation is likely to be its inhalation toxicity.

25.6.2 *Hazard classification*

This hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) for acute oral toxicity and eye irritation. Tetrasodium EDTA is also recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances for respiratory irritation and the adopted Globally Harmonised System of Classification (GHS (United Nations Economic Commission for Europe (UNECE) 2009) for acute oral toxicity, eye irritation and respiratory irritation as shown inTable A25.6. These NICNAS recommendations do not consider physical or environmental hazards.

Table A25.6 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful if swallowed (X_n; R22)*	Harmful if swallowed – Cat. 4 (H302)
Irritation/ Corrosivity	Irritating to the respiratory system (X_i; R37) Risk of serious damage to eyes (X_i; R41)*	May cause respiratory irritation – Specific target organ toxicity, single exposure - Cat. 3 (H335) Causes serious eye damage – Cat. 1 (H318)

*[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009); * Existing hazard classification. No change recommended by NICNAS to this classification.*

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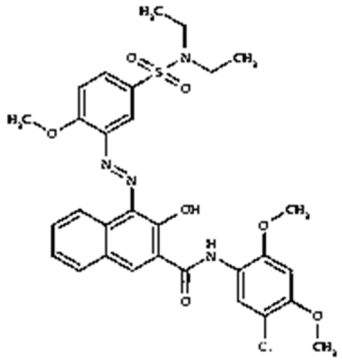
A26 Pigment Red 5

CAS No.	CAS Name
6410-41-9	2-Naphthalenecarboxamide, N-(5-chloro-2,4-dimethoxyphenyl)-4-[2-[5-[(diethylamino)sulfonyl]-2-methoxyphenyl]diazenyl]-3-hydroxy-

26.1 Chemical identity

Details of the chemical identity provided in Table A26.1 were obtained from the web-based database ChemID*plus* (2012) and an industry registration dossier submitted under the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (REACH 2013a).

Table A26.1 Chemical identity

	Pigment Red 5
Synonyms	C.I. 12490 C.I. Pigment Red 5
Structural formula	
Molecular formula	$C_{30}H_{31}ClN_4O_7S$
Molecular weight	627.12
Appearance and odour	Red powder with a non-specific odour
SMILES Notation	c1cc(S(=O)(=O)N(CC)CC)cc(c1OC)\N=N\c1c(c(cc2c1cccc2)C(=O)Nc1cc(c(cc1OC)OC)Cl)O

26.2 Physical properties

For the purposes of this assessment, the chemical will be referred to by the synonym Pigment Red 5.

The following information on physical properties of Pigment Red 5 presented in Table A26.2 was compiled from an industry registration dossier submitted under the EU REACH program (REACH 2013a).

Table A26.2 Physical properties

Property	Value
Melting point	Not available - decomposes at approx. 292 °C
Density	1.4 x 10^3 kg/m^3 at 23 °C
Vapour pressure	<0.001 kPa at 20 °C (calculated)
Water solubility	7.8 x 10^{-6} g/L at 23 °C
Partition coefficient n-octanol/water (log K_{ow})	1.22

26.3 Current regulatory controls

26.3.1 *Hazard classification for occupational health and safety*

Pigment Red 5 is not classified as hazardous for human health in the Safe Work Australia Hazardous Substances Information System (HSIS) (Safe Work Australia 2013a).

26.3.2 *Occupational exposure standards*

26.3.2.1 Australia

There is no specific exposure standard for Pigment Red 5. However, the permissible exposure limits (as the Time Weighted Average (TWA)) for dusts apply (10 mg/m^3 measured as inspirable dust) (Safe Work Australia 2013b).

26.3.2.2 International

There are no specific exposure standards for Pigment Red 5. However, the following exposure standards for particulates are identified (Galleria Chemica 2013).

TWA:

- 10 mg/m^3 [Canada, Singapore]
- 3 to 10 mg/m^3 [Germany, Indonesia, Spain]
- 4 to 10 mg/m^3 [Ireland]
- 0.15 to 10 mg/m^3 [Norway]
- 5 to 15 mg/m^3 [US].

Short Term Exposure Limit (STEL):

- 10 to 20 mg/m^3 [US].

Some countries publish separate exposure standards for inhalable and respirable particulate fractions.

26.3.3 *Australian food standards*

Pigment Red 5 is not listed as a colour permitted in processed foods (Australia New Zealand Food Standards Code – Standard 1.3.1 – Food Additives, Schedule 3 and 4) (Food Standards Australia and New Zealand 2013).

26.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for Pigment Red 5 in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

26.3.5 *Additional controls*

26.3.5.1 Australia

No additional controls were identified. A general exemption is noted in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) for pigments when immobilised in a polymer (Appendix A) (Therapeutic Goods Administration 2014).

26.3.5.2 International

In the US, Pigment Red 5 is permitted for use in pesticides, but only for non-food applications (US Environmental Protection Agency-US EPA 2012).

In the European Union, Pigment Red 5 is listed as a substance banned for use in hair dye products but is permitted as a colourant in cosmetic products more broadly (European Union 2013).

26.4 Use

The use of this chemical in coal seam gas extraction processes is described in the following National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

26.5 Health hazard characterisation

Little health hazard information is currently available for Pigment Red 5. Accordingly, an analogue approach for data gap filling was adopted for Pigment Red 5 by read-across of information. In this assessment, read-across is a technique used to predict endpoint information for Pigment Red 5 by using data (for the same endpoint) from other tested chemicals which are considered to be structurally similar. Data for read-across are available from a Canadian group assessment of monoazo pigments, which includes a substance grouping containing Pigment Red 5.

The grouping containing Pigment Red 5 is based on a common structural element - Naphthol AS (CAS No. 92-77-3) (Figure A26.1) (Environment Canada/Health Canada 2013). Members of this naphthol AS grouping for which human health data were available for read across are shown in Table A26.3. Data from two additional monoazo pigments – Pigment Red 22 and 23, which were used to fill data gaps for this naphthol AS grouping are also displayed in Table A26.3.

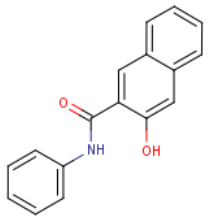
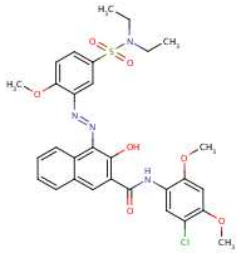
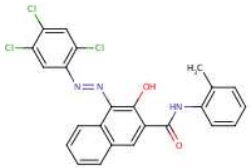
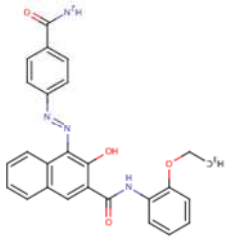
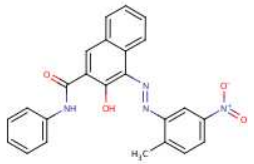
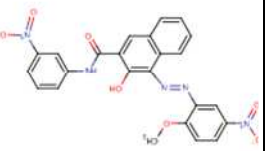


Figure A26.1 Naphthol AS CAS No. 92-77-3

The following information has been sourced primarily from the Environment Canada/Health Canada (2013) screening assessment and separate industry registration dossiers for pigments submitted under the EU REACH program.

Table A26.3 Substances for read-across for health hazard information

	Pigment Red 5	**Pigment Red 112**	**Pigment Red 120 (170)**	**Pigment Red 268**	**Pigment Red 22**	**Pigment Red 23**
CAS No.	6410-41-9	6535-46-2	2786-76-7	16403-84-2	6448-95-9	6471-49-4
Structure						
Acute toxicity		✓	✓			
Irritation	✓	✓	✓			
Sensitisation		✓	✓			
Repeat dose toxicity		✓✓	✓✓			✓
Genotoxicity		✓	✓	✓	✓	
Carcinogenicity						✓
Reproductive toxicity			✓		✓	

✓- *data available (Environment Canada/Health Canada 2013);* ✓- *data available (REACH dossier).*

26.5.1 *Justification for analogue approach*

26.5.1.1 Structure

All pigments used as analogues for read-across in this assessment feature the same core structure consisting of a phenyl derivative (amino-sulfonated in the case of Pigment Red 5) which is azo coupled to a naphthol AS moiety (CAS No. 92-77-3) (Figure A26.1).

Available analogues, however, possess considerable variability amongst substitutions on both sides of the azo bond (Table A26.2).

26.5.1.2 Physico-chemical properties

Naphthol AS pigments identified by Environment Canada/Health Canada are considered to have reasonably similar physico-chemical properties. However, structural differences are expected to contribute to variability. For example, data available for Pigment Red 5, 112 and 120 indicate similar water solubilities (7.8 to 11.9 µg/L) but greater differences in octanol solubilities - 1.3 x 10^{-4} g/L for Pigment Red 5 (REACH 2013a) compared to 3.3 x 10^{-3} g/L for Pigment Red 112 (REACH 2013b).

26.5.1.3 Read-across uncertainty

Heterogeneity in structure and physicochemical properties for naphthol AS-based analogues are sources of uncertainty in read-across for health hazard characterisation of Pigment Red 5. Such variabilities may lead to differences in absorption and azo bond cleavage metabolites. Consequently, because the potential toxicity of aromatic azo substances can be attributed in part to their aromatic amine metabolites, there may be significant uncertainty in the toxicological profile of Pigment Red 5 inferred from these analogues. Some aromatic amines are known or suspected genotoxins and carcinogens. It has been noted that both Pigment Red 22 and 23 contain nitroaniline groups which may be released if azo cleavage occurs. Therefore, these analogues may not be as applicable to read-across as other naphthol AS substances not containing these groups (Environment Canada/Health Canada 2013).

26.5.2 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

26.5.2.1 Oral absorption

No data were available for Pigment Red 5.

For Pigment Red 23, a limited toxicokinetic study in rats reported only minimal absorption following oral administration (El Dareer et al. 1984). Also, the equivocal results of a carcinogenicity study in rats suggested only limited amounts of Pigment Red 23 were absorbed and / or metabolised to the carcinogenic metabolite 5-nitro-*o*-anisidine following oral administration (NTP 1992).

On the basis of an overall lack of data on oral absorption, for human risk assessment purposes, a conservative oral absorption of 100% is assumed.

26.5.2.2 Dermal absorption

No data were available for dermal absorption. For human risk assessment purposes, a conservative dermal absorption of 100% is therefore assumed.

26.5.2.3 Inhalation absorption

No data were available for inhalation absorption. For human risk assessment purposes, a conservative inhalation absorption of 100% is therefore assumed.

26.5.2.4 Distribution

No data were available.

26.5.2.5 Metabolism

No data were available for Pigment Red 5.

In mammals, azo dyes are metabolised by cleavage of the azo bond to the corresponding amines. This can occur by cytosolic and microsomal enzymes in the liver or by microorganisms in the intestines or skin (Stingley et al. 2010; Feng et al. 2012).

Reductive cleavage of azo dyes by epidermal cells during percutaneous absorption has also been demonstrated for mice, guinea pigs and human skin *in vitro* (Collier et al. 1993). Ring oxidation, N-glucuronidation, N-acetylation and N-oxidation are the major metabolic pathways for aromatic amines in mammals (SCCNFP 2002).

Reductive azo bond cleavage of Pigment Red 5 would potentially give rise to 3-amino-(N,N-diethyl)-4-methoxybenzenesulphonamide (C.I. 37150; CAS 97-35-8). However, available, albeit limited, analogue data on the likelihood of azo cleavage indicate only limited potential for formation of this metabolite. In a microbial azo reduction study, only low levels of azo reduction were observed for Pigment Red 112 in comparison with a β-naphthol pigment Pigment Orange 5 (Pearce et al. 2008). For Pigment Red 23, an oral carcinogenicity study in rats suggested only limited amounts were absorbed and / or metabolised to the carcinogenic metabolite 5-nitro-*o*-anisidine (NTP 1992).

26.5.2.6 Excretion

No data were available.

26.5.3 *Acute toxicity*

26.5.3.1 Oral

No data were available for Pigment Red 5.

A rat oral toxicity study of Pigment Red 112 was conducted in 1983 according to OECD Test Guideline (TG) 401 (REACH 2013b). Rats (five per sex) received Pigment Red 112 via gavage at a single dose of 5000 mg/kg bw. Reduced spontaneous activity was observed during the first hour following dosing. After 2 to 4 hours, animals exhibited hunched posture and diarrhoea with stained faeces. No clinical signs were noted one day following dosing or at further timepoints. On the basis of no mortality, the study established a median Lethal Dose (LD50) of >5000 mg/kg bw.

A rat oral toxicity study conducted in 1976 was also available for Pigment Red 120 (REACH 2013c). This study was performed to company test guidelines similar to OECD TG 401. A single dose of 15 000 mg/kg bw administered via gavage caused no mortality in rats. The study established an LD50 of >15 000 mg/kg bw.

26.5.3.2 Dermal

No data were available for Pigment Red 5.

A dermal toxicity study of Pigment Red 112 in rats conducted in accordance with OECD TG 402 was reported in 2007 (REACH 2013b). Rats (five males) received an aqueous paste containing Pigment Red 112 at a single dose of 5000 mg/kg bw applied to the skin under occlusive dressing. The test substance was removed after 24 hours. No clinical signs were noted at any time during a 14 day observation period commencing 30 minutes after substance removal. On the basis of no mortality, the study established an LD50 of >5000 mg/kg bw.

A dermal toxicity study conducted in 2012 in accordance with OECD TG 402 was also available for Pigment Red 120 (REACH 2013c). Rats (five eachsex) received dermal semi-occlusive application of Pigment Red 120 in cottonseed oil at a dose of 2000 mg/kg bw for 24 hours. No mortality or signs of toxicity were noted. The study established a dermal LD50 of >2000 mg/kg bw.

26.5.3.3 Inhalation

No data were available.

26.5.3.4 Observation in humans

No data were available.

26.5.4 *Irritation / Corrosivity*

26.5.4.1 Skin irritation

In a study conducted in a similar fashion to OECD TG 404 (but with exposure for 24 hours rather than the guideline four hours) 0.5 g of Pigment Red 5 in water was applied to the intact skin of two male and one female New Zealand White rabbits under semi-occlusive conditions for 24 hours (REACH 2013a). A red discoloration was noted on the treated area. No skin reactions or signs of systemic toxicity were observed at any time point from 1 to 72 hours after removal of the applied chemical. The report concluded that the test substance was not irritating to the skin.

Pigment Red 120 was tested for skin irritancy in 1976 according to US Food and Drug Administration (FDA) test guidelines (REACH 2013c). Both intact and scarified skin sites of six rabbits were exposed to 0.5 g Pigment Red 120 for 24 hours under occlusive conditions. Animals were observed for 48 hours after the end of exposure. In animals with intact skin, no oedema was seen at any time point (score 0), slight erythema was seen in one animal after 24 hours (score 1) and in two animals after 48 hours. No erythema evaluation was possible immediately after end of exposure due to discoloration of the skin. Effects on scarified skin were comparable to those observed on intact skin. It was concluded that Pigment Red 120 was not irritating to the skin.

26.5.4.2 Eye irritation

No data were available for Pigment Red 5.

In a study conducted in a similar fashion to OECD TG 405, 0.1 g of Pigment Red 112 in polyethylene glycol was applied to the conjunctival sacs of the left eyes of three New Zealand White rabbits for 24 hours (REACH 2013b). A red stained eye discharge was noted one hour after application. One hour after washing following the 24 hour application, mild chemosis (grade 1) was observed in one animal and mild conjunctival reddening (grade 1)

was observed in all three animals. After 24 hours, chemosis and conjunctival reddening were absent other than in one animal which still showed mild conjunctival reddening (grade 1). No reactions were observed at any subsequent timepoint up to 72 hours after removal of the test substance. The report concluded that the test substance was not irritating to the eye.

Pigment Red 120 was tested for eye irritancy in 1976 according to US FDA guidelines. 100 mg of Pigment Red 120 were applied without vehicle to one eye of six rabbits (REACH 2013c). The eyes were washed 24 hours after application and eye responses were noted for 72 hours. One animal showed conjunctival redness (score 1) at seven and 24 hours. This effect was completely reversible within 48 hours. Two animals showed eye discharge (score 1) at one hour. No other effects were observed. It was concluded that Pigment Red 120 was not irritating to the eyes.

26.5.4.3 Respiratory irritation

No data were available.

26.5.4.4 Observation in humans

No data were available.

26.5.5 *Sensitisation*

26.5.5.1 Skin sensitisation

No data were available for Pigment Red 5.

A Local Lymph Node Assay (LLNA) conducted in accordance with OECD TG 429 was performed in 2008 for Pigment Red 112 (REACH 2013b). Mice were treated with Pigment Red 112 in a dimethyl sulphoxide vehicle at test concentrations of 0.5, 10 and 20%. No cases of mortality or clinical signs were observed during the course of the study. Due to the colour of the test substance, local irritant reactions such as ear redness could not be determined. However, no ear swelling was evident. The maximum stimulation index reported was 1.16 at a test concentration of 10%. Consequently, EC3 values (the effective concentration required to produce a three-fold increase in stimulation index) could not be calculated. The study concluded that Pigment Red 112 was not a skin sensitiser.

A similar LLNA conducted in accordance with OECD TG 429 was reported in 2005 for Pigment Red 120 (REACH 2013c). Mice were treated with Pigment Red 120 in a dimethyl sulphoxide vehicle at test concentrations of 0.5, 10 and 20%. No clinical signs or mortality were reported. Due to the colour of the test substance, local irritant reactions such as ear redness could not be determined. The maximum stimulation index reported was 2.0 (at 20%). Consequently, no EC3 could be calculated. The study concluded that Pigment Red 120 was not a skin sensitiser.

A Buehler skin sensitisation test conducted in guinea pigs in accordance with OECD TG 406 was also available for Pigment Red 112 (REACH 2013b). No signs of skin sensitisation were observed. The study did not conform fully to the TG as the concentration used for induction (20%) was not maximised.

26.5.5.2 Respiratory sensitisation

No data were available.

26.5.5.3 Observation in humans

No data were available.

26.5.5.4 Summary of acute toxicity

Few acute toxicity data were available for Pigment Red 5.

Data for structurally similar analogues, such as those listed in Table A26.3, indicate low acute oral toxicity (LD50 >5 000 mg/kg bw) and low acute dermal toxicity (LD50 >5000 mg/kg bw). Skin irritation studies for Pigment Red 5 and analogues and eye irritation studies with analogues alone indicate low skin and eye irritancy potential. Similarly, skin sensitisation studies with analogues indicate low sensitisation potential.

26.5.6 *Repeat dose toxicity*

26.5.6.1 Oral

No data were available for Pigment Red 5.

A 28 day repeat dose toxicity test with Pigment Red 112 conducted in 2008 in accordance with OECD TG 407 was available (REACH 2013a). Rats received Pigment Red 112 in propylene glycol via gavage at doses of 100, 300 and 1000 mg/kg bw/day. Doses were selected on the basis of a preliminary five-day dose range finding study. No toxicologically significant changes were noted in clinical appearances, functional observations, body weights, food consumption, clinical laboratory findings, organ weights or macroscopic and microscopic examinations. Red staining of various body parts, faeces and gastrointestinal tract contents was noted amongst all tested groups. This was regarded as an artefact of the test substance and not a consequence of systemic toxicity. No correlating histopathological abnormalities were noted. On the basis of no systemic toxic effects seen at the highest dose (1000 mg/kg bw/day), no No Observed Adverse Effect Level (NOAEL) was established from this study.

A similar 28 day repeat dose toxicity test published in 1993 conducted to OECD TG 407 was available for Pigment Red 120 (REACH 2013c). Rats received Pigment Red 120 via diet at doses of 500, 2500 and 12 500 mg/kg food. There were no changes in clinical appearance, functional observations, body weights, food consumption, clinical laboratory investigations, macroscopic and microscopic examination or organ weights that were considered treatment-related. On the basis of no effects observed at the highest dose of 12 500 mg/kg food (equivalent to 1172 mg/kg bw/day in males and 1193 mg/kg bw/day in females), no NOAEL could be established from the study.

A reproductive/developmental toxicity study conducted to OECD TG 422 was described for Pigment Red 22 (Environment Canada/Health Canada 2013). Rats (12 per sex per group) were exposed to Pigment Red 22 via gavage at doses of 0, 100, 300 or 1000 mg/kg bw/day for 37 days in males and approximately 40 days in females. No consistent treatment-related changes were observed in haematology, urinary or clinical chemistry parameters or from gross pathology or histopathology. However, a dose-dependent increase in liver weight was observed in both male and female rats which reached statistical significance at the highest dose (the magnitude of these increases was not stated). The No Observed Effect Level (NOEL was considered to be 300 mg/kg bw/day for this study.

Both 17 day and 90 day repeat dose studies in rats and mice were available for Pigment Red 23 (NTP 1992). For the 17 day studies, groups of five rats and five mice of each sex were fed diets containing 0, 6000, 12 500, 25 000, 50 000 or 100 000 ppm Pigment Red 23 for 15 to 17 days. There were no treatment-related mortalities. Food consumption was unaffected by treatment. At the end of the study, body weights of treated rats and mice were within 10% of those of controls. Haematocrit values, haemoglobin concentrations and erythrocyte counts decreased in 50 000 and 100 000 ppm rats. No such decreases were seen in mice. Organ

weights were similar to that of controls. No treatment-related gross lesions were seen in either rats or mice.

For 90 day studies, groups of five rats and five mice of each sex were fed diets containing 0, 3000, 6000, 12 500, 25 000 or 50 000 ppm Pigment Red 23 (NTP 1992). No mortality was observed. Food consumption was unaffected by treatment. At the end of the study, body weights of treated rats and mice were within 10% of those of controls. In male rats, haematocrit and haemoglobin concentrations and erythrocyte counts were significantly decreased at 50 000 ppm only. In female rats receiving 3000, 6000 and 50 000 ppm, lymphocyte counts were significantly increased (not dose-related). White blood cell counts were also increased in 3000 ppm female rats. There were no biologically significant changes in organ weight related to treatment. No treatment-related gross or histopathological lesions were observed. Changes in haematological parameters in male rats at the highest dose were regarded as indicative of haemolytic anaemia typically seen with aromatic amines. Female mice at 6000 ppm showed decreased haematocrit and haemoglobin concentrations. In male mice, absolute and relative liver weights were increased (not dose-related). In all female mice, except those fed diets containing 12 500 ppm, absolute and relative thymus weights were decreased (not dose-related). No treatment-related gross or histopathological lesions were observed. In conclusion, haematological changes seen at the highest dose in the 90 day study in male rats suggests a NOAEL for repeat dose effects for Pigment Red 23 at 25 000 ppm (approximately 1250 mg/kg bw/day).

In conclusion, repeat dose toxicity studies for structurally similar analogues noted no adverse effects with oral doses of 1000 to 1200 mg/kg. A lower NOEL was described for one analogue (Pigment Red 23) but the magnitude of changes was not reported (NTP 1992). Overall, a conservative NOAEL for repeat dose toxicity is established from a 90 day rat study at 1250 mg/kg bw/day based on decreased haematocrit and haemoglobin concentrations and erythrocyte counts at higher doses (NTP 1992).

26.5.6.2 Dermal

No data were available.

26.5.6.3 Inhalation

No data were available.

26.5.6.4 Observation in humans

No data were available.

26.5.7 *Genotoxicity*

No data were available for Pigment Red 5.

A bacterial reverse mutation assay (Ames test) conducted in 1996 according to OECD TG 471 was available for Pigment Red 112 (Prival and Mitchell 1982). The test item did not induce gene mutations in *Salmonella typhimurium* strains TA 1535, 1537, 98 and 100 including with the azo-reductive flavin mononucleotide (FMN) Prival modification to the testing protocol (REACH 2013b). The Prival modification for testing the mutagenic activity of azo dyes in *Salmonella typhimurium* uses flavin mononucleotide instead of riboflavin and hamster liver S9 for metabolic activation.

A mammalian cell gene mutation assay for Pigment Red 112 in Chinese hamster lung fibroblasts, conducted in 2008 according to OECD TG 476, was negative (REACH 2013b). Similarly, an *in vitro* micronucleus test in 2009 in Chinese hamster lung fibroblasts, conducted according to a draft OECD TG 487, was also negative (REACH 2013b).

A bacterial reverse mutation assay (Ames test), conducted in 2005 according to OECD TG 471, was available for Pigment Red 120 (REACH 2013c). The test item did not induce gene mutations in *Salmonella typhimurium* strains TA 1535, 1537, 98 and 100 including with FMN Prival modification. A mammalian cell gene mutation assay for Pigment Red 120 in Chinese hamster lung fibroblasts, conducted in 2008 according to OECD TG 476, was also negative (REACH 2013c), as was a chromosome aberration test for Pigment Red 120 in Chinese hamster lung fibroblasts conducted in 2008 according to OECD TG 473 (REACH 2013c).

Negative results were also noted for Pigment Red 268 in *Salmonella typhimurium* strains TA 98 and 100, including with the FMN Prival modification (ILS 2011).

In contrast to Pigment Red 112, 120 and 268, both positive and negative results have been noted in Ames tests for Pigment Red 22 (Environment Canada/Health Canada 2013).

Similarly, both positive and negative results were reported for Pigment Red 23. Pigment Red 23 was positive in Salmonella *typhimurium* strains TA 100, 1537 and 98 but not in strain TA 1535 (NTP 1992). For Pigment Red 23, a sister chromatid exchange test was reported to be positive but only without metabolic activation., Additionally, a chromosome aberration test in Chinese hamster ovary cells was reported to be negative with and without metabolic activation (NTP 1992).

In conclusion, available data indicate that Pigment Red 112, 120 and 268 are not mutagenic. Both positive and negative results were observed with Pigment Red 22 and 23. Positive results for genotoxicity are consistent with the presence of nitro groups (NTP 1992; Environment Canada/Health Canada 2013). Based on these analogue data, Pigment Red 5 is not regarded as mutagenic.

26.5.8 *Carcinogenicity*

No data were available for Pigment Red 5. However, a long term carcinogenicity study in rats and mice was available for Pigment Red 23 (NTP 1992). Groups of 60 rats and 60 mice of each sex received Pigment Red 23 at doses of 0, 10 000, 25 000 or 50 000 ppm in feed for 103 weeks. In rats, no treatment-related decreases in survival rates were observed. Survival rates of mid and high dose males and high dose females were increased due to decreased incidence of mononuclear cell leukaemia in these groups. There were no clinical signs associated with treatment. The study reported equivocal evidence of carcinogenic activity based on marginally increased incidences of renal tubule hyperplasia and neoplasms (adenoma and / or carcinoma) in male rats receiving 50 000 ppm (approximately 2500 mg/kg bw/day). No such neoplasms were observed in female rats.

In mice, there were no clinical signs associated with treatment and survival rates were unaffected. No treatment-related increases in the incidence of neoplasms were observed.

It has been noted that 5-nitroanisidine, a possible microbial azo bond cleavage metabolite of Pigment Red 23, has been shown to be carcinogenic in rats and mice at doses lower to those of the mid and high dose animals in this study (NTP 1992). Therefore, given only equivocal evidence of carcinogenicity of Pigment Red 23 for which metabolites have been shown to be carcinogenic, the absence of such carcinogenic metabolites for Pigment Red 5, and the lack of carcinogenicity in mice, Pigment Red 5 is unlikely to be carcinogenic.

26.5.9 *Reproductive toxicity*

No fertility or developmental toxicity data were available for Pigment Red 5.

A reproductive/developmental toxicity study conducted to OECD TG 422 was identified for Pigment Red 22 (Environment Canada/Health Canada 2013). Rats (12 per sex per group) were exposed to Pigment Red 22 via gavage at doses of 0, 100, 300 or 1000 mg/kg bw/day

for 37 days in males and approximately 40 days in females (14 days premating, 22 days of gestation to day four of lactation). No treatment-related changes in reproductive or developmental parameters were reported.

A reproductive/developmental toxicity screening study reported in 2013 conducted to OECD TG 421 was available for Pigment Red 120 (REACH 2013c). Pigment Red 120 was administered daily to male and female rats via gavage during a 14 day pre-mating period, a 14 day mating period, during gestation and up to postnatal day three in females. Females were dosed for up to 54 days and males were dosed for 28 to 31 days. Doses were 0, 100, 300 and 1000 mg/kg bw/day. No clinical signs or mortality were observed in males or females. No statistically significant effects on food consumption or body weight were observed. Litter weights were unaffected. Precoital intervals and duration of gestation were unaffected. Group mean numbers of corpora lutea, implantation sites, per cent preimplantation and post-implantation losses were unaffected. Litter parameters were unaffected. No treatment-related effects on copulation, delivery, fertility or viability indices were observed. Overall, pup survival was unaffected. A few external spontaneous findings were observed in some pups but these were not considered related to the test substance. Sperm indices were unaffected. Gross pathological and histopathological findings were unremarkable. Organ weights were unaffected. In conclusion, no treatment-related effects were observed even at the highest dose of 1000 mg/kg bw/day. Consequently, no NOAEL was established.

Overall, analogue data from combined reproductive/developmental studies do not suggest that Pigment Red 5 is lkely to have effects on fertility or development.

26.5.10 *Other health effects*

No data were available.

26.6 Health hazard summary

26.6.1 *Critical health effects*

Limited health hazard data were available for Pigment Red 5. Therefore, read across of data from several structurally similar azo pigments was used to build a human health hazard profile for the chemical.

On the basis of analogue data, Pigment Red 5 is of low acute oral and dermal toxicity (LD50 >5000 mg/kg bw). No acute inhalation toxicity data were available. Also, it is not a skin or eye irritant or a skin sensitiser.

Repeat dose toxicity studies for structurally similar analogues noted no adverse effects with oral doses of approximately 1000 – 1250 mg/kg.

A majority of analogue genotoxicity studies reported negative results. Both positive and negative results were reported for analogues containing functional groups known to be associated with genotoxicity. Overall, Pigment Red 5 is not regarded as mutagenic.

A single carcinogenicity study was available for an analogue containing functional groups likely to give rise to metabolites known to be carcinogenic. Despite the presence of such groups, the study only reported equivocal evidence of carcinogenic activity in rats. No evidence of carcinogenicity was seen in mice. Consequently, Pigment Red 5 is not regarded as carcinogenic.

Analogue reproductive toxicity studies reported no adverse effects at doses of 1000 mg/kg bw/day (highest dose tested).

The choice of NOAEL for risk assessment is complicated by findings in studies of no adverse effects even at the highest doses tested. Overall, for the purposes of risk assessment, a no effect level of 1000 mg/kg bw/day is established. This is the highest dose associated with an absence of adverse effects across analogue studies for both repeat dose toxicity and reproductive toxicity.

26.6.2 *Hazard classification*

Pigment Red 5 is currently not classified as hazardous for human health in the Safe Work Australia Hazardous Substances Information System (HSIS 2013). This assessment confirms this current classification. The chemical is not recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (Approved Criteria) (NOHSC 2004) or under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009).

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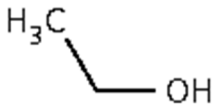
A27 Ethanol

CAS No.	CAS Name
64-17-5	Ethanol

27.1 Chemical identity

Details of the chemical identity provided in Table A27.1 were obtained from the Hazardous Substances Data Bank (HSDB) (2013).

Table A27.1 Chemical identity

	Ethanol
Synonyms	Alcohol Ethyl alcohol Ethyl hydroxide
Structural formula	
Molecular formula	C_2H_6O
Molecular weight	46.07
Appearance and odour	Clear colourless liquid with a weak ethereal vinous odour
SMILES notation	C(C)O

27.2 Physical properties

The physical properties presented in Table A27.2 were obtained from the following comprehensive data sources: an Organisation for Economic Co-operation and Development (OECD) *Screening Information Data Set (SIDS) Initial Assessment Report* (OECD 2005), HSDB (2013) and ChemID*plus* (2012).

Table A27.2 Physical properties

Property	**Value**
Melting point	-114.14 °C
Boiling point	78.92 °C
Density	780 kg/m^3 at 20 °C
Vapour pressure	7.91 kPa at 25 °C
Water solubility	1 x 10^3 g/L at 25 °C
pKa	15.9 at 25 °C

Property	Value
Partition coefficient n-octanol/water (log K_{ow})	-0.31
Flash point	14 °C
Conversion factor	1 ppm = 1.92 mg/m^3

27.3 Current regulatory controls

27.3.1 *Hazard classification for occupational health and safety*

Ethanol is not classified as hazardous for human health in the Safe Work Australia *Hazardous Substances Information System* (HSIS) (Safe Work Australia 2013).

27.3.2 *Occupational exposure standards*

27.3.2.1 Australia

The following exposure standard was identified (Safe Work Australia 2013):

- Time Weighted Average (TWA) of 1880 mg/m^3.

No Short-Term Exposure Limit (STEL) has been assigned.

27.3.2.2 International

The following exposure standards were identified (Galleria Chemica 2013).

TWA:

- 950 mg/m^3 [Norway]
- 960 mg/m^3 [Germany, Switzerland]
- 1000 mg/m^3 [Sweden]
- 1500 mg/m^3 [Chile]
- 1880 mg/m^3 [Canada]
- 1900 mg/m^3 [Canada (Yukon), Denmark, France, Greece, Hungary, Iceland, Mexico, Poland, US]
- 1920 mg/m^3 [United Kingdom).

Short-term Exposure Limit (STEL):

- 1900 mg/m^3 [Canada, Sweden]
- 1920 mg/m^3 [Switzerland]
- 7600 mg/m^3 [Hungary]
- 9500 mg/m^3 [France].

27.3.3 *Australian food standards*

Ethanol has the following listings in the *Australia New Zealand Food Standards Code* (Food Standards Australia and New Zealand 2013):

- as a permitted food additive subject to GMP (ethanol) (Standard 1.3.1 *Food additives*)
- as a generally permitted processing aid (ethyl alcohol) (Standard 1.3.3 *Processing aids*)
- as a permitted component of wine (alcohol) (Standard 2.7.3 *Fruit wine and vegetable wine*)
- as subject to a composition limit in brewed soft drinks (no more than 1.15% alcohol/volume) (Standard 2.6.2 *Non-alcoholic beverages and brewed soft drinks*)
- As subject to a composition limit in:
  - wine and sparkling wine (no less than 45mL ethanol/L and not to contain added ethanol)
  - fortified wine (no less than 150 mL ethanol/L and no more than 220 mL ethanol/L)
  - brandy (must contain no less than 250 mL/L of the spirit distilled at a strength of no more than 830 mL ethanol/L at 20˚C (Standard 4.5.1 *Wine production requirements*).

27.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the *Australian Drinking Water Guidelines* (NHMRC 2011).

27.3.5 *Additional controls*

27.3.5.1 Australia

Denatured ethanol (methylated spirits) is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (TGA 2014) in Schedule 5 with the following entry:

- METHYLATED SPIRIT(S) (being ethanol denatured with denatonium benzoate, methyl isobutyl ketone and fluorescein) except:
  a) when included in preparations or admixtures
  b) when packed in containers having a capacity of more than 5 L.

Ethanol (ethyl alcohol) is also listed in the SUSMP in Schedule B (*Substances considered not to require control by scheduling*). The reason for entry is low toxicity and covers any use.

Ethanol is included in the *Australian Dangerous Goods Code Edition* 7 (ADG7) (National Transport Commission 2007), with UN Number 1170. It is listed as a Class 3 ‘Flammable Liquid’ and is assigned to Packaging Group II. The ADG7 contains detailed provisions for the packaging, transport and marking of containers in Class 3.

27.3.5.2 International

Ethanol (ethyl alcohol) is listed in the *Immediately Dangerous to Life or Health* (IDLH) documentation of the US *National Institute for Occupational Safety and Health* (NIOSH) *Centers for Disease Control and Prevention* (CDC). The IDLH value is 3300 ppm (6336

mg/m^3) based on safety considerations (being 10% of the lower explosive limit of 3.3%) (NIOSH 2013).

27.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

27.5 Health hazard characterisation

The information on health hazards is obtained from the following comprehensive peer reviewed data sources:

- an International Agency for Research on Cancer (IARC) summary and evaluation of alcohol drinking (IARC 1988)
- an IARC monograph on alcohol consumption and ethyl carbamate (IARC 2010)
- an OECD Screening Information Assessment Report on ethanol (OECD 2005)
- HSDB (2013).

In addition, data were also obtained from a registration dossier on ethanol submitted by industry under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (REACH 2013). Unless otherwise noted, references to individual studies below are taken from these data sources.

27.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

27.5.1.1 Oral absorption

Acute and chronic toxic effects observed after ingestion indicate that ethanol is readily and rapidly absorbed via the oral route in humans. For human risk assessment purposes, an oral absorption of 100% is assumed.

27.5.1.2 Dermal absorption

In an *in vitro* dermal penetration study, the movement of ^{14}C- labelled ethanol through pig skin was shown to be greater through occluded skin than non-occluded skin (2.19 mg/cm^2 and 0.1 mg/cm^2 over 24 hours respectively) (Pendlington 2001). In a comparative human dermal study, none of the blood samples taken from 16 volunteers following dermal application of an alcohol-based deodorant spray exhibited detectable levels of ethanol (Pendlington 2001). These studies concluded that ethanol is poorly absorbed via intact skin.

In a subsequent human study, the dermal absorption of ethanol was assessed following hand disinfection using alcohol based hand rubs (Kramer et al. 2007). Twelve volunteers applied three different hand rubs containing 55%, 85% or 95% ethanol. For hygienic hand disinfection, 4 mL were applied 20 times for 30 seconds with a one minute break between applications. For surgical hand disinfection, 20 mL were applied to hands and arms 10 times for three minutes with a break of five minutes between applications. Blood samples were taken between 2.5 and 90 minutes after the last application. For hygienic hand disinfection, the maximum proportion of absorbed ethanol was 2.3% (60 g ethanol initially applied). For surgical hand disinfection, the maximum proportion of absorbed ethanol was 1.1% (140 g ethanol initially applied).

Ethanol has a very low octanol/water partition coefficient and this is seen as a contributor to a poor dermal uptake of ethanol through intact human skin (OECD 2005).

For human risk assessment purposes, a dermal absorption of 10% is assumed.

27.5.1.3 Inhalation absorption

In humans, approximately 60% of inhaled ethanol vapour is absorbed (Lester and Greenberg1951; Kruhøffer 1983). A large proportion of inspired ethanol is deposited in airway linings to be released to expired ethanol-free alveolar air (Kruhøffer 1983).

For human risk assessment purposes, a conservative inhalation absorption of 100% is assumed.

27.5.1.4 Distribution

Following absorption, in accordance with its very low octanol/water partition coefficient, ethanol is widely distributed in body water.

27.5.1.5 Metabolism

Following absorption, ethanol is metabolised mainly in the liver (OECD 2005). Other tissues such as kidney, stomach and intestines also metabolise ethanol but to a lesser extent.

The first metabolic step is oxidation within the cytosol of hepatocytes to acetaldehyde by alcohol dehydrogenase followed by rapid conversion to acetate via acetaldehyde dehydrogenase mainly in the mitochondria. Acetate is then released into the blood stream to be oxidised in peripheral tissues to acetic acid and ultimately to CO_2 and water. Although metabolism of ethanol proceeds mainly via alcohol dehydrogenase, other hepatic pathways for ethanol oxidation have also been described. These include a microsomal system in endoplasmic reticulum and a catalase system in peroxisomes (OECD 2005).

The capacity of the alcohol dehydrogenase enzyme system is saturable at low blood ethanol levels. Accordingly, following saturation, metabolism moves from first-order to zero-order kinetics with metabolism occurring at a constant rate independent of blood concentrations. In humans, there is considerable individual variation in rates of ethanol metabolism (Goldfrank 2002). Ethnic sensitivities to ethanol have been linked to genetic polymorphisms of acetaldehyde dehydrogenase and increased blood acetaldehyde levels following ethanol ingestion (Bingham et al. 2001).

27.5.1.6 Excretion

The predominant route of excretion of ethanol is via urine (OECD 2005). Ethanol is also excreted via exhaled air and sweat. Excretion occurs mainly as metabolites with a small amount (5 to 10%) excreted unmetabolised. Ethanol does not accumulate in the body.

27.5.2 *Acute Toxicity*

27.5.2.1 Oral

Ethanol has a low order of toxicity in animals following acute oral exposure.

The following figures for acute oral toxicity are reported from robust studies: Rat median Lethal Dose (LD50) = 15 010 mg/kg bw (Youssef et al. 1992); Mouse LD50 = 8300 mg/kg bw (Bartsch et al. 1976). In rats, the main symptoms reported following acute exposure were central nervous system depression e.g. inebriation, disturbances of gait and dose-related decreases in responses to painful stimuli, respiratory depression and coma. Deaths were reported due to cardiorespiratory failure (Youssef et al. 1992).

27.5.2.2 Dermal

Few studies are available on the dermal toxicity of ethanol. A poorly documented rabbit study reported death in one of four animals following a dose of 20 000 mg/kg bw (Monick 1968). Although poorly reported, the apparent low dermal toxicity from this study is regarded as consistent with poor uptake of ethanol through intact skin. Accordingly, the LD50 is greater than 20 000 mg/kg bw.

27.5.2.3 Inhalation

Ethanol has shown a low order of acute toxicity in inhalation studies. In a study regarded as well reported but with noted deviations from OECD test guidelines, no deaths were reported in CD-1 mice exposed for 60 minutes to up to 60 000 ppm ethanol by inhalation (Moser 1985). Slight to moderate ataxia was observed and recovery exceeded four hours at all exposure levels. The LC50 was more than 60 000 ppm (115 g/m^3).

27.5.2.4 Observation in humans

Symptoms of intoxication (e.g. drowsiness and loss of concentration) are associated with oral consumption of beverages containing ethanol. However, there is no evidence of such symptoms occurring following dermal or inhalational exposures (OECD 2005).

27.5.3 *Irritation / Corrosivity*

27.5.3.1 Skin irritation

An early skin irritation study in rabbits with application of ethanol under occlusion for 24 hours showed only very slight skin irritation (Phillips 1972). A subsequent study in six New Zealand White rabbits conducted in accordance with OECD Test Guideline (TG) 404 also noted only very slight irritation (Jacobs and Martens 1992). In conclusion, ethanol is not regarded as irritating to skin.

27.5.3.2 Eye irritation

In a study conducted to OECD TG 405, application of 0.1 mL ethanol to the eyes of six New Zealand White rabbits produced moderate irritation (Jacobs and Guido 1987). Reported mean Draize scores at 24, 48 and 72 hours were: 2.5, 2.61, 2.06 for conjunctivitis, 1.67, 1.17, 0.83 for chemosis, 0.50, 0.33, 0.00 for iritis and 1.00, 1.50, 1.00 for corneal opacity. In this study, conjunctivitis persisted for more than 24 hours with mean scores in two animals greater than, or equal to, 2.5.

In a study reported in a reference handbook of peer reviewed eye irritation studies conducted to OECD TG 405, instillation of 0.1 mL ethanol in three rabbits caused eye irritation (ECETOC 1998). Mean Draize scores following grading at 24, 48 and 72 hours were 2.11 for conjunctivitis (two out of three animals with a mean score >2), 1.33 for chemosis, 0.44 for iritis, and 1.11 for corneal opacity. All symptoms had subsided by day 14.

In conclusion, data from animal studies indicate that ethanol is irritating to the eye.

27.5.3.3 Respiratory irritation

No data were available.

27.5.3.4 Observation in humans

Ethanol is frequently applied to skin as a biocidal surgical wipe and as a component of cosmetics and personal care products (OECD 2005). Few concerns regarding skin irritation arising from these uses have been documented. Direct contact of the eye with liquid ethanol

causes immediate discomfort accompanied by reflex closure of the eye. Foreign body type discomfort may persist for a day or two. However, recovery is complete (OECD 2005). In humans, inhalation of 5000 ppm (9600 mg/m^3) ethanol has been reported as irritating (Lester and Greenberg 1951).

27.5.4 *Sensitisation*

27.5.4.1 Skin sensitisation

Ethanol was used as a solvent in a Magnusson and Kligman guinea pig maximisation test of a polyalkalene glycol (BP Chemicals 1984). No skin reactions were observed at challenge with the polyalkalene glycol in 75% ethanol in either test or negative control animals. No positive controls were used in this study and no detailed information on the conduct of the study was available.

No increase in ear thickness was observed following challenge application of 95% ethanol in a mouse ear swelling test (Descotes 1988).

In a dossier submitted under REACH, a test is described to evaluate the effect of vehicles (ethanol or diethyl phthalate) for use in a mouse local lymph node assay (REACH 2013). The assay was conducted according to OECD TG 429 with minor deviations. The level of induced T-lymphocyte proliferation was low for ethanol compared to that for fragrance materials known to be mild to moderate skin sensitisers and comparable to the other negative control vehicle diethyl phthalate. On the basis of a lack of sensitising potential, the test concluded that ethanol is an appropriate vehicle for use in the local lymph node assay.

Overall, available data indicate that ethanol does not induce skin sensitisation in animals.

27.5.4.2 Respiratory sensitisation

No data were available.

27.5.4.3 Observation in humans

A literature review of contact reactions to ethanol has noted that ethanol can induce immediate and delayed hypersensitivity reactions in humans following external and internal exposures (Ophaswongse and Maibach 1994). A single case report notes that a patient using a transdermal drug delivery system with ethanol as a solvent experienced erythematous and itchy lesions at patch sites after continuous use (Pitarch and de la Cuadra 2010). The authors concluded that such adverse effects are only likely under occluded conditions and for prolonged periods.

27.5.5 *Repeat dose toxicity*

Many repeat dose studies of ethanol have been conducted in a number of species, predominantly with the aim of assessing adverse effects associated with the consumption of alcoholic beverages. Consequently, these are mostly conducted via the oral route and with doses well in excess of those that might be encountered via occupational exposures or use of consumer products (OECD 2005) or unintentional public exposures via the environment.

27.5.5.1 Oral

In 90-day oral toxicity studies conducted to national test guidelines (EPA OPPTS 870.3100), a single dose of 5% ethanol in drinking water was assessed in rats and mice as a vehicle for long-term toxicity and carcinogenicity studies (REACH 2013).

Male rats showed minor changes in thymus weights and slight, inconsistent changes in haematology and clinical chemistry. Minor changes in clinical chemistry were also seen in female rats. Some female rats (4/10) exhibited liver nodules and small increases in liver weights. Both sexes showed increases in nephropathy. Based on water consumption data, this single dose study established a nominal No Observed Adverse Effect Level (NOAEL) for male rats at approximately 3250 mg/kg bw/day. No Lowest Observed Adverse Effect Level (LOAEL) was established. For female rats, a LOAEL was established at 4400 mg/kg bw/day. No NOAEL was established.

In another study in male mice, organ weights (liver, heart, kidney and lung) were increased and sperm counts in the cauda epididymis were decreased (REACH 2013). For male mice, this single dose study established a LOAEL at 9700 mg/kg bw/day. No NOAEL was established. Female mice showed no effects apart from small changes in the length of the dioestrus and pro-oestrus phases of the oestrus cycle. Cycle length was unchanged. The biological significance of these changes was unclear. A NOAEL for female mice was established at 9400 mg/kg bw/day. No LOAEL could be established.

In a 90-day oral study regarded as well-conducted, male and female rats were administered ethanol (1%, 2%, 3%, 4%, 5% and 10% w/w) via drinking water (Holmberg et al. 1986). Water consumption in the 10% group was reduced relative to controls. Serum liver enzymes were unaffected by treatment and kidney findings were reported to be minimal. A LOAEL was established at 3% (approximately 3600 mg/kg bw/day). This was based on dose-related hepatic yellowing, centrilobular steatosis and increased frequency and severity of Mallory bodies (hyaline) and acidophilic degeneration and necrosis. The NOAEL was 2% (approximately 2400 mg/kg bw/day).

A two-year oral carcinogenicity study in mice conducted to national test guidelines (EPA OPPTS) exposed mice to either 2.5% or 5% ethanol in drinking water (NTP 2002). A marginal dose-related increase in survival in males but not females was reported. An ethanol-induced reduction in water consumption was also reported, more marked in males than females.

In conclusion, ethanol appears to be of low repeat dose oral toxicity. The critical study for oral repeat dose effects is the 90-day drinking water study of Holmberg et al. (1986) which was well conducted and in which dose selection was sufficient to reliably distinguish effect levels. From this study, a NOAEL of 2400 mg/kg bw/day and a LOAEL of 3600 mg/kg bw/day were established.

27.5.5.2 Dermal

No data were available.

27.5.5.3 Inhalation

No data were available.

27.5.5.4 Observations in humans

Concentrations of ethanol attained in humans in the upper gastrointestinal tract after consumption of alcoholic beverages can cause local irritation. Long-term excessive consumption of alcoholic beverages is also associated with liver effects – fatty liver, alcoholic hepatitis, cell necrosis, fibrosis and cirrhosis (IARC 1988).

27.5.6 *Genotoxicity*

27.5.6.1 *In vitro* studies

The results from numerous bacterial mutation assays of ethanol have generally been negative (OECD 2005). A very weak positive effect of ethanol in an *Escherichia coli* DNA repair test was found but not in Ames tests with *Salmonella typhimurium* by the same authors (De Flora et al. 1984a). In separate studies, there have been positive results reported in Ames tests but only at ethanol concentrations that were significantly greater than those specified in test guidelines (De Flora et al. 1984b; Hayes 1985). Ethanol is not considered mutagenic in bacteria.

Ethanol has also been tested in several chromosome aberration assays (OECD 2005). Many of these studies have limitations such as insufficient dose ranges and lack of metabolic activation. Accordingly, a weight of evidence approach is required to draw conclusions regarding clastogenic potential. No chromosomal aberrations were found in testing with human lymphocyte cultures (Banduhn and Obe 1985), lymphocyte cell lines (Brown et al. 1992) or Chinese hamster ovary (CHO) cells (Lin et al. 1989). Chromosomal aberrations were detected in CHO cells but only in the presence of metabolic activation using plant microsomal extracts (Darroudi and Natarajan 1987).

Collectively, there is little evidence that ethanol is clastogenic *in vitro*. It has been considered that positive responses with high ethanol concentrations may be an artefact, attributable to damage from high osmotic pressures.

Ethanol has also been tested in cell mutation (mouse lymphoma) assays with negative results (Amacher et al. 1980; Friedrich and Nass 1983). A statistically significant increase in mutations was reported both in the presence and absence of metabolic activation in a mouse lymphoma assay designed to assess false positive results. However, the magnitude of mutant frequencies was small and the result was regarded as negative (Wangenheim and Bolcsfoldi 1988).

27.5.6.2 *In vivo* studies

Several *in vivo* micronucleus assays have assessed the potential for ethanol to induce damage to chromosomes of erythroblasts. No effect was reported in rats when administered at 5% (approximately 4 g/kg bw/day) in drinking water (Tates 1980) or mice at up to 40% (approximately 31 g/kg bw/day) (Chaubey et al. 1977). Ethanol-related mortality was observed in this latter study. Marginal statistically significant increases in the incidence of micronucleated bone marrow erythrocytes were reported in rats fed for six weeks with a diet containing ethanol at 12 to 16 g/kg/day (Baraona 1981). More recently, a mouse micronucleus drinking water study examined the impact of prolonged exposures (21 days) to a single high dose of ethanol (>20 g/kg bw/day). A positive result was obtained but only with exposures to this very high dose (Cebral et al. 2011). Overall, available data from some (but not all) studies suggest a potential for ethanol at very high doses to induce micronuclei in bone marrow erythrocytes.

No chromosomal aberrations were found in bone marrow or peripheral blood lymphocytes of rats receiving ethanol at up to 15.7 g/kg bw day in drinking water (Tates 1980). Similarly, no chromosomal aberrations were found in the bone marrow of Chinese hamsters receiving ethanol in drinking water at up to 20% for 12 weeks (Korte et al. 1981a) or 10% for 46 weeks, (Korte and Obe 1981b).

Results of dominant lethal assays with ethanol have been mixed. Interpretation of results has been confounded by inadequacies in methodologies and use of high ethanol doses often producing confounding toxicological effects. The most robust dominant lethal testing was identified as a collaborative inter-laboratory study conducted to OECD test guidelines (James

and Smith 1982). In this study, male mice were exposed via intubation to doses of ethanol at and below the maximally tolerated dose. No evidence of dominant lethality was reported.

Increased frequencies of chromosomal aberrations have been reported in several studies of peripheral blood lymphocytes in alcoholics (IARC 1998, 2010).

In conclusion, the interpretation of studies on the genotoxicity of ethanol is confounded by methodological inadequacies in many studies. *In vitro*, ethanol was not shown to be mutagenic in bacteria, mutagenic in animal cells or clastogenic in human or animal cells. *In vivo*, ethanol was not mutagenic or clastogenic in animals in the majority of studies. Clastogenicity was reported in some micronucleus assays at very high doses and in assays examining peripheral blood lymphocytes of alcoholics. Overall, data do not suggest that ethanol should be regarded as a mutagen. For studies showing positive results, it has been questioned whether ethanol is genotoxic to somatic cells other than at very high doses achievable in humans only by deliberate oral ingestion (Phillips and Jenkinson 2001).

27.5.7 *Carcinogenicity*

27.5.7.1 Animal studies

In a similar fashion to studies of repeat dose toxicity, studies of carcinogenicity have been conducted in experimental animals often with the aim of assessing risks from consumption of alcoholic beverages. However, many early studies have been criticised on methodological grounds with the result that despite the number of studies conducted, evidence for carcinogenicity in experimental animals was previously concluded by IARC to be inadequate (IARC 1988).

In a subsequent review by IARC, studies of ethanol exposures in animals additional to those assessed by IARC in 1988 including studies of the modifying effects of ethanol on the activity of various carcinogens, were noted (IARC 2010). In the mouse, oral studies have been conducted with ethanol administered via drinking water, gavage or diet. Doses ranged from 1 to 20% of drinking water to a total of 30% of total dietary calories. Exposure periods ranged from 4 to 104 weeks. Many studies were criticised on the basis of methodological shortcomings such as inadequate numbers of animals or failure to measure blood ethanol concentrations. The majority of studies failed to detect increases in tumour incidence.

In one study, groups of 20 female ICR mice received 10% ethanol in drinking water for two months and then 15% ethanol in drinking water for 23 months (NTP 2002). Beginning eight months after treatment, mammary gland tumours (papillary or medullary adenocarcinoma) were detected in 45% (9/20) mice receiving ethanol compared to 0/20 control mice receiving drinking water alone. The dose of ethanol was estimated at 13.2 g/kg bw/day (Watabiki et al. 2000). In another long term oral study, mice were exposed to 2.5% and 5% ethanol in drinking water (equivalent to 80 to 100 mg/day and 155 to 180 mg/day respectively) for 104 weeks. The study revealed only equivocal evidence of carcinogenic activity, based on increased incidence of hepatocellular neoplasms in males. Females showed no evidence of these effects (NTP 2002).

Similarly, as described by IARC (2010), several additional oral studies in the rat have been conducted with ethanol administered via drinking water or diet. Doses ranged from 1 to 10% of drinking water to 3% of diet. Exposure periods ranged from 51 to 179 weeks. The lack of measurement of blood ethanol concentrations was a common criticism of these studies, among which the majority failed to detect increases in neoplasms.

In a single high dose, chronic multigenerational study, male and female rats and their offspring received 10% ethanol in drinking water (Soffritti et al. 2002). Administration of ethanol resulted in an increase in the incidence of head and neck carcinomas in male and female rats and the incidence of forestomach carcinomas, testicular interstitial cell adenomas

and osteosarcomas of the head, neck and other sites in male rats. Conclusions from this study are limited because of the single high dose, insufficient data reporting and inconsistencies between conclusions and statistical analyses (OECD 2005; IARC 2010). In another long term (104 week) study of up to 3% ethanol in drinking water (Holmberg and Ekström 1995), a significant decrease in tumours in females was noted. The ethanol dose was estimated at 480 to 560 mg/day.

Other animal studies have been performed to determine whether ethanol modifies chemically induced carcinogenesis (IARC 2010). In these studies, known carcinogens were administered orally with ethanol as a vehicle or administered by different routes at various times with ethanol administered via drinking water or liquid diets. Some studies have been criticised because of methodological shortcomings. Positive results are reported in some studies whilst others report negative findings (IARC 2010). Overall, increases in tumours (mostly in target organs characteristic of the carcinogens used) were observed in experiments in which ethanol was used as a vehicle for N-nitrosamines and 7,12-dimethylbenz[*a*]anthracene (DMBA). Similar results were obtained in some but not all experiments when animals received ethanol just before administration of the carcinogen or separately but at the same time as the carcinogen. There was no effect on carcinogenesis in most experiments when ethanol was given separately and after administration of the carcinogen or when ethanol concentrations were low e.g. 5%. This has been interpreted as indicating that ethanol may influence initiation of carcinogenesis, or influence mechanistic events such as entry of the carcinogen into target cells or intracellular metabolism or suppression of DNA repair. Competitive inhibition of hepatic metabolism of the carcinogen, allowing it to reach target organs, has also been proposed (IARC 2010).

In contrast to earlier conclusions in 1988, IARC has now determined that there is sufficient evidence for the carcinogenicity of ethanol in experimental animals (IARC 2010). However, the extent to which carcinogenicity seen in animals with ethanol at doses associated with beverage consumption can inform the carcinogenic potential of ethanol via other types of exposures in humans has been questioned. Studies conducted mostly via the oral route at high doses provide scant data to inform risks associated with occupational exposures or use of consumer products containing ethanol (OECD 2005). In the same way, these may be of little relevance to a hazard assessment of low level public exposures to ethanol via environmental contamination from industrial activity.

27.5.7.2 Human studies

There are a large number of human studies on the effects of alcoholic beverages which indicate that consumption is causally related to cancers of the oral cavity, pharynx (excluding the nasopharynx), larynx and oesophagus (IARC 1988). The aetiology is thought to be linked to persistent irritation, hyperplasia and finally tumour formation (Greim 1999). Consumption in excess of 10 to 40 g ethanol/day appears necessary before there is an appreciable increase in relative risk for these cancer types (UK Department of Health 1995; Greim 1999).

Early human studies also indicate a causal relationship between alcoholic beverage consumption and liver cancer (IARC 1988). In this case, aetiology is commonly linked to cirrhosis, normally seen only following chronic intakes of greater than 80 g ethanol/day (UK Department of Health 1995; Greim 1999). However, the evidence did not suggest that carcinogenicity is linked to mutagenic effects of ethanol (UK Department of Health 1995).

Since the conclusion of a causal relationship between consumption of alcoholic beverages and carcinogenicity (IARC 1988), a large number of additional epidemiological studies have reported on the association between alcohol consumption and cancers at various sites (IARC 2010). These indicate that regular alcoholic consumption is associated with increased risk of malignant tumours of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast. Daily consumption of 50 g ethanol was associated with a two- to three-fold

increase in risk of upper digestive tract tumours compared to non-drinkers. Similarly, daily consumption of 50 g ethanol was associated with relative risks for colorectal cancer and breast cancer of 1.4 and 1.5 respectively, compared to non-drinkers. The risk for liver tumours was more difficult to estimate due to confounding effects of cirrhosis and other liver diseases which often occur before the cancer becomes manifest and lead to reductions in alcohol intake in patients.

Consequently, IARC more recently concluded that alcoholic beverages are carcinogenic to humans. This conclusion was supported by an analysis of the expanded human dataset that carcinogenic effects appeared independent of the type of alcoholic beverage (IARC 2010).

27.5.8 *Reproductive toxicity*

27.5.8.1 Fertility

There are few fertility studies in males that provide sufficient dose information from which to conclude effect levels associated with ethanol exposures. Also, there are few studies on fertility effects in females (OECD 2005).

In a robust two-generation study in mice, ethanol in drinking water at concentrations of 5%, 10% and 15% (approximately 21 g/kg bw/day at 15%) had no effect on fertility indices in P and F1 generations (George et al. 1985). However, F1 males exposed to 15% ethanol showed significantly decreased per cent motile sperm and decreased testis, epididymis and seminal vesicle weights. Clinical signs were not evaluated. Data on fertility effects in females were also not evaluated.

In rats, an adverse effect on male fertility was noted with administration of 10% ethanol via diet for 15 days prior to and during the mating period (Klassen and Persaud 1976). However, this study was confounded by paternal toxicity manifesting as ataxia, lethargy and weight loss during the study period. In contrast, no effect on fertility was reported in male rats exposed via oral intubation to either 2000 mg or 3000 mg ethanol/kg bw/day for nine weeks (Abel 1993).

In another well-reported one-generation study, no effect on fertility was reported in male rats exposed to 2500 mg or 5000 mg ethanol/kg bw/day for three or nine weeks (Abel 1995).

Male rats exposed to 16 000 ppm (30 400 mg/m^3) ethanol by inhalation for seven hours/day for six weeks in a combined fertility and developmental toxicity study showed no effects on fertility (Nelson et al. 1985a, 1985b, 1988). This level of exposure is associated with a blood alcohol concentration of 500 mg/L.

From available data, the most reliable oral NOAEL for fertility effects was 5000 mg/kg bw/day (Abel 1995).

27.5.8.2 Developmental toxicity

Many studies of developmental toxicity have investigated effects of high dose oral ethanol intake (OECD 2005). However, such studies often dose animals well above the maximum 1 g/kg bw/day recommended in current OECD test guidelines with ethanol then representing a significant portion of daily caloric intake. Consequent reductions in nutrient intake, especially during critical periods of gestation, can produce significant postnatal effects which can confound interpretation of such studies.

In female mice treated pre- and post-gestation with ethanol via diet at doses representing 15 to–30% caloric intake, skeletal abnormalities were seen in all offspring (Chernoff 1977). In a robust study in mice, malformations were significantly increased by maternal diets containing 25% or more of ethanol-derived calories (Randall and Taylor 1979). Rats treated with 12.5%

ethanol in water by gavage throughout gestation and gestation plus lactation showed impaired learning at nine weeks compared to controls, with impairment still evident in males at five months (Vaglenova and Petkov 1998).

In a developmental toxicity study in mice, ethanol was administered daily via gavage at doses of 2.2, 3.6, 5.0, 6.4 and 7.8 g/kg bw/day on gestation days 8 to 14 (Wier et al. 1987). Maternal toxicity (lethargy, staggered gait and laboured breathing) was seen commencing at 3.6 g/kg bw/day. At 7.8 g/kg bw/day all dams died. There were no significant dose-related adverse effects on foetuses even at doses associated with maternal toxicity. On this basis, a NOAEL for developmental effects was reported at 6400 mg/kg bw/day (the highest dose for which developmental data could be obtained).

In the first of a series of inhalation developmental toxicity studies, groups of rats were exposed seven hours/day throughout gestation to ethanol concentrations of 0, 10 000, 16 000 or 20 000 ppm (Nelson et al. 1985a). Ethanol induced severe maternal toxicity at 20 000 ppm, but dams also appeared hyperactive after exposures at the lower exposure levels. Foetal weights were slightly reduced at 16 000 and 20 000 ppm but the differences were not statistically significant. There were also no significant differences in incidences of external, visceral or skeletal malformations or variations at these doses. No developmentally toxic effects were seen in this study, including at doses associated with maternal toxicity.

Similar studies were conducted with ethanol doses of 0, 10 000 and 16 000 ppm in which rats were allowed to litter in order to assess behavioural effects in offspring. Litter size, birth weights, offspring survival, growth and behaviour were unaffected even at the highest dose (Nelson et al. 1985b).

In conclusion, oral administration of ethanol showed developmental effects in some but not all studies. Developmental effects, where seen, were associated with maternal toxicity. The results of inhalation studies showed no developmental toxicity from ethanol exposures even at maternally toxic doses. On the basis of a lack of developmental effects seen in inhalation studies, no NOAEC for developmental toxicity could be established.

27.5.8.3 Observations in humans

Effects of alcoholic beverages on reproduction in humans have been reviewed extensively. Alcohol consumption can interfere with both male and female reproductive function through effects on reproductive cells and adverse regulation of sex hormones. Ethanol is a recognised human teratogen. Multiple terms are used to describe a continuum of effects that result from prenatal exposure to ethanol. Foetal alcohol syndrome is the most common description of a collection of the most severe abnormalities linked with alcohol abuse. Abnormalities include pre- and / or postnatal growth retardation, characteristic craniofacial dysmorphology, mental retardation, cardiac septal defects, joint abnormalities and additional alterations in multiple organs and systems (IARC 2010).

27.5.9 *Other health effects*

No other health effects were identified.

27.6 Health hazard summary

27.6.1 *Critical health effects*

Ethanol has low acute toxicity by all exposure routes. It is not irritating to skin and is irritating to eyes. It is not a skin sensitiser.

Many repeat dose studies have been conducted, predominantly with the aim of assessing effects associated with the consumption of alcoholic beverages. Overall, ethanol has low

repeat dose oral toxicity. The critical study for oral repeat dose effects is a 90-day drinking water study which established a NOAEL of 2400 mg/kg bw/day. The LOAEL was 3600 mg/kg bw/day based on hepatic effects.

In *in vitro* genotoxicity tests, ethanol was shown not to be mutagenic in bacteria, mutagenic in animal cells or clastogenic in human or animal cells. In *in vivo* tests, ethanol was not mutagenic or clastogenic in animals in the majority of studies. Clastogenicity was reported in some micronucleus assays at very high doses and in studies of chromosomal aberrations in alcoholics. Overall, data do not suggest that ethanol is a mutagen.

Numerous studies of carcinogenicity have been conducted in experimental animals via the oral route, often with the aim of assessing risks associated with regular consumption of alcoholic beverages. In a review of more recent reports, the majority of repeat dose studies of oral administration of ethanol failed to show increases in tumour incidence. A two-year study in mice reported that male (but not female) animals showed increased incidence of hepatocellular neoplasms with oral exposures equivalent to 155 to 180 mg/day. Another study in mice detected increases in mammary gland tumours beginning eight months after commencement of administration of ethanol via drinking water. The dose of ethanol was estimated at 13.2 g/kg bw/day. In rats, a 104-week study of up to 3% ethanol in drinking water reported a significant decrease in the incidence of tumours in female animals. In contrast, in an insufficiently reported multigenerational study, an increase in tumours in male and female rats was reported with 10% ethanol in drinking water. In experiments testing whether ethanol modifies chemically induced carcinogenesis, increases in tumours were observed in some instances. There was commonly no effect on carcinogenesis in experiments when ethanol was given separately and after administration of the carcinogen, or when ethanol concentrations in drinking water or diet were low e.g. 5%.

In humans, regular consumption of alcoholic beverages is associated with increased risk of malignant tumours of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast. Accordingly, there appears sufficient evidence for carcinogenicity of alcoholic beverages in humans. A question remains as to whether carcinogenicity is linked with ethanol exposures other than doses associated with regular alcoholic beverage consumption.

Current data indicate that, other than at very high doses, ethanol is not associated with effects on fertility. In a well-reported study, no effects on fertility were reported in male rats exposed to up to 5000 mg ethanol/kg bw/day for up to nine weeks.

Developmental effects have been reported for ethanol in some, but not all, animal studies. Effects were compounded by the potential for high ethanol doses to produce postnatal effects through reduced maternal nutrient intake. In a well-conducted mouse developmental study, no developmental effects were seen at oral doses of up to 6400 mg/kg bw/day (highest dose for which developmental data could be obtained) despite maternal toxicity at this dose. Consequently, other than at very high doses, ethanol is not regarded as a developmental toxin.

Overall, the most sensitive endpoint for ethanol appears to be repeat dose toxicity. The oral NOAEL was 2400 mg/kg bw/day. The LOAEL was 3600 mg/kg bw/day based on hepatic effects.

27.6.2 *Hazard classification*

Available data indicate that ethanol should be classified as an eye irritant according to the approved criteria and under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009).

In addition to acute effects, ethanol has been tested extensively for repeat dose toxicity, carcinogenicity and reproductive toxicity. To date, such testing for repeated exposures has been conducted predominantly to inform an understanding of risks associated with consumption of alcoholic beverages. Accordingly, the majority of testing has been conducted via the oral route and at high doses, with selected doses frequently exceeding 1000 mg/kg/day, which is the normal limit dose for toxicity testing in the absence of evidence of the possibility of higher human exposures.

For ethanol used within the workplace, repeated high dose oral exposures are unlikely and descriptions of toxic effects from such exposures are of limited relevance to classification and labelling for workplace hazards.

Similarly, for ethanol in consumer products not intended for deliberate oral ingestion, repeated, high dose oral exposures are unlikely and, therefore, evidence of toxic effects at high oral doses is of limited relevance for scheduling of such consumer products.

On the basis of low repeat dose toxicity, ethanol is not classified for effects from repeated exposures according to the Approved Criteria or adopted GHS.

On the basis of carcinogenic effects seen in animals only at high oral doses and in humans only with ingestion of alcoholic beverages at high levels and that these exposure patterns and doses are inappropriate for potential workplace exposures, ethanol is not classified as a workplace carcinogen according to the approved criteria or adopted GHS.

Similarly, on the basis of reproductive toxicity seen with animals only at high oral doses and in humans with ingestion of alcoholic beverages at high levels and these exposure patterns and doses being inappropriate for potential workplace exposures, ethanol is not classified as a reproductive toxicant according to the approved criteria or adopted GHS.

The chemical is therefore recommended by NICNAS to Safe Work Australia for the following classification and labelling under the approved criteria and adopted GHS (Table A27.3). These NICNAS recommendations do not consider physical or environmental hazards.

Table A27.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Eye irritation	Irritating to eyes (X_i; R36)	Irritating to eyes – Cat. 2A (H319)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

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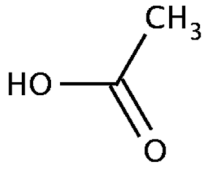
A28 Acetic acid

CAS No.	CAS Name
64-19-7	Acetic acid

28.1 Chemical identity

The following chemical identity information was obtained from ChemID*plus* (2012) and Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (REACH 2013) and other resources identified in brackets. Table A28.1 provides details of the chemical identity.

Table A28.1 Chemical identity

	Acetic acid
Synonyms	Ethanoic acid Acetic acid, glacial Vinegar acid Ethylic acid Methane carboxylic acid
Structural formula	
Molecular formula	$C_2H_4O_2$
Molecular weight	60
Appearance and odour	Clear colourless liquid with a pungent vinegar smell
SMILES notation	C(C)(=O)O

28.2 Physical properties

Information regarding the physical properties of Acetic acid was obtained from Haynes (2011) and is presented in Table A28.2.

Table A28.2 Physical properties

Property	**Value**
Melting point	16.6 °C
Boiling point	117.9 °C
Density	1.05 kg/m^3 at 25 °C
Vapour pressure	1.5 kPa at 20 °C

Property	Value
Water solubility	1000 g/L at 25 °C
Partition coefficient n-octanol/water (log K_{ow})	-0.17

28.3 Current regulatory controls

28.3.1 *Hazard classification for occupational health and safety*

Acetic acid is classified as hazardous, with the following risk phrase for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013):

- C; R35 (Corrosive, causes severe burns).

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures:

- Conc >=90%: C; R35 (Corrosive, causes severe burns)
- ≥25% Conc <90%: C; R34 (Corrosive, causes burns)
- ≥10% Conc <25%: Xi; R36/38 (Irritant, Irritating to eyes and skin).

28.3.2 *Occupational exposure standards*

28.3.2.1 Australia

The chemical has an exposure standard of 25 mg/m³ (10 ppm) Time Weighted Average (TWA) and 37 mg/m³ (15 ppm) Short-Term Exposure Limit (STEL) (Safe Work Australia 2013).

28.3.2.2 International

The following exposure standards are identified in Galleria Chemica (2013).

Occupational Exposure limit (TWA):

- 10 to 25 mg/m³ [China, Canada, Denmark, Germany, Ireland, South Africa, Spain, Sweden, Switzerland, and the US].

An exposure limit (STEL):

- 15 to 50 mg/m³ [China, Canada, France, Ireland, Singapore, South Africa, Spain, Sweden, Switzerland, and the US].

28.3.3 *Australian food standards*

Acetic acid is allotted the following International Numbering System of food additives number:

- INS 260 (Food Standards Australia New Zealand 2013).

28.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

28.3.5 *Additional controls*

28.3.5.1 Australia

Acetic acid is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) as follows:

> Schedule 2: ACETIC ACID (excluding its salts and derivatives) and preparations containing more than 80% of acetic acid for therapeutic use. Schedule 2 chemicals are labelled 'Pharmacy medicine' and may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person.

- Schedule 5: ACETIC ACID (excluding its salts and derivatives) in preparations containing more than 30% of acetic acid (CH3COOH), except:
    a) when included in Schedule 2 or 6 or
    b) for therapeutic use.

  Schedule 5 chemicals are labelled with 'Caution'. These are substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

  Schedule 6: ACETIC ACID (excluding its salts and derivatives) and preparations containing more than 80% of acetic acid (CH3COOH) except when included in Schedule 2. Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.

28.3.5.2 International

The US Cosmetic Ingredient Review (CIR) concluded that a cosmetic ingredient can contain up to 0.3% for safe use (CIR 2010).

28.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

28.5 Health hazard characterisation

The information on health hazards is obtained from REACH dossiers on the chemical (REACH 2013). Unless otherwise noted, references to individual studies below are taken from these sources.

28.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

Acetic acid and its salts (acetates) are common constituents of animal and plant tissues and are formed during the metabolism of food substances. Typical concentrations of acetic acid occurring naturally in foods are 2.8 mg/kg in fresh orange juice, 700 to 1200 mg/kg in wines, and up to 860 mg/kg in aged cheeses (EFSA 2012). Estimated average daily intake of acetic acid and sodium acetate (based on food intake concentrations) are 2.1 g/day and 0.23 g/day, respectively. Acetates are also produced as major intermediates in normal metabolic processes and are rapidly metabolised (EFSA 2012). Various isotope experiments have shown that the different carbon atoms of the acetate molecule are used in glycogen formation, as intermediates of carbohydrates and fatty acid synthesis, as well as in cholesterol synthesis. In addition, the chemical also participates in the acetylation of amines and formation of proteins of plasma, liver, kidney, gut mucosa, muscle and brain (WHO 1966). The level of the acetate ion in humans has been estimated at about 50 to 60 µmol/L (3.0 to 3.6 mg/L) in plasma and 116 µmol/L (7 mg/L) in cerebrospinal fluid. Daily turnover of the acetate ion in humans is estimated at about 7.5 µmol/kg/minute representing about 45 g/day (EC 2012).

28.5.1.1 Oral absorption

The rate of absorption of acetic acid by the stomach was determined in rats (Hertling 2001). Single doses of 20 to 400 mg acetic acid in water (six doses) were injected into the pylorus ligated stomachs of Sprague-Dawley (SD) rats (details of injection not provided). The recovery of acetic acid from the treated stomachs was determined immediately after administration and after six hours using a titrametric method. Acetic acid was rapidly absorbed from the stomach of rats, the percentage absorbed decreased with increasing dose. At 20 mg/rat dose, the absorption was 100%.

A 100% oral absorption for acetic acid is assumed for human health risk assessment.

28.5.1.2 Dermal absorption

In an *in vitro* dermal absorption study, conducted according to the Organisation for Economic Cooperation and Development (OECD) Test Guidelines (TG), different concentrations of radio-labelled acetic acid were applied to human skin placed in a diffusion cell (experimental details not provided) (REACH 2013). The skin was exposed to the chemical for eight hours under occlusive conditions. Dermal absorption was measured by the analysis of the labelled acetic acid in the membranes and receptor fluid of the chamber. The potential dermal absorption of acetic acid was calculated to be 43% in *in vitro* conditions.

Considering that the above dermal absorption rate was achieved in an *in vitro* system, the dermal absorption of acetic acid in the intact skin under physiological conditions is assumed to be 100% for human health risk assessment.

28.5.1.3 Inhalation absorption

Information on absorption of acetic acid by inhalation route is not available. However, based on adverse effects noted in a mouse acute toxicity study (see Section A28.5.2.3), 100% inhalation absorption is assumed for human health risk assessment.

28.5.1.4 Distribution

No data were available. Since acetic acid is metabolised by most tissues in the body (see Section A28.5.1.5), it is assumed that following absorption acetic acid is rapidly distributed throughout the body.

28.5.1.5 Metabolism

Following absorption, acetic acid is almost completely metabolised to carbon dioxide and water by most tissues and may give rise to ketone bodies as intermediates (CIR 2010). It is also rapidly oxidised to carbon dioxide in the body. The general tissues of the body have a high potential capacity to oxidise acetate and probably at least half the energy needs of the tissues can be supplied in this manner (Wick and Drury 1952). The amount of acetic acid or acetate oxidised in a given period is proportional to the amount injected and indicates that the rate of oxidation of the substance is proportional to its concentration in the animal. A considerable fraction (30 to 40%) of administered acetate appears to be converted into other forms (Wick and Drury 1952). For instance, in many *in vitro* studies using human and animal tissue preparations, acetate was found to be incorporated into phospholipids, neutral lipids, steroids, sterols and fatty acids in a variety of tissues. Metabolism of ^{14}C-acetate in mice resulted in radioactivity associated with the protein fractions of most major tissues (EC 2012; Hazardous Substances Data Bank (HSDB) 2013).

28.5.1.6 Excretion

Most of the acetic acid taken internally is either utilised in the body or oxidised to carbon dioxide. Only small amounts are excreted in urine. Following administration of large doses (1 to 2 g/kg) of sodium acetate in dogs, only very small amounts were detected in the urine, indicating rapid utilisation of the acetate ion (HSDB 2013). In rats given radiolabelled acetate in the diet, 50% of the radiolabel was excreted as carbon dioxide (EC 2012).

28.5.1.7 Summary of toxicokinetics

Acetate is produced as a major intermediate in normal metabolic processes in the body. Acetic acid is rapidly absorbed by oral, dermal and inhalation routes. The ingested acetic acid is rapidly metabolised into carbon dioxide and also gets incorporated in larger biomolecules such as phospholipids and proteins. As a result of metabolism, only little amounts of acetic acid are excreted in the urine, the majority being excreted as carbon dioxide.

28.5.2 *Acute toxicity*

28.5.2.1 Oral

Acetic acid was of low acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) observed in two rat studies is greater than 2000 mg/kg bw (REACH 2013). In one study, groups of unfasted rats were fed 2239, 2512, 2859, 3100, 3500, 4000, 4467 mg/kg bw sodium acetate and observed for six days (REACH 2013). No further details of the study are provided. Results from the study are summarised below (Table A28.3) Based on these results, the acute oral median lethal dose (LD50) of the sodium salt of acetic acid was found to be 3310 mg/kg bw for rats.

Table A28.3 Results from a six-day study of sodium acetate acute oral toxicity in rats (REACH 2013)

Dose	2239	2512	2859	3100	3500	4000	4467

	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
No rats in dose group	10	10	5	10	10	10	10
No of deaths after six days	1	0	3	5	6	7	8

28.5.2.2 Dermal

Acetic acid was of moderate acute toxicity in rabbits following dermal exposure. The LD50 in rabbits was 1060 mg/kg bw (HSDB 2013). Details regarding the concentration of the administered test substance were not provided. The moderate acute dermal toxicity is believed to be due to its local corrosive effects rather than any systemic toxicity (see Section A28.5.3 Irritation / Corrosivity)**.**

28.5.2.3 Inhalation

Acetic acid was of low acute toxicity in animal tests following inhalation exposure. In an acute inhalation study, mice were exposed to various concentrations of acetic acid (experimental details and concentration range not provided) (HSDB 2013). Clinical signs of respiratory irritation were evident at concentrations of 2.46 mg/L and higher. Animals exposed to concentrations higher than 11.07 mg/L died within 27 hours of exposure. Surviving mice recovered quickly and showed no abnormalities three days after exposure. The median lethal concentration (LC50) was determined by the Weil's method and was estimated to be 13.8 mg/L in the mouse.

28.5.2.4 Observation in humans

Severe health effects have been reported in humans following accidental exposure to acetic acid by different routes, mainly due to the local corrosive effects of the chemical leading to systemic effects (HSDB 2013). Dietary ingestion of vinegar, where the chemical is present at non-corrosive concentrations does not cause harm.

Perforation of the oesophagus has been reported following accidental ingestion of as little as 1 mL of the chemical at high concentrations. In other cases, ingestion has resulted in severe corrosion of the mouth, perforation of the oesophagus, severe corrosion of the gastrointestinal tract, bloody vomiting, diarrhoea, shock, haemolysis, haemoglobinuria and death (HSDB 2013).

Haemolysis and slight intravascular coagulation have been reported in one patient following ingestion of an 80% solution of the chemical.

Accidental rectal administration of 50 mL of 9% chemical to a five-year-old male resulted in necrosis of the colon, acute renal failure, acute liver dysfunction, disseminated intravascular coagulopathy (DIC) and sepsis (HSDB 2013). The enhanced toxicity of the chemical, without the benefit of dilution and neutralisation in the upper intestine, is evident in this case. Poisoning following incidental or accidental ingestion of concentrated acetic acid has often been reported (SCOEL 2012). Doses of 20 to 50 g or 60 to 70 mL concentrated acetic acid have been calculated to be lethal. Survivors were treated for oesophageal constriction (SCOEL 2012).

28.5.3 *Irritation / Corrosivity*

28.5.3.1 Skin irritation

In animal studies, severe skin burns were reported in guinea pigs following application to intact or abraded skin of patches of 80% solution of the chemical, moderate to severe burns at 50 to 80% solution, mild injury at 50% solution, and no effect at 10% solution (HSDB 2013).

In a study with rabbits, the chemical was considered to be slightly irritating at concentrations of 3.3% and 10% (REACH 2013). In another study with rabbits, a concentration of 2.5% of the chemical was not irritating while concentrations of 10 to 25% caused moderate to severe erythema, slight to severe oedema, skin lesions over the application site and eschar formation (REACH 2013). A 10% solution was therefore considered a skin irritant.

Pure acetic acid is corrosive to skin.

28.5.3.2 Eye irritation

As part of a study to select the optimum testing conditions for predicting hazard to the human eye, 3%and 10% aqueous acetic acid were tested in rabbit eyes (REACH 2013). Materials were applied directly to the central corneal surface. Irritation was followed for up to 21 days and scored according to the Draize scale. The 3% acetic acid gave moderate irritation and 10% acetic acid was severely irritating or corrosive. In other studies, instillation of 0.5 mL of a 1% acetic acid solution in the eyes of rabbits caused a severe burn (Smyth et al. 1951). Solutions of 5% induced injury in eyes of rabbits which healed by 14 days, while a 10% solution resulted in severe permanent damage (Henschler 1973).

Based on the results of the studies pure acetic acid is considered to be corrosive to eyes.

28.5.3.3 Respiratory irritation

In an acute inhalation study in mice, clinical signs of respiratory irritation were evident at concentrations of 2.46 mg/L and higher (see Section A28.5.2.3). Acetic acid vapours were reported to cause damage to nose, throat and lungs in humans (SCOEL 2012).

Acetic acid is considered to be a respiratory tract irritant.

28.5.3.4 Observation in humans

A case of chemical burns (necrosis, ulceration) has been reported in humans following treatment, under occlusion with gauze, with a 50:50 mixture of flour and rice vinegar, containing 4.5% acetic acid. However, a 10% solution of acetic acid in patch tests over a period of 48 hours caused slight skin irritation in human volunteers (EC 2012; HDSB 2013; REACH 2013).

Extreme eye and nasal irritation has been experienced by unaccustomed humans at vapour concentrations in excess of 25 ppm, and 50 ppm reported to be 'unendurable' (SCOEL 2012). Conjunctivitis from concentrations below 10 ppm has also been reported (EC 2012). A splash of vinegar (4% to 10% solution) in the human eye caused immediate pain and conjunctival hyperaemia, and in some cases injury of the corneal epithelium (HSDB 2013). Contact with the concentrated form of the chemical can lead to severe skin and eye damage and vapours of the chemical can also damage nose, throat and lungs (SCOEL 2012). In two patients, accidental application of acetic acid to the eyes followed very quickly by irrigation with water resulted in immediate corneal opacification (HSDB 2013). The corneas cleared sufficiently in a few days to reveal severe iritis and small pupils fixed by

posterior synechiae. Regeneration of the epithelium took many months, but corneal anaesthesia and opacity were permanent.

28.5.4 *Sensitisation*

28.5.4.1 Skin sensitisation

No experimental data were available, however the US National Institute of Occupational Safety and Health (NIOSH) *Pocket Guide to Chemical Hazards* mentions skin sensitisation as one of the symptoms of acetic acid exposure (NIOSH 2010). A 1994 report (Kivity et al. 1994) describes a late asthamatic response to inhaled glacial acetic acid by an asthma patient.

28.5.4.2 Respiratory sensitisation

No data were available.

28.5.4.3 Observation in humans

A 68-year-old female experienced type-1 hypersensitivity-like reactions to a number of acid-based food items (EC 2012). It was concluded that acetic acid (vinegar) was the likely causative agent for these reactions. This conclusion was based on the patient's history as well as the results of various allergy tests.

Based on reports of patients with bronchial asthma reacting to acetic acid challenge, it is believed that acetic acid may cause allergic reactions in humans (HSDB 2013). Some researchers consider acetic acid capable of causing a syndrome known as ‘reactive airways dysfunction’, which resembles bronchial asthma. Symptoms include dyspnoea, wheezing, and cough.

28.5.5 *Summary of acute toxicity*

Acetic acid has low acute oral and inhalation toxicity but moderate dermal toxicity. In laboratory animals, LD50 for oral, dermal and inhalation routes were >3100 mg/kg bw, 1060 mg/kg bw and 13.8 mg/L, respectively. Acetic acid is corrosive to the skin and eyes and its vapours caused respiratory tract irritation in mice. Data on the sensitisation effect of acetic acid in animals are not available, although some reports suggest that acetic acid could cause sensitisation in humans.

28.6 Repeat dose toxicity

28.6.1.1 Oral

Studies on repeated dose toxicity are limited. In a six-month repeat dose oral toxicity study (Lamb and Evard 1919), pigs were initially fed acetic acid at 155 mg/kg bw/day with the dose was raised every 10 to 30 days until a final dose of 380 to 450 mg/kg bw/day was reached after 60 days. There was no mortality and no effects on body weight or acid-base balance noted in this study (REACH 2013). A no observed adverse effect level (NOAEL) was not established in this study.

Repeated intra-gastric administration of the chemical at 3% concentration in animals (unspecified) for six months resulted in chronic inflammation of the oesophageal mucosa (HSDB 2013). Similarly, intra-gastric administration to rats of 3 mL of a 10% solution for 90 days produced a drop in haemoglobin concentration and erythrocyte count (HSDB 2013).

In another similar study, pigs were fed daily diets containing the chemical at 0, 240, 720, 960 and 1200 mg/kg bw/day for successive 30-day periods for a total of 150 days (HSDB 2013).

There were no significant differences in growth rate, weight gain, early morning urinary ammonia and terminal blood pH between controls and test groups. A NOEL or NOAEL was not indicated by the authors. Based on the available information and taking a conservative approach, the NOAEL in the study is considered to be 1200 mg/kg bw/day, the highest tested dose with no adverse effects. This NOAEL will be used for human health risk assessment.

28.6.1.2 Dermal

In the only available dermal repeat dose toxicity study (Slaga et al. 1975) (described in more detail in Section A28.5.8), acetic acid was applied dermally to mice at doses of 1 to 40 mg/animal, one to three times/week for 32 weeks. Single dermal applications of acetic acid at doses of up to 40 mg/animal did not induce mortality. However, more than one application per week of 10 mg acetic acid or more caused excessive mortality. Thirty three per cent of mice died when 10 mg acetic acid/animal was applied dermally three times/week and approximately 50% of mice died when 20 mg was applied twice a week.

No biochemical or histopathological effects were reported. A LOAEL of 10 mg/animal was suggested by the authors, however it was expressed in terms of ‘mg/animal’ rather than ‘mg/kg bw/day’ and it therefore cannot be adopted.

Dermal NOAEL or LOAEL for acetic acid are not available.

28.6.1.3 Inhalation

No data were available.

28.6.1.4 Observations in humans

Low concentrations of acetic acid in vinegar and other items of food and drink has been consumed by humans for centuries, apparently without causing any adverse effects (WHO 1966). Estimations of the daily intake of acetic acid have been reported to vary from 1 to 2.1 gram/day. No adverse health effects at these doses have been reported (EC 2012), however, continued ingestion of large doses of the chemical has been regarded as a contributing factor in the development of the Laennec type of liver cirrhosis (WHO 1966).

Repeated oral, inhalation and dermal exposure of humans to pure acetic acid has been reported to have effects on the gastrointestinal tract and to cause digestive disorders including heartburn and constipation, chronic inflammation of the respiratory tract, pharyngitis, catarrhal bronchitis, darkening of skin, skin dermatitis and erosion of the exposed front teeth enamel. In addition, skin on the palms of hands can become dry, cracked and hyperkeratotic. These observed effects were not associated with any systemic findings, suggesting the effects observed could be due to its corrosive action (EC 2012; HSDB 2013).

In a study of five workers from a cellulose acetate chemical plant, reported effects included blackening and hyperkeratosis of the skin of the hands, conjunctivitis, pharyngitis, bronchitis, and blackening and erosion of the teeth (EC 2012). Specific details about exposure duration and the concentration of the chemical were not available.

Workers exposed to concentrations of 60 ppm during their working hours plus one hour daily at 100 to 200 ppm, for 7 to 12 years developed conjunctivitis, bronchitis, pharyngitis, and erosion of exposed teeth (HSDB 2013). In addition, workers exposed for a number of years to concentrations of up to 200 ppm have been found to suffer from palpebral oedema with hypertrophy of the lymph nodes, conjunctival hyperaemia, chronic pharyngitis, chronic catarrhal bronchitis, in some cases asthmatic bronchitis and traces of erosion on the vestibular surface of teeth (incisors and canines) (HSDB 2013). A further study of 12 workers exposed long term to the chemical (at least two years) with an average vapour exposure of

0.125 mg/L (including peaks of 0.44 mg/L) reported skin irritation (hyperkeratotic dermatitis with cracked and irritated lesions of the palmar skin) (REACH 2013). Respiratory and eye irritation was reported for eight of the workers. Five workers also had some erosion on their incisors.

28.6.2 *Genotoxicity*

Acetic acid was not mutagenic in bacterial reverse mutation assays using *Salmonella typhimurium* strains TA100, TA1535, TA97 and TA98 with and without metabolic activation (Ishidate et al. 1984). Acetic acid was negative in the chromosome aberration assay using Chinese hamster lung fibroblasts at concentrations of up to 1 mg/mL with or without metabolic activation. In one study using Chinese hamster ovary Kl cells, acetic acid induced chromosomal aberrations at the initial pH of 6.0 or below (about 10 to 14 mM of acid) both with and without S9 mix (REACH 2013). However, when the culture medium was neutralised to pH 7.2 with sodium hydroxide, no clastogenic activity was observed. Moreover, pH lower than 6.0 (pH 5.7 or below) were also found to be cytotoxic. Chromosomal aberrations induced at these high concentrations were therefore considered to be artifacts due to acidification of the culture medium. Acetic acid was concluded not to be clastogenic when tested in cultured Chinese hamster K1 cells (REACH 2013; HSDB 2013). It was concluded that acetic acid is not mutagenic.

28.6.3 *Carcinogenicity*

Studies on carcinogenic effect of acetic acid are limited. In a carcinogenicity study (Slaga et al. 1975), acetic acid was tested as the promoter for tumour development in mice. Acetic acid was applied dermally to mice initiated with a carcinogenic agent, dimethylbenz(a)anthracene (DMBA) at doses of 1 to 40 mg/animal, one to three times/week for 32 weeks. Control animals received acetic acid dermally once per week. No further details were provided about the exposure duration. Single dermal application of acetic acid at doses of up to 40 mg/animal did not induce mortality. However, more than one application per week of 10 to 40 mg acetic acid caused excessive mortality. Thirty three per cent of mice died when 10 mg acetic acid/animal was applied dermally three times/week and approximately 50% of mice died when 20 mg was applied twice a week.

No biochemical or histopathological effects were reported. Acetic acid did not produce any carcinogenic effects in mice (REACH 2013).

In another study, oral administration of the chemical as a 3% solution in rats, three times/week for eight months did not induce tumours in the oesophagus and fore-stomach, although epithelial hyperplasia was observed. When dosed in combination with the known carcinogen, N-nitrososarcosine ethyl ester (positive control), there was an increase in oesophageal/stomach tumour formation (REACH 2013).

Based on the limited available data, acetic acid is not likely to be a carcinogen.

28.6.4 *Reproductive toxicity*

28.6.4.1 Fertility

No data were available.

28.6.4.2 Developmental toxicity

In two developmental toxicity studies conducted according to the EU Method B.31 (prenatal developmental toxicity study), acetic acid was administered by gavage to pregnant female Wistar rats and CD-1 mice at 16, 74.3, 345, and 1600 mg/kg bw/day during gestation days 6 to 15 (10 consecutive doses) (REACH 2013). In a similar study, the chemical was

administered by gavage to female Dutch rabbits at 16, 74.3, 345, and 1600 mg/kg bw/day during gestation days 6 to 18 (13 consecutive doses) (REACH 2013). There were no clearly discernible effects on implantation, maternal survival or foetal survival in any species at any of the doses. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ significantly from those occurring spontaneously in the controls. No NOAEL could be established for maternal toxicity or foetal developmental effects.

Based on the available data, the chemical does not show developmental toxicity.

28.7 Health hazard summary

28.7.1 *Critical health effects*

Acetic acid has low acute oral and inhalation toxicity but moderate dermal toxicity. LD50 for oral, dermal and inhalation routes were >3100 mg/kg bw, 1060 mg/kg bw and 13.8 mg/L, respectively in laboratory animals. It is corrosive to skin, eyes and respiratory tract. Acetic acid has low repeat dose toxicity by oral and dermal routes. Information on toxicity by the inhalation route is not available. It is not genotoxic or carcinogenic and does not have any developmental effects in animals. Information on effects on fertility is not available.

A NOEL or NOAEL was not established in any of the repeat dose studies. Based on the available information and taking a conservative approach, the highest tested dose with no adverse effects in the repeat dose oral study (1200 mg/kg bw/day) was taken as the NOAEL for human health risk assessment.

The critical health effect of acetic acid for risk characterisation is its corrosivity.

28.7.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004). Although the dermal LD50 was <2000 mg/kg bw the effects are considered to be due to its local corrosive effects rather than any systemic toxicity, the chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A28.4. This NICNAS recommendation does not consider physical or environmental hazards.

Table A28.4 Recommended hazard classification

	GHS* classification
Irritation / Corrosivity	Causes severe skin burns and eye damage - Cat. 1A (H314)

** Globally Harmonised System (UNECE 2009)*

28.8 References

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A29 Deodorised kerosene

CAS No.	CAS Name
64742-47-8	Distillates (petroleum), hydrotreated light

29.1 Chemical identity

Distillates (petroleum), hydrotreated light (CAS No. 64742-47-8) is a petroleum substance, It is considered as a substance of unknown or variable composition, complex reaction products or biological materials (UVCB). It is a complex product of hydro treatment, which involves removal of olefins, sulfur- and nitrogen-containing components of kerosenes by hydrogenation (API 2010). Hydro treatment of kerosene gives a de-sulfurised product (KEMI 2013).

The Chemical Abstract Service (CAS) defines the substance as:

> *'a complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C9 through C16 and boiling points in the range of approximately 150°C to 290°C (302°F to 554°F).'*
>
> *Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013).*

The CAS definition of a petroleum substance generally identifies the starting material and the last process step that the substance has undergone during its manufacture or production, as well as physical-chemical parameters such as boiling range and / or carbon number range (International Petroleum Industry Environmental and Conservation Association (IPIECA) 2010; Comber and Simpson 2006).

Identity information of distillates (petroleum), hydrotreated light was obtained from REACH (2013). The Simplified Molecular Input Line Entry System (SMILES) notation for the substance was obtained from the Organisation for Economic Co-operation and Development (OECD) Toolbox version 3.1 (OECD 2013). Details are provided in Table A29.1.

Table A29.1 Substance identity

	Deodorized kerosene
Synonyms	Distillates (petroleum), hydrotreated light Hydrotreated light distillates (petroleum) Deodorised kerosene Dearomatised kerosine
Appearance and odour	Odourless, low viscosity liquid
SMILES notation	C(C)CCCCCCCCCC

29.2 Physical properties

The physical properties of the substance are presented in Table A29.2. The information was obtained from REACH (2013).

Table A29.2 Physical properties

Property	Value
Melting point	-49 °C
Boiling point	146 to 299 °C
Density	770 to 850 kg/m^3 at 15 °C
Vapour pressure	1 to 3.7 kPa at 37.8 °C
Viscosity	1 to 2.4 cSt at 40 °C 2.8 to 4.3 cSt at -20 °C

29.3 Current regulatory controls

The document refers to distillates (petroleum), hydrotreated light (CAS No. 64742-47-8) as 'deodorized kerosene', one of the synonyms of the substance.

29.3.1 *Hazard classification for occupational health and safety*

The substance is classified as hazardous for human health in the *Hazardous Substances Information System* (HSIS) (Safe Work Australia 2013) with the following risk phrase:

- X_n (Harmful): R65

Mixtures containing the substance are classified as hazardous with the following risk phrase based on the concentration (Conc) of the substance in the mixtures:

- Conc ≥10%: X_n; R65 (May cause lung damage if swallowed)

29.3.2 *Occupational exposure standards*

29.3.2.1 Australia

No specific exposure standards were available.

29.3.2.2 International

No specific exposure standards were available.

29.3.3 *Australian food standards*

No Australian food standards were identified.

29.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this substance in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

29.3.5 *Additional controls*

29.3.5.1 Australia

The specific substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014). Liquid hydrocarbons are listed in Schedule 5 with the following entry:

- Schedule 5: HYDROCARBONS, LIQUID, including kerosene, diesel (distillate), mineral turpentine, white petroleum spirit, toluene, xylene and light mineral and paraffin oils (but excluding their derivatives), except:
  a. toluene and xylene when included in Schedule 6
  b. benzene and liquid aromatic hydrocarbons when included in Schedule 7
  c. food grade and pharmaceutical grade white mineral oils
  d. in solid or semi-solid preparations
  e. in preparations containing 25% or less of designated solvents
  f. in preparations packed in pressurised spray packs
  g. in adhesives packed in containers each containing 50 grams or less of adhesive
  h. in writing correction fluids and thinners for writing correction fluids packed in containers having a capacity of 20 mL or less or
  i. in other preparations when packed in containers with a capacity of 2 mL or less.

29.3.5.2 International

No international restrictions for the substance were identified. However, there are restrictions for kerosene substances which may not be specifically referring to the substance.

29.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

29.5 Health hazard characterisation

The information on health hazards of deodoriszed kerosene is obtained from the OECD *Screening Information Data Set Initial Assessment Profiles* (SIAPs) for C_9–C_{14} Aliphatic (≤2% aromatic) hydrocarbon solvents category (OECD 2012) and C_{14}–C_{20} Aliphatic (≤2% aromatic) hydrocarbon solvents category (OECD 2011).

The groupings in the OECD report are based on specific carbon ranges of aliphatic carbon compounds ranging from C_9–C_{14} and C_{14}–C_{20} with a common feature of having aromatic content of ≤2%. UVCBs with the same CAS numbers, but not meeting the category definitions of C_9–C_{14} aliphatic hydrocarbons with ≤2% aromatic, and C_{14}–C_{20} aliphatic hydrocarbons with ≤2% aromatic, were not considered in the category assessments (OECD 2011, 2012). The aromatic content of deodorized kerosene is not known and may be higher than 2%, which may exclude an unknown proportion of the substance from the OECD category assessments. The toxicity data for the chemicals or substances used in the OECD report to read across to deodorized kerosene may not be applicable to the substance with a much higher aromatic content.

The European Union Council adopted the grouping of petroleum substances as developed by the Conservation of Clean Air and Water in Europe (CONCAWE). The grouping was established based on the refinery processing history of the substances (CONCAWE 2012). Petroleum substances listed in the *European Inventory of Existing Commercial Chemical Substances* (EINECS) were categorised into groups and subgroups to facilitate the evaluation of hazard data, as indicated in the European Union Council Regulation EEC No. 793/93 of 23 March 1993 (European Union Council 1993). The grouping was established

based on the similar manufacturing process for each group/subgroup. In addition, the Regulation stated that data for one substance in each specific group or subgroup can be submitted for hazard assessment purposes for all the substances in that group or subgroup on the presumption that the hazards are similar across all the substances in each category (Comber and Simpson 2006; CONCAWE 2012). Deodorized kerosene belongs to the kerosines group. Substances in this group are derived from crude petroleum, with carbon numbers ranging from C5 to C17, and are composed of the following hydrocarbon types:

- branched and straight chain paraffins and naphthenes (cycloparaffins)
- aromatic hydrocarbons (alkylbenzenes and alkylnaphthalenes).

The typical boiling range of the kerosines group is from 90°C to 320°C, and is such that components of specific toxicological concern such as benzene (boiling point 80°C) and n-hexane (boiling point 69°C) are typically only present at trace concentrations (CONCAWE 2012). The CONCAWE grouping is similar to the Petroleum Sector Stream Approach by the Canadian government, wherein 160 petroleum substances identified as priorities through Canada's chemical categorisation process are being assessed in a sectoral approach based on the production and uses of the substances (Government of Canada 2013).

Similarly, the American Petroleum Institute (API) Petroleum High Production Volume (HPV) Testing Group included deodorized kerosene in the Kerosene/Jet fuel category assessment in a submission to the United States Environmental Protection Agency (API 2010). The grouping is based on process history, physical properties and product-use specifications, but not on detailed composition data. The category members are known by the generic term kerosene, which is defined as 'complex petroleum substances, with boiling ranges of approximately C_9–C_{16} with less than 25% by volume aromatic hydrocarbons, such as single ring alkylbenzenes and double ring alkylnaphthalenes'.

This assessment will read across data from similar substances from the CONCAWE and API Petroleum HPV grouping where data were not available for certain endpoints of deodorized kerosene (i.e. skin sensitisation, repeat dermal dose toxicity, carcinogenicity, and reproductive toxicity). The aromatic content of deodorized kerosene is not known and some substances from the OECD grouping (aromatic content ≤2%) may not be applicable. However, as noted above from the CONCAWE classifications, components of specific toxicological concern such as benzene (boiling point 80°C) and n-hexane (boiling point 69°C) are typically only present at trace concentrations.

Available data for kerosine (petroleum) CAS No. 8008-20-6 were used to read across toxicity information for deodorized kerosene. The US EPA Substance Registry Services (SRS) defined kerosine (petroleum) as 'a complex combination of hydrocarbons produced by the distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C_9 through C_{16} and boiling in the range of approximately 180°C to 300°C (356°F to 572°F).' (US EPA 2013). Deodorized kerosene and kerosine (petroleum) belong to the same petroleum group 'kerosines' (CONCAWE 2012) and 'kerosene/jet fuel' category (API 2010). Based on the similar properties of the substances in each group (CONCAWE 2012; European Union Council 1993) and the broadly overlapping chemical composition and the closely related physical properties (API 2010), the applicability of the read across approach is justified.

Information on health hazards of kerosine (petroleum) is obtained from REACH (2013). Unless otherwise noted, references to individual studies below are taken from OECD (2011, 2012), API (2010) and REACH (2013).

29.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

29.5.1.1 Oral absorption

No data were available for the deodorized kerosene, although an estimated 61–81% of the C_9–C_{14} aliphatic (≤2% aromatic) hydrocarbon solvents category would be absorbed following ingestion (OECD 2012).

For the purposes of risk assessment, 100% oral absorption in humans is assumed.

29.5.1.2 Dermal absorption

No data were available for the substance.

In vitro dermal absorption studies of C_9–C_{14} aliphatic hydrocarbon substances containing 20% aromatics reported low absorption (OECD 2012). Similar results were obtained from *in vitro* studies of C_{14}–C_{20} aliphatic (≤2% aromatic) hydrocarbon solvents with 0.18% of the applied dose absorbed for one of the category members (OECD 2011).

Based on this, 10% dermal absorption in humans is assumed for the purposes of risk assessment.

29.5.1.3 Inhalation absorption

No data were available for the substance, however C_9–C_{14} aliphatic (≤2% aromatic) hydrocarbon solvents are readily and rapidly absorbed following inhalation (OECD 2012).

For the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

29.5.1.4 Distribution

No data were available for the substance, however C_9–C_{14} aliphatic (2–25% aromatic) hydrocarbon solvents are widely distributed in human and animal tissues following absorption (OECD 2012).

29.5.1.5 Metabolism

No data were available for the substance.

The C_{14}–C_{20} aliphatic (≤2% aromatic) hydrocarbon solvents are metabolised to alcohol and carboxylic acid derivatives by side chain oxidation. The metabolites can either be glucuronidated and excreted, or undergo further metabolism before being excreted (OECD 2011).

29.5.1.6 Excretion

No data were available for the substance.

The majority of metabolites of C_{14}–C_{20} aliphatic (≤2% aromatic) hydrocarbon solvents are anticipated to be excreted in the urine and to a lesser extent in the faeces (OECD 2011).

29.5.2 *Acute toxicity*

29.5.2.1 Oral

Two studies cited in OECD (2012), conducted similarly to OECD Test Guideline (TG) 401, in rats (strain not specified) administered commercial grade deodorized kerosene by gavage reported acute oral medial lethal doses (LD50s) of >5000 mg/kg bw and >15 000 mg/kg bw. No other details were provided.

Deodorized kerosene has low acute oral toxicity in rats.

29.5.2.2 Dermal

An occlusive application of commercial grade deodorized kerosene in rats (strain not specified), conducted similarly to OECD TG 402, reported LD50 >2000 mg/kg bw in a study cited in OECD (2012). No other details were provided.

Deodorized kerosene has low acute dermal toxicity in rats.

29.5.2.3 Inhalation

A study reported no mortality from six-hour exposures of rats (strain not specified) to aerosolised deodorized kerosene at mean concentrations of 7.5 mg/L (REACH 2013). Rats showed slight loss of coordination in the first three hours of exposure and flaking of the skin. The reported acute median lethal concentration (LC50) was >7.5 mg/L.

Deodorized kerosene has low acute inhalation toxicity in rats.

29.5.2.4 Observation in humans

No data were available.

29.5.3 *Irritation / Corrosivity*

29.5.3.1 Skin irritation

Semi-occlusive applications of commercial grade deodorized kerosene produced slight irritation in New Zealand White and SPF rabbits in dermal irritation studies conducted in accordance with OECD TG 404. The studies reported the range of erythema and oedema scores to be 0.3–0.9 and 0.2–1.0, respectively, based on Draize scoring at 24, 48 and 72 hours.

Deodorized kerosene is slightly irritating to rabbit skin.

29.5.3.2 Eye irritation

Several studies conducted similarly to OECD TG 405 showed minimal effects to the eye with the reported range of conjunctival redness score to be 0–0.2 from instillation of undiluted deodorized kerosene in the eyes of New Zealand White and SPF rabbits (OECD 2011).

Deodorized kerosene is slightly irritating to rabbit eye.

29.5.3.3 Respiratory irritation

No data were available.

29.5.3.4 Observation in humans

Deodorized kerosene, 10% in petrolatum, was applied to 53 individuals in semi-occlusive patches for 24 hours. There were no skin reactions seen in any of the individuals (OECD 2011).

29.5.4 *Sensitisation*

29.5.4.1 Skin sensitisation

No data were available for the substance.

C_9–C_{14} aliphatic (≤2% aromatic) hydrocarbon solvents and C_{14}–C_{20} aliphatic (≤2% aromatic) hydrocarbon solvents are not sensitising to the skin (OECD 2011, 2012). Skin sensitisation was negative for the kerosene/jet fuel category (API 2010).

Four Buehler tests conducted in accordance with US EPA guideline reported that undiluted kerosine (petroleum) applied in occlusive patches on male Hartley guinea pigs was negative for sensitisation (REACH 2013).

Deodorized kerosene is not sensitising, based on reading across data available for kerosine (petroleum).

29.5.4.2 Respiratory sensitisation

No data were available.

29.5.4.3 Observation in humans

No sensitisation was reported in volunteers following application of occlusive patches of deodorized kerosene in (OECD 2011). No other details were provided.

29.5.5 *Repeat dose toxicity*

29.5.5.1 Oral

In a 90-day study conducted in accordance with OECD TG 408, Sprague-Dawley rats were administered deodorized kerosene by gavage at doses of 0, 100, 500 or 1000 mg/kg bw/day (REACH 2013). Microscopic changes, such as incidence of α2μ-globulin, were seen in male kidneys. These effects are not considered relevant to humans. No other treatment-related effects were observed. No Lowest Observed Adverse Effect Level (LOAEL) or No Observed Adverse Effect Level (NOAEL) could be established in this study.

29.5.5.2 Dermal

No data were available for the substance.

Repeated dermal exposures to members of the kerosene/jet fuel category showed minimal systemic effects (API 2010).

Animal data on repeat dermal toxicity of kerosine (petroleum) are summarised from REACH (2013) and presented in Table A29.2. The LOAELs and NOAELs are indicated for each study.

Table A29.3 Repeat dermal toxicity studies with kerosene (petroleum)

Species	Method, study duration and doses	Results	Remarks	Reference
Sprague-Dawley rats	Occlusive 28-day study (similar to OECD TG 410) 0, 0.01, 0.25 or 0.5 mL/kg bw/day	No systemic LOAEL/NOAEL established LOAEL (local irritation) = 0.01 mL/kg bw/day	Dose-dependent irritation, such as erythema, eschar and skin dryness was observed at the site of application. There were no significant changes seen in bodyweight, organ weights, haematology and histopathology.	REACH (2013)
Sprague-Dawley rats	Occlusive 28-day study (similar to OECD TG 410) 0, 0.5, 2.0 or 5.0 mL/kg bw/day	No LOAEL/NOAEL established	Local signs of irritation were seen at the application site at all doses. No treatment-related systemic effects observed.	REACH (2013)
Sprague-Dawley rats	Occlusive 28-day study (similar to OECD TG 410) 0, 0.01, 0.1 or 1.0 mL/kg bw/day	No systemic LOAEL/NOAEL established LOAEL (local irritation) = 0.01 mL/kg bw/day	Skin irritation at the site of application was observed in a dose-dependent manner in all treated groups. The type of irritation seen was not specified. No treatment-related systemic effects.	REACH (2013)
New Zealand White rabbits	Occlusive 28-day study 0, 200, 1000 or 3000 mg/kg bw/day	LOAEL = 1000 mg/kg bw/day NOAEL = 200 mg/kg bw/day	At the top dose, treatment-related mortality and decreased bodyweight in both sexes were reported. At the mid- and top doses, effects included increased relative heart weight in both sexes, and increased absolute and relative spleen weights for females only. Dose-dependent irritation at the application site was seen in all treated animals.	REACH (2013)

Prolonged skin exposure to kerosine (petroleum) in rats and rabbits were consistently associated with local irritation. In rabbits only, systemic effects included changes in bodyweight and organ weights. It is expected that deodorized kerosene would have similar effects in the animals.

29.5.5.3 Inhalation

In a 13-week study, rats (strain not specified) were exposed to deodorized kerosene vapour at concentrations of 0, 0.02, 0.048 or 0.10 mg/L for six hours/day, five days/week. No treatment-related effects were reported (REACH 2013).

29.5.5.4 Observation in humans

No data were available.

29.5.6 *Genotoxicity*

In vitro tests reported deodorized kerosene as negative both with and without metabolic activation in Ames tests conducted in accordance with OECD TG 471 (REACH 2013; OECD 2011) and in chromosomal aberration tests conducted in accordance with OECD TG 473 (OECD 2011, 2012).

In an *in vivo* study, deodorized kerosene was negative in a dominant lethal assay, conducted in accordance with OECD TG 478, in male Swiss mice and Long Evans rats administered 10% deodorized kerosene intraperitoneally (REACH 2013).

These studies demonstrate that deodorized kerosene is not genotoxic.

29.5.7 *Carcinogenicity*

A study for deodorized kerosene is available in the REACH Dossier (REACH 2013) but was not reported in enough detail to be able to determine the carcinogenicity of the substance.

In a study conducted similarly to OECD TG 451, B6C3F1 mice were applied 0, 250 or 500 mg/kg bw/day kerosine (petroleum) in the interscapular region (type of wrapping not specified) for 103 weeks (REACH 2013). At the end of the study, less than 10% decrease in bodyweight gain was observed at the top dose in both sexes. Mortality in females was significantly higher at the two doses compared to controls. Increased incidence and severity of chronic dermatitis was seen in all treatment groups. At the top dose, increased incidence of the following non-neoplastic lesions was reported: amyloid in the liver, kidney, adrenal cortex (males only), spleen; granulocytic hyperplasia in the bone marrow; and hyperplasia of the axillary lymph nodes (females only). The only indication of neoplastic lesions was an increased incidence of malignant lymphomas observed in treated female animals but the values were within the range of historical controls. Under the conditions of the test, kerosine (petroleum) was not carcinogenic. The LOAEL for systemic effects is 250 mg/kg bw/day.

The International Agency for Research on Cancer (IARC) concluded that there is inadequate evidence for the carcinogenicity of kerosine (petroleum) in experimental animals and humans, placing the chemical in Group 3 (Not classifiable as to its carcinogenicity to humans) (IARC 1989).

Deodorized kerosene is not carcinogenic, based on reading across the information available for kerosine (petroleum).

29.5.8 *Reproductive toxicity*

29.5.8.1 Fertility

No data were available for the substance.

C_9–C_{14} aliphatic (≤2% aromatic) hydrocarbon solvents and C_{14}–C_{20} aliphatic (≤2% aromatic) hydrocarbon solvents are not toxic to fertility (OECD 2011, 2012). Members of the kerosine/jet fuel category are not toxic to fertility (API 2010).

Sprague-Dawley rats were administered undiluted kerosine (petroleum) by gavage at doses of 0, 750, 1500 or 3000 mg/kg bw/day in males treated for 70–90 days and 0, 325, 750 or 1500 mg/kg bw/day in females treated for 21 weeks. At 750 and 1500 mg/kg bw/day, increased absolute liver weight was observed in females but with no corresponding changes in clinical chemistry or histopathology. In females only, other effects included perianal dermatitis at 1500 mg/kg bw/day and stomach hyperplasia at 750 and 1500 mg/kg bw/day. These parameters were not measured in males. In males, the study indicated dose-dependent decrease in male bodyweight that was linked to nephropathy specific to male rats.

Data for this effect were not provided in the study description. There were no treatment-related effects on fertility in both sexes (REACH 2013). The NOAEL for systemic effects in females only was 325 mg/kg bw/day. No NOAEL can be established for fertility effects.

Deodorized kerosene is not considered toxic to fertility, based on reading across data available for kerosine (petroleum).

29.5.8.2 Developmental toxicity

No data were available for the substance.

C_9–C_{14} aliphatic (≤2% aromatic) hydrocarbon solvents and C_{14}–C_{20} aliphatic (≤2% aromatic) hydrocarbon solvents are not developmental toxicants (OECD 2011, 2012). Members of the kerosine/jet fuel category are not developmental toxicants (API 2010).

In a study conducted in accordance with OECD TG 414, Sprague-Dawley rats were administered kerosine (petroleum) by gavage on gestation days (GD) 6 to 15 at doses of 0, 500, 1000, 1500 or 2000 mg/kg bw/day (REACH 2013). Bodyweight gain was decreased at 1500 and 2000 mg/kg bw/day. Foetal weight was decreased at 1500 and 2000 mg/kg bw/day which may be attributed to decreased maternal bodyweight gain. No malformations were reported. The maternal NOAEL is 1000 mg/kg bw/day. In another study, Sprague-Dawley rats were exposed (whole body) to kerosine (petroleum) in air at concentrations of 0, 106 or 364 ppm on GD 6–15. There were no treatment-related effects observed in the dams and offspring (REACH 2013).

Deodorized kerosene is not considered a developmental toxicant, based on reading across data available for kerosine (petroleum).

29.5.9 *Other health effects*

No data were available.

29.6 Health hazard summary

29.6.1 *Critical health effects*

Deodorized kerosene is an aspiration hazard since it has low viscosity and is composed of aliphatic and aromatic hydrocarbons up to 10%.

Deodorized kerosene has low acute oral, dermal and inhalation toxicity, and is slightly irritating to the skin and eye. The substance is not a skin sensitiser, based on reading across data available for kerosine (petroleum).

No treatment-related effects were reported in repeated oral and inhalation exposures to deodorized kerosene. Prolonged dermal exposure to kerosine (petroleum) reported local irritation in rats and rabbits, and changes in bodyweight and organ weights in rabbits. It is expected that these effects would be similar for deodorized kerosene.

The substance is not genotoxic. It is neither a carcinogen nor a reproductive toxicant, based on reading across data available for kerosine (petroleum).

The most appropriate NOAEL for risk assessment, determined from the developmental toxicity study cited in REACH (2013) of the gavage administration of kerosine (petroleum) in rats conducted in accordance with OECD guideline, is 1000 mg/kg bw/day based on decreased bodyweight gain at the LOAEL of 1500 mg/kg bw/day. This NOAEL will be adopted for deodorized kerosene.

29.6.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004).

The equivalent classification and labelling under the adopted *Globally Harmonised System of Classification* (GHS) (UNECE 2009) is shown in Table A29.4. This NICNAS recommendation does not consider physical or environmental hazards.

Table A29.4 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* Classification
Aspiration hazard	May be fatal if swallowed and enters airways – Cat. 1 (H304)

** Globally Harmonised System (UNECE 2009)*

29.7 References

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A30 Methanol

CAS No.	CAS Name
67-56-1	Methanol

30.1 Chemical identity

The following chemical identity information was obtained from ChemID*plus* (2012) and Organisation for Economic Co-operation and Development (OECD) (OECD 2004). Table A30.1 provides details of the chemical identity.

Table A30.1 Chemical identity

	Methanol
Synonyms	Methyl alcohol Methyl hydroxide Monohydroxymethane Carbinol; Methylol Wood alcohol
Structural formula	HO – CH_3
Molecular formula	CH_3OH
Molecular weight	32.04
Appearance and odour	Clear colourless liquid
SMILES notation	CO

30.2 Physical properties

Information on the physical properties of methanol was obtained from OECD (2004) and is presented in Table A30.2.

Table A30.2 Physical properties

Property	**Value**
Melting point	approx. –98 °C
Boiling point	65 °C
Density	0.79 g/cm^3 at 20 °C
Vapour pressure	12.8 kPa 20 °C
Water solubility	Miscible at 20 °C
Partition coefficient n-octanol/water (log K_{ow})	–0.82 to –0.64

30.3 Current regulatory controls

30.3.1 *Hazard classification for occupational health and safety*

Methanol is classified as hazardous for human health in the *Hazardous Substances Information System* (HSIS) with the following risk phrases (Safe Work Australia 2013):

- T; R23/24/25 (Toxic; Toxic by inhalation, in contact with skin and if swallowed)
- T; R39/23/24/25 (Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed).

Mixtures containing the chemical are classified as hazardous based on the concentration (Conc) of the chemical in the mixtures. The risk phrases for this chemical are:

- Conc ≥20%: T; R23/24/25; (Toxic: Toxic by inhalation, in contact with skin and if swallowed); R39/23/24/25; (Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed)
- 10% ≤Conc <20%: T; R20/21/22; (Toxic: Harmful by inhalation, in contact with skin and if swallowed); R39/23/24/25; (Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed)
- 3% ≤Conc <10%: Xn; R20/21/22; (Harmful: Harmful by inhalation, in contact with skin and if swallowed); R68/20/21/22; (Harmful: possible risk of irreversible effects through inhalation, in contact with skin and if swallowed).

30.3.2 *Occupational exposure standards*

30.3.2.1 Australia

Methanol has an exposure standard of 262 mg/m³ Time Weighted Average (TWA) and 328 mg/m³ Short-Term Exposure Limits (STEL) (Safe Work Australia 2013).

30.3.2.2 International

The following occupational exposure standards were identified (Galleria Chemica 2013).

TWA:

- 250 to 270 mg/m³ [US, Canada, Denmark, United Kingdom, Germany, France, Estonia, Greece, Hungary, South Africa, Spain, Singapore, Taiwan, Sweden, Malta, Malaysia, Latvia, Japan, Indonesia, India, Iceland, Egypt, Ireland, Mexico, Philippines and Switzerland]
- 50 mg/m³ [Bulgaria]
- 100 mg/m³ [Poland]
- 25 mg/m³ [China]
- 133 mg/m³ [Netherlands].

STEL:

- 250 to 350 mg/m³ (250 to 328 ppm) [US, Canada, United Kingdom, Greece, South Africa, Singapore, Sweden, India, Egypt and Mexico]
- 1300 mg/m³ (1000 ppm) [France]
- 1040 mg/m³ [Hungary and Switzerland]

- 300 mg/m³ [Poland]
- 50 mg/m³ [China].

30.3.3 *Australian food standards*

No Australian food standards were identified (FSANZ 2013)

30.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for methanol in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

30.3.5 *Additional controls*

30.3.5.1 Australia

Methanol is included in Schedule 5 and Schedule 6 of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

- Schedule 5: METHANOL (excluding its derivatives) in preparations containing 10% or less of methanol except in preparations containing 2% or less of methanol.
- Schedule 6: METHANOL (excluding its derivatives) except:
  - when included in Schedule 5 or
  - in preparations containing 2% or less of methanol.

The SUSMP also recommends appropriate 'Warning Statements' and 'Safety Directions' for methanol when used in consumer products.

Methanol is included in the *Australian Dangerous Goods Code* Edition 7 (ADG7) (National Transport Commission 2007), with UN Number 1230. It is listed as a '*flammable liquid'*, in Class 3 and Packaging Group II. The ADG7 contains detailed provisions for the packaging, transport and marking of containers in Class 3.

30.3.5.2 International

Methanol is listed on the following lists:

- *European Union Cosmetic Directive* 76/768/EEC Annex III Part 1 (European Commission 2013):
  - List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down
  - Restriction: maximum authorised concentration in the finished cosmetic product is 5% calculated as a percentage of ethanol and isopropyl alcohol.
- *New Zealand Cosmetic Products Group Standard* - Schedule 5 (NZ EPA 2012):
  - Components Cosmetic Products May Contain With Restrictions - Maximum authorised concentration in the finished cosmetic product is 5% calculated as a percentage of ethanol and isopropyl alcohol.
- *Association of Southeast Asian Nations (ASEAN) Cosmetic Directive* Annex III Part 1 (Galleria Chemica 2013):
  - List of substances which cosmetic products must not contain except subject to

restrictions and conditions laid down

- Restrictions - Maximum authorised concentration in the finished cosmetic product is 5% calculated as a percentage of ethanol and isopropyl alcohol.

- Health *Canada List of Prohibited and Restricted Cosmetic Ingredients* (The Cosmetic Ingredient "Hotlist") (Health Canada 2011).

30.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

30.5 Health hazard characterisation

The information on health hazards is obtained from the OECD SIDS Initial Assessment Report (SIAR) on methanol (OECD 2004), Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers on the chemical (REACH 2013) and published papers. Unless otherwise noted, references to individual studies below are taken from these sources.

30.5.1 *Toxicokinetics*

Methanol occurs naturally in humans, animals and plants. It is a natural constituent in blood, urine, saliva and expired air. A mean urinary methanol level of 0.73 mg/L (range 0.3 to 2.61 mg/L) in unexposed individuals and a range of 0.06 to 0.32 µg/L in expired air, have been reported (IPCS 1997). The two most important sources of background body burdens for methanol are diet and metabolic processes.

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

30.5.1.1 Oral absorption

Methanol is rapidly absorbed from the gastrointestinal tract with peak absorption occurring in 30 to 60 minutes depending on how much food is in the stomach (Becker 1983).

After a single oral exposure of rats and mice to methanol, absorption was rapid and nearly complete. In rats, single doses of 100 and 2500 mg methanol/kg led to maximum blood concentrations of 100 and 2000 mg methanol/L, respectively (Pollack and Brouwer 1996).

In human volunteers, oral doses of 71 to 84 mg methanol/kg resulted in blood levels of 47 to 76 mg/L within two to three hours. The urinary concentrations of methanol rapidly reached a peak capacity within one hour and then declined exponentially, reaching control values in 13 to 16 hours. The urine/blood concentration ratio was found to be relatively constant at 0.30 (Leaf and Zatman 1952; EHC 1997).

An oral absorption of 100% of methanol is assumed for human health risk assessment.

30.5.1.2 Dermal absorption

Pure methanol diffuses rapidly through the epidermis and has a biphasic absorption profile through the skin. In an *in vitro* study comparing dermal absorption of methanol in various species including humans (cadaver), skin penetration of methanol reached a plateau within two to four hours (Clary 2013). Permeability was low for swine, medium for rabbits, guinea

pigs and monkeys and high for humans and nude mice. The permeability of the epidermis for pure methanol is 10.4 mg/cm^2/hour (Scheuplein and Blank 1971).

Following dermal exposure in human volunteers, average skin absorption rates of methanol were reported to be 0.192 mg/cm^2/minute (Dutkiewicz et al. 1980). Exposure of one hand to liquid methanol for two minutes resulted in a body burden of 170 mg, which is similar to that resulting from exposure to an approximate air concentration of 0.050 mg/L (38 mL/m^3) for eight hours (Dutkiewicz et al. 1980).

In another report studying dermal absorption of methanol, 12 human volunteers (seven males and five females) were exposed to methanol via one hand for durations of 0 to 16 minutes in a total of 65 sessions (Batterman and Franzblau 1997). In each session, 14 blood samples were collected sequentially and analyzed for methanol. These data were used to derive absorption rates and delivery kinetics using a two compartment model that accounts for elimination and pre-exposure levels. The maximum methanol concentration in blood reached 1.9 mg/L one hour after exposure. Delivery rates from skin into blood lagged exposure by half an hour while methanol continued to enter the systemic circulation for four hours following exposure. The mean derived absorption rate was 8.1 mg/cm^2/hour.

The rate of absorption of M-85 (85% methanol-15% gasoline) through the skin has been found to be higher than that of pure methanol (Machiele 1990). The higher absorption rate was reportedly due to the gasoline drying out the skin, allowing the methanol to be more readily absorbed.

Gummer and Maibach (1986) have reported a 45% penetration of methanol in excised skin of guinea pigs under occluded conditions.

The Danish Ministry of Environment's *Survey of Methanol* (2013) reported that methanol had an anomalously high diffusion rate through human skin. Methanol is marked in the *Danish Occupational Threshold Limit Value List* as a substance that is permeable through skin. The United States Environment Protection Agency (USEPA) in the *Toxicological Review of Methanol (Non Cancer)* (US EPA 2013) concluded that studies conducted in humans and animals demonstrated rapid absorption of methanol by inhalation, oral and dermal routes of exposure. The *Poisons Information Monograph 335* (International Programme on Chemical Safety (IPCS)), based on the dermal absorption study by Dutkiewicz et al. (1980), also concluded that methanol is readily absorbed by the dermal route (IPCS 1997).

Based on the above information, a 100% dermal absorption for methanol will be assumed for human health risk assessment.

30.5.1.3 Inhalation absorption

In experimental studies, the mean fractional respiratory absorption of methanol in rats and mice was 85% at air concentrations ranging from 1.3 to 6.5 mg/L (Perkins et al. 1996). At higher concentrations of 13 to 26 mg/L, absorption tended to be lower in rats (60 to 70%), but not in mice. The lower absorption efficiency from the upper respiratory tract in rats was mainly attributed to a lower breathing rate.

Around 60 to 85% of inhaled methanol is absorbed in the human lung (Sedivec et al. 1981). After a single inhalation exposure to 0.26 mg/L methanol in humans for four hours, blood methanol increased several fold above the endogenous blood concentration of 1.8 to 7.0 mg/L (Lee et al. 1992; Chuwers et al. 1995).

On the basis of these observations, 100% absorption through the inhalation route will be assumed for human health risk assessment.

30.5.1.4 Distribution

Methanol distributes readily and uniformly to organs and tissues in direct relation to their water content (Haggard and Greenberg 1939). The apparent volume of distribution of methanol is 0.6 to 0.7 L/kg, which is similar to that of ethanol. In methanol inhalation studies conducted in dogs, Bartlett (1950) reported that the highest concentrations of methanol were found in the blood, vitreous and aqueous humour, bile and urine, while the lowest concentrations were found in bone marrow and fatty tissue.

30.5.1.5 Metabolism

Most of the methanol is metabolised in the liver to carbon dioxide (96.9%), while a small fraction is excreted directly through urine (2.0%) and lungs (EHC 1997). In all mammalian species studied, methanol is metabolised in the liver by sequential oxidative steps to form formaldehyde, formic acid and CO_2 (shown in Table A30.3, and dicussed in further detail below). However, there are profound differences in the rate of formate oxidation in different species that determine the sensitivity to methanol (Eells et al. 1983). In Table A30.3, the first and third columns depict the enzyme/co-enzyme systems involved in methanol metabolism in primates and rodents.

Table A30.3 Steps in methanol metabolism in primates and rodents

Primates		**Rodents**
Enzyme/Co-enzyme	*Metabolites*	*Enzyme/Co-enzyme*
	Methanol Ch_3OH	
Alcohol dehydrogenase	↓	Catalase
	Formaldehyde HCHO	
Formaldehyde dehydrogenase	↓	Formaldehyde dehydrogenase
	Formate HCOO	
Folate (limited)	↓	Folate (abundant)
	CO_2 Carbon dioxide	

Step 1: Methanol is oxidised to formaldehyde. In humans and monkeys, this reaction is mediated by alcohol dehydrogenase (ADH). In rodents, the oxidation of methanol occurs mainly through a catalase-peroxidase system and is a rate-limiting step in methanol metabolism (Medinsky et al. 1997), which means that at a critical dose, methanol will accumulate and cause effects that may not occur in humans. In humans, ADH levels are high enough so that accumulation of methanol does not occur except at dose levels that are lethal or near-lethal.

Step 2: Formaldehyde is oxidised to formate. This step occurs as a two-reaction process. Formaldehyde is catalysed by the formaldehyde dehydrogenase in the presence of glutathione to form the intermediate, S-formylglutathione. This intermediate is then hydrolysed to formic acid by an associated thiolase. Formaldehyde is rapidly oxidised (with a

half-life of approximately one minute) to formate in all species. It is the rate at which formate is oxidised to CO_2 that accounts for the pronounced species difference in the toxicity of methanol (NTP 2003).

Step 3: Formate is oxidised to carbon dioxide and water. The folate-mediated oxidation of formate proceeds about twice as slowly in primates (including humans) compared to rat due to limited amounts of folate in the primates. This explains the susceptibility of primates to the accumulation of formate, which is seen to occur at doses of methanol greater than 0.5 g/kg (Tephly and McMartin 1984). There is substantial clinical and experimental evidence that, formic acid is the toxic metabolite responsible for the metabolic acidosis observed in methanol poisoning in humans, in non-human primates and in folate-depleted rodents (IPCS 1997). It is also believed to be the toxic metabolite responsible for ocular toxicity in methanol-poisoned humans (Sharpe et al. 1982).

A comparative metabolism study between rodents and non-human primates showed that formic acid concentration in blood of rats and monkeys was similar at doses of 25, 125 and 600 mg methanol/kg, but became substantially higher in monkeys at 3000 mg/kg (EHC 1997).

The critical methanol dose that saturates the folate pathway in humans is estimated to be 200 mg/kg bw. Based on data from studies in monkeys, metabolic saturation in humans is also less likely during inhalation if the amount is divided over a prolonged time and not incorporated as a bolus (OECD 2004).

30.5.1.6 Excretion

Methanol is either excreted unchanged (direct excretion) in urine or exhaled breath or enters a metabolic pathway in the liver with carbon dioxide the ultimate product. The time course of the disappearance of methanol from the circulation is dependent upon the combined action of both direct excretion and metabolism. Monkeys and rodents showed different excretion patterns for methanol (Katoh 1989). As the dose increased, monkeys tended to excrete an increasing percentage of methanol in urine, whereas in rats, the percentage of methanol excreted in expired air increased. Additionally, rats excreted much higher levels of carbon dioxide (as a percentage of dose) in expired air than monkeys.

In humans, methanol is primarily eliminated as formic acid in the urine or further oxidised to carbon dioxide. Only 2% of a given dose of methanol is excreted unchanged by the kidneys and lungs (Leaf and Zatman 1952). The small excretion of unchanged methanol was also observed in methanol-poisoned subjects (Jacobsen et al. 1983).

The clearance of methanol from the circulation following low-level exposures by oral or inhalation routes indicated that methanol disappearance follows first-order kinetics with a half-time of about 2.5 to 3 hours (Leaf and Zatman 1952) as determined by blood and urinary methanol concentrations.

30.5.2 *Acute toxicity*

30.5.2.1 Oral

In rats, mice, rabbits and dogs, the LD50 values after single oral administration range from about 5600 to 14 400 mg/kg bw (EHC 1997). Adverse effects noted in these animals were ataxia, narcosis and coma after high methanol doses. The animals did not exhibit acidosis and ophthalmologic changes typically seen in humans at high lethal and sub-lethal doses.

In rhesus monkeys, no deaths were reported at doses of 1000 to 2000 mg/kg bw, while animals receiving 3000 to 8000 mg/kg bw died within two days (OECD 2004). Treated animals showed acidosis, and some exhibited semi-coma and ophthalmologic changes.

Human data, however, indicate acute oral toxicity at comparatively lower doses of 300 to 1000 mg/kg bw (EHC 1997).

The reported median lethal doses (LD50) for experimental animals are 7300 mg/kg bw (mouse), 5628 mg/kg bw (rat), 14 200 mg/kg bw (rabbit) and 7000 mg/kg bw (monkey). The lowest lethal dose (LDLo) for humans ranges from 143 to 428 mg/kg bw (ChemID*plus* 2012).

30.5.2.2 Dermal

There are limited available dermal toxicity studies in animals. In one dermal exposure study all the rats survived after application of 35 000 mg/kg bw methanol to the skin under occlusive conditions, while deaths were reported at 45 000 mg/kg bw (Eulner and Gedicke 1955). In rabbits, a dermal LD50 of 17 000 mg/kg bw was reported although no details of the study were provided (Carnegie-Mellon 1981). Limited data in monkeys indicate that the chemical is toxic via the dermal route (McCord 1931). Humans have been found to be more susceptible to methanol as compared to monkeys. Therefore, acute dermal toxicity with methanol is expected in humans (OECD 2004).

The lowest reported dermal LD50 is 17 000 mg/kg bw, which was recorded in rabbits.

30.5.2.3 Inhalation

Median lethal concentrations (LC50) of 87.5 and 128.2 mg/L were reported in rats following six and four hour inhalation exposures to methanol, respectively (BASF 1980a, 1980b). Clinical signs of toxicity were secretions from eyes and nose, laboured breathing, staggering, apathy and narcosis.

A similar LC50 value (79 mg/L) was reported for mice following 2.25 hours exposure (Von Burg 1994). In cats, LC50 values after six-hour exposures ranged from 26 to 48 mg/L. A shorter duration of 4.5 hours led to an LC50 of 85.4 mg/L (Von Burg 1994).

Studies in Rhesus monkeys indicated lethal concentrations (percent mortality not reported) at 13 mg/L after 18 hour exposure and 52 mg/L after one to four hour exposure (OECD 2004).

30.5.2.4 Observation in humans

Oral ingestion is the most frequent route of poisoning, but percutaneous absorption or inhalation of vapours is shown to be as effective as the oral route in producing methanol acute toxic syndrome (refer to Section A30.5.2.3).

Wood and Buller (1904) published a series of 235 case studies that characterised many of the key presenting features of acute methanol poisoning. A vast majority of poisonings occurred from drinking adulterated beverages or wood alcohol products.

The largest single episode of methanol poisoning occurred in Atlanta (US) in 1951 when 323 people ingested bootlegged whisky contaminated with methanol within a five-day period and 41 of these poisonings were fatal (Bennett et al. 1953).

Human data indicate acute oral toxicity at comparatively lower doses of 300 to 1000 mg/kg bw (EHC 1997). Autopsies from victims of lethal methanol poisonings have revealed gross pathology in the visceral organs, the lung and the central nervous system (CNS) with a variety of oedematous, haemorrhagic and degenerative changes (Kavet and Nauss 1990).

Acute methanol intoxication (including acidosis and visual effects) follows a well-defined pattern (OECD 2004). First, a mild depression of the CNS occurs followed by an asymptomatic latent period commonly lasting 12 to 14 hours. Clinical symptoms include headache, dizziness, nausea and vomiting, abdominal pain and laboured, periodic breathing (Kussmaul breathing), which may progress to coma and death from respiratory failure. Methanol exposure results in ocular effects ranging from mild photophobia, misty or blurred vision to markedly reduced visual acuity and total blindness. Severe visual disturbances have been reported in workers who were exposed to methanol air levels of about 1.5 mg/L (1200 mL/m^3) or more (OECD 2004).

Generally, transient CNS effects appear above blood methanol levels of 200 mg/L, ocular symptoms appear above 500 mg/L and fatalities have often occurred in untreated patients with initial methanol levels in the range of 1500 to 2000 mg/L (OECD 2004). Ophthalmologic examination revealed hyperaemia of the optic disc, followed by the appearance of oedema projecting into the surrounding of the retina from the optic disc (Dethlefs and Naraqi 1978). The incidence of permanent ocular abnormalities was found to correlate with the incidence of metabolic acidosis and with the amount of methanol consumed.

Giminez et al. (1968) reported a case of 48 children intoxicated with percutaneously applied alcohol with 30 of these patients having severe respiratory depression. Among the 48 children 14 were comatose, 11 had seizures, 7 had anuria or severe oliguria, and there were 12 deaths.

30.5.3 *Irritation / Corrosivity*

30.5.3.1 Skin irritation

The irritation potential of an unspecified dose of undiluted methanol in rabbits was examined under occlusive conditions after exposure periods of 1, 5, and 15 minutes and 20 hours (BASF 1975). No signs of irritation (erythema, edema) were apparent after 24, 48 and 72 hours and after six and eight days. Rabbits exposed to 500 mg methanol showed moderate skin irritation (NIOSH 1982, as cited in DGMK 1982). However, because these data were from a secondary source, they could not be verified (OECD 2004).

Methanol is not considered to be a skin irritant.

30.5.3.2 Eye irritation

There is limited information on the eye irritation effect of methanol. In a study comparable to international guidelines and current standards, 0.05 mL undiluted methanol was instilled in to the eyes of two rabbits (strain not mentioned) (BASF 1975). Slight erythema, corneal opacity and moderate oedema were observed one hour after instillation (Draize equivalent scores less than 2). After 24 hours the effects were assessed as mild and after eight days the animals had no symptoms. No further details were provided.

In another study conducted according to OECD Test Guidelines (TG) 405, 0.1 mL undiluted methanol was instilled in to the left eyes of six New Zealand White rabbits (Jacobs 1990). Untreated eyes of the same animals served as controls. The animals were observed at 1, 4, 24, 48, 72 hours and at 8 and 14 days. Mild to moderate conjunctivitis, oedema and mild iritis, were observed one and four hours after instillation. Average scores after 24, 48, and 72 hours were approximately two for conjunctival effects and less than one for all other effects (chemosis, iritis, corneal opacity). Primary irritation subsided after 72 hours, although redness of the conjunctivae persisted at that time. Information on eight-day and 14-day observations was not available. The authors concluded that the mean scores of the symptoms did not exceed the respective limits for classification. The results were interpreted as indicating that the substance has mild irritation potential.

Based on these studies, methanol is not considered to be an eye irritant.

30.5.3.3 Respiratory irritation

High concentration of methanol vapours may cause irritation of the respiratory tract. In a short-term exposure study (details not available), exposure of rats to an atmosphere saturated with methanol vapours produced severe irritation of mucous membranes and milky corneal opacity (BASF 1975). All animals died after eight hours (BASF 1975).

30.5.3.4 Observation in humans

Information on eye and skin irritation cases in humans is not available.

30.5.4 *Sensitisation*

30.5.4.1 Skin sensitisation

A guinea pig maximisation bioassay gave no evidence of contact sensitisation in 10 female guinea pigs after induction and challenge with a 50% aqueous methanol solution (0.1 mL) (BASF 1979a). Only 3/10 animals exhibited slight skin response (erythema score 1) 24 hours after challenge.

In a study using 24 female Pirbright White guinea pigs (two tests with 12 animals each), only one animal in Test 1 and two animals in Test 2 exhibited a slight skin response (erythema score 1) after 24 and 48 hours after challenge with 50% methanol (BASF 1979b). This was interpreted as indicating a weak sensitising potential and it was concluded that methanol is not a skin sensitiser.

30.5.4.2 Respiratory sensitisation

Animal studies for the respiratory sensitisation effect of methanol are not available.

30.5.4.3 Observation in humans

Skin sensitisation has not been reported in workers exposed to methanol during handling of methanol at worksites.

30.5.5 *Summary of acute toxicity*

In conclusion, methanol showed low acute oral, dermal and inhalation toxicity in experimental animals but moderate to high acute oral and dermal toxicity in humans. A low lethal dose (LDLo) of 143 to 428 mg/kg bw (humans) has been reported. It is not a skin or eye irritant but is expected to be a moderate respiratory irritant based on its effect on the mucous membrane in rats exposed to methanol vapours and on the effects observed in repeat dose inhalation studies. Tests with guinea pigs indicated that methanol is not a skin sensitiser.

30.5.6 *Repeat dose toxicity*

30.5.6.1 Oral

Repeat dose toxicity studies by oral route are limited. In a single study, rats fed 100, 500 and 2500 mg/kg bw/day methanol by gavage for 90 days showed increased liver enzymes (enzymes not specified) and decreased absolute brain weights at the highest dose (US EPA 1995). An oral No Observed Adverse Effect Level (NOAEL) of 500 mg/kg bw/day was established in this study.

30.5.6.2 Inhalation

Several short and long-term inhalation studies have been conducted with methanol in rats, mice and monkeys. The key animal data on inhalation repeat dose toxicity are summarised from OECD (2004) and are presented below (Table A30.4).

Table A30.4 Repeat dose inhalation studies with methanol

Species	Method, study duration and doses	Results	Remarks	Reference
SD rats (both sexes)	Inhalation exposure; 0.66, 2.7, and 6.6 mg/L for 6 hours/day, 5 days/week over 4 weeks	NOAEL could not be established for systemic toxicity	No significant histopathological changes. Increased frequencies of nasal and eye discharge were noted in the treated groups. Only mucoid nasal discharge appeared to be dose-related Relative spleen weights were increased significantly only at 2.7 mg/L but not at 6.6 mg/L.	Andrews et al. (1987)
Fischer-344 rat (both sexes)	Inhalation exposure; 0.013, 0.13, and 1.3 mg/L for ~20 hours/day, 7 days/week, for 12 months	NOAEL could not be established	No significant clinical or histopathological effects. Slight body and organ weight changes within a 5% limit in the high-dose group only.	NEDO (1987)
B6C3F1 mice (both sexes)	Inhalation exposure; 0.013, 0.13, and 1.3 mg/L for ~20 hours/day, 7 days/week, for 12 months	NOAEL could not be established	Slight body and organ weight changes within 5% limit, After 12 months, increased incidence of severe fatty degeneration of hepatocytes in high-dose males with 16/20 versus 10/20 in controls. Female mice showed no difference among the groups compared to control. These changes were therefore considered incidental.	NEDO (1987)
Macaca fascicularis monkeys	Inhalation exposure; 3.9, 6.5, 9.1, and 13 mg/L for up to 20 days, 21 hours/day. 4 animals per group	LOAEL = 3.9 mg/L	Blood levels of methanol at 3.9 and 6.5 mg/L were 80 and 5250 mg/L, respectively. At and above 3.9 mg/L hyperplasia and fibrosis around myelin sheets of basal ganglia with slight to moderate increase in the astroglia, incipient atrophy of optic nerve and reduction in myelinated fibres. Fibrosis in liver and partly vacuolar degeneration in kidneys at 6.5 mg/L. Severe oedema and necrosis in basal ganglions of cerebrum were also noted. Coma and lethality at doses ≥9.1 mg/L. (histopathological information and statistical results lacking)	NEDO (1987)

Species	Method, study duration and doses	Results	Remarks	Reference
Macaca fascicularis monkey	Inhalation exposure; 0.013, 0.13, and 1.3 mg/L (21 h/d, 7 d/wk) for 7, 19 and 29 months; 8 animals per group, 2, 3 and 3 for indicated intervals, respectively	NOAEC = 0.013 mg/L	Increased hyperplastic responsiveness of the astroglia in some parts of the brain's white substance was observed at all dose levels (not considered degenerative). Slight degeneration of the inside nucleus of the thalamus at 0.13 and 1.3 mg/L after 7 months or more. One monkey at 0.13 mg/L and two at 1.3 mg/L showed slight but clear changes in peroneal nerves indicating damage to peripheral nerves. In the kidney, Sudan positive granules appeared on the renal tubule epithelium at 0.13 and 1.3 mg/L. Some additional effects (hyalinisation of glomeruli) and some signs of fibrosis were observed at 1.3 mg/L, which were considered borderline. Some effects were observed on the ECG at 0.13 and 1.3 mg/L, which were described by the authors as a slight myocardial disorder. Histologically, a significant increase of Sudan positive granules was noted in the 1.3 mg group without pathological manifestations (e.g. fibrosis) In the trachea, atrophy of the epithelium of the mucous membrane and a decrease in goblet cells was seen in four cases (doses were not shown, although effects were not observed in controls). The effect was localised.	NEDO, (1987)

LOAEL = Lowest Observed Adverse Effect Level

In a 20-day study in monkeys, 3.9 mg/L (3000 mL/m^3) was identified as the LOAEL (continuous exposure) where neurotoxic lesions appeared to progress in monkeys (according to NEDO 1987). This exposure concentration correlated with methanol blood levels 80 mg/L and formate levels 30 mg/L.

There was no evidence of adverse effects in rats exposed to methanol up to 6.6 mg/L, six hours/day for 28 days, except local nasal irritation and increased relative spleen weights, which were observed only at the middle dose and not considered treatment-related (Andrews et al. 1987). A NOAEL could not be established in this study.

In the chronic exposure studies in rats and mice, slight treatment-related decreases in body and organ weights were reported at the highest dose. These are however not considered as 'adverse' effects. In monkeys, slight degeneration of the inside nucleus of the thalamus was observed at 0.13 and 1.3 mg/L after seven months or more (NEDO 1987). One monkey at 0.13 mg/L and two at 1.3 mg/L showed slight but clear changes in peroneal nerves indicating damage to peripheral nerves. Some signs of fibrosis at 1.3 mg/L, which were considered borderline. There were mild but significant effects on heart and kidney at 0.13 and 1.3 mg/L.

Histologically, a significant increase of Sudan positive granules was noted in the 1.3 mg group without pathological manifestations (e.g. fibrosis). Although the authors considered the lowest dose (0.013 mg/L) as the LOAEL, it was observed that effects at this dose were very mild and reversible and therefore not considered to be adverse effects. Based on these observations, a NOAEL of 0.013 mg/L was established in this study.

30.5.6.3 Dermal

No data were available on repeated dose toxicity by the dermal route for methanol.

30.5.6.4 Observation in humans

A health survey of duplicating machine operators who handled a 99% methanol duplicator fluid and teacher aides who worked near spirit duplicator machines and experienced exposures to 0.48 to 4.0 mg/L (mean 1.38 ±0.75 mg/L) suggested that symptoms relevant to methanol toxicity such as headache, dizziness and eye irritation were significantly increased among exposed staff compared with a non-exposed teacher control group at the same institute (Frederick et al. 1984).

Male and female workers exposed to methanol for long periods (up to 7.8 years), complained more often of blurred vision, headache and nasal irritation during or after work (EHC 1997). No retinal changes were observed. Among four workers exposed to 1.0 to 3.6 mg/L, two showed retarded pupil reflex and one exhibited mild mydriosis, but no permanent eye damage. Forgetfulness and skin sensitivity were other common complaints. Additional studies also showed that headaches were associated with occupations that involve the operation of duplicating machines (National Toxicology Program (NTP) 2003).

30.5.7 *Genotoxicity*

Methanol has been examined in numerous *in vitro* and *in vivo* test systems, including bacterial, mammalian and fungal test systems. Most *in vitro* studies did not demonstrate mutagenic activity. A small number of studies gave ambiguous results. All other studies produced negative results consistently. The majority of *in vivo* assays were negative for mutagenicity and clastogenicity (OECD 2004).

Methanol was therefore concluded to be not mutagenic.

30.5.8 *Carcinogenicity*

In a chronic inhalation study, Fisher rats and B6C3F1 mice were exposed to 0.013, 0.13, and 1.3 mg/L methanol for 24 and 18 months, respectively (NEDO 1987). No differences in survival were noted in the treatment groups compared with the control group. There was no evidence of an increase in liver tumours in rats or in the spontaneous liver tumour rate in mice. In the rats, some tumours such as papillary lung adenomas (males only), adrenal phaeochromocytomas (females only) and metastatic (transition) tumours appeared at a somewhat higher incidence in high-dose group rats after week 79 and 104 without clear dose-response relationship. However these tumour incidences were not statistically significantly different from those in the control group. In the mice, there were no appreciable differences from the control in either numbers of animals with tumours or in degree of malignancy observed.

Proliferative effects on the astroglia cells were observed in monkeys continuously exposed to 0.013, 0.13 and 1.3 mg/L methanol by the inhalation route (NEDO 1987). These effects however were of a transient nature and disappeared after a six-month recovery period. There were no signs of histological degeneration.

Based on these studies, methanol is not considered to be carcinogenic.

30.5.9 *Reproductive toxicity*

30.5.9.1 Fertility

No impairment of fertility and reproductive performance was found in male and female rats (parent and second generation) exposed continuously to high doses of methanol (NEDO 1987).

In male mice after repeated oral dosing at 1000 mg/kg bw/day, insignificant increases in morphological anomalies in spermatozoa were reported (Ward et al. 1984). The key animal data on reproductive toxicity are summarised from OECD (2004) and presented below (Table A30.4).

Table A30.5 Effect of methanol on fertility in animals

Species	Method, study duration and doses	Results	Remarks	Reference
Sprague-Dawley rats (both sexes)	Two-generation inhalation study; 0.013, 0.13, and 1.3 mg/L, 20 hours/day, 7 days/week F0: 103-108 days; F1: 61-62 days + 145-153 days; F2: 54-56 days	NOAEL not established	No treatment-related alterations in F0 and F1 for all reproductive parameters.	NEDO (1987); Takeda and Katoh (1988)
Macaca fascicularis monkey 9-12 females per group	Inhalation exposure; 0.26, 0.78, and 2.34 mg/L for 2.5 h/day *before*, and during pregnancy.	NOAEL not established	Maternal toxicity: none Menstrual cycles, conception rate and live-birth delivery rate not affected; dose-unrelated reduction of gestation length of about 6 to 8 days in all exposed animals.	Burbacher et al. (1999)
B6C3F1 mice	Oral exposure; 10 males, exposed to 1000 mg/kg bw/day, five days, after testicular spermatid maturation	NOAEL not established	No significant morphological abnormalities in sperms. In spermatozoa isolated from dissected cauda epididymis for light microscopy, slight, statistically insignificant increase in sperm abnormalities	Ward et al. (1984)

30.5.9.2 Developmental toxicity

Methanol has been tested in numerous developmental toxicity studies using rat, mouse and monkey. The number of classic developmental investigations following oral administration is limited or poorly documented. Most of the studies looked at effects of methanol inhalation. The key animal data on developmental effects of methanol are summarised from OECD (2004) and are presented in Table A30.6.

Table A30.6 Developmental toxicity studies with methanol

Species	Method, study duration and doses	Results	Remarks	Reference
Macaca fascicularis monkey 9-12 females per group	Inhalation exposure, 0.26, 0.78, and 2.34 mg/L for 2.5 h/day before, and during pregnancy.	LOAEL (devel) = 0.26 mg/L.	Blood methanol levels: 5 mg/L (1- to 2-fold), ~10 mg/L (3- to 4-fold), and 40 – 50 mg/L (13- to 16-fold), respectively Maternal toxicity: none Dose-unrelated reduction of gestation length in all methanol-exposed animals of about 6 to 8 days. Vaginal bleeding, probably due to detachment of the placenta in two monkeys at 0.26 mg/L, 2 at 0.78 mg/L, and 1 at 2.34 mg/L. Delay in early sensorimotor development was observed at all doses. Delay in visual recognition memory was noted (but no clear dose response was observed). 2/7 female offspring showed growth retardation at 12 and 17 months in the 2.34 mg/L group.	Burbacher et al. (1999)
SD rat	Inhalation; 6.5, 13, and 26 mg/L 7 hours/day, gestation day 1-19 for the two lowest doses and gestation day 7-15 for the highest dose	NOAEL (maternal) = 13 mg/L NOAEL (devel) = 6.5 mg/L	Methanol blood levels: 1000 – 2170 mg/L, 1840 – 2240 mg/L, and 5250 – 8650 mg/L, respectively. Maternal toxicity: slight, unsteady gait at the highest concentration Fetal body weight: slight decrease at ≥13 mg/L ($p<0.05$) Malformations: At 26 mg/L; Visceral defects: 15/96 malformed fetuses vs. 0/107 malformed fetuses in the untreated control Skeletal defects: 72/92 malformed fetuses vs. 0/98 malformed fetuses in the untreated control At 13 mg/L, visceral malformations in 2/107 fetuses and skeletal malformations in 2/115 fetuses (not statistically significant): At 6.5 mg/L, visceral defects in 2/90 fetuses and skeletal defects in 1/90 fetuses (not statistically significant)	Nelson et al. (1985)
Crl:CD SD Rats 36/group	Inhalation; 0.26, 1.3, and 6.5 mg/L for 22.7 hours/day, gestation	NOAEL (devel) = 1.3 mg/L	Dams: reduced food and water intake and bodyweight gain at 6.5 mg/L. Prenatal Development: At 6.5 mg/L increased late resorptions, reduced number of live foetuses, decreased foetal weight, increased numbers of	NEDO (1987)

Species	Method, study duration and doses	Results	Remarks	Reference
	days 7-17		litters with foetuses that have malformations (ventricular septal defect), variations (thymus, vertebrae, ribs), delayed ossification. Postnatal Development: At 6.5 mg/L prolonged gestation, reduced post-implantation embryo survival and number of live pups/litter, decreased survival rate on postnatal day 4 were observed. Brain, thyroid, thymus, and testes weights were decreased at 8 weeks of age, but not overall body weight.	
CD-1 mice	Inhalation; 1.3, 2.6, 6.5, 9.75, 13, and 19.5 mg/L for 7 hours/day, gestation days 6-15	NOAEL (devel) = 1.3 mg/L (based on cervical-rib defect)	Mean blood methanol levels: 100 mg/L, 540 mg/L, 1600 mg/L, 3200 mg/L, 4200 mg/L and 7300 mg/L, respectively, with the background level at about 1.6 mg/L Maternal toxicity: none At ≥13 mg/L: Statistically-significant decrease in foetal body weight, dose-related statistically significant increase in females with fully resorbed foetuses. At ≥9.75 mg/L: Dose-related statistically significant decrease in number of live pups/litter At ≥6.5 mg/L: Increase in exencephaly and cleft palate (approx. 10% foetuses vs. 0.3% in the control) At ≥ 2.6 mg/L dose-related increase in extracervical ribs or ossification sites lateral to the 7th cervical vertebra ($p<0.01$) (approx. 50% per litter vs. 26 to 34% in the controls and approx. 34% per litter at 1.3 mg/L)	Rogers et al. (1993)

There was no clear evidence of malformations or variations in the pre- and post-natal development of the progeny of two rat generations (NEDO 1987). However, slight but significant retardation in brain growth (F1 and F2) led to the conclusion of the NOAEL (20 hours/day) being 0.13 mg/L. This corresponds to a blood level of 1 to 4 mg/L, which is not statistically different from the 0. 13 mg/L group and the untreated control. There were also some statistically significant differences in time to descent of the testes, although the biological significance of this difference is not clear because the differences were so slight. Due to experimental dose selection, the NOAEL happened to be very low compared with the LOAEL.

High concentrations of methanol may cause specific malformations in organogenesis in pre-natal development of rodents. In the rat, the NOAEL (inhalation for seven hours/day) was

determined to be 6.5 mg/L, based on observance of malformations as well as slight decreased body weights. This corresponds to a maternal methanol blood level of 1000 to 2170 mg/L (Nelson et al. 1985).

Studies in monkeys (Burbacher et al. 1999) provided some evidence of effects by prenatal methanol exposure on the neurobehavioral development of non-human primate infants during the first nine months of life. Based on these neurobehavioral results and the observance of neurological effects in other studies, the LOAEL for developmental effects was determined to be 0.26 mg/L.

30.5.9.3 Observation in humans

The limited data available in humans exposed to methanol during pregnancy do not show an association with methanol and developmental effects (NTP 2003). Occupational exposure of 851 females to methanol during the first trimester of pregnancy did not show increased risk for orofacial clefts (Lorente et al. 2000). The authors reported no association between methanol exposure and oral clefts.

30.5.9.4 Summary of reproductive toxicity

No impairment of fertility or reproductive performance was reported in male and female rats exposed to the chemical, except at very high doses. Male mice had morphological anomalies in spermatozoa after repeated oral dosing at 1000 mg/kg bw/day (blood level > 500 to 1000 mg/L in mice) (OECD 2004).

Rodent studies indicate that methanol has developmental toxicity effects. The rodent data on developmental toxicity are relevant for humans despite the known differences in methanol metabolism between the two species. However, rodents are considered adequate models for humans only at levels where formate does not accumulate (NTP 2003). Blood methanol levels associated with serious developmental effects in rodents were in the range associated with formate accumulation (1000 to 2000 mg methanol per litre of blood), which is likely to result in metabolic acidosis, and visual and clinical effects in humans (NTP 2003; OECD 2004).

The limited data available in humans do not show an association between reproductive and developmental toxicity and methanol (NTP 2003). Following a review of the developmental toxicity studies, the NTP concluded that there is evidence to suggest that females with low folate levels may be more susceptible to the adverse developmental effects of methanol, but more information was necessary to clarify this issue (NTP 2003).

Based on the data available, the chemical is not considered to have reproductive or developmental toxicity in humans.

30.5.10 *Other health effects*

No data were available.

30.6 Health hazard summary

30.6.1 *Critical health effects*

The critical effects to human health are acute toxicity from inhalation, contact with skin and if swallowed. There are possible irreversible effects from acute oral exposure. Experimental

animals did not exhibit acidosis and ophthalmologic changes typically seen in humans at high lethal and sub-lethal doses.

No deaths were reported in Rhesus monkeys at 1000 to 2000 mg/kg bw. Treated animals showed acidosis and some exhibited semi-coma and ophthalmologic changes. Human data, however, indicate acute oral toxicity at comparatively lower doses of 300 to 1000 mg/kg bw.

Methanol is not considered to be a skin or eye irritant or a skin sensitiser. Information on repeated dose toxicity by the dermal route is not available. An oral NOAEL of 500 mg/kg bw/day was established in rats in a 90-day oral study. In the chronic inhalation exposure studies in rats, body and organ weight changes and treatment-related histopathological changes were noted at high dose (6.5 mg/L). These were not considered as adverse effects and a NOAEL could not be established. In monkeys, a NOAEL of 0.013 mg/L was established in a chronic inhalation exposure study based on adverse effects on brain, kidney and heart.

Methanol was found to be not genotoxic or carcinogenic. Reproductive and developmental toxicity studies did not show any significant effects of relevance to humans.

30.6.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004).

The chemical is classified with the risk phrase 'Toxic in contact with skin' (R24) in Australia (Safe Work Australia 2013). The rat and rabbit LD50 values available do not support this classification. However, the limited data available on monkeys indicate that the chemical is toxic via the dermal route and the oral data indicate that humans have higher susceptibility when compared with monkeys. Therefore, NICNAS has not recommended to Safe Work Australia that the existing hazard classification be amended.

Reproductive and developmental toxicity studies did not show any significant effects of relevance to humans. The Safework Australia's *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004) states that even when clear effects have been demonstrated in animal studies the relevance for humans may be doubtful where effects have been demonstrated only at high doses, where marked toxicokinetic differences exist or the route of administration is inappropriate. For these or similar reasons it may be that classification in Category 3, or even no classification, will be warranted.

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted *Globally Harmonised System of Classification* (GHS) (UNECE 2009) as shown in Table A30.7. These NICNAS recommendations do not consider physical or environmental hazards.

Table A30.7 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Acute toxicity	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Toxic if inhaled - Cat. 3 (H331)
Specific target organ toxicity, single exposure	Causes damage to organs - Specific target organ tox, single exp Cat. 1 (H370)

** Globally Harmonised System (UNECE 2009)*

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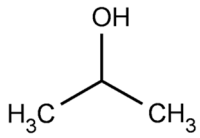
A31 Isopropanol

CAS No.	CAS Name
67-63-0	2-Propanol

31.1 Chemical identity

Information on chemical identity was obtained from ChemID*plus* (2012) and the International Program on Chemical Safety (IPCS) (1990b) and is presented in Table A31.1.

Table A31.1 Chemical identity

	Isopropanol
Synonyms	Isopropanol Isopropyl alcohol Propan-2-ol
Structural formula	
Molecular formula	C_3H_8O
Molecular weight	60.09
Appearance and odour	Colourless liquid with a pleasant odour
SMILES notation	C(C)(C)O

31.2 Physical properties

The physical properties of the chemical are presented below (Table A31.2). The information was obtained from the Organisation for Economic Co-operation and Development (OECD) (2002).

Table A31.2 Physical properties

Property	**Value**
Melting point	-90 °C
Boiling point	82 °C
Density	785 kg/m^3 at 20 °C
Vapour pressure	4.3 kPa at 20 °C
Water solubility	Miscible at 20 °C
Partition coefficient n-octanol/water (log K_{ow})	0.05 at 25 °C
Flash point	12 °C

Property	Value
Conversion factor	1 ppm = 2.46 mg/m^3 1 mg/m^3 = 0.41 ppm

31.3 Current regulatory controls

The chemical 2-Propanol (CAS No. 67-63-0) is referred to in this document as isopropanol, one of the synonyms of the chemical.

31.3.1 *Hazard classification for occupational health and safety*

The chemical is classified as hazardous for human health in the *Hazardous Substances Information System* (HSIS) (Safe Work Australia 2013) with the following risk phrases:

- X_i (Irritant); R36, R67.

Mixtures containing the chemical are classified as hazardous with the following risk phrase based on the concentration (Conc) of the chemical in the mixtures. The risk phrase for this chemical is:

- Conc >=20%: X_i: R36 (Irritating to eyes).

31.3.2 *Occupational exposure standards*

31.3.2.1 Australia

The following exposure standards were identified (Safe Work Australia 2013):

- Time Weighted Average (TWA): 983 mg/m³ (400 ppm).
- Short-Term Exposure Limit (STEL): 1230 mg/m^3 (500 ppm).

31.3.2.2 International

The following occupational exposure standards were identified (Galleria Chemica 2013).

- TWA:
  - 150 ppm (350 to 500 mg/m³) [Sweden, Denmark, Iceland, Peru, Turkey]
  - 400 ppm (980 to 999 mg/m³) [Korea, Mexico, Philippines, New Zealand, Belgium, UK]
- Threshold Limit Value (TLV):
  - 983 mg/m^3 [US]
- STEL:
  - 250–400 ppm (600 to 983 mg/m^3) [Sweden, Peru]
  - 500 ppm (1225 to 1250 mg/m^3) [Korea, Mexico, Belgium, New Zealand, UK]
  - 1230 mg/m^3 [US].

31.3.3 *Australian food standards*

Isopropanol is listed in Standard 1.3.1 of the Australia *New Zealand Food Standards Code* and has a permitted use as a food additive at a maximum permitted level of 1000 mg/kg (Food Standards Australia New Zealand 2013). The chemical is also listed in Standard 1.3.3 as a generally permitted processing aid (Food Standards Australia New Zealand 2012) with a maximum permitted level of 1000 mg/kg in carriers, solvents and diluents (Food Standards Australia New Zealand 2006).

31.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

31.3.5 *Additional controls*

31.3.5.1 Australia

The chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

31.3.5.2 International

No international restrictions were identified.

31.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

31.5 Health hazard characterisation

The information on health hazards is obtained from the following comprehensive reviews: OECD (2002), IPCS (1990a, 1990b), European Food Safety Agency (EFSA) (2005) and Kapp et al. (1996). Unless otherwise noted, references to individual studies below are taken from these reviews.

31.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

31.5.1.1 Oral absorption

Numerous toxicokinetic studies conducted from 1944 to 1986, and evaluated by the IPCS, indicated that isopropanol is readily absorbed in animals and humans through the gastrointestinal (GI) tract (IPCS 1990a, 1990b).

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

31.5.1.2 Dermal absorption

Numerous toxicokinetic studies conducted from 1944 to 1986, and evaluated by the IPCS indicated that isopropanol is readily absorbed in animals and humans through the skin (IPCS 1990a, 1990b).

For the purposes of risk assessment, 100% dermal absorption in humans is therefore assumed.

31.5.1.3 Inhalation absorption

Numerous toxicokinetic studies conducted from 1944 to 1986 and evaluated by the IPCS indicated that isopropanol is readily absorbed in animals and humans through the lungs (IPCS 1990a, 1990b).

For the purposes of risk assessment, 100% inhalation absorption in humans is therefore assumed.

31.5.1.4 Distribution

Isopropanol was recovered from the blood, spinal fluid, liver, kidneys and brain, half an hour after the chemical was injected into the GI tract of dogs (Wax et al. 1949). The chemical was found in the blood, liver, kidneys, and brain in rats after three hours of a single oral administration (Idota 1985). Approximately 99% of the chemical exchanged freely with the brain after a single injection of ^{11}C-labelled isopropanol into the carotid artery of anaesthetised monkeys, followed by an injection of ^{15}O-labelled water. The blood-brain barrier permeability for isopropanol was estimated as 5 cm/s (Raichle et al. 1976).

31.5.1.5 Metabolism

Figure A31.1 shows an outline of the metabolism and elimination of isopropanol (IPCS 1990a).

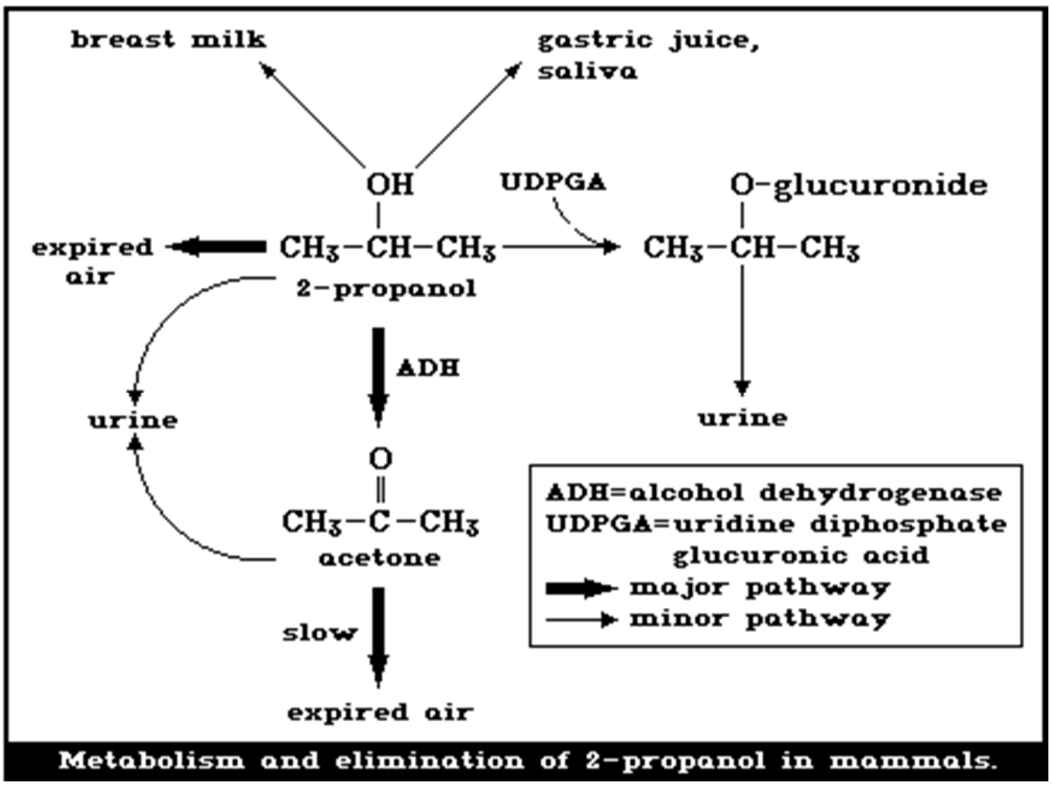
Isopropanol is metabolised to acetone predominantly by the enzyme alcohol dehydrogenase in both animals and humans (Abshagen and Rietbock 1969; Nordmann et al. 1973; Laham et al. 1980; Brugnone et al. 1983).

Dose-related increases in blood levels of isopropanol and acetone were reported following oral administration of up to 1 mL and four-hour inhalation exposure of up to 8000 ppm (19 680 mg/m^3) in rats (Laham et al. 1980). The acetone/isopropanol ratio in blood decreased with increasing isopropanol levels following inhalation exposure, which indicates saturation of the oxidative metabolic pathway above levels of approximately 4000 ppm (9840 mg/m^3). The metabolic oxidation to acetone was estimated to be 64 to 84% of the administered dose following an intravenous injection in rabbits of 750 or 1300 mg/kg bw/day (Siebert et al. 1972).

A minor metabolic pathway is the conjugation of isopropanol by glucuronic acid.

Isopropanol was not detected in the blood or urine. The levels of acetone ranged from 0.76 to 15.6 mg/L in blood, 3 to 93 mg/m^3 in alveolar air, and 0.85 to 53.7 mg/L in urine (Brugnone et al. 1983). Isopropanol and acetone have also been reported in gastric lavage (Agarwal 1979) and in saliva (Tomita and Nishimura 1982).

Acetone levels were measured in the blood, alveolar air and urine of 12 printing workers.



Source: IPCS (1990a)

Figure A31.1 Metabolism and elimination of Isopropanol

31.5.1.6 Excretion

Isopropanol was excreted in the gastric juice and saliva in the dog and through breast milk in the rat (Lehman et al. 1945). No other details were provided.

Beta-isopropyl-glucuronide was detected at a concentration of 10.2% in the urine of rabbits given an oral dose of 3000 mg/kg bw isopropanol (Kamil et al. 1953).

In a more recent study on disposition and pharmacokinetics of isopropanol in Fischer 344 rats and B6C3F1 mice, the animals were administered 300 mg/kg bw isopropanol intravenously and exposed to 500 or 5000 ppm for six hours by inhalation (Slauter et al. 1994). Isopropanol was also administered by gavage to rats only in single and multiple 300 or 3000 mg/kg bw doses. In the rat, an estimated 81 to 89% of the administered dose was exhaled as acetone, carbon dioxide and unmetabolised isopropanol. In the mice, approximately 76% was exhaled after intravenous bolus and 92% following inhalation exposure. An estimated 3 to 8% of the administered dose was excreted in the urine as isopropanol, acetone and the glucuronide conjugate of isopropanol. Only 0.5 to 1.7% of the dose was excreted in the faeces. The elimination half-life in blood of isopropanol ranged from 0.7 to 2 hours, but a value of 5.4 hours was reported at the 3000 mg/kg bw dose in rats. There were no main differences in the rates of excretion between sexes or between administration routes.

In humans, pulmonary and renal clearance of acetone in eight workers showed that acetone is mainly excreted in the lungs (Brugnone et al. 1983). Elimination half-lives of 2.5 to 3 hours in blood were reported from two individuals after ingesting isopropanol (no other details provided) (Daniel et al. 1981). Another study reported a half-life of 6.4 hours in blood in an

individual following ingestion of isopropanol (no other details provided) (Natowicz et al. 1985).

Following consumption of orange juice containing 3.75 mg isopropanol by 10 volunteers, the chemical was detected in blood and in urine partly as glucuronide after two hours. The total urinary excretion of isopropanol was 1.9% of the ingested dose (Bonte et al. 1981a, 1981b).

31.5.2 *Acute toxicity*

31.5.2.1 Oral

The reported acute oral median lethal doses (LD50s) of isopropanol solutions were:

- 4 475 mg/kg bw in mice (Guseinov 1985)
- 5 280 to 5500 mg/kg bw in rats (strain not specified) (Guseinov 1985; Lehman and Chase 1944)
- 5 480 mg/kg bw in Sherman rats (Smyth and Carpente 1948)
- 4 710 mg/kg bw in Sprague-Dawley rats (Kimura et al. 1971)
- 4 475 to 5000 mg/kg bw in rabbits (strain not specified) (Lehman and Chase 1944; Munch 1972).

An acute oral LD50 value for an isopropanol solution in dogs was reported as 4 830 mg/kg bw (Lehman and Chase 1944). For undiluted isopropanol, an acute oral LD50 in rabbits of 4 396 mg/kg bw was established (Kimura et al. 1971). The effects from acute oral exposures to isopropanol included irritation and respiratory arrest while under narcosis. Necropsy showed oedema, haemorrhage, inflammation and dystrophy in the interstitial tissues of parenchymal organs. Infiltration, oedema and thinning of the alveolar walls were also seen in the lungs of rats (IPCS 1990a, 1990b).

The studies show that isopropanol has low acute toxicity by the oral route in rodents, rabbits and dogs.

31.5.2.2 Dermal

An acute dermal LD50 of 12 870 mg/kg bw of isopropanol solution was reported in rats (Smyth and Carpenter 1948). The effects were not specified.

The study shows that isopropanol has low acute toxicity by the dermal route in rats.

31.5.2.3 Inhalation

The acute inhalation median lethal concentrations (LC50s) for an eight-hour isopropanol exposure were 46 740 and 55 350 mg/m^3 in male and female Sprague-Dawley rats, respectively (Laham et al. 1979). Another study reported LC50s of 53 000 and 72 600 mg/m^3 for unspecified strains of mice and rats, respectively (Guseinov 1985). Severe irritation of the mucous membranes and central nervous system depression as indicated by ataxia, prostration and narcosis were reported. These effects were seen at very high doses of the chemical. At non-lethal levels, congestion of the liver, lung and spleen was seen, especially in male animals (IPCS 1990a, 1990b).

The studies show that isopropanol has low acute toxicity by the inhalation route in rodents.

31.5.2.4 Other routes

The ranges of acute LD50s for intravenous and intraperitoneal dosing of isopropanol in animals (rodents, rabbits and hamsters) were 1088 to 1860 mg/kg bw and 2830 to 4868 mg/kg bw, respectively (Chvapil et al. 1962; Tichy et al. 1985).

31.5.2.5 Observation in humans

The IPCS (1990a) summarised acute intoxication incidents from isopropanol. The incidents were mostly cases of oral ingestion of the chemical by alcoholics. A few cases of isopropanol sponging for fever reduction in children have also been reported. Excessive intoxication with the chemical caused unconsciousness, decreased or absent reflexes, GI problems, hypothermia and some cardiovascular effects such as hypotension and shock.

31.5.3 *Irritation / Corrosivity*

31.5.3.1 Skin irritation

In primary irritation tests, no skin irritation was observed in rabbits (Nixon et al. 1975) or guinea pigs (Steele and Wilhelm 1966) following patch applications of undiluted isopropanol.

The studies show that isopropanol is not a skin irritant in rabbits and guinea pigs.

31.5.3.2 Eye irritation

Studies on eye irritation of isopropanol in rabbits are summarised from IPCS (1990a) and OECD (2002) and presented in Table A31.3.

Table A31.3 Eye irritation studies of isopropanol in rabbits

Rabbit strain	Test method	Results	Reference
New Zealand White	Draize test	Highly irritating at high doses and moderately irritating at low doses; Reversible effects	Marzulli and Ruggles (1973)
Not specified	Draize test	Moderately irritating	Griffith et al. (1980)
Not specified	Draize test	Irritating	Exxon Biomedical Sciences Inc (1986)
Stauffland albino	Draize test	Corrosive with effects that persisted for more than 21 days	Morgan et al. (1987)

The studies show that isopropanol is irritating to rabbit eyes.

31.5.3.3 Respiratory irritation

The 50% reflex decrease in the respiratory rate of mice (RD50) to isopropanol was found to range from 12 300 mg/m^3 (Cupitt 1980) to 43 525 mg/m^3 (Kane et al. 1980). Effects seen on acute and repeated inhalation exposures to isopropanol indicate that the chemical is a respiratory irritant.

31.5.3.4 Observation in humans

In a dermal irritation study, isopropanol (concentration or quantity not specified) was applied to the back of individuals (number not reported) with an abraded and intact size area of 4 cm^2 (Nixon et al. 1975). The mean scores for irritant response in intact and abraded skin were 0 and 0.8, respectively. The primary irritation index was 0.4. In another dermal irritation study conducted in 1987, a 50% solution of isopropanol was applied to the skin of 24 individuals. Negligible skin responses were reported in this study (REACH 2013).

31.5.4 *Sensitisation*

31.5.4.1 Skin sensitisation

No data were available.

31.5.4.2 Respiratory sensitisation

No data were available.

31.5.4.3 Observation in humans

No data were available.

31.5.5 *Repeat dose toxicity*

31.5.5.1 Oral

Wistar rats were administered 0, 870, 1390, 1700 or 2500 mg/kg bw/day isopropanol in drinking water for 12 weeks (Pilegaard and Ladefoged 1993). Decreased bodyweights were seen at the two highest doses and decreased relative liver and kidney weights were observed at doses of 1390 mg/kg bw/day and above. Increased relative adrenal weights were seen at the two highest doses and increased testes weight at the top dose. The No Observed Adverse Effect Level (NOAEL) is 870 mg/kg bw/day based on effects observed at the Lowest Observed Adverse Effect Level (LOAEL) of 1390 mg/kg bw/day.

In another study, rats (strain not specified) were administered the chemical in drinking water at doses of 600 or 2300 mg/kg bw/day for males and 1000 or 3900 mg/kg bw/day for females for 27 weeks (Lehman and Chase 1944). Male rats showed decreased bodyweight gain during the first 13 weeks and increased bodyweight gain for the remainder of the treatment. Female rats showed decreased bodyweight gain throughout the dosing. No other effects were reported. The NOAELs were 2300 and 1000 mg/kg bw/day for males and females, respectively. The LOAEL in females was 3900 mg/kg bw/day and could not be established in males (OECD 2002).

31.5.5.2 Dermal

No data were available.

31.5.5.3 Inhalation

The key animal data on inhalation repeat dose toxicity of isopropanol are summarised from OECD (2009) and EFSA (2005), and presented in Table A31.4. The Lowest Observed Adverse Effect Concentrations (LOAECs) and No Observed Adverse Effect Concentrations (NOAECs) are indicated for each study.

Table A31.4 Repeat inhalation toxicity studies with isopropanol

Species	Method, study duration and doses	Results	Remarks	Reference
Fischer 344 rats	US EPA TSCA Guidelines, 13 weeks 0, 100, 500, 1500 or 5000 ppm	LOAEC = 1500 ppm NOAEC = 500 ppm	No mortality. Narcotic effects seen at 1500 and 5000 ppm and ataxia at 5000 ppm; Increased mean corpuscular volume (both sexes) and mean corpuscular haemoglobin (males) at 5000 ppm; hyaline droplets in kidneys of all male rats including controls with the size and frequency of droplets were increased in the treated groups.	Burleigh-Flayer et al. (1994)
Wistar rats, males only	Method not specified, 13 weeks 400, 1000, 4000, or 8000 ppm for 13 weeks	LOAEC = 1000 ppm NOAEC = 400 ppm	Decrease in bodyweight and local irritation at 1000 ppm and higher; decreased erythrocyte and haemoglobin at 4000 ppm and higher; increased serum aspartate transaminase (AST) and alanine transaminase (ALT) and cholesterol at 8000 ppm.	Nakaseko et al. (1991)
Fischer 344 rats	Method not specified, 104 weeks 0, 500, 2500, or 5000 ppm	LOAEC = 2500 ppm NOAEC = 500 ppm	Increased mortality and decreased mean survival time at top dose. At the mid- and top doses, increase in bodyweight gain and in absolute and relative liver weights. Changes in urine chemistry indicative of impaired kidney function (decreased osmolality and increased total protein, volume and glucose) were seen in males at the mid-dose and in females at the top dose; kidney lesions seen at the mid- and top-doses were tubular dilation, mineralisation, glomerulosclerosis, interstitial nephritis, interstitial fibrosis, hydronephrosis and cell hyperplasia.	Burleigh-Flayer et al. (1997)
CD-1 mice	US EPA TSCA Guidelines, 13 weeks 0, 100, 500, 1500, or 5000 ppm	LOAEC = 1500 ppm NOAEC = 500 ppm	No mortality. Narcotic effects seen at 1500 and 5000 ppm; increased bodyweight gain (>10%) for females at 5000 ppm; 10 and 21% increase in relative liver weight in females at 1500 and 5000 ppm, respectively; increased mean corpuscular volume (females) and mean corpuscular haemoglobin (females) at 5000 ppm.	Burleigh-Flayer et al. (1994)
CD-1 mice	Method not specified, 78 weeks 0, 500, 2500, or 5000 ppm	LOAEC = 2500 ppm NOAEC = 500 ppm	At the top dose, clinical signs were hypoactivity, lack of startle reflex, ataxia and narcosis; increased bodyweight gain, increased relative liver weight and enlargement of seminal vesicles and renal tubular dilation (males only) reported at the mid- and top-dose groups.	Burleigh-Flayer et al. (1997)

US EPA TSCA = United States Environmental Protection Agency Toxic Substances Control Act

The critical study for determining the effects of repeated exposures to the chemical is the more recent investigation by Burleigh-Flayer et al. (1997), which showed chronic kidney effects in rodents and is the only study that conducted lifetime rodent exposure to isopropanol. The kidney effects seen in this study were not reported in the 13-week studies,

which possibly indicates that longer term exposure is necessary for the development of the lesions. The increased hyaline droplets in the kidney observed in the study of Burleigh-Flayer et al. (1994) are a male rat-specific nephropathy and is not considered to be relevant to humans.

The LOAEC and NOAEC established from the critical study were 2500 and 500 ppm, respectively, which are equivalent to 1275 and 255 mg/kg bw/day, respectively.

31.5.5.4 Observation in humans

Two studies were available but the IPCS reported that the methodologies and results were poor due to the subjectivity of the adopted criteria and the unreliability of the exposure levels (IPCS 1990a).

31.5.6 *Genotoxicity*

Isopropanol did not induce gene mutations *in vitro* (with or without metabolic activation) in Ames assays (Florin et al. 1980; Zeiger et al. 1992), sister chromatid exchange assay (Von der Hude et al. 1987) and hypoxanthine-guanine phosphoribosyltransferase (HGPRT) assay (Kapp et al. 1993). An *in vivo* micronucleus assay at levels up to 2500 mg/kg was also negative (Kapp et al. 1993).

Based on the available studies, isopropanol is not considered to be genotoxic.

31.5.7 *Carcinogenicity*

Animal data on carcinogenicity of isopropanol are summarised from IPCS (1990a) and OECD (2002) and is presented below (Table A31.5).

Table A31.5 Carcinogenicity studies with isopropanol

Species	Method, exposure period and doses	Results	Reference
Fischer 344 rats	Inhalation, 24 months 0, 500, 2500 or 5000 ppm	Increased (77.3%, 86.7% and 94.7% at low, mid- and top dose groups, respectively) interstitial Leydig cell adenoma of the testis. The authors did not consider the tumours to be treatment-related since incidence in the control group (64.9%) was lower than the mean incidence (88%) of control groups from other studies conducted in the same laboratory.	Burleigh-Flayer et al. (1997)
C3H, ABC, and C57/BL mice	Inhalation, 5–8 months 0 or 7700 mg/m3	No excess of lung tumours seen. High lung tumour incidence in the control group.	Weil et al. (1952)
Mice (strain not specified)	Dermal, 52 weeks Doses not specified	No treatment-related skin tumours seen.	US NIOSH (1976)
CD-1 mice	Inhalation, 18 months 0, 500, 2500 or 5000 ppm	No increase in neoplastic changes at any dose group.	Burleigh-Flayer et al. (1997)

The International Agency for Research on Cancer (IARC) concluded that there is inadequate evidence for the carcinogenicity of isopropanol in experimental animals and humans, placing the chemical in Group 3 (Not classifiable as to its carcinogenicity to humans) (IARC 1999).

31.5.8 *Reproductive toxicity*

31.5.8.1 Fertility

Animal data on reproductive toxicity of isopropanol are summarised from IPCS (1990a) and OECD (2002), and is presented in

Table A31.6. The LOAELs and NOAELs for each study are provided in the table.

Table A31.6 Studies for fertility effects with isopropanol

Species	Test, doses	Results	Remarks	Reference
Wistar rats	One-generation drinking water study 0, 0.5, 1, or 2%	Systemic effects: LOAEL = 2%, NOAEL = 1% Fertility LOAEL = 2%, NOAEL = 1% 1% equivalent to 825 and 625 mg/kg bw/day in females and males, respectively	Parents at top dose had decreased bodyweight gain. At the top dose, pups had decreased bodyweight gain, decreased survival, increased relative liver weight.	BIBRA (1988)
Wistar-derived rats	One-generation drinking water study 0, 0.5, 1.25, 2.0, or 2.5%	Systemic effects LOAEL = 1.25%, NOAEL = 0.5% Fertility LOAEL = 1.25%, NOAEL = 0.5% 0.5% equivalent to 517 and 325 mg/kg bw/day in females and males, respectively	At doses of 1.25% and higher, red cell numbers were reduced in a dose-related manner (females only) and mean cell volume was reduced (males only); increased liver and kidney weights at top 2 doses. Pup weights and pup survival lower at the top two doses; foetal weight gain reduced at 1.25% and higher.	US EPA/OTS (1986)
Wistar rats	One-generation drinking water study 0, 2 or 3%	Systemic effects LOAEL = 3%, NOAEL = 2% Fertility LOAEL = 3%, NOAEL = 2%	Parents at 3% had decreased bodyweight gain. Litter size and pup weights were reduced at 3%.	Gallo et al. (1977)
Rats (strain not specified)	Three generation drinking water study 1470 (P1), 1380 (P2), 1290 (P3) mg/kg bw/day	Thresholds could not be established since study description was lacking.	No fertility effects reported. Details were not provided.	Lehman et al. (1945)

Species	Test, doses	Results	Remarks	Reference
Sprague-Dawley rats	Two-generation gavage study, (US EPA TSCA Test Guidelines) 100, 500, or 1000 mg/kg bw/day	Parental LOAEL = 1000 mg/kg bw/day, NOAEL = 500 mg/kg bw/day Fertility LOAEL = 1000 mg/kg bw/day, NOAEL = 500 mg/kg bw/day	At the top dose, effects in the male parents included centrilobular hypertrophy (P1 and P2) and increased (>10%) relative liver weight (P2 only). Offspring in both generations had 5–12% decrease in bodyweights at the top dose; 14% increased mortality in F1 offspring.	Bevan et al. (1995)

P1 – first parent generation; P2 – second parent generation; P3 – third parent generation; F1 – first offspring generation

The studies show that isopropanol does not have any effects on fertility.

31.5.8.2 Developmental toxicity

Animal data on developmental toxicity of isopropanol are summarised from OECD (2002) and IPCS (1990a), and presented in Table A31.7. The LOAEL/C and NOAEL/C for each study are indicated.

Table A31.7 Developmental toxicity studies with isopropanol

Species	Method, exposure period and doses	Results	Remarks	Reference
Wistar rats	Drinking water, GD6-15 0, 596, 1242, or 1605 mg/kg bw/day	Maternal NOAEL = 596 mg/kg bw/day Developmental LOAEL = 1242 mg/kg bw/day NOAEL = 596 mg/kg bw/day	At the mid and top doses, maternal effects were decreased bodyweights and reduced food and water consumption. At the mid and top doses, effects included reduced foetal bodyweight on a per foetus basis and delayed ossification of the skeleton.	BIBRA (1988)
Sprague-Dawley rats	Gavage (US EPA TSCA Guidelines), GD6-15 0, 400, 800, or 1200 mg/kg bw/day	Maternal NOAEL = 400 mg/kg bw/day Developmental LOAEL = 800 mg/kg bw/day NOAEL = 400 mg/kg bw/day	Mortality at mid and top doses; Decreased gestational weight associated with decreased gravid uterine weights at the top dose. Reduced foetal bodyweight per litter at mid- and top doses.	Tyl et al. (1994)
Sprague-Dawley rats	Gavage (US EPA TSCA Guidelines), GD6-21 200, 700 or 1200 mg/kg bw/day	Maternal NOAEL = 700 mg/kg bw/day Developmental NOAEL = 1200 mg/kg bw/day	Dam mortality at top dose. No developmental effects observed at all doses.	Bates et al. (1994)

Species	Method, exposure period and doses	Results	Remarks	Reference
Sprague-Dawley rats	Inhalation, GD1-19 3500, 7000, or 10 000 ppm	Maternal NOAEC = 3500 ppm Developmental LOAEC = 3500 ppm	Maternal effects at the mid and top dose groups were unsteady gait and narcotisation, decreased bodyweight gain and food consumption. Foetal bodyweight per litter were decreased at all doses; at the top dose, effects were reduced implantation, fully resorbed litters, increased resorptions per litter and increased incidence of cervical ribs.	Nelson et al. (1988)
New Zealand White rabbits	Gavage (US EPA TSCA Guidelines), GD6-18 120, 240, or 480 mg/kg bw/day	Maternal NOAEL = 240 mg/kg bw/day Developmental NOAEL = 480 mg/kg bw/day	Decreased maternal bodyweight and clinical signs of toxicity seen at the top dose. No developmental effects observed at all doses.	Tyl et al. (1994)

The studies demonstrate that effects on the foetus, such as decreased foetal bodyweights, occurred only at maternally toxic doses with no accompanying malformations and are considered to be secondary to maternal toxicity.

These studies indicate that isopropanol is not a developmental toxicant.

31.5.9 *Other health effects*

31.5.9.1 Neurotoxicity

Animal data on neurotoxicity of isopropanol are summarised from OECD (2002) and Kapp et al. (1996), and presented in Table A31.8. The neurotoxicity LOAEL/C and NOAEL/C for each study are indicated.

Table A31.8 Neurotoxicity studies with isopropanol

Species	Method, exposure period and doses	Results	Remarks	Reference
Fischer 344 rats	Inhalation, 6 hours 0, 100, 500, 1500, 5000, or 10 000 ppm	LOAEC = 1500 ppm NOAEC = 500 ppm	All animals at 10 000 ppm were prostrate after one hour of exposure and functional observation battery (FOB) was not done at this group; At 5000 ppm, behavioural alterations after one hour of exposure included altered gait, decreased toe and nail withdrawal reflexes, decreased mean rearing events, decreased rectal temperature and grip strength and increased mean hind limb splay; motor activity	Gill et al. (1994); Gill et al. (1995)

Species	Method, exposure period and doses	Results	Remarks	Reference
			decreased at 5000 and 10 000 ppm (both sexes) and at 1500 ppm for males.	
Male SPF rats	Drinking water, 12 weeks 0, 870, 1390, 1700, or 2500 mg/kg bw/day	NOAEL = 2500 mg/kg bw/day	No treatment-related evidence of astrogliosis in the form of increased glial fibrillary acidic protein in dorsal hippocampus reported.	Pilegaard and Ladefoged (1993)
Fischer 344 rats	Inhalation, 13 weeks 0, 100, 500, 1500, or 5000 ppm	LOAEC = 5000 ppm NOAEC = 1500 ppm	No treatment-related effects on FOB or neuropathologic lesions in the central or peripheral nervous systems; narcotic effects at the top two doses; increased motor activity at the top dose in females.	Burleigh-Flayer et al. (1994); Gill et al. (1994)
Female Fischer 344 rats	Inhalation, 13 weeks 0 or 5000 ppm	NOAEC = 5000 ppm	Increased motor activity, such as ambulation, rearing and fine movements, was seen at 5000 ppm which was reversible after treatment.	Burleigh-Flayer et al. (1998)
Jcl-Wistar rats (sex not specified)	Inhalation, 20 weeks 1000 or 8000 ppm	LOAEC = 8000 ppm NOAEC = 1000 ppm	Increased motor and sensory nerve conduction velocity at 8000 ppm. No effect on conduction velocity at the 1000 ppm dose.	Teramoto et al. (1993)
Male Wistar rats	Inhalation, 21 weeks 0 or 300 ppm	LOAEC = 300 ppm	Decreased enzyme activity of superoxide dismutase and azoreductase in cerebellar homogenate; increased acid protease activity in glial cells; open field tests showed changes in urination and defaecation.	Savolainen et al. (1979)
Sprague-Dawley rats	Gavage (US EPA TSCA Guidelines), GD6-21 200, 700 or 1200 mg/kg bw/day	NOAEL = 1200 mg/kg bw/day	No treatment-related effects on developmental neurotoxicity parameters tested (i.e. motor activity, auditory startle and active avoidance) at any dose.	Bates et al. (1994)

Based on the available neurotoxicity studies on adult rats, inhalation of isopropanol vapour produces reversible central nervous system depression. Increased motor activity was seen in adult rats exposed to high doses of the chemical.

31.6 Health hazard summary

31.6.1 *Critical health effects*

Isopropanol has low acute oral, dermal and inhalation toxicity, is not skin irritant and demonstrates eye and respiratory irritation. The chemical is not a skin sensitiser.

The most appropriate NOAEC for risk assessment, determined from the 104-week study by Burleigh-Flayer et al. (1997), is 255 mg/kg bw/day based on kidney effects at the LOAEC of 1275 mg/kg bw/day.

The chemical is not genotoxic or a carcinogen based on available data. Developmental toxicity occurred only at maternally toxic doses.

31.6.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A31.9. These NICNAS recommendations do not consider physical or environmental hazards.

Table A31.9 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Acute toxicity	May cause drowsiness or dizziness – STOT SE 3 (H336)
Irritation / Corrosivity	Causes serious eye irritation – Cat. 2A (H319)

** Globally Harmonised System (UNECE 2009)*

31.7 References

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A32 C6-C10 linear alkyl sulfate, ammonium salt

CAS No.	CAS Name
68187-17-7	Sulfuric acid, mono-C6-10-alkyl esters, ammonium salts

32.1 Chemical identity

The chemical belongs to a widely used class of anionic surfactants called alkyl sulphates (AS) in which fatty aliphatic alcohols are sulphated and then neutralised with a base to produce sodium, potassium or ammonium salts. The basic structure of AS is $CH_3(CH_2)_nOSO_3^-$, where *n+1* is the carbon chain length. The CAS No. 68187-17-7 denotes alkyl sulfate ammonium salts with carbon chain lengths ranging between six and ten carbons (ie C6-C10) and is referred to in this report as AS C6-10.

The identity information was obtained from *Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products – Alcohol Sulphates* (HERA 2002) and the United States Environmental Protection Agency (US EPA 2006). A description of the chemical identity is provided in Table A32.1.

Table A32.1 Chemical identity

	C6-C10 linear alkyl sulfate, ammonium salt
Synonyms	(C6-C10) Linear alkyl sulfate, ammonium salt Ammonium (C6-10) alcohol sulphated Alkyl sulphate
Structural formula	CH_3-$(CH_2)_nOSO_3^-NH_4^+$
Molecular weight	200 to 255 (with n=5-9) Mol. Wt of an average AS C8 is 227
Appearance and odour	Not available
SMILES notation	HN(H)(H)OS(=O)(=O)OCCCCCCCCCC (AS C10)

32.2 Physical properties

The physical properties of the substance are presented in Table A32.2. The information was obtained from HERA (2002). Data on the physical properties of AS C6-10 were not available. The following modelled data (using EPI Suite) were provided for a C8 alkyl sulphate.

Table A32.2 Physical properties

Property	Value
Melting point	181-183 °C (AS C12)
Boiling point	542 °C (AS C12)
Bulk density	Not available

Property	Value
Vapour pressure	2.0 x 10^{-12} kPa
Water solubility	Soluble in water
Partition coefficient n-octanol/water (log K_{ow})	Not applicable as substance is a surfactant

32.3 Current regulatory controls

32.3.1 *Hazard classification for occupational health and safety*

The substance is not listed on the *Hazardous Substances Information System* (HSIS) (Safe Work Australia 2013).

32.3.2 *Occupational exposure standards*

32.3.2.1 Australia

No specific exposure standards were available.

32.3.2.2 International

No specific exposure standards were available.

32.3.3 *Australian food standards*

No Australian food standards were identified.

32.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the substance in the *Australian Drinking Water Guidelines* (NHMRC 2011).

32.3.5 *Additional controls*

32.3.5.1 Australia

The substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (TGA 2014).

32.3.5.2 International

No international restrictions were identified.

32.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

32.5 Health hazard characterisation

Toxicology information specifically on alkyl sulphates AS C6-10 ammonium (NH_4) salts is not available. However, toxicological information is available for alkyl sulphates with carbon

chain lengths ranging from C8 to C18, sodium or ammonium salts (AS C8-18) (HERA 2002). The chemical structures of the two groups of alkyl sulphates (AS C6-10 and AS C8-18) are similar and compounds with carbon chain lengths 8-10 (AS C8-10) are common to both groups of AS. Therefore, it is considered appropriate to apply the available toxicological information on AS C8-18 to assess the toxicity of AS C6-10, with preference for data on C8-C12 chain lengths. However, for repeat dose studies, only data on C12 and longer chain AS were available. Toxicity information was sourced primarily from HERA (2002) and from the Organisation for Economic Co-operation and Development (OECD) *Screening Information Data Set (SIDS) Initial Assessment Report* (SIAR) (OECD 2007).

32.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

32.5.1.1 Oral absorption

Information on oral absorption of AS C6-10 is not available. Generally, AS are rapidly absorbed from the gastrointestinal tract in mammals and humans (Burke, Olavesen et al. 1976). Plasma concentrations of AS reached a maximum within 30 minutes to two hours after oral administration (Denner et al. 1976). Studies with radiolabeled AS (ranging in chain length from C10 to C18) showed that, irrespective of chain length or counter ion, over 80% to 90% of the administered dose was excreted in the urine in rats, pigs and humans (Burke et al. 1976).

Based on these observations, 100% oral absorption in humans is assumed for the purposes of risk assessment.

32.5.1.2 Dermal absorption

Dermal absorption of AS has been found to be limited, which was considered to be most likely because the anionic surfactants tend to bind to the skin surface (Black and Howes 1980). Early studies with isolated human skin were unable to detect penetration of a homologous series of AS, which ranged from C8 to C18 (Blank and Gould 1961). Animal studies confirmed a low level of percutaneous absorption of AS. Less than 0.4% of a 3 µmol dose of ^{35}S-labeled AS C12 Na salt was percutaneously absorbed in guinea pigs, based on recovery of the radiolabel in urine, faeces and expired air (Prottey and Ferguson 1975). Studies with rats indicated that pre-washing of the skin with surfactant enhanced AS skin penetration (Black and Howes 1980).

Based on these observations, a 1% dermal absorption is assumed for AS C6-10.

32.5.1.3 Inhalation absorption

No data were available for inhalation absorption. Considering the relatively small size of the AS molecules and their water solubility, a 100% inhalation absorption in humans is assumed for the purposes of risk assessment.

32.5.1.4 Distribution

Tissue disposition studies with AS C12 in rats indicated that 36% of an intravenous dose reached the liver within 15 minutes, followed by the intestine, the kidney and the blood (Greb and Wingen 1980). Studies with potassium salts of ^{35}S-labeled AS C10 and C18 in the rat

also indicated that liver and kidney were early sites of labelling. The shorter chain length surfactant was cleared from tissues more rapidly: after six hours, only traces of the C10 salt remained in the kidney, whereas it took 12 hours for the C18 salt to be cleared from the kidney (Burke et al. 1972; Burke et al. 1975).

The systemic disposition of percutaneously absorbed surfactants was similar to other routes of administration, with the highest percentage of the dose recovered in the liver and kidneys.

32.5.1.5 Metabolism

Studies with radiolabeled even-chain AS (specifically, C12, C16 and C18) indicate extensive metabolism in rats, dogs and humans to yield a sulphate ester as the final degradation product (Burke et al. 1975; Merits 1975). The major metabolite was identified as the 4-carbon compound, butyric acid 4-sulphate. Butyric acid 4-sulphate is highly polar and excreted in the urine.

For odd-numbered AS, the major urinary metabolite was propionic acid-3-sulphate. The postulated mechanism for AS is degradation by a common pathway involving ω-oxidation of the terminal methyl group to a carboxyl group, followed by β-oxidation that removes two carbons at a time, to yield metabolites with chain lengths of C2 and C4. Metabolism of odd numbered chains (specifically, C11) also yielded pentanoic acid-5-sulphate and inorganic sulphate as minor metabolites (Burke et al. 1975; Burke et al.1976).

Biotransformation of the hydrocarbon chain of AS is via the metabolic pathway of cytochrome P450 dependent ω-oxidation of aliphatic fatty acids (Klassen et al. 1996). Furthermore, the distribution of label in urine and faeces from orally administered potassium dodecyl ^{35}S-sulphate (C12) was similar in both antibiotic-treated and untreated rats, indicating that the intestinal flora do not play a significant role in the metabolism of this compound (Denner et al. 1969).

32.5.1.6 Excretion

Studies with radiolabeled AS (ranging in chain length from C10 to C18) showed that, irrespective of chain length or counter ion, over 80% to 90% of the administered dose was excreted in the urine in rats, pigs and humans (Denner et al. 1969; Merits 1975; Burke et al. 1975; Burke et al.1976). However, in the dog, a significant proportion of the administered AS dose was excreted unchanged in the faeces (Merits 1975). Studies with C10, C11, C12 and C18 AS indicate that the proportion of the dose excreted in urine and faeces is not significantly altered by the route of administration (oral, intravenous, or intraperitoneal) (Denner et al. 1969; Burke et al. 1975).

32.5.2 *Acute toxicity*

32.5.2.1 Oral

Information on acute oral toxicity of AS C6-10 is not available. Generally, alkyl sulphates (AS) displayed a low order of toxicity when tested in rodents.

In studies performed with rats, 25% aqueous solutions of AS C10-16 alkyl sulphates (separately administered as AS C10-16 NH_4-salt, AS C10-16 sodium-salt and AS C10-16 acid) had median lethal dose (LD50) values of 1827, 1830 and 1780 mg active substance/kg bw (Procter and Gamble Co. 1974). The clinical signs were decreased motor activity, decreased respiratory rate, abdominal cramps and diarrhoea. Stomach ulcers were found at necropsy only in the study with AS C10-16 acid.

In one study, AS C10 Na salt was administered as a 30% aqueous solution to two to five rats per sex per dose at 1000 and 2000 mg/kg bw (Henkel KGaA 1985). Clinical signs included

piloerection, diarrhoea, paleness, blood in urine and cramps. At necropsy, anaemia of internal organs, peritonitis and inflammation and haemorrhages in the gastrointestinal tract were found. The approximate LD50 was between 290 and 580 mg active substance/kg bw for females, and 580 mg active substance/kg bw for males (OECD 2007).

There was also some evidence of decreasing toxicity with increasing chain length. Acute oral LD50 values in rats of alkyl sulphates were between 290 and 580 mg/kg bw for AS C10, between 1000 and 2000 mg/kg bw for C10-16, greater than 2000 mg/kg bw for C12-14, C12-15, C12-16, C12-18 and C18, and greater than 5000 mg/kg bw for C16-18 alkyl sulphates. The counter ion does not appear to influence the toxicity in a substantial way (OECD 2007).

Based on these observations that shorter chain alkyl sulphates are likely to be more toxic than the longer chain alkyl sulphates, AS C6-10 is considered to have moderate acute toxicity by the oral route.

32.5.2.2 Dermal

The acute dermal toxicity profile of this chemical class has been adequately characterised. Studies are available for three alkyl sulphates, AS C10 potassium salt and AS C10-16 magnesium and ammonium salts. The chemicals caused no deaths and showed no evidence of systemic effects when administered at doses ranging from 0.5 g/kg to 2 g/kg, depending on the active concentration of the raw material.

Although none of the studies were conducted according to OECD guidelines, their conduct was scientifically sound, with methodology comparable to the OECD standards except for a smaller group size (three animals per sex perdose) (HERA 2002). The results showed skin irritation at the site of surfactant application but limited systemic toxicity by the percutaneous route. Therefore, based on the available data, no significant percutaneous toxicity is expected for this class of materials beyond local irritant effects.

Based on these observations, AS C6-10 is considered to have low acute dermal toxicity.

32.5.2.3 Inhalation

Detailed information on inhalation effects is not available. Inhalation of aerosolised solutions of AS C12 Na and NH_4, triethanolamine (TEA) salts caused irritation of the respiratory tract in mice (OECD 2007). Inhalation LD50s for alkyl sulphates have not been established.

32.5.2.4 Observation in humans

No data were available.

32.5.3 *Irritation / Corrosivity*

32.5.3.1 Skin irritation

Alkyl sulphates produce dermal irritation in a dose-dependent manner that is consistent with their surfactant properties. Acute and repeated dermal application of anionic surfactants to mammalian tissue causes de-lipidation of the skin surface, increased cellular and tissue permeability, inflammation, tissue edema and ulceration of the skin, the severity of which is highly dependent on concentration, duration of exposure and occlusion (Little 1991).

Skin irritation tests in rabbits with three different materials, conducted according to OECD guidelines, were sourced from HERA (2002). The results are summarised in Table A32.3.

Table A32.3 Skin irritation studies in rabbits for alkyl sulphates of various chain lengths

Chemical	Concentration	Result	Reference
C_{8-14} (NH_4 salt)	32.9% (4 hours, semi-occlusive)	Corrosive	Henkel KGaA (1991a)
C_{8-16} (Na salt)	29 – 31% (4 hours, semi-occlusive)	Corrosive	Henkel KGaA (1991b)
C_{12-14} (Na salt)	90% (4 hours, semi-occlusive)	Corrosive	Henkel KGaA (1994)
AS C12 sodium salt	25%	Severe erythema and oedema Mean erythema for the test animals over three scoring time points (24, 48 and 72 hours) was 2.0. Mean oedema was 0.7.	Henkel KGaA (1972)
AS C12 Na salt	5% and 1%	Mild irritation at 5%. No reaction at 1%.	Henkel KGaA (1972)
AS C12-14 TEA salt	25%	Severe erythema and oedema Mean erythema for the test animals over three scoring time points (24, 48 and 72 hours) was 3.7. Mean oedema was 2.1.	Henkel KGaA (1987a)
AS C12-18 Na salt	88.7% 43-46% 5%	Severe erythema and oedema Moderate erythema, slight oedema Slight erythema and oedema.	Henkel KGaA (1994)

Overall, AS with longer carbon chains (C16-18) tend to be less irritating than AS with carbon chains of C12-15 (results not shown). Test results indicated that for the shorter carbon chain length AS (C12 and C13-15), concentrations of 10% or greater consistently produced moderate to severe irritation reactions. Responses to lower concentrations (1 to 5%) tend to vary from none to moderate. The longer carbon chain length materials (C16-18) produce severe reactions at concentrations above 25% and no or slight reactions at lower concentrations.

Based on these observations AS C6-10 is considered corrosive.

32.5.3.2 Eye irritation

Several eye irritation studies were conducted with AS of different carbon chain lengths. As with skin irritation, the longer carbon chain length AS (C16-18) tended to produce less irritation than the shorter chains. In studies with AS C12 Na salt, concentrations greater than 2% produced moderate to severe irritation (HERA 2002). Symptoms persisted for as long as 21 days. Testing with lower concentrations, ie, 2%, resulted in only slight irritation. For the longer chain C16-18 AS, 5% dilutions produced only slight eye irritation; these AS were moderate to severe irritants only above 25%. Table A32.4 summarises eye irritation effects of different AS at varying concentrations (BUA 1996).

Table A32.4 Eye irritation studies in rabbits for alkyl sulphates of various chain lengths

Substance	Test concentration	Finding	Reference
AS C12, Na salt	25%	Irreversible effects	Henkel KGaA (1987b)
AS C12-14, Mg salt	10%	Irreversible effects	Henkel KGaA (1987c)
AS C12-14, TEA salt	25%	Irreversible effects	Henkel KGaA (1987d)
AS C12, Na salt	20% 10% 20% 10% 2%	Strongly irritating Moderately irritating Moderately irritating Moderately irritating Slightly irritating	Henkel KGaA (1977) Ciuchta and Dodd (1978)
AS C12, TEA salt	20% 10% 2% 2.5%	Moderately irritating Moderately irritating Slightly irritating Moderately irritating	Ciuchta and Dodd (1978) Serrano, et al. (1977)
AS C12-16, Na salts	20% 10% 5%	Strongly irritating Moderately irritating Slightly irritating	Henkel KGa(1977)
AS C16-18, Na salts	25% 5%	Irritating Slightly irritating	Henkel KGa(1987e)

Based on these studies, AS C6-10 is considered to be severely irritating to the eyes.

32.5.3.3 Respiratory irritation

No data were available. Based on severe skin and eye irritation AS C6-10 are likely to be respiratory irritants.

32.5.3.4 Observation in humans

Reports from controlled human exposures to AS confirm that low concentrations are non-irritating. Concentrations of 10% are moderate to strong irritants while, concentrations of 1% are only slightly irritating (Little 1991). In a Burckhardt Test (Burckhardt 1970), 1% AS C12 Na was applied repeatedly to the skin of human volunteers. There were no adverse reactions (Henkel 1978).

32.5.4 *Sensitisation*

32.5.4.1 Skin sensitisation

Alkyl sulphates are universally considered non-sensitising skin irritants. In a maximisation study, 20 guinea pigs were treated at induction with 5% AS C12-14 Na salts (HERA 2002). This concentration was used for both the induction injections (alone and mixed with Freund's complete adjuvant) and the induction patch, which was applied one week after the injections.

A challenge patch with 1% test material was applied two weeks after the induction patch. No skin reactions were observed after challenge in any of the 20 test animals or the 10 control animals.

In a Buehler sensitisation study, three induction patches of 12.5% AS C12-14 Na salts were applied (six hours, occluded) to guinea pig skins (HERA 2002). The challenge substance was 6.25% AS C12-14 Na salts, which produced slight erythematous responses in both the test and control groups that were consistent with irritation responses. Four of the 20 animals in the test group, and two of 10 animals in the control group exhibited scores of "1" (slight erythema) at 24 hours. By 48 hours, the reactions had resolved on both control animals and on two of the four test animals.

In a Local Lymph Node Assay (LLNA), equivocal results were obtained with sodium dodecyl sulphate (AS C12, Na salt) (Basketter et al. 1996). However, the observed positive reactions were regarded as a non-antigen-specific proliferative stimulus induced by the irritating effect of the tested concentrations. Further, cell typing studies on lymph node changes induced by AS indicated that the cell changes were characteristic of irritation, not sensitisation (Sikorski et al. 1996).

From the above studies, it is concluded that AS C6-10 does not have skin sensitisation potential.

32.5.4.2 Respiratory sensitisation

No data were available.

32.5.4.3 Observation in humans

The known irritancy potential of high concentrations of AS can easily confound the reading of diagnostic patch tests in human subjects. Indeed there have been rare reports of human subjects reacting to diagnostic patch tests with AS C12, Na salt. Skin reactions to the common detergent, sodium dodecyl sulphate (SDS, AS C12, Na salt) are believed to be irritant reactions rather than any sensitisation effects (Reitschel and Fowler 2001). There are no chemical structural alerts for SDS for sensitisation (Barratt et al. 1994). This further supports the conclusion that these materials are non-sensitisers.

32.5.5 *Summary of acute toxicity*

Available studies of AS indicate that AS C6-10 is likely to have moderate acute oral toxicity and low dermal and inhalation toxicity. It is likely to be a skin irritant and a severe eye irritant. Information on the respiratory irritant potential is not available. Based on skin irritation and severe eye irritation AS C6-10 are likely to be respiratory irritants. AS C6-10 was considered to be non-sensitising to skin based on animal and human tests with other closely related AS.

32.5.6 *Repeat dose toxicity*

32.5.6.1 Oral

Repeat dose oral studies with AS C6-10 are not available. Several repeat dose oral toxicity studies on AS with chain lengths C12 and above have been reported (HERA 2002). The following table (Table A32.5) lists some of the studies carried out in rats with AS of carbon chain lengths C12 or mixtures of AS with carbon chains C12 to C18.

Table A32.5 Repeat dose oral studies in rats

Substance	Sample size, duration and doses (mg/kg bw/day)	NOAEL / LOAEL (mg/kg bw/day)	Effects at LOAEL	Reference
AS C12 Na	10/sex/ dose 28-days, gavage 0, 30, 100, 300	LOAEL = 300	Decreased food consumption and body weight gains, increase in relative liver, kidney, brain, and gonad weights. Ulceration of stomach, partially reversible at the highest dose.	Henkel KGa (1987f)
AS C12-14 TEA	10/sex/dose; 28-days, gavage 0, 70, 250, 750	NOAEL not established	Local effects (inflammation and oedema of forestomach).	Henkel KGa (1988)
AS C12 Na	10/sex/dose; 90-days 0, 59, 116, 230, 470, 950, 1900	230	Increase in relative weights of liver, kidneys, adrenals, brain and testes. Decreased weight gains and depleted body fat. Serum triglyceride decreased in the three highest dose groups and some serum enzymes were elevated. Livers of rats in the two highest dose groups showed prominent periportal and diffuse hypertrophy, reduced glycogenic vacuolation and cytoplasmic neural fat. Haemosiderin content of parenchymal and Kupfer cells was reduced. Periportal and diffuse parenchymal hypertrophy, reduced cytoplasmic fat and glycogenic vacuolation in females at four highest doses.	Unilever Research (1977a)
AS C12-15 Na	10/sex/dose; 90-days, 0 62, 122, 245, 488, 1016, 2081	488	Increased relative liver, kidneys and testes weights. Liver cell hypertrophy, elevated serum glutamic-pyruvic transaminase (GPT) and alkaline phosphatase (ALP); periportal parenchymal hypertrophy; increase in serum enzymes; decrease in serum magnesium, protein, cholesterol , changes in colour and consistency of intestinal contents, reduced incidence/severity of nephrocalcinosis; lymphatic dilation of small intestine.	Unilever Research (1976a)
AS C13-15 Na	10/sex/dose; 90-days 0, 64, 134, 253, 512, 1007, 2096	253	Increase in serum AP, aspartate aminotransferase (AST), serum cholinesterase, absolute/relative liver, brain, kidney and testes weights, absolute spleen weights; periportal parenchymal hypertrophy and lymphatic dilation of the intestine. Decrease in serum cholesterol and serum triglycerides and nephrocalcinosis.	Unilever Research (1977b)

Substance	Sample size, duration and doses (mg/kg bw/day)	NOAEL / LOAEL (mg/kg bw/day)	Effects at LOAEL	Reference
AS C16-18 Na	10/sex/dose; 90-days, gavage 0, 61, 123, 230, 482, 970, 2067	230	Increased relative liver, brain, testes weights, ALP, alanine aminotransferase (ALT). Decreased packed cell volume (PCV)/haemoglobin levels, serum total protein, cholesterol , triglyceride, AST, absolute spleen weights, cytoplasmic basophilia, neutral fat content and hemosiderin content of parenchymal and Kupffer cells and incidence and / or severity of nephrocalcinosis. Parenchymal hypertrophy, glycogenic vacuolation in the liver.	Henkel KGa (1987g)
AS C12-15 Na	45/sex/ dose; 2 years (dietary) 0, 11, 113 or 1125	113	Increased AST, ALT, lactate dehydrogenase (LDH) and ALP values, absolute and relative weights of liver and zonal/diffuse parenchymal hypertrophy. Enhanced pigmented lipid granulomata and focal coagulative/ haemorrhage necrosis. Increased severity and / or incidence of arterial medial hypertrophy and patchy myocardial fibrosis; increased haemosiderin deposition and decreased myelopoiesis and stem cell hyperplasia,	Unilever Research (1995)

NOAEL = No Observed Adverse Effect Level; LOAEL = Lowest Observed Adverse Effect Level

Strains of rats were not specified for any of the studies. The liver appeared to be the primary target organ following oral administration of alkyl sulphates of different chain length, with increases in liver weight, histological evidence of cellular enlargement and altered clinical chemistry parameters observed across several studies. Gastrointestinal irritation was observed after gavage but not dietary administration.

In these studies, hepatocellular hypertrophy seen at low doses in the absence of adverse, degenerative changes confirmed by histological observations or suggestive changes in clinical chemistry parameters is regarded as an adaptive non-adverse response.

A recent expert working group on interpreting the toxicological significance of liver hypertrophy noted that hepatocellular hypertrophy without histologic or clinical pathological indications of liver toxicity should be regarded as an adaptive response. However, non-adverse adaptive changes at low doses may become adverse at higher doses (Hall et al. 2012). The expert group also noted that changes in single clinical chemistry parameters can normally be regarded as non-adverse in the absence of adverse histopathological evidence. However, multiple changes in clinical chemistry parameters of sufficient magnitude such as a two- to three-fold increase in serum ALT together with biologically significant changes in other liver enzymes (ALP, AST etc.) or other clinical pathology markers such as cholesterol, triglycerides or serum proteins may be interpreted as indicating hepatocyte injury.

Notwithstanding a general lack of information on the magnitude of changes in the studies of alkyl sulphates, changes in clinical chemistry parameters accompanying liver weight

increases were reported for several repeat dose studies of alkyl sulphates of different chain length. For C12 alkyl sulphates, regarded as most relevant for sulphated C6-10 alkyl sulphates, a 13-week rat dietary study reported, in addition to liver hypertrophy, changes in liver enzyme increased serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) and decreased serum triglycerides. At lower doses, the only liver effects reported were histological evidence of liver hypertrophy and increased serum ALP. Doses higher than 230 mg/kg bw/day were associated with additional changes in clinical chemistry (decreases in serum total protein, cholesterol, triglycerides, AST) as well as histological changes in the liver.

Decreased serum protein and increased aspartate aminotransferase (AST), ALT and ALP were also reported at a similar dose of 482 mg/kg bw/day in 13-week gavage study of C16-18 alkyl sulphates. At a lower dose, the only liver changes reported were increased relative liver weight and increased serum ALT. Consequently, these multiple changes in clinical chemistry parameters commencing at approximately 470 to 480 mg/kg bw/day reported in these two 13-week oral studies of C12 and C16-C18 alkyl sulphates are interpreted as indicative of adverse liver effects and are considered LOAELs.

For the purposes of risk assessment of alkyl sulphates, the critical study is the 13-week dietary study of C12 alkyl sulphate (Unilever Research 1977b). This study was of 13 weeks duration, was reportedly well-conducted and tested an alkyl sulphate of chain length closest to C6-C10 alkyl sulphate. From this study, based on adverse liver effects, the LOAEL was 470 mg/kg bw/day and the NOAEL was 230 mg/kg bw/day.

The oral repeat dose NOAEL of 230 mg/kg bw/day from the 13-week study (supported by the same NOAEL from the 104-week study) will be used for human risk assessment of the related alkyl sulphates.

32.5.6.2 Dermal

In a 21-day repeat dermal exposure study (Unilever 1976b), 0%, 5%, 10%, 15% and 18% AS C12-15 sodium salt solutions were applied to the shaved backs of mice (strain not reported) twice weekly. No further details were provided. The results were consistent with the irritant properties of the surfactants. All mice in the highest dose group died due to dehydration caused by fluid loss through skin lesions. At the 10% concentration, oedema, hyperkeratosis and acanthosis of the epidermis were observed at the site of application. Responses increased in severity at 15% to include ulceration and necrosis, with inflammatory exudate in decedents and epidermal thickening due to hyperkeratosis and acanthosis in survivors. These were due to sustained skin irritation induced by the test materials. There were no systemic histopathological changes in other organs or tissues. A NOAEL for systemic effects was not established in this study.

In a 90-day dermal study, AS C12-15 Na salt was applied to the skin of mice (strain not reported) at doses of 0%, 5%, 10%, 12.5% and 15% of the substance (Unilever 1977c). No further details were provided. Skin effects at the application site were consistent with the irritant properties of the test material. Dose-related ulceration of the epidermis with inflammatory exudate was observed at the 12.5% and 15% concentrations. Dose-dependent increases in oedema, vascular dilatation, epidermal acanthosis, hyperkeratosis and hypergranulosis were prominent at the 10% treatment level and above. Increases were noted in liver-to-body weight ratios in both sexes at the 15% concentration and in females at the 12.5% concentration. Absolute kidney weights increased in males and kidney-to-body weight ratios increased in females at the 15% treatment level. These effects are consistent with those observed in the oral studies. The systemic effects suggest that a higher level of percutaneous absorption of the test material may have occurred at high doses with ulceration of the skin at the higher doses in this study. However, a NOAEL could not be deduced from this study due to lack of detailed information, such as the exact dose applied (mg/kg bw/day),

number of applications (daily or weekly) and the incidence of skin damage (ulceration) during the study.

32.5.6.3 Inhalation

Long-term inhalation studies on AS were not available.

32.5.6.4 Observation in humans

No data were available.

32.5.7 *Genotoxicity*

A substantial database of reliable studies exists on the *in vitro* genetic toxicity of AS. Results in the Ames reverse mutation assay were consistently negative with or without metabolic activation (HERA 2002). No evidence of mutagenic activity was observed, irrespective of carbon chain length, unsaturation or the nature of the countervalent moiety that neutralised the anionic surfactant.

Negative results were found in *in vivo* rodent studies for chromosomal aberrations for several different AS carbon chain lengths. A small number of less reliable studies showed equivocal results at high doses; however these studies did not meet scientific standards (HERA 2002). The *in vivo* dominant lethal mutation assays on AS C12 and AS C12-15 showed essentially negative results, as expected based on the *in vitro* Ames assay results for the category.

Alkyl sulphates with fully saturated carbon chains are not metabolised to reactive electrophiles. Hence, the lack of mutagenic activity for this chemical class is predictable based on the absence of highly reactive electrophilic centres capable of interacting with nucleophilic sites on DNA (direct acting agents) (HERA 2002).

Based on the above observations, it was concluded that AS C6-10 are not likely to be genotoxic, noting that the above studies considered C12 as the shortest chain length.

32.5.8 *Carcinogenicity*

Carcinogenicity studies for AS C6-10 are not available. In the two lifetime (two-year) feeding studies with AS C12-15 Na (as described in Section A32.5.6.1), there was no increase in tumour incidence or any impact on tumour type in either study. For both studies, approximately 70% of animals survived to study termination and mortality was similar across dosage groups and controls (Kritchevsky 1995). Animals in the 1.5% dose groups in both studies exhibited reduced food and water consumption, and slower growth rates. Within these high dose groups, there was a decreased number of total tumours and tumour-bearing animals.

Based on these two-year feeding studies, and the absence of any tumour effects of the test materials, the NOAEL and LOAEL for carcinogenicity is greater than the highest dose of 1.5%.

Overall, the results of the chronic feeding studies together with the absence of a mutagenic response in *in vitro* and *in vivo* tests suggest that a carcinogenic potential for AS C6-10 specifically is considered unlikely, noting the shortest chain length studied was C12.

32.5.9 *Reproductive toxicity*

32.5.9.1 Fertility

In the only available fertility study on AS, Hemsworth et al. (1981) fed groups of 10 male Swiss albino mice with either 1% of AS C12 Na for two weeks or with 0.1% of AS C12 Na for

six weeks to ensure that germ cells were exposed at any stage of development. One, two or three weeks after dosing, the animals of each group were mated with females. At the highest dose level, body weights were significantly decreased, while the treatment caused no adverse effects on fertility (i.e. impairment of epididymal spermatozoa).

Repeated oral dose 90-day studies with AS C12-15 Na, AS C16-18 Na and AS C13-15 Na gave no indication of adverse effects on reproductive organs (Unilever Research 1976a, 1977a, 1977b). At very high doses (around or above 1000 mg/kg bw/day), increases in relative (but not absolute) testes weights were noted. This effect was not considered to be adverse but was attributed to a decreased body fat/body weight. There were also no adverse histopathological findings at necropsy.

Based on these studies, AS C6-10 is considered unlikely to be toxic to fertility, noting the shortest chain length studied was C12.

32.5.9.2 Developmental toxicity

Developmental toxicity studies have consistently shown that AS have no major skeletal or visceral effects on the developing foetus. In some studies, there was evidence of slightly delayed foetal development; however, this effect was observed at dose levels that caused maternal toxicity as well (HERA 2002).

A developmental toxicity study assessed the teratogenic potential of AS in rats, mice and rabbits following oral (gavage) administration (Palmer et al. 1975a, 1975b). The doses were 0, 0.2, 2, 300 and 600 mg/kg/day administered during the appropriate days of gestation. The protocol was comparable to OECD TG 414. The chain length of the AS evaluated for teratogenicity was not specified in the study report. Mice and rabbits were more sensitive to maternal toxicity induced by the test material. At the 600 mg/kg dose, marked maternal toxicity was evident in mice and rabbits, while slight to moderate toxicity was observed in rats at the same dose. An increased incidence of total litter loss occurred at doses that caused maternal toxicity. When dams showing total litter loss were excluded from the analysis, litter parameters were unchanged by treatment. In mice, a higher incidence of minor skeletal anomalies occurred at 600 mg/kg of the test material; however, in all species, the incidence of major or minor visceral or skeletal anomalies was unaffected by treatment at non-maternally toxic doses.

In these studies, a NOAEL for developmental toxicity could not be established as maternal toxicity was also noted at doses that caused litter loss.

Based on available data, AS C6-10 is considered unlikely to be a developmental toxicant, noting the carbon chain range of the AS in these studies was not specified.

32.5.10 *Other health effects*

No data were available.

32.6 Health hazard summary

32.6.1 *Critical health effects*

No health hazard data were available for sulfuric acid, mono-C6-10-alkyl esters, ammonium salts (AS C6-10). However, data on alkyl sulphates (AS) were available from *Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products – Alkyl Sulphates* (HERA 2002) and OECD *Screening Information Data Set (SIDS) Initial Assessment Report* (OECD 2007) for the alkyl sulphates chemical category.

AS are well absorbed via the oral route and poorly absorbed by the dermal route. Data were unavailable for inhalation absorption, but these chemicals are expected to be well absorbed also via this route.

Available studies of AS indicate moderate acute oral toxicity and low dermal toxicity. AS cause skin irritation and are severe eye irritants, but are not regarded as skin sensitisers.

In repeat dose toxicity studies of AS of at least 12 carbon chain length, the liver appears to be the primary target organ, with increases in liver weight, cellular enlargement and elevated levels of liver enzymes observed consistently. A NOAEL for repeat dose toxicity was established from a 90-day rat feeding study on AS C12 Na at 230 mg/kg bw/day. A NOAEL for dermal repeat dose toxicity could not be established.

Genotoxicity testing *in vitro* and *in vivo* did not suggest that AS of at least C12 chain length possess genotoxic potential. Carcinogenicity studies for AS are not available. Short- or long-term oral studies for AS did not report any evidence of carcinogenicity.

Available studies do not show evidence of fertility or developmental toxic effects in the absence of maternal toxicity for AS of at least C12 carbon chain length.

32.6.2 *Hazard classification*

Based on the above studies, alkyl sulphate C6-12 is recommended by NICNAS to Safe Work Australia for classification and labelling under the current *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004) and under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A32.6. These NICNAS recommendations do not consider physical or environmental hazards.

Table A32.6 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed – Cat. 4 (H302)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage irritation – Cat. 1C (H314)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

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Unilever Research (1977c) Examination of Dobanol-25-sulphate, high conversion bleached for biological effects on skin, including carcinogenicity. 2. Thirteen week mouse test (Unpublished report no. PCW 77 1137). Unilever Research, Colworth/Welwyn, 47 pp.

Unilever Research (1995) Two year rat feeding study with Dobanol-25-sulphate, high conversion, bleached (HCB) (Unpublished Report No. RG 954). Unilever Research, Colworth/Welwyn, 131 pp.

US EPA (2006) Reassessment of three exemptions for the requirement of a tolerance of alkyl sulphates. Office of the Prevention, Pesticides and Toxic Substances. United States Environment Protection agency, Washington.

A33 C6-12 ethoxylated alcohols

CAS No.	CAS Name
68439-45-2	Alcohols C6-12, ethoxylated

33.1 Chemical identity

Alcohol ethoxylates (AE) is a widely used class of non-ionic surfactants produced by the addition of ethylene oxide to fatty alcohols. The basic structure is $C_{X-Y}O(CH_2CH_2)_nOH$, where "X-Y" indicates the range of carbon atoms in the fatty alkyl chain and "n" represents the average degree of ethoxylation. The alkyl chain can vary in length and in the degree of linearity, but is typically between six and 18 carbons long. The ethylene oxide (EO) chain ($(CH_2CH_2)_nOH$) can also vary in length from one to 40 EO units. An AE with the structure C9-11 EO6.5, for example, contains a range of alkyl chain lengths of 9-11 and averages 6.5 EO units per alkyl chain (Environment Canada 2013). The CAS No. 68439-45-2 depicts alcohol ethoxylates with carbon chain length ranging between six and 12 carbons (referred to in this report as AE C6-12). The number of ethylene oxide units in the AEC6-12 molecule is not specified, although commercial alcohol ethoxylates used in household products have an average ethylene oxide chain length ranging from 3-12 units (HERA 2009). Surfactants used for industrial purposes, where a stronger surfactant activity would be required, can be expected to have a greater degree of ethoxylation.

The identity information (Table A33.1) was obtained from ChemID*plus* (2012).

Table A33.1 Chemical identity

	C6-12 ethoxylated alcohols
Synonyms	Ethoxylated alcohols (C=6-12) Polyoxyethylene C6-12 fatty alcohol ether Alfonic 810-40
Structural Formula	HO—[—CH2—CH_2—O—]$_n$— $(CH_2)_{5-11}$-CH_3
Molecular weight	230 to 714 (C6 with 3 EO units to C12 with 12 EO units) Mol. Wt. of an average C10 with 8 EO units is 510
Appearance and odour	Clear to slightly hazy liquid with sweet pungent odour
SMILES Notation	CCCCCCCCOCCOCCOCCO (C8 ethoxylated alcohol, 3 ethoxylate units)

33.2 Physical properties

The physical properties of the substance are presented in Table A33.2. The information was obtained from H*uman and Environmental Risk Assessment on Ingredients of Household Cleaning Products (Alcohol Ethoxylates)* (HERA) (2009).

Table A33.2 Physical properties

Property	Value
Boiling Point	367-543 °C depending on chain length and ethylene oxide units (calculated by EPIWIN program, HERA 2009)
Bulk density	951 kg/m^3 at 20 °C
Vapour pressure	Extremely low (HERA 2009)
Water solubility	Not available. However based on solubility of long chain alcohols and ethylene oxide moieties, solubility is expected to be as high as 551 mg/L.
Partition coefficient n-octanol/water (log K_{ow})	3.15 to 5.36 depending on the C chain length*
Flash Point	114 °C

**Not applicable as the substance is a surfactant.*

33.3 Current regulatory controls

33.3.1 *Hazard classification for occupational health and safety*

The substance is not listed on the *Hazardous Substances Information System (HSIS)* (Safe Work Australia 2013).

33.3.2 *Occupational exposure standards*

33.3.2.1 Australia

No specific exposure standards were available.

33.3.2.2 International

No specific exposure standards were available.

33.3.3 *Australian food standards*

No Australian food standards were identified.

33.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the substance in the *Australian Drinking Water Guidelines* (National Health and Medical Research Council (NHMRC) 2011).

33.3.5 *Additional controls*

33.3.5.1 Australia

The substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

33.3.5.2 International

No international restrictions were identified.

33.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports;Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

Health hazard characterisation

Very little toxicology information is available on AE C6-12. Toxicological information is available for a number of alcohol ethoxylate classes with a carbon chain length distribution ranging from C8 to C18. Given that the chemical structures of the two groups of alcohol ethoxylates (AE C6-12 and AE C8-18) are very similar and the compounds with carbon chain lengths 8-12 (AE C8-12) are common to both groups of AEs, the available toxicological information on AEs that collectively covers the C8-18 range and similar number of ethoxylated units was used to read across for AE C6-12 toxicity. Toxicity information was sourced primarily from the HERA report (2009).

From a structural activity point of view, the length of the alkyl chain does not exert any meaningful influence on the acute toxicity. The degree of ethoxylation of the AE appear to be the only factor found to be of relevance in acute oral toxicity with the compounds with ethoxylate chains between five and 14 being more toxic by the oral route than those with less than four or more than 21 ethoxy units (HERA 2009).

33.4.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

33.4.1.1 Oral absorption

Oral absorption of three ^{14}C-labelled alcohol ethoxylates C12, with different degree of ethoxylation (3, 6 and 10 ethylene oxide units) was determined in female Colworth Wistar rats (Unilever 1978a). The test solution was administered by oral intubation and faeces, urine and air were monitored for ^{14}C activity. At the end of the study period various tissues and organs were removed and analysed for radioactivity. ^{14}C was excreted mainly in the urine after oral administration of the compound. Small proportions were recovered as $^{14}CO_2$ and in the faeces. ^{14}C-labelled AE C12-15 was administered orally to rats to evaluate its absorption and excretion. The orally dosed material was absorbed quickly and extensively (>75% of the dose). In most of the experiments about half of the ^{14}C that was absorbed by the oral route was excreted promptly in the urine; smaller amounts appeared in the faeces and CO_2

The relative proportions of compounds found in the urine, faeces, air and carcass did not differ with the route of administration and the recoveries were close to 100% for all routes. The results suggested an almost complete absorption of the compound from the alimentary tract.

The absorption of ^{14}C labelled AE C12 was also examined in human volunteers (Drotman 1980). Six adult human males were given a capsule containing 50 mg of the radio-labelled surfactant. Urine and faeces were collected for the next 144 hours. Blood samples and expired CO_2 were also collected regularly. Most of the radioactivity (about 75%) was excreted via the urine within the first 24 hours, while faecal and air eliminations were very low at 5% and 4%, respectively. Amounts in the blood were also low and never exceeded 1%.

Based on these observations, 100% oral absorption in humans is assumed for the purpose of risk assessment.

33.4.1.2 Dermal absorption

Dermal penetration of AE C12 was investigated in human male volunteers (Drotman 1980). A solution of 100 mg ^{14}C-labelled AE C12 (with six ethoxy units) dissolved in 1 mL ethanol was applied dermally over a 90 cm^2 area to the outer part of the forearm of two male subjects. The treated skin was protected by a non-occlusive metal shield for eight hours. After 144 hours the application site was repeatedly washed to remove any remaining product. Blood, urine, faeces and expired air were monitored as described for the oral application (see Section A33.5.1.1). Recovery of the total applied radioactivity was 82.4 to 95%.Most of the radioactivity (74 to 88%) applied to the skin was removed by cleaning the application site with alcohol soaked gauze. Less than 2% radioactivity was detected in the urine and none found in faeces or in the form of CO_2. The study demonstrated poor absorption of AE C12 with six ethoxy units through human skin.

For the purposes of risk assessment, 10% dermal absorption in humans is assumed.

33.4.1.3 Inhalation absorption

No data were available for inhalation absorption.

For human risk assessment purposes, inhalation absorption of 100% is therefore assumed.

33.4.1.4 Distribution

No data were available.

33.4.1.5 Metabolism

The major metabolic pathway of alcohols ethoxylated appears to be the degradation of the ether linkage and oxidation of the alkyl chain to form lower molecular weight polyethylene glycol-like materials and ultimately carbon dioxide and water (HERA 2009). Studies with radio-labelled compounds showed that both the alkyl and the ethylene oxy chains are sites of attack. Moreover, by labelling the compounds with ^{14}C either on the alkyl group or the ethoxylate moiety, it was shown that the metabolism of their alkyl chains was a function of chain length, where longer alkyl chains gave rise to a higher percentage of $^{14}CO_2$ in the expired air and a lower percentage in urine (HERA 2009).

33.4.1.6 Excretion

In animal studies, orally or parentally administered ^{14}C-labelled alcohol ethoxylates were excreted mainly in the urine and only small proportions were recovered in faeces or as CO_2 (HERA 2009). The ^{14}C in the faeces probably results from biliary excretion (Drotman 1980) In the toxicokinetics study described previously (Unilever 1978a), the test substance was also administered through intraperitoneal and subcutaneous injections. The relative proportions of compounds found in the urine, faeces, air and carcass did not differ with the route of administration. Total recoveries were close to 100% for all routes of administration.

33.4.2 *Acute toxicity*

33.4.2.1 Oral

Several acute oral toxicity studies have been conducted with AEs differing in carbon chain lengths and number of ethylene oxide (ethoxy) units. In general, the acute oral toxicity of AEs appeared to be related to the number of ethoxy units rather than the carbon chain length. AEs containing more than five ethoxy units appeared to be of higher acute oral toxicity than those containing four or less. For example, median lethal dose (LD50) values for alcohol ethoxylates C9-11 with 2.5 ethoxy units ranged from 2.7 to 10 g/kg (Shell Research Ltd. 1980) compared to 1.2 to 2.7 g/kg for alcohol ethoxylates C9-11 with eight ethoxy units (Shell Research Ltd. 1976, 1991). As noted, it is expected that alcohols C6-12, ethoxylated would have a larger number of ethoxy units.

In an acute oral toxicity study, conducted according to the Organisation for Economic Cooperation and Development (OECD) test guidelines (TG), groups of male and female rats (species not specified) received a dose of 1.3, 1.6 or 2 g/kg bw AE C7-9 with six ethoxy units (Shell International BV. 1996). Compound-related clinical signs (prone posture, ataxia and changes to breathing pattern) appeared in all treated animals within four hours of dosing, but recovery was complete by day three. No macroscopic changes were apparent in the majority of rats subject to necropsy on day 15. Some changes that were apparent at the end of the experimental period showed no treatment-related trend. For both sexes combined, the LD50 was determined to be greater than 2 g/kg bw.

In another study, conforming to OECD TG 401, an LD50 value of 1.1 g/kg was calculated for AE C11 with nine ethoxy units (HERA 2009). In the study, groups of five male and five female fasted rats (species not specified) were tested with three different doses of 0.89, 1.5 and 2 g/kg of AE C11. All deaths occurred within two days of dosing. There were 4/10, 6/10 and 9/10 deaths (out of 10 animals) in the 0.89, 1.5 and 2.0 g/kg dose groups, respectively. At the low dose all mortalities were female rats indicating that female rats were more sensitive. Gastrointestinal and lung abnormalities, foamy tracheal contents and kidney changes were observed in rats that died. Hypothermia, prostration and / or laboured respiration were also noted in these animals.

Based on these observations AE C6-12 is considered to have low to moderate acute toxicity by the oral route.

33.4.2.2 Dermal

Several studies have been conducted in rats and rabbits on acute dermal toxicity of alcohol ethoxylates. No mortalities occurred in any of these studies, even at very high doses (HERA 2009). The test materials applied were typically solutions containing 19 to 100% w/v active ingredient at doses ranging from 1.3 to 10.2 g/kg wt. Rat and rabbit studies with AE C7-9 and AE C9-11 produced dermal LD50 greater than 2 g/kg bw.

Based on these observations, AE C6-12 is considered to have low acute dermal toxicity.

33.4.2.3 Inhalation

Limited studies are available on the inhalation toxicity of alcohol ethoxylates. None of these studies followed OECD TG nor were they GLP compliant (HERA 2009). In one study, five rats of each sex were exposed for four hours to two different concentrations of AE C9-11, five ethoxy units, generated as a mist (Shell Research Ltd. 1980). The mass median diameter of the particles was 3.4 ± 2.0 µm. There were no mortalities or signs of toxicity observed during the study.

Talmage (1994) reported that alcohol ethoxylates were not acutely toxic to rats at concentrations less than or equal to their saturated vapour concentrations in air. Acute toxic thresholds were reached only when animals were exposed to the undiluted test chemical in the form of a respirable mist or aerosol. Under these conditions, one- or four-hour inhalation LC50 values ranged from 1.5 to 20.7 mg/L. Some studies reported no mortalities at concentrations as high as 52 mg/L.

Based on these observations, AE C6-12 is considered to have low acute toxicity by the inhalation route.

33.4.2.4 Observation in humans

No data were available.

33.4.3 *Irritation / Corrosivity*

33.4.3.1 Skin irritation

Several studies following OECD TG 404 were conducted in rabbits to evaluate the potential of alcohol ethoxylates to cause skin irritation (HERA 2009). Two studies used alcohol ethoxylates C9-11 (with eight ethoxy units) and one study used C11 (with nine ethoxy units) to determine their skin irritation potential. In all three studies, slight erythema was noted at the application sites, which resolved within seven days after application, indicating that alcohol ethoxylates C9-11 are slightly irritating to skin (HERA 2009).

In a series of OECD TG 404 compliant studies investigating the dermal irritation potential of a range of AEs with varying degree of ethoxylation (alcohol ethoxylates ranging between C9-11 to C23-25 with 2.5 to 20 ethoxylate units) were applied to shorn intact skin of rabbits as single doses under semi-occlusive dressing for four hours. Twenty four, 48 and 72 hours after removal of the patch, the skin reaction was evaluated for erythema and oedema. Each of the two factors was scored on a basis of 0 (no change) to 4 (severe reaction) and these scores were combined to give a maximum value of 8. A primary irritation index (PII) was calculated as the average of the scores assigned at three time periods (ECETOC 1995). Under the test conditions, the responses to the test materials ranged from slightly irritating (PII of 0.6 to 1.6 for AE C13, 20 ethoxy units and AE C12-14, 15 ethoxy units) through moderately irritating (PII of 4.1 to 5.6 for; AE C12-14, 10 ethoxy units; AE C13, 6 ethoxy units and AE C13, 5 to 6.5 ethoxy units) to extremely irritating (AE C12-14, 6 ethoxy units, AE C12-14, 3 ethoxy units and AE C13, 3 ethoxy units). The data indicated a trend of lower irritation effect with increasing degree of ethoxylation. The effects caused by the slightly irritating materials in these studies reversed six days after exposure. For those that resulted in moderate to severe irritation, signs of irritation, such as fissures and scaly skin, persisted until the end of the 14-day observation period (HERA 2009).

Based on these observations, AE C6-12, which reportedly contains 3 to 12 ethoxy units, is considered a moderate skin irritant.

33.4.3.2 Eye irritation

The potential for AEs to produce eye irritation has been widely examined in rabbits. Several reviews (Talmage 1994) found that alcohol ethoxylates range from mildly to severely irritating to rabbit eyes when applied undiluted. Very low concentrations (0.1%) were non-irritating, while concentrations between 1 and 10% were slightly to moderately irritating. With some AEs the eyes of the treated animals recovered a few days after exposure. In others, exposure caused irreversible damage to the eyes. No relationship between the alcohol chain length or the number of ethoxylate groups and degree of irritation could be established.

In a GLP compliant study, AE C7-9 was tested for its eye irritation potential. Details of the study are not provided and the study was conducted in only one animal (Shell International BV. 1995). Initial extensive corneal damage was followed by regeneration of the corneal epithelium. On day 7, neovascularisation of the cornea developed which became marked by day 11. As a consequence of this irreversible damage, the study was terminated and the test animal euthanised. In another GLP-compliant study, six rabbits were treated with undiluted C9-11 AE6 (Shell Development Company 1981). All six animals developed corneal opacities which were not completely cleared within 14 days after treatment. Consequently AE C7-9 and C9-11 AE6 were assessed to be severely irritating to the rabbit eye (HERA 2009).

Based on these studies, AE C6-12 is considered to be severely irritating to the eyes.

33.4.3.3 Respiratory irritation

No data were available.

33.4.3.4 Observation in humans

Basketter et al. (2004) collated the results of six AEs (C11AE3, C11AE7, C12-15AE5, C12-15AE7, C16-18AE5, C16-18AE14) tested undiluted in a standard human four-hour patch test in which 0.2 mL of the substance was applied to the skin of the upper outer arm of 30 human volunteers. The treatment sites were assessed for the presence of irritation using a four-point scale, ranging from no reaction to strongly positive reaction at 24, 48 and 72 hours. Twenty per cent sodium dodecyl sulphate was used as a positive control. The study results indicated that none of the alcohol ethoxylates were skin irritants.

In a similar GLP-compliant study according to COLIPA testing guidelines, the skin irritation potential of neat and 20% diluted C16-18AE12 and C16-18AE20 was tested over a 24 hour application on 20 volunteers (Henkel KGaA 2000). Skin reactions were evaluated 6, 24, 48 and 72 hours after removal of the patch for erythema, oedema and scaling. The test substance C16-18AE20 was found to be slightly irritating. Two out of the 20 persons tested with C16-18AE20 developed very mild erythema which had cleared by the end of the 72 hours observation period. One out of twenty persons developed slight erythema resulting from application of the 20% diluted C16-18AE12. The erythema cleared very quickly in all cases.

Talmage (1994) reported several studies evaluating skin irritation properties of AEs in humans. Using the Draize patch test, AE surfactants at dilutions of 60% produced no to slight skin irritation in human subjects.

Little (1977) cites a study in which 10 human volunteers were exposed for four hours a day on three alternate days to undiluted or a 25% aqueous solution of C14-15AE7 under an occlusive patch. Slight to negligible skin irritation was noted. In another study, slight skin irritation was observed in eight subjects exposed for 24 hours to an occluded patch containing a 10% aqueous solution of C12-13AE6.5.

33.4.4 *Sensitisation*

33.4.4.1 Skin sensitisation

The skin sensitisation potential of a whole range of alcohol ethoxylates was evaluated in the guinea pig maximisation test (HERA 2009). Of the 25 studies conducted on different AEs (C9 to C21 with 2 to 21 ethoxy units), 22 studies revealed no evidence for skin sensitisation, two studies concluded that there was ‘essentially’ no evidence for skin sensitisation and only one AEs (C7-9 AE6) was found to exert weak skin sensitisation potential. Although preliminary dose-range finding studies were conducted to determine the appropriate dose levels for intradermal and topical induction and topical challenge, the review concluded that it is

conceivable that the minor signs of erythema in a few animals in this study may be signs of irritation and not of sensitisation.

Additionally, a review of 13 available Buehler studies covering the range of C9 to C15 with 3 to 13 ethoxy units revealed no evidence for skin sensitisation (HERA 2009).

From the above studies, it is concluded that AE C6-12 does not have skin sensitisation potential.

33.4.4.2 Respiratory sensitisation

No data were available.

33.4.4.3 Observation in humans

Two alcohol ethoxylates, AE C12-15 with seven ethoxy units and AE C12-15 with nine ethoxy units, were evaluated in a Human Repeated Insult Patch Test (HRIPT) to determine their skin irritation and sensitising properties (Shell Chemical Company 1969). Each test material was evaluated as an aqueous solution at concentrations of 5% w/v, 10% w/v up to 25% w/v. A patch with 0.03 mL of the test material was allowed to contact the skin for 24 hours, after which the skin site was graded for irritation. Twenty four hours later, a second patch was placed on the same site for 24 hours. This procedure was repeated nine times followed by a two week rest period after which, a final 24 hour challenge patch was applied to an alternative site to determine if a sensitising reaction to the test material occurred. The evaluation of the skin sites after challenge revealed no evidence of skin sensitisation for either of the materials.

During the induction phase, the patches containing the highest concentration of the test material (25%) caused slight primary skin irritation.

33.4.5 *Repeat dose toxicity*

33.4.5.1 Oral

Several repeat dose oral toxicity studies on alcohol ethoxylates with varying chain lengths and ethoxy units have been reported (HERA 2009). The following table lists only those studies that used alcohol ethoxylates with carbon chain lengths between C6 and C12 or mixtures of alcohol ethoxylates that contained members of this class of alcohol ethoxylate, such as AE C12-15 (which contains C12). The ethoxy units in the AE reported in Table A33.3 ranged from 3 to 11. For most studies, the oral doses were reported only as percent dietary concentrations. However, the No Observed Adverse Effect Levels (NOAEL) in these studies have been calculated as ‘mg/kg bw/day’ based on the body weight of the animals.

Table A33.3 Repeated dose oral toxicity studies

Alcohol ethoxylate	Species, group size	Study duration/dose	NOAEL	Effects at LOAEL	Reference
C12-14 E7	Wistar rats 10/sex	90 days; 0, 0.03, 0.063, 0.125, 0.25, 0.5, 1.0%	110 mg/kg bw/d (0.125%)	Reduced body weight, increases in relative liver weight (hypertrophy), and alkaline phosphatase at doses ≥0.25%.	Unilever (1978a)
C12-15 E7	Wistar rats	90 days; 0, 0.03, 0.063, 0.125, 0.25,	102 mg/kg bw/d	Reduced body weight, increased relative liver weight (hypertrophy), and	Unilever (1978b)

Alcohol ethoxylate	Species, group size	Study duration/dose	NOAEL	Effects at LOAEL	Reference
	10/sex	0.5, 1.0%	(0.125%)	alkaline phosphatase	
C12-13 E6.5	Sprague-Dawley rats	104 weeks; 0, 0.1, 0.5, 1%	50 mg/kg bw/d (0.1%)	Reduced bodyweight gain, Increased relative liver, kidney and brain weight	Talmage (1994)
C14-15 E7	Sprague-Dawley rats 20/sex	90 days; 0, 0.1, 0.5, 1.0%	No NOAEL/ LOAEL established	No treatment-related changes	Procter and Gamble (1974)
C14-15 E7	Wistar rats 6/sex	90 days; 0, 300, 1000, 3000, and 10 000 ppm	50 mg/kg bw/d (1000 ppm)	Reduced body weight gain. Increases in liver and spleen weights, urea, chloride and cholesterol. Elevated white blood cell counts.	Shell Research Ltd (1982)
C14-15 E7	Sprague-Dawley rats	104 weeks; 0, 0.1, 0.5, 1%	50 mg/kg bw/d (0.1%)	Reduced bodyweight gain, Increased relative liver, kidney and brain weight	Talmage (1994)
C14-15 E7	Charles River rats n=520	104 weeks; 0, 0.1, 0.5, 1%	160 mg/kg bw/d (0.5%)	Reduced bodyweight gain, Increased relative organ weights	Little (1981) Talmage (1994)

Growth retardation and organ weight changes were the most common observations in animals in all repeat dose studies. The liver appeared to be the major target however the observed changes (increased relative liver weight and hepatocytic hypertrophy) were considered to be indicative of an adaptive response rather than a true adverse effect. If the liver changes were accompanied by other effects, such as variation in triglycerides, cholesterol or urea concentrations, then the observed changes in liver and other organs were considered as adverse effects and NOAELs from these studies were derived accordingly.

NOAELs of 50 to 700 mg/kg bw/day have been established in studies (of at least 90 days) with various AEs based mostly on changes in relative organ weights and liver hypertrophy. A NOAEL of 1000 ppm (50 mg/kg bw/day) was established in a good quality 90-day oral feeding study with Wistar rats (Shell Research Ltd 1982). In this study, rats fed with C14-15 AE7 showed dose-related reduction in mean body weights, increased liver and spleen weights accompanied by higher urea, chloride, potassium (males) and cholesterol (females) levels. Haematological changes (increased leukocytes and lymphocytes) were noted in males at 3000 ppm (150 mg/kg bw/day) and in both sexes at the top dose with decreased neutrophils, cell volumes and haemoglobin also seen in females at the top dose. A NOAEL of 50 mg/kg bw/day was also established in a 104-week rat study of C12-13 E6.5 or C14-15 E7, based on reduced body weight gain and elevated relative organ weights at 250 mg/kg bw/day (Talmage 1994).

The oral repeat dose NOAEL of 50 mg/kg bw/day from the 90-day study (supported by the same NOAEL from the 104-week study) will be used for human risk assessment of the related alcohol ethoxylates.

33.4.5.2 Dermal

In a dermal repeat dose study conducted according to OECD TG (Gingell and Lu 1991), 10 rats per sex per group were treated dermally with 1%, 10% and 25% AE C9-11 for 90-days (methodology details not provided). In-life observations included body weights, urine and blood collection and analysis and skin irritation. At necropsy, organs and tissues collected were preserved in buffered formalin and histopathologically examined. Dermal treatment did not result in any significant compound-related effects. Scores for signs of irritation at the application site throughout the study were zero, however, dry and flaky skin was noted at the 10% and 25% treatment levels. Relative kidney weights were increased in both sexes at the 25% treatment level, but no histological lesions could be determined. A NOAEL of about 80 mg/kg bw/d (10% treatment level) was established by the study authors based on observed increases in relative kidney weight. However this NOAEL is not considered appropriate for human risk assessment because it is based only on changes in relative kidney weights while no other effects or histological lesions were detected in treated rats. No other suitable NOAEL underpinned by significant adverse changes could be derived.

33.4.5.3 Inhalation

Long-term inhalation studies on alcohol ethoxylates were not available.

33.4.5.4 Observation in humans

No data were available.

33.4.6 *Genotoxicity*

Several reliable and well documented *in vitro* and *in vivo* genotoxicity assays covering the whole spectrum of alcohol ethoxylates were conducted to assess their potential to induce genotoxicity (HERA 2009). The range of evaluated surfactants spanned C7-9 E2 to C22 E10. For ethoxy units, a similarly broad range was evaluated: C12-14 E3 to C16-18 E20. In all *in vitro* and *in vivo* genotoxicity assays, there was no indication of genetic toxicity of the broad range of structurally different alcohol ethoxylates. The structure of alcohol ethoxylates are not of concern for potential genotoxicity.

Based on these it was concluded that there is no evidence that AE C6-12 is genotoxic.

33.4.7 *Carcinogenicity*

Carcinogenicity studies for AE C6-12 are not available. The carcinogenic potential of a closely related compound, AE C12-13, was tested in rats in a two-year oral feeding study. Sprague-Dawley rats were fed AE C12-13 (with 6.5 ethoxy units) in their diet at doses up to 1% (500 mg/kg bw/day) for two years (Talmage 1994). Reduced food consumption was noted at the higher dose levels (0.5 and 1% for females and 1% for males), resulting in a lower body weight gain compared to the control group. No treatment-related histopathology was found and no increase in tumour incidence was observed. On the basis of this study, C12-13 was not considered to be carcinogenic.

In a similar study (Procter and Gamble Ltd. 1979), AE C14-15 (with seven ethoxy units) was administered in the diet at 0, 0.1, 0.5 and 1% to four groups of Charles River rats for a period of one or two years. Fifteen males and females from each group were sacrificed after an interim of one-year exposure. The remaining animals were treated for the full two-year period. Administration of AE C14-15 for a period of one or two years did not produce any compound-related changes in general behaviour and appearance. The survival rate of the test animals was comparable to those of the controls. At necropsy, no compound-related effects were observed in organ to body weight determinations. In conclusion, there was no

evidence to indicate that treatment-related changes of a carcinogenic nature were produced in rats by repeated ingestion of 0.1, 0.5 and 1% C14-15.

Based on the observations, AE C6-12 is not considered to have carcinogenic potential.

33.4.8 *Reproductive toxicity*

33.4.8.1 Fertility

The reproductive toxicity and developmental effects of AE C12 with unspecified ethoxylate units was evaluated in a two-generation feeding study (Little 1977). Full details of the study were not provided. Rats were exposed to the compound at dose levels of 25, 50 or 250 mg/kg bw/d. Specific observations for the reproduction phase of this study included observations for fertility, litter size, numbers of male and female pups, viability of the newborn, survival of pups to weaning and growth of the pups. No treatment-related changes in behaviour or appearance were observed in the parental rats or pups throughout the study. Fertility of treated groups was comparable with the controls. The only observation was a reduced weight gain of parental rats and pups relative to the control at the highest dose level. A NOAEL for fertility was not established.

In a two-generation reproduction study, Fisher 344 rats (30 per sex per group) were dermally exposed to 1 mL/kg bw AE C9-11 at concentrations of 0, 1, 10 or 25% w/v three times a week except during the mating period (Shell Development Company 1985). This treatment equals exposure levels of about 0, 10, 100 or 250 mg/kg bw/d. No mortalities were observed in the F0 generation. There was no effect on maternal body weight during gestational and lactational periods in either generation. At necropsy, organ weight differences in liver, lung, kidney and heart were observed in the F1 generation. However no pathological findings were associated with these affected organs. There were no compound-related effects on mating and fertility indices and mean gestational length in both generations. No effects on testicular weights and sperm counts in F0 and F1 male adults were observed. Macroscopic and microscopic examination of the reproductive organs did not reveal significant differences in the treated groups compared to the controls. A NOAEL for reproductive and developmental toxicity was not established in this study.

AE C6-12 is not considered to be toxic to fertility.

33.4.8.2 Developmental toxicity

In a two-generation developmental and teratogenicity study, Charles River CD rats (25 per sex per group) were fed AE C12 in the diet at dosage levels of 0.05, 0.1 and 0.5% (corresponding to about 25, 50 and 250 mg/kg bw/d) (Talmage 1994). Rats in the three test groups received the test compound continuously during the study. General behaviour, appearance and survival were not affected by treatment. At the 0.5% dose level, adults and pups gained less weight than the control rats and there was also a statistical increase in embryo lethality and soft tissue anomalies. At the 0.1% dose, there was a statistical decrease in mean foetal liver weight. Neither of these effects was considered to be treatment-related by the authors as they showed no dose response characteristics. A NOAEL for developmental and teratogenic toxicity was not established.

In another study with AE C12, 25 female rabbits were orally administered doses of 0, 50, 100 or 200 mg/kg bw/d from day 2 to day 16 of gestation (Shell Chemicals Ltd. 2002). Caesareans were performed on the 28th day of pregnancy. A definite increase in maternal toxicity, evidenced by ataxia and a slight decrease in body weight, was observed at 100 and 200 mg/kg bw/d. No effects were observed for parameters such as the number of corpora lutea, implantations, live foetuses and spontaneous abortions. Nine control rabbits and 31 treated rabbits (dose groups not specified) died during the study. Surviving rabbits at the 200 mg/kg bw/d dose level generally showed slight losses of body weight. In seven treated

rabbits (dose groups not specified) and two control rabbits, early deliveries were recorded. A NOAEL of 50 mg/kg bw/d for maternal toxicity was established in this study. No NOAEL for developmental toxicity was established.

Based on available data, alcohol ethoxylates C6-12 are not considered to be developmental toxicants.

33.4.9 *Other health effects*

No data were available.

33.5 Health hazard summary

33.5.1 *Critical health effects*

Alcohol ethoxylates C6-12 is considered to have low to moderate acute oral and low acute dermal toxicity. Based on studies on closely related compounds, AE C6-12 is expected to be a skin irritant and severe eye irritant but not a skin sensitiser.

Repeat dose oral studies indicated effects on organ weights and liver hypertrophy. A NOAEL of 50 mg/kg bw/d for systemic toxicity was determined in a 90-day study based on reduced mean body weights, increased liver and spleen weights, high urea, chloride and cholesterol and increased leucocytes and lymphocytes at the next higher dose. This NOAEL will be used for human risk assessment.

Alcohol ethoxylates were not genotoxic or carcinogenic. Reproductive and developmental studies with a range of alcohol ethoxylates indicated no adverse effects on these parameters.

33.5.2 *Hazard classification*

Based on the above studies, alcohol ethoxylated C6-12 is recommended by NICNAS to Safe Work Australia for classification and labelling under the current *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004) and the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A33.4. These NICNAS recommendations do not consider physical or environmental hazards.

Table A33.4 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful if swallowed (X_n; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Irritating to skin (X_i; R38) Risk of serious eye damage (X_i; R41)	Causes skin irritation – Cat. 2 (H315) Causes serious eye irritation – Cat. 1 (H318)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

Mixtures containing the chemical are classified as hazardous based on the concentration (Conc) of the chemical in the mixtures. The NICNAS recommended risk phrases for this chemical are:

- 5% ≤Conc <10%: Xi R36 (Irritant: Irritating to eyes)
- Conc ≥10%: Xi; R41; (Irritant: Risk of serious eye damage)

- Conc ≥20%: Xi; R41, R38; (Irritant: Risk of serious eye damage; Irritating to skin)

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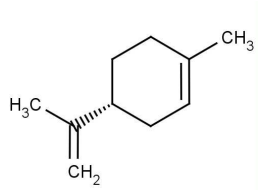
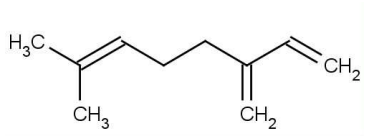
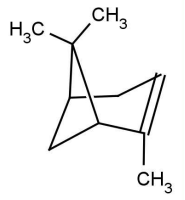
A34 Sweet orange oil terpenes

CAS No.	CAS Name
68647-72-3	Terpenes and terpenoids, sweet orange oil

34.1 Chemical identity

Terpenes and terpenoids, sweet orange oil (CAS No. 68647-72-3) are substances of unknown or variable composition, complex reaction products or biological materials (UVCB), having biological origins. They are composed of approximately 97.1% monoterpene hydrocarbons, at least 91% of which consists of *d*-limonene (United States Environmental Protection Agency (US EPA) 2009). The chemical constituents presented in Table A34.1 are mostly monoterpene hydrocarbons. The chemical structures were obtained from ChemID*plus* (2012).

Table A34.1 Chemical constituents of terpenes and terpenoids, sweet orange oil

Chemical constituents
91-95% *d*-Limonene [Cyclohexene, 1-methyl-4-(1-methylethenyl)-, (R)-, CAS No. 5989-27-5, MW = 136.236, $C_{10}H_{16}$]  2.0-2.1% Myrcene [1,6-Octadiene, 7-methyl-3-methylene-, CAS No. 123-35-3, MW = 136.236, $C_{10}H_{16}$]  1-2% *alpha*-Pinene [Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl-, CAS No. 80-56-8, MW = 136.236, $C_{10}H_{16}$] 

The National Industrial Chemicals Notification and Assessment Scheme's (NICNAS) Priority Existing Chemical (PEC) report on limonene indicated that myrcene and *alpha*-pinene were impurities of *d*-limonene (NICNAS 2002).

The information on the identity of terpenes and terpenoids, sweet orange oil was obtained from US EPA (2009). Details are provided in Table A34.2.

Table A34.2 Chemical identity

Attribute	Identifier
Synonyms	Terpenes and terpenoids, orange oil Sweet orange oil terpenes
Appearance	Colourless liquid

34.2 Physical properties

There is no information on the physical properties for terpenes and terpenoids, sweet orange oil; however, physical properties of some of the chemical constituents of terpenes and terpenoids, sweet orange oil are provided in Table A34.3. The information was obtained from US EPA (2009).

Table A34.3 Physical properties of the chemical constituents of terpenes and terpenoids, sweet orange oil

Property	Values: *d*-limonene	Values: myrcene
Melting Point	-97 to -74 °C	<-10 °C
Boiling Point	175-179 °C	167-172 °C
Vapour Pressure	0.19 kPa at 20 °C	0.27 kPa at 25 °C
Water Solubility	0.0138 g/L at 25 °C	0.0056 g/L at 25 °C
Partition coefficient n-octanol/water (log K_{ow})	4.57	4.17

34.3 Current regulatory controls

The document from here on refers to terpenes and terpenoids, sweet orange oil (CAS No. 68647-72-3) as 'sweet orange oil terpenes', one of the synonyms. Sweet orange oil terpenes are also referred to as 'the substance' in this document.

34.3.1 *Hazard classification for occupational health and safety*

The substance is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

The major constituent of sweet orange oil terpenes, *d*-limonene, is classified as hazardous for human health in the HSIS (Safe Work Australia 2013) with the following risk phrases:

- X_i (Irritant); R38 (Irritating to skin), R43 (May cause sensitisation by skin contact)

Mixtures containing *d*-limonene are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures. The risk phrases for different concentration ranges are:

- Conc ≥20%: X_i; R38, R43
- 1% ≤Conc <20%: X_i; R43.

34.3.2 *Occupational exposure standards*

34.3.2.1 Australia

No specific exposure standards were available for the substance or the chemical constituents.

34.3.2.2 International

No specific exposure standards were available for the substance or the chemical constituents.

34.3.3 *Australian food standards*

No Australian food standards were identified for the substance or the chemical constituents.

34.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the substance or the chemical constituents in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

34.3.5 *Additional controls*

34.3.5.1 Australia

The substance or its chemical constituents are not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

34.3.5.2 International

No international restrictions were identified for the substance or its chemical constituents.

34.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

34.5 Health hazard characterisation

The information on health hazards was obtained from a comprehensive review by the US EPA (2009) and the NICNAS PEC report on limonene (NICNAS 2002). Unless otherwise noted, references to individual studies below are obtained from these reviews.

NICNAS conducted a risk assessment of limonene as a PEC. Limonene occurs as the *d* and *l* isomers, as well as the racemic mixture *dl*-limonene. The PEC report indicated that commercial grades of limonene may also be introduced in Australia as Hydrocarbons, terpene processing by-products (NICNAS 2002).

The US EPA evaluated 10 chemicals as part of the monoterpene hydrocarbon category assessment. The category included the following:

- *d*-limonene
- *dl*-limonene

- terpinolene
- myrcene
- dihydromyrcene (CAS No. 2436-90-0)
- hydrocarbons, terpene processing by-products (CAS No. 68956-56-9)
- oils, orange, sweet (CAS No. 8008-57-9)
- terpenes and terpenoids, sweet orange oil (CAS No. 68647-72-3)
- terpenes and terpenoids, limonene fraction (CAS No. 65996-98-7)
- terpenes and terpenoids, turpentine oil, limonene fraction (CAS No. 65996-99-8).

The last five chemicals are considered complex mixtures composed of two or more monoterpene hydrocarbons as constituents (US EPA 2009).

There are no toxicity data available for sweet orange oil terpenes. However, several toxicity studies are available for the main component of the substance, *d*-limonene. In addition, toxicity data were available for oils, orange, sweet (CAS No. 8008-57-9), which is similarly composed of 91-94% limonene and 2.0-2.1% myrcene (US EPA 2009). Oils, orange, sweet is referred to as 'sweet orange oil' from here on.

Information available for sweet orange oil and *d*-limonene is presented in

Table A34.4. Accordingly, the data gaps for sweet orange oil terpenes are read across from data available for sweet orange oil and *d*-limonene.

Table A34.4 Summary of available toxicity endpoint data

	Sweet orange oil terpenes (CAS No. 68647-72-3)	**Sweet orange oil (CAS No. 8008-57-9)**	***d*-limonene (CAS No. 5989-27-5)**
Acute oral toxicity	×	✓	✓
Acute dermal toxicity	×	✓	✓
Acute inhalation toxicity	×	×	×
Skin irritation	×	×	✓
Eye irritation	×	×	✓
Respiratory irritation	×	×	✓
Skin sensitisation	×	×	✓
Respiratory sensitisation	×	×	×
Repeat dose toxicity (oral)	×	✓	✓
Repeat dose toxicity (dermal)	×	×	×
Repeat dose toxicity (inhalation)	×	×	×
Genotoxicity *in vitro*	×	✓	✓
Genotoxicity *in vivo*	×	×	✓
Carcinogenicity	×	×	✓

	Sweet orange oil terpenes (CAS No. 68647-72-3)	Sweet orange oil (CAS No. 8008-57-9)	*d*-limonene (CAS No. 5989-27-5)
Reproductive toxicity	×	✓	✓

✓*Existing data point;* ×*Missing data point;*

34.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

34.5.1.1 Oral absorption

No data were available for the substance.

Toxicokinetic studies evaluated by the NICNAS indicated that *d*-limonene is readily absorbed by ingestion, with almost complete uptake of orally administered *d*-limonene in rats and humans (NICNAS 2002). Sweet orange oil terpenes are expected to be absorbed by the oral route since the substance consists of at least 91% *d*-limonene.

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed for sweet orange oil terpenes.

34.5.1.2 Dermal absorption

No data were available for the substance.

The dermal absorption of *d*-limonene in mice was rapid, with peak levels reached within 10 minutes. One study in humans noted that the dermal absorption is lower than in the inhalation route, although quantitative data were not provided (NICNAS 2002). Sweet orange oil terpenes are expected to be absorbed by the dermal route since the substance consists of at least 91% *d*-limonene.

For the purposes of risk assessment, 100% dermal absorption in humans is assumed for sweet orange oil terpenes.

34.5.1.3 Inhalation absorption

No data were available for the substance.

Toxicokinetic studies evaluated by NICNAS for d-limonene indicated that *d*-limonene is readily absorbed by inhalation. The two-hour net uptake in humans exposed by inhalation to 10, 225, or 450 mg/m^3 *d*-limonene was reported to average 65% (NICNAS 2002). Sweet orange oil terpenes are expected to be absorbed by the inhalation route since the substance consists of at least 91% *d*-limonene.

For the purposes of risk assessment, 100% inhalation absorption in humans is therefore assumed for sweet orange oil terpenes.

34.5.1.4 Distribution

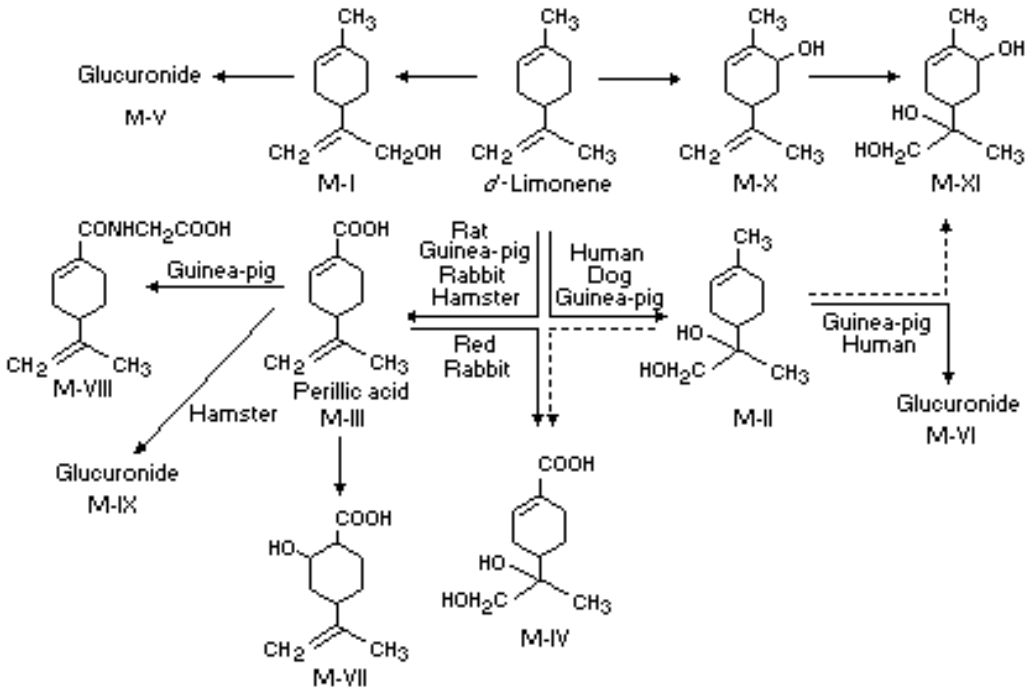
No data were available for the substance.

Toxicokinetic studies showed that *d*-limonene is rapidly distributed to different tissues in the body. Tissue distribution of radioactivity was high in the liver, kidneys and blood following oral administration of [^{4}C] *d*-limonene in rats after 24 hours, with negligible radioactivity levels after 48 hours. Sex-related differences in the distribution of *d*-limonene were reported in rats, with up to three times higher concentration in males than females and approximately 40% of *d*-limonene reversibly bound to the male rat-specific protein, α2μ-globulin (NICNAS 2002). Sweet orange oil terpenes are expected to be rapidly distributed since the substance consists of at least 91% *d*-limonene.

34.5.1.5 Metabolism

No data were available for the substance.

d-Limonene was readily metabolised with the possible metabolic pathways indicated in Figure A34.1. The major plasma metabolites were perillic acid (in humans and rats), dihydroperillic acid (in humans), limonene-1,2-diol (in humans), a previously undescribed analogue of perillic acid (in humans), and limonene-8,9-diol (in humans). The major urinary metabolites in humans were glucuronide conjugates of perillic acid, dihydroperillic acid, limonene-8,9-diol, and a monohydroxylimonene (NICNAS 2002).



Source: International Programme on Chemical Safety (ICPS) (1998)

Figure A34.1 Possible metabolic pathways of *d*-limonene

34.5.1.6 Excretion

No data were available for the substance.

Approximately 50 to 80% of radioactivity was eliminated in the urine within 48 hours following gavage administration of 1.6 g ^{14}C-*d*-limonene (NICNAS 2002). Sweet orange oil terpenes are expected to be eliminated in the urine since *d*-limonene forms a major component of the substance.

34.5.2 *Acute toxicity*

34.5.2.1 Oral

No data were available for the substance.

Administration of a single dose of 5000 mg/kg bw sweet orange oil by gavage to male Wistar rats reported no mortality (US EPA 2009). No other details were provided.

The ranges of acute oral median lethal doses (LD50) from *d*-limonene studies evaluated by NICNAS (2002) were 4400 to 5300 mg/kg bw in rats and 5300 to 6800 mg/kg bw in mice. The effects from acute oral administration of *d*-limonene were not provided.

The substance is expected to have low acute oral toxicity based on read-across data available for sweet orange oil and *d*-limonene. Read-across is a technique used here to predict acute toxicity for sweet orange oil terpenes by using acute toxicity data from other two tested chemicals which comprise the major common component of sweet orange oil terpenes.

34.5.2.2 Dermal

No data were available for the substance.

In two studies, 24-hour applications of 5000 mg/kg bw sweet orange oil and *d*-limonene to the clipped, abraded, abdominal skin of New Zealand White rabbits reported no mortality (US EPA 2009). No other details were provided.

The substance is expected to have low acute dermal toxicity based on reading across the results of the data available for sweet orange oil and d-limonene.

34.5.2.3 Inhalation

No data were available for sweet orange oil terpenes, sweet orange oil, and *d*-limonene.

34.5.2.4 Observation in humans

No data were available for sweet orange oil terpenes, sweet orange oil, and *d*-limonene.

34.5.3 *Irritation / Corrosivity*

34.5.3.1 Skin irritation

No data were available for the substance.

The skin irritancy potential of *d*-limonene was moderate in guinea pigs and low in rabbits. The primary irritation index of *d*-limonene applied to rabbit skin was ranked 3.5 out of 8 (NICNAS 2002). No other details were provided.

The substance is expected to be a skin irritant based on reading across the results of the data available for *d*-limonene.

34.5.3.2 Eye irritation

No data were available for the substance.

NICNAS (2002) indicated that *d*-limonene was an eye irritant in rabbits. No other study details were provided.

A conclusion cannot be made on the eye irritancy potential of the substance based on the limited information.

34.5.3.3 Respiratory irritation

No data were available for the substance.

NICNAS (2002) indicated a potential for limonene to cause respiratory irritation. The exposure concentration producing a 50% respiratory rate decrease (RD_{50}) values for the first 10 minutes of exposure of *d*-limonene and *l*-limonene were reported as 1076 ppm (5983 mg/m^3) and 1467 ppm (8156 mg/m^3), respectively. Testing of other terpenes and mixtures estimated a range of RD_{50} values of limonene enantiomers to be between 1279 ppm (7111 mg/m^3) and 4663 ppm (25 926 mg/m^3).

It is expected that sweet orange oil terpenes may have the potential to cause respiratory irritation since *d*-limonene is the main component of the substance.

34.5.3.4 Observation in humans

No data were available for the substance.

Volunteers presented skin irritation to *d*-limonene within 10 to 15 minutes of exposure using four different patch testing systems (i.e. Finn chamber, Hill Top patch, Van der Bend chamber and Webril patch). Urticarial responses persisted for 24 to 72 hours after patch removal in many of the volunteers (NICNAS 2002).

Based on the available human studies, it is expected that sweet orange oil terpenes may have the potential to cause skin irritation since *d*-limonene is the main component of the substance.

34.5.4 *Sensitisation*

34.5.4.1 Skin sensitisation

No data were available for the substance.

The autoxidised products of *d*-limonene have the potential to be skin sensitisers. Autoxidation of limonene occurs in the presence of light and air, forming a variety of oxygenated monocyclic terpenes (NICNAS 2002).

Limonene (unspecified isomer, form and purity) was tested in four different guinea pig sensitisation assays (i.e. open epicutaneous test, maximisation test, Draize test and Freund's complete adjuvant). Positive results were reported in all of the studies except for the Draize test (NICNAS 2002).

Sweet orange oil terpenes are expected to be skin sensitisers based on reading across the data available for the unspecified limonene isomer.

34.5.4.2 Respiratory sensitisation

No data were available for sweet orange oil terpenes, sweet orange oil, and *d*-limonene.

The potential for limonene to cause respiratory sensitisation cannot be determined based on the limited data available (NICNAS 2002).

34.5.4.3 Observation in humans

No data were available for sweet orange oil terpenes and sweet orange oil.

Human volunteer studies show that limonene has a low skin sensitising capacity and the sensitisation is due to oxidation of products containing limonene when in contact with air (NICNAS 2002).

34.5.5 *Repeat dose toxicity*

34.5.5.1 Oral

No data were available for the substance.

Data for sweet orange oil and *d*-limonene are summarised from US EPA (2009) and NICNAS (2002), and presented in Table A34.5. The Lowest Observed Adverse Effect Level (LOAEL) and No Observed Adverse Effect Level (NOAEL) are indicated for each study.

Table A34.5 Repeat oral toxicity studies with sweet orange oil and d-limonene

Substance	Species, study, method and doses	Results	Remarks	Reference
Sweet orange oil	Sprague-Dawley rats 28-day gavage study (guideline not specified) 0, 240, 600, or 1500 mg/kg bw/day	LOAEL = 600 mg/kg bw/day; NOAEL = 240 mg/kg bw/day in females LOAEL = 1500 mg/kg bw/day; NOAEL = 600 mg/kg bw/day in males	Treatment-related effects included decrease in glucose levels in males at top dose and in females at mid and top doses and lesions in the non-glandular stomach in both sexes at the top dose. Hyaline droplet formation and α2μ-globulin accumulation was reported in males at the top dose. Nephropathy associated with α2μ-globulin formation in male rats is not considered relevant to humans.	US EPA (2009)
d-limonene	Fischer 344 rats 13-week gavage study (United States National Toxicology Program, US NTP, method) 0, 150, 300, 600, 1200, or 2400 mg/kg bw/day	LOAEL = 1200 mg/kg bw/day; NOAEL = 600 mg/kg bw/day in females LOAEL = 1200 mg/kg bw/day; NOAEL = 600 mg/kg bw/day in males	At 2400 mg/kg bw/day, 90 and 50% mortality was reported for females and males, respectively. At 1200 and 2400 mg/kg bw/day, rough hair coats, lethargy and excessive lacrimation were reported in all animals. In males only, there were 6, 12 and 23% decreases in bodyweight at 600, 1200 and 2400 mg/kg bw/day, respectively. Also in males, there were dose-dependent increases in epithelial degeneration in convoluted tubules, granular casts with tubular lumens, and tubular	US EPA (2009)

Substance	Species, study, method and doses	Results	Remarks	Reference
			epithelium regeneration associated with hyaline droplet formation and α2μ-globulin formation. Nephropathy associated with α2μ-globulin formation in male rats is not considered relevant to humans.	
d-limonene	Male rats (strain not specified) 13-week gavage (guideline not specified) 0, 2, 5, 10, 30, or 75 mg/kg bw/day	LOAEL = 75 mg/kg bw/day; NOAEL = 30 mg/kg bw/day	Pathological formation of granular casts at the outer zone of the renal medulla at unspecified dose. Increased relative liver and kidney weights reported at 75 mg/kg bw/day. No other study details were provided.	NICNAS (2002)
d-limonene	Fischer 344 rats 2-year gavage study (US NTP method) 0, 75, or 150 mg/kg bw/day in males 0, 250, or 500 mg/kg bw/day in females	No LOAEL or NOAEL could be determined due to limited reporting of the study.	Slightly lower bodyweights at the top dose for both sexes. No other study details were provided.	NICNAS (2002)
d-limonene	Dogs (unspecified breed) 6-month oral administration 0.4, 1.2, or 3.6 mg/kg bw/day	No LOAEL or NOAEL could be determined due to limited reporting of the study.	Treatment caused nausea and vomiting. No other study details were provided.	NICNAS (2002)
d-limonene	B6C3F1 mice 13-week gavage study (US NTP method) 0, 125, 250, 500, 1000, or 2000 mg/kg bw/day	LOAEL = 1000 mg/kg bw/day; NOAEL = 500 mg/kg bw/day	At 1000 and 2000 mg/kg bw/day, reported effects were 10% decrease in bodyweight in males, rough hair coats and decreased activity in both sexes.	US EPA (2009)
d-limonene	B6C3F1 mice 2-year gavage study (US NTP method) 0, 250, or 500 mg/kg bw/day in males 0, 500, or	No LOAEL or NOAEL could be determined due to limited reporting of the study.	Slightly lower bodyweights at the top dose in females. No other study details were provided.	NICNAS (2002)

Substance	Species, study, method and doses	Results	Remarks	Reference
	1000 mg/kg bw/day in females			

The critical study for determining the effects of repeated oral exposures is the 13 week gavage study, which was conducted in accordance with a national guideline, on *d*-limonene cited in US EPA (2009). The LOAEL and NOAEL established from this study were 1200 and 600 mg/kg bw/day, respectively, based on rough hair coats, lethargy, and excessive lacrimation.

It is expected that these LOAEL and NOAEL values can be applied to sweet orange oil terpenes since *d*-limonene is the main component of the substance.

34.5.5.2 Dermal

No data were available for sweet orange oil terpenes, sweet orange oil, and *d*-limonene.

34.5.5.3 Inhalation

No data were available for sweet orange oil terpenes, sweet orange oil, and *d*-limonene.

34.5.5.4 Observation in humans

No data were available for sweet orange oil terpenes, sweet orange oil, and *d*-limonene.

34.5.6 *Genotoxicity*

No data were available for the substance.

In an Ames test with sweet orange oil, all *Salmonella typhimurium* strains showed negative responses with and without metabolic activation. Sweet orange oil was also negative with and without metabolic activation in a gene mutation test in mouse lymphoma cells (US EPA 2009).

Based on available *in vitro* and *in vivo* data, there is no evidence that *d*-limonene or its metabolites are genotoxic (US EPA 2009; NICNAS 2002).

Sweet orange oil terpenes are not expected to be genotoxic based on reading across the data available for the sweet orange oil.

34.5.7 *Carcinogenicity*

No data were available for the substance.

In a two-year study in accordance with US NTP methodology, *d*-limonene was administered by gavage to Fischer 344 rats (0, 75 or 150 mg/kg bw/day in males; and 0, 300 or 600 mg/kg bw/day in females), and B6C3F1 mice (0, 75, or 150 mg/kg bw/day in males; and 0, 500 or 1000 mg/kg bw/day in females). In the kidney, increased incidences of tubular cell adenomas and adenocarcinomas were reported in male rats. These effects were not seen in female rats, and male and female mice (NICNAS 2002; US EPA 2009). The kidney tumours seen in male rats are associated with α2μ-globulin formation and are not considered relevant to humans (US EPA 1991; NICNAS 2002).

Sweet orange oil terpenes are not considered to be carcinogenic based on reading across the data available for *d*-limonene.

34.5.8 *Reproductive toxicity*

34.5.8.1 Fertility

No data were available for sweet orange oil terpenes, sweet orange oil, and *d*-limonene.

34.5.8.2 Developmental toxicity

No data were available for sweet orange oil terpenes.

Developmental toxicity studies for sweet orange oil and *d*-limonene are summarised from US EPA (2009) and NICNAS (2002), and are presented in Table A34.6. The LOAEL and NOAEL for each study are indicated.

Table A34.6 Developmental toxicity studies with sweet orange oil and *d*-limonene

Substance	Species, method, duration and doses	Results	Remarks	Reference
Sweet orange oil	Sprague-Dawley rats Gavage, 7 days prior to and through mating, gestation, delivery, and 4 days of lactation 0, 375, 750, or 1500 mg/kg bw/day	Maternal: • NOAEL = 750 mg/kg bw/day Developmental: • LOAEL = 1500 mg/kg bw/day • NOAEL = 750 mg/kg bw/day	Decreased dam bodyweight and food consumption at mid and top doses. At 1500 mg/kg bw/day, increased stillbirths and pup mortality were observed. No other treatment-related developmental effects were reported.	US EPA (2009)
d-limonene	Wistar rats Gavage, gestation day (GD) 9-15 0, 591 or 2869 mg/kg bw/day	Maternal: • NOAEL = 591 mg/kg bw/day Developmental: • LOAEL = 2869 mg/kg bw/day • NOAEL = 591 mg/kg bw/day	Dam mortality and decreased bodyweight were observed at 2869 mg/kg bw/day. At 2869 mg/kg bw/day, effects were decreased foetal bodyweights, delayed ossification of foetal metacarpal bones and proximal phalanx, and decreased weights of thymus, spleen and ovaries.	US EPA (2009); NICNAS (2002)
d-limonene	ICR mice Gavage, GD 7-12 0, 591 or 2363 mg/kg bw/day	Maternal: • NOAEL = 591 mg/kg bw/day Developmental: • LOAEL = 2363 mg/kg bw/day • NOAEL = 591 mg/kg bw/day	Decreased dam bodyweight gain at 2363 mg/kg bw/day. At 2363 mg/kg bw/day, effects in the offspring were increased incidence of fused ribs, delayed ossification of some bones, and decreased bodyweight gain.	US EPA (2009)
d-limonene	Japanese White	Maternal:	Increased dam mortality at	US EPA

Substance	Species, method, duration and doses	Results	Remarks	Reference
	rabbits Gavage, GD 6-18 0, 250, 500, or 1000 mg/kg bw/day	• NOAEL = 250 mg/kg bw/day Developmental: • No LOAEL or NOAEL can be established	1000 mg/kg bw/day. Decreased dam bodyweight gain and food consumption at 500 and 1000 mg/kg bw/day. No treatment-related effects observed in the offspring.	(2009); NICNAS (2002)

The studies on sweet orange oil and *d*-limonene demonstrate that developmental effects occurred only at maternally toxic doses and are considered to be secondary to maternal toxicity.

Sweet orange oil terpenes are not developmental toxicants based on reading across the data available for sweet orange oil and *d*-limonene.

34.5.9 *Other health effects*

No data were available for sweet orange oil terpenes, sweet orange oil, and *d*-limonene.

34.6 Health hazard summary

34.6.1 *Critical health effects*

Sweet orange oil terpenes have low acute oral and dermal toxicity based on reading across the data available for sweet orange oil and *d*-limonene. Based on reading across the data available for *d*-limonene, the substance is a skin irritant and a skin sensitiser.

The most appropriate NOAEL for risk assessment, determined from the 13-week study on *d*-limonene cited in US EPA (2009), is 600 mg/kg bw/day based on decreased bodyweight at the LOAEL of 1200 mg/kg bw/day. This NOAEL will be applied to sweet orange oil terpenes.

Sweet orange oil terpenes are neither genotoxic nor a developmental toxicant based on data available for sweet orange oil and *d*-limonene. The substance is not carcinogenic based on reading across the data available for *d*-limonene.

34.6.2 *Hazard classification*

The substance is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A34.7. These NICNAS recommendations do not consider physical or environmental hazards.

Table A34.7 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	GHS[b] classification
Irritation / Corrosivity	Irritating to skin (X_i; R38)	Causes mild skin irritation – Cat. 3 (H316)
Sensitisation	May cause sensitisation by skin contact (X_i; R43)	May cause an allergic skin reaction – Cat. 1B (H317)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

34.7 References

ChemID*plus* (2012). Accessed 11 September 2013 at http://chem.sis.nlm.nih.gov/chemidplus/

IPCS (1998) Concise International Chemical Assessment Document No. 5: Limonene. World Health Organization.

NHMRC (2011) Australian Drinking Water Guidelines 6 2011. National Health and Medical Research Council. Accessed in September 2013 at http://www.nhmrc.gov.au/guidelines/publications/eh52

NICNAS (2002) Limonene: Priority Existing Chemical Assessment Report No. 22. National Industrial Chemicals Notification and Assessment Scheme.

NICNAS (2017a) Identification of chemicals associated with coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NICNAS (2017b) Human health hazards of chemicals used in coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. National Occupational Health and Safety Commission.

Safe Work Australia (2013) Hazardous Substances Information System. Accessed 26 June 2013 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

TGA (2014) Poisons Standard 2014. Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Therapeutic Goods Administration.

UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe, New York and Geneva. Accessed in June 2013 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

US EPA (1991) α2μ-globulin: association with chemically induced renal toxicity and neoplasia in the rat. United States Environmental Protection Agency, EPA/625/3-91/019F.

US EPA (2009) Screening level hazard characterization: monoterpene hydrocarbons category. United States Environmental Protection Agency. Accessed at http://www.epa.gov/chemrtk/hpvis/hazchar/Category%20Monoterpenes_Sept2009.pdf

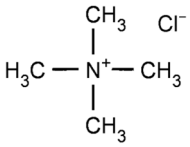
A35 Tetramethylammonium chloride

CAS No.	CAS Name
75-57-0	Methanaminium, N, N, N-trimethyl-, chloride (1:1)

35.1 Chemical identity

Information on chemical identity was obtained from ChemID*plus* (2012) and the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier (REACH 2013). Details are provided in Table A35.1.

Table A35.1 Chemical identity

	Tetramethylammonium chloride
Synonyms	Methanaminium, N, N, N-trimethyl-, chloride Tetramethylammonium chloride
Structural formula	
Molecular formula	$C_4H_{12}NCl$
Molecular weight	109.6
Appearance and odour	Hygroscopic white powder with unspecified odour
SMILES notation	CN{+}(C)(C)(C).Cl{-}

35.2 Physical properties

The physical properties of the chemical were obtained from REACH (2013) and are presented in Table A35.2.

Table A35.2 Physical properties

Property	**Value**
Melting point	268 °C
Boiling point	300 °C (thermal decomposition)
Density	1190 kg/m^3 at 20 °C
Vapour pressure	<1.6 x 10^{-11} kPa at 25 °C <1.3 x 10^{-11} kPa at 20 °C
Water solubility	>1000 g/L at 20 °C
Partition coefficient n-octanol/water (log K_{ow})	<-1.6 at 20 °C

35.3 Current regulatory controls

The document from here on refers to methanaminium, N, N, N-trimethyl-, chloride (1:1) (CAS No. 75-57-0) as 'tetramethylammonium chloride', one of the synonyms of the chemical.

35.3.1 *Hazard classification for occupational health and safety*

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

35.3.2 *Occupational exposure standards*

35.3.2.1 Australia

No specific exposure standards were available.

35.3.2.2 International

No specific exposure standards were available.

35.3.3 *Australian food standards*

No Australian food standards were identified.

35.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

35.3.5 *Additional controls*

35.3.5.1 Australia

The chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014); however, tetramethylammonium chloride is a quaternary ammonium compound and quaternary ammonium compounds are listed in Schedules 5 and 6. The SUSMP (TGA 2014) has the following entries:

Schedule 5:

> *'Quaternary ammonium compounds in preparations containing 20 per cent or less of quaternary ammonium compounds except:*
>
> - *when separately specified in these Schedules;*
> - *dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or*
> - *in preparations containing 5 per cent or less of such quaternary ammonium compounds.'*

Schedule 6:

> *'Quaternary ammonium compounds except:*
>
> - *when separately specified in these Schedules;*

- *when included in Schedule 5;*
- *dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or*
- *in preparations containing 5 per cent or less of such quaternary ammonium compounds.'*

35.3.5.2 International

No international restrictions were identified.

35.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

35.5 Health hazard characterisation

The information on health hazards were obtained from REACH (2013).

Available data for tetramethylammonium hydroxide [Methanaminium, N,N,N-trimethyl-, hydroxide, CAS No. 75-59-2, MW 91.15, $C_4H_{12}NOH$], an analogue of the chloride, were used where data were not available for certain endpoints of tetramethylammonium chloride (i.e. repeat oral and dermal dose toxicity, and toxicity to fertility and development). The information on repeat oral and dermal dose toxicity, and toxicity to fertility and development was obtained from the Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set Initial Assessment Report (SIAR) for tetramethylammonium hydroxide (OECD 2007).

Tetramethylammonium hydroxide and tetramethylammonium chloride have similar molecular weights and are both composed of a functional amine group that is quaternary in nature. In addition, once the two chemicals enter the body, tetramethylammonium hydroxide will dissociate into the tetramethylammonium and hydroxide ions, and tetramethylammonium chloride will dissociate into the tetramethylammonium and chloride ions; the toxicity of both the chemicals is mainly attributed to the tetramethylammonium ion. Thus, the use of tetramethylammonium hydroxide as analogue for tetramethylammonium chloride is appropriate.

Unless otherwise noted, references to individual studies below are taken from REACH (2013) and OECD (2007).

35.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

35.5.1.1 Oral absorption

No data were available.

The International Chemical Safety Card (ICSC) for tetramethylammonium chloride indicated that the substance can be absorbed into the body by ingestion (International Programme on Chemical Safety (IPCS) 2003).

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

35.5.1.2 Dermal absorption

No data were available.

High potential uptake of tetramethylammonium chloride through the skin is expected due to the chemical's low molecular weight, high water solubility, and low vapour pressure.

For the purposes of risk assessment, 100% dermal absorption in humans is therefore assumed.

35.5.1.3 Inhalation absorption

No data were available.

The ICSC for tetramethylammonium chloride indicated that the substance can be absorbed into the body by inhalation (IPCS 2003).

For the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

35.5.1.4 Distribution

Human erythrocytes were isolated from freshly collected blood in a 1966 *in vitro* cellular uptake study (REACH 2013). Results showed that 0.08% of the total activity of ^{14}C-tetramethylammonium chloride was taken up by the cells. The uptake of the chemical showed a linear increase with increasing external concentration. The study concluded that the tetramethylammonium ions are taken up intracellularly both by passive diffusion and by a receptor-mediated mechanism.

35.5.1.5 Metabolism

In the *in vitro* cellular uptake study above, the chemical was not converted to any other metabolites (REACH 2013).

35.5.1.6 Excretion

No data were available.

35.5.2 *Acute toxicity*

35.5.2.1 Oral

An aqueous solution of 15% tetramethylammonium chloride was administered by gavage to female Sprague-Dawley rats at doses of 300, 550, or 2000 mg/kg bw (REACH 2013). The study was conducted in 2010 in accordance with OECD Test Guideline (TG) 425. Clinical signs included prostration and lethargy, few faeces, chromorhinorrhoea, and wetness of the anogenital area. No abnormalities were reported at necropsy. The reported acute oral median lethal dose (LD50) was 1146 mg/kg bw, equivalent to 171.9 mg/kg bw tetramethylammonium chloride.

In a 2007 study conducted in accordance with OECD TG 425, the chemical was administered by gavage to female Wistar rats at doses of 17.5, 55, or 175 mg/kg bw (REACH 2013). Clinical signs included convulsions, tremors, sagging eyelids, wet nose/mouth area, flaccid muscle tone, prostration, lethargy, spasms, ataxia, and eye closure. Necropsy revealed abnormalities in the thymus, kidneys, spleen, intestines, pancreas, and ovaries. The reported acute oral LD50 was 55 mg/kg bw tetramethylammonium chloride.

In a 1978 study similar to OECD TG 401, an unspecified concentration of the chemical was administered by gavage to Wistar rats at doses of 30, 36, 43, 52, or 62 mg/kg bw

(REACH 2013). Clinical signs included sedation, convulsions, dacryorrhoea, and coma. No abnormalities were reported at necropsy. The reported acute oral LD50 was 47 mg/kg bw tetramethylammonium chloride.

The studies show that the chemical has moderate to high acute toxicity by the oral route in rats.

35.5.2.2 Dermal

Single doses of 200 or 500 mg/kg bw were applied semi-occlusively in the dorsal area of the trunk of rabbits (strain not specified) for 24 hours in a 2007 study, conducted in accordance with OECD TG 402 (REACH 2013). Clinical signs included lethargy, wetness of the nose/mouth area, few faeces, and diarrhoea. No dermal effects were seen. Necropsy revealed abnormalities of the treated skin area and in the lungs, intestines, spleen, thymus, pancreas, and kidneys. The acute dermal LD50 was between 200 and 500 mg/kg bw.

The study found that the chemical has moderate acute toxicity by the dermal route in rabbits.

35.5.2.3 Inhalation

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.5.2.4 Observation in humans

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.5.3 *Irritation / Corrosivity*

35.5.3.1 Skin irritation

Two *in vitro* tests conducted in accordance with OECD TG 439 (skin irritation) and 431 (skin corrosion) were available for the chemical. A poorly described supporting *in vivo* study conducted similar to OECD TG 404 with deviations, was also available.

In the first *in vitro* study, tetramethylammonium chloride powder was liquefied and 10.5 to 11.8 mg applied to 0.38 cm^2 cultured human skin for 15 minutes (REACH 2013). A positive control was established using 5% aqueous sodium dodecyl sulfate. The cell viability of unexposed skin was set at 100%. The mean cell viabilities of the positive control and the test substance were 5 and 28%, respectively. The chemical was reported to be irritating since the mean cell viability was below 50%. In the second *in vitro* study, tetramethylammonium chloride powder was crushed, ground, and applied to 0.6 cm^2 cultured human skin for three minutes or one hour (REACH 2013). The positive control used was 8N potassium hydroxide. The mean cell viabilities at three minutes exposure of the positive control and the test substance were 26 and 98%, respectively. At one hour exposure, the mean cell viabilities of the positive control and the test substance were 10 and 92%, respectively. The chemical was found to be not corrosive since the mean cell viability was above 50 and 15% after three minutes and one hour exposure, respectively.

In the *in vivo* study, a 50% aqueous solution of the chemical was applied occlusively to 6.45 cm^2 of New Zealand White rabbit skin for 24 hours (REACH 2013). The observation time was 48 hours and the reversibility of effects was not tested. Signs of intoxication, such as excessive salivation and apathy, were reported in four out of six rabbits. One animal died and slight erythema was seen in one animal. After patch removal, another animal died, and slight erythema and slight ischaemia were reported. The chemical was found to be slightly irritating based on the conditions of the test.

The tests demonstrate that tetramethylammonium chloride is irritating to the skin.

35.5.3.2 Eye irritation

In an eye irritation test conducted in accordance with OECD TG 405, 0.1 mL of liquefied tetramethylammonium chloride powder was instilled in the eyes of male New Zealand White rabbits (REACH 2013). The treated eye of one animal showed slight dulling of the normal corneal lustre on day one. Conjunctival redness and chemosis were reported in all treated eyes with mean scores of 1.1 and 0.3, respectively. All effects were reversible after seven days. The chemical was found to be not irritating based on the conditions of the test.

In an *in vitro* bovine corneal opacity test conducted in accordance with OECD 437, corneas were incubated with an aqueous solution of 20% tetramethylammonium chloride for 240 minutes (REACH 2013). A positive control was established using 20% imidazole. The negative and positive control responses were within the historical data range which indicated that the test system was valid. The chemical did not induce ocular irritation or corrosion.

The tests demonstrate that the chemical is not an eye irritant.

35.5.3.3 Respiratory irritation

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.5.3.4 Observation in humans

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.5.4 *Sensitisation*

35.5.4.1 Skin sensitisation

Tetramethylammonium chloride in propylene glycol vehicle was applied at concentrations of 5, 10, or 25% in a Local Lymph Node Assay (LLNA) conducted in accordance with OECD TG 429 (REACH 2013). A positive control group was established using hexyl cinnamic aldehyde. The observations for the high dose group were not considered in the interpretation since two of the three animals were sacrificed on days three and four due to severe systemic toxicity. Clinical signs before mortality included flat posture, ptosis, tremors, and irregular breathing. The auricular lymph nodes of the surviving animals treated at 10 and 25% were larger in size compared to the other dose groups. No ear irritation and no macroscopic abnormalities of the surrounding ear area were seen in the surviving animals. The stimulation indices at the 5 and 10% doses were reported as 0.5 and 1.1, respectively. The chemical was not sensitising up to 10% based on the conditions of the test.

The study shows that the chemical is not a skin sensitiser in mice.

35.5.4.2 Respiratory sensitisation

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.5.4.3 Observation in humans

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.5.5 *Repeat dose toxicity*

35.5.5.1 Oral

No data were available for tetramethylammonium chloride with a proposal for testing the repeat oral toxicity indicated by REACH (2013).

Data for tetramethylammonium hydroxide, an analogue of tetramethylammonium chloride, was read across to tetramethylammonium chloride.

In a study conducted in accordance with OECD TG 407, an aqueous solution of 20.19% tetramethylammonium hydroxide was administered by gavage to Sprague-Dawley rats for 28 days at doses of 0, 5, 10, or 20 mg/kg bw/day (Ministry of Health, Labour and Welfare (MHLW) Japan 2001). In the first week, decreased food consumption was observed in males at 10 mg/kg bw/day and in both sexes at 20 mg/kg bw/day. This effect was attributed to the alkalinity of the test substance. Decreased absolute and relative heart weight in males was reported at 10 and 20 mg/kg bw/day but with no dose-response relationship and with no associated histopathological findings. Salivation was observed at the top two doses on the 6th day of administration but this was attributed to the strong alkaline characteristic of tetramethylammonium hydroxide and not as a direct toxic effect. The No Observed Adverse Effect Level (NOAEL) for this study could not be established.

35.5.5.2 Dermal

No data were available for tetramethylammonium chloride.

Data for tetramethylammonium hydroxide, an analogue of tetramethylammonium chloride, was read across to tetramethylammonium chloride.

In a 28-day study comparable to OECD TG 410, an aqueous solution of 25% tetramethylammonium hydroxide was applied on the shaved skin behind the shoulder blades of Sprague-Dawley rats (IBM Corp. 1999). The doses were 0, 5.5, 50, 120, or 250 mg/kg bw/day in males, and 0, 2.5, 5.5, 10, or 50 mg/kg bw/day in females. Skin irritation, such as erythema, oedema and / or scabbing at the application site was seen in all treated animals at all dose groups. The severity of irritation was not specified for the different doses. Scabbing was also seen in the control group. The authors indicated that scabbing could be associated with the instinctive grooming behaviour of the animals. At 120 and 250 mg/kg bw/day, all males died within three hours of application. At 50 mg/kg bw/day, all males died within one week and all females died within two weeks of application. There were no deaths or overt clinical signs of toxicity seen in the lower doses. At 5.5 mg/kg bw/day and above, red ovaries were observed in females. At 50 mg/kg bw/day and above, red lungs, urinary bladder calculus dark eye and small seminal vesicles were observed in males and females. No other effects were observed. The Lowest Observed Adverse Effect Level (LOAEL) is 50 and 5.5 mg/kg bw/day for males and females, respectively. The NOAEL is 5.5 and 2.5 mg/kg bw/day for males and females, respectively.

35.5.5.3 Inhalation

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.5.5.4 Observation in humans

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.5.6 *Genotoxicity*

In an Ames test with tetramethylammonium chloride, conducted in accordance with OECD TG 471, all bacterial strains showed negative responses with and without metabolic activation (REACH 2013).

No *in vivo* data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

The chemical is considered to be not genotoxic based on the *in vitro* study.

35.5.7 *Carcinogenicity*

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.5.8 *Reproductive toxicity*

35.5.8.1 Fertility

No data were available for tetramethylammonium chloride.

Data for tetramethylammonium was read across to tetramethylammonium chloride for this endpoint.

In a reproductive/developmental toxicity screening study conducted in accordance with OECD TG 421, tetramethylammonium hydroxide was administered by gavage to Sprague-Dawley rats at doses of 0, 1, 5, or 20 mg/kg bw/day (TMAH Consortium 2005). Males were treated from 14 days before mating through to mating. Females were treated from 14 days before mating through mating and gestation periods. At the top dose, effects included mortality of two females, decreased food consumption, decreased locomotor activity, incomplete eyelid opening or eyelid closure, loss of hair, and decreased bodyweight after parturition. Salivation was observed at 5 and 20 mg/kg bw/day on the fourth day of administration but this was attributed to the strong alkaline characteristic of tetramethylammonium hydroxide and not as a direct toxic effect. Tetramethylammonium hydroxide showed no effects on fertility parameters. The NOAEL for parental toxicity was 5 mg/kg bw/day. The NOAEL for fertility could not be established.

35.5.8.2 Developmental toxicity

No data were available for tetramethylammonium chloride.

Data for tetramethylammonium was read across to tetramethylammonium chloride.

In the reproductive/developmental toxicity screening study with tetramethylammonium hydroxide described above, there were no treatment-related malformations in the external features of the offspring (TMAH Consortium 2005). The NOAEL for maternal toxicity was 5 mg/kg bw/day. The NOAEL for development could not be established.

35.5.9 *Other health effects*

No data were available for tetramethylammonium chloride and tetramethylammonium hydroxide.

35.6 Health hazard summary

35.6.1 *Critical health effects*

Tetramethylammonium chloride has moderate to high acute oral toxicity, moderate acute dermal toxicity, is irritating to the skin, and is not an eye irritant or a skin sensitiser.

There was no NOAEL established since no adverse effects were observed for tetramethylammonium hydroxide at a maximum dose of 20 mg/kg bw/day from the 28-day rat study by MHLW Japan (2001). This will be applied to tetramethylammonium chloride.

The chemical is not genotoxic or carcinogenic. Tetramethylammonium chloride is not a reproductive toxicant based on read across data available for tetramethylammonium hydroxide.

35.6.2 *Hazard classification*

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A35.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A35.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Toxic if swallowed (T; R25) Toxic in contact with skin (T; R24)	Toxic if swallowed – Cat. 3 (H301) Toxic in contact with skin – Cat. 3 (H311)
Irritation / Corrosivity	Irritating to skin (X_i; R38)	Causes skin irritation – Cat. 2 (H315)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

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A36 Hydrochloric acid

CAS No.	CAS Name
7647-01-0	Hydrochloric acid

Hydrochloric acid is a solution of hydrogen chloride gas (HCl) in water. Both have the same CAS Registry number.

36.1 Chemical identity

The chemical identity information was obtained from ChemID*plus* (2012) and O'Neil (2001). A description of the chemical identity is provided in Table A36.1.

Table A36.1 Chemical identity

	Hydrochloric acid
Synonyms	Muriatic acid, Aqueous hydrogen chloride
Structural formula	H-Cl
Molecular formula	ClH
Molecular weight	36.46
Appearance and odour	Colourless –yellow solution (due to traces of iron, chlorine and organic matter)
SMILES notation	Cl

36.2 Physical properties

Information regarding the physical properties of hydrochloric acid was obtained from O'Neil (2001) and is shown in Table A36.2.

Table A36.2 Physical properties

Property	**Value**
Melting point	-114.22 °C (gas) -42°C (32% solution)
Boiling point	-85.05 °C (gas) 108.6 °C (20.22% solution)
Density – kg/m^3 (degrees C)	1.491 kg/m^3 at 25 °C (gas) 1100 kg/m^3 at 15 °C (20% solution)
Vapour pressure	4220 kPa at 20 °C (gas) 1.4 kPa at 20 °C (30% concentration) 43 kPa at 40 °C (36% concentration)
Water solubility	673 g/L at 30 °C gas)
Partition coefficient (log K_{ow})	Not applicable

36.3 Current regulatory controls

36.3.1 *Hazard classification for occupational health and safety*

Separate listings for 'hydrogen chloride' and 'hydrochloric acid' are provided in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013). Hydrochloric acid is classified as hazardous for human health with the following risk phrases:

- C (Corrosive); R34 (Causes burns)
- X_i (Irritant); R37 (Irritating to respiratory system).

Mixtures containing hydrochloric acid are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures:

- Conc ≥25%: C; R34, R37
- 10% ≤Conc <25%: X_i; R36/37/38 (Irritating to eyes, respiratory system and skin).

36.3.2 *Occupational exposure standards*

36.3.2.1 Australia

There are no specific exposure standards for hydrochloric acid. However, the permissible exposure limits for hydrogen chloride gas apply (Safe Work Australia 2013):

- Time Weighted Average (TWA) of 7.5 mg/m^3 (5 ppm).

36.3.2.2 International

The following exposure standards were identified for hydrogen chloride (Galleria Chemica 2013).

TWA:

- 7 to 8 mg/m^3 (5 ppm) [Austria, Belgium, Denmark, EU, Hungary, Japan, Korea, Mexico, The Netherlands, New Zealand, Norway, Sweden, Turkey]
- 2 to 5 mg/m^3 (1-2 ppm) [Germany, Poland, Switzerland, UK].

Short Term Exposure Limit (STEL):

- 15 mg/m^3 (10 ppm) [Austria, Belgium, EU, Hungary]
- 7.6 to 8 mg/m^3 (5 ppm) [Finland, Iceland, UK].

36.3.3 *Australian food standards*

Hydrochloric acid is an additive permitted in accordance with Good Manufacturing Practice (GMP) in processed foods specified in Schedule 1 of the *Australia New Zealand Food Standards Code – Standard 1.3.1 – Food Additives* (Food Standards Australia New Zealand 2013).

36.3.4 *Australian drinking water guidelines*

Hydrochloric acid is listed as an endorsed drinking water treatment chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

36.3.5 *Additional Controls*

36.3.5.1 Australia

Hydrochloric acid is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedule 5 and 6 with the following entries.

Schedule 5:

> *'Hydrochloric acid (excluding its salts and derivatives) in preparations containing 10 per cent or less of hydrochloric acid (HCl) except:*
>
> - *in preparations containing 0.5 per cent or less of hydrochloric acid (HCl); or*
> - *for therapeutic use.'*

Schedule 6:

> *'Hydrochloric acid (excluding its salts and derivatives) except:*
>
> - *when included in Section 5;*
> - *in preparations for therapeutic use; or*
> - *in preparations containing 0.5 per cent or less of hydrochloric acid (HCl).'*

Hydrochloric acid is included in the Australian Dangerous Goods Code Edition 7 (ADG7) (National Transport Commission 2007) under hydrochloric acid (UN No. 1789) as a 'corrosive substance' in Class 8 with limited quantities of 1 L and 5 L. The ADG7 contains detailed provisions for the packaging and marking of containers in Class 8.

36.3.5.2 International

Hydrochloric acid is listed as a hazardous substance under Section 102(a) of the *Comprehensive Environmental Response, Compensation, and Liability Act* (CERCLA) (United States Environmental Protection Agency (US EPA) 2012). Hydrochloric acid is also listed as a hazardous substance under Section 311(B)(2)(a) of the *Clean Water Act* (US EPA 2011).

36.4 Use

The use of this chemical in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

36.5 Health hazard characterisation

Information on hydrochloric acid or hydrogen chloride gas was sourced primarily from the Organisation for Economic Co-operation and Development (OECD) (2005). Additional sources of hazard information include the International Agency for Research on Cancer (IARC) (1992), US EPA (1995) and Hazardous Substances Data Bank (HSDB) (2013).

As the chemical under assessment is hydrochloric acid, in general, only those studies where the distinction can be made (and the test substance identified as the aqueous form) will be referenced in this assessment.

36.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

Following absorption, the chemical dissociates rapidly into hydrogen ions (protons) and chloride ions, which are both normal, homeostatically regulated components of the human body.

Hydrochloric acid is a direct acting corrosive and irritant and adverse effects are caused at the site of contact by deposition of protons (causing pH change) rather than effects of the chloride ion. Exposure by inhalation, dermal or oral route at high concentrations has therefore been considered as inappropriate.

36.5.1.1 Oral absorption

No data were available.

The adult human secretes hydrochloric acid into the stomach at a concentration of 0.05 to 0.10 N (Rosenberg 1980) and uptake is buffered by the simultaneous endogenous production of bicarbonate. Injury to the gastric mucosa from ingested hydrochloric acid would therefore presumably eventuate at dose levels where the ingested protons exceed the stomach's natural protective mechanisms.The uptake of chloride ions from the consumption of sodium chloride in food is 2.1 to 5.5 g chloride per person per day (OECD 2005).

For human risk assessment purposes, 100% oral absorption is assumed.

36.5.1.2 Dermal absorption

No data were available.

In a skin irritation test, OECD test guideline (TG) 404, 37% hydrochloric acid caused severe damage when applied to rabbits (Potokar 1985). Under these conditions it is expected that damage of the superficial layers of the skin will enhance dermal penetration of the chemical.

For the purposes of risk assessment, given the corrosivity of the chemical as well as its low molecular weight, 100% dermal absorption in humans is assumed.

36.5.1.3 Inhalation absorption

No data were available.

Inhaled hydrogen chloride gas or mist is partially neutralised before it reaches the lower respiratory tract by naturally occurring ammonia gas in the respiratory system (Soskolne et al. 1989). However for human risk assessment purposes, 100% inhalation absorption of the acid is assumed.

36.5.1.4 Distribution

No data were available.

Hydrogen chloride will rapidly dissociate on administration and the chloride ion will enter the body's electrolyte pool. The body pool of the chloride anion is large and regulated by processes well known from human physiology. The hydrogen ions react with various buffering components in biological fluids to form water.

36.5.1.5 Metabolism

No data were available.

Absorbed protons and chloride ions will not be metabolised.

36.5.1.6 Excretion

Following intravenous infusion of 0.15 M hydrochloric acid into rats (50 mL/kg bw/hr) and dogs (20 mL/kg bw/hr), urinary excretion of the chloride ion was increased in both species (Kotchen et al. 1980). With regard to protons, changes in the pH of the body fluids are buffered and regulated within a narrow range to maintain homeostasis which ultimately depends on respiratory excretion of carbon dioxide and bicarbonate regeneration through proton secretion in the urine (Ganong 2001).

36.6 Acute toxicity

36.6.1.1 Oral

Female rats orally administered 3.3% hydrochloric acid yielded an acute oral median lethal dose (LD50) in a range from 238 to 277 mg/kg bw (Hoechst 1966). No details of the study were available. In another study in rats, administration of a solution of undisclosed concentration induced stomach ulceration, inflammation of the intestine, discolouration of the liver and hyperaemia of the lung (Monsanto 1976). An LD50 of 700 mg/kg bw was reported.

36.6.1.2 Dermal

An acute dermal LD50 was established as >5010 mg/kg bw in rabbits however the dose levels administered were not reported (Monsanto 1976).

36.6.1.3 Inhalation

Acute median lethal concentration (LC50) values of 8.3 mg/L and 3.2 mg/L were observed in rats and mice respectively after a 30 minute inhalation exposure to aerosolised hydrochloric acid (Darmer et al. 1974). Clinical signs observed were irritation and corrosion to the eye, skin and respiratory tract with animals succumbing to respiratory failure shortly after exposure.

36.6.1.4 Observation in humans

Mortality has been observed following ingestion of hydrochloric acid. A female died 29 hours after ingestion of 60 mL of a 35% hydrochloric acid solution, although toxic effects were not described (Hashimura et al. 1996). A 29-year-old male presented to hospital after ingesting approximately 200 mL of a cleaning solution containing 36% hydrochloric acid (Kanne et al. 2005). Initial clinical effects included mucosal injury in the oropharynx, hypopharynx, supraglottic region and oesophagus. Further examination at two days post-ingestion revealed gastric necrosis and perforation and the patient died shortly thereafter.

36.6.2 *Irritation / Corrosivity*

36.6.2.1 Skin irritation

In a skin irritation test in rabbits performed according to OECD TG 404, 37% hydrochloric acid (0.5 mL) was applied by both semi-occlusion and occlusion (Potokar 1985). The chemical was found to be corrosive under both conditions after one hour exposure. Corrosion was also seen in a poorly reported study after 17% hydrochloric acid was applied to rabbits for four hours (Vernot et al. 1977).

A 3.3% hydrochloric acid solution (0.5 mL) was found to be moderately irritating after application to rabbits for five days (Hoechst 1966). Slight to marked reddening, isolated small necrosis and slightly cracked and bloody flank skin were observed in 1/3 animals. A 1% solution was non-irritating in the same study.

Based on the three studies the chemical is corrosive to the skin.

36.6.2.2 Eye irritation

In a Draize test (OECD TG 405), eye instillation of a 10% hydrochloric acid solution in rabbits produced severe irritation with conjunctivitis, chemosis, iritis and corneal opacity from 4 to 96 hours after dosing with the severity of irritation increasing over time (Jacobs 1992).

In a method comparable to OECD TG 405, ocular irritancy was tested by instilling 0.33% and 3.3% hydrochloric acid to the conjunctival sac of rabbits and evaluated over 28 hours. At the high dose, very slight to slight reddening and opaque swelling of the conjunctiva with a slight corneal opacity were observed. No irritation was observed at the low dose (Hoechst 1966).

Four eye irritation studies showed that hydrochloric acid (0.3 to 5%) caused mild to severe irritating effects. Overall, the OECD (2005) concluded that severe effects can be expected from exposure of the chemical to the eyes; some inter-study variation in effect was attributed to factors including dose, duration and the buffering/diluting effects of tears.

36.6.2.3 Respiratory irritation

No data were available; however, inhalation of hydrochloric acid vapours is expected to cause irritation.

36.6.2.4 Observation in humans

Patch testing of 30 individuals with 10% hydrochloric acid was conducted in a clinic. Based on the reactions in six volunteers, scored as milder than that of the positive control (20% sodium dodecyl sulfate), the chemical was determined to be ‘irritating to skin’ (York et al. 1996).

Occlusive patches of 4% hydrochloric acid were applied to the skin of 20 individuals for four days. Scores obtained after 24 hours showed that the test substance was a slight irritant with 14/20 volunteers displaying very weak to weak erythema (Agner and Serup 1988).

36.6.3 *Sensitisation*

36.6.3.1 Skin sensitisation

Only poorly described studies were available. Both a guinea pig maximisation test (1% hydrochloric acid in both sensitisation and challenge phases) and a mouse ear swelling test (1% acid in sensitisation and 5% acid for challenge) showed negative results (Gad et al. 1986).

36.6.3.2 Respiratory sensitisation

No data were available.

36.6.3.3 Observation in humans

Occlusive patches of hydrochloric acid (undisclosed concentration) were applied to the skin of 50 individuals for nine 24-hour periods over three weeks (Gad et al. 1986). None gave positive reactions on challenge 10 to 14 days after the final induction application.

36.6.4 *Repeat dose toxicity*

36.6.4.1 Oral

In a study judged to be unreliable (OECD 2005), rats were fed diets containing 312, 625, 937 and 1250 mmol hydrochloric acid/kg diet (180, 349, 366, 466 mg per animal per day) for nine weeks (Upton and L'Estrange 1977). In the groups fed a diet containing 312 mmol/kg and above, an increase in water intake was observed. A No Observed Adverse Effect Level (NOAEL) of 625 mmol/kg diet (870 to 1160 mg/kg bw/day) was determined based on mortalities, decreased body weight and food consumption and changes to blood pH and femur length observed in all groups fed a diet containing 937 mmol/kg and above.

In an oral study with rats over 21 weeks, hydrochloric acid was administered via drinking water (acidified to pH 2 to 3). Decreased protein levels in urine and decreased urine volumes were observed in the treatment groups. A NOAEL could not be established as dose levels were not reported (Clausing and Gottschalk 1989).

36.6.4.2 Dermal

No data were available.

36.6.4.3 Inhalation

Only studies reporting exposure to hydrogen chloride gas were available.

In a Good Laboratory Practice (GLP) compliant study (CIIT 1984), rats and mice were exposed to the gas at concentrations of 0, 10, 20 and 50 ppm (0, 15, 30, 75 mg/m^3) for 90 days. For mice at 50 ppm, a decrease in body weight gain, food consumption and liver weight (male) was noted. For rats, a decrease in body weight gain was observed in males at 50 ppm and a decrease in food consumption was observed in both sexes at 20 and 50 ppm. Inflammatory histopathological changes in lips or nasal cavity were observed in mice and rats above 10 ppm. No histopathological changes were reported in reproductive organs. The No Observed Adverse Effect Concentration (NOAEC) was determined to be 20 ppm (equivalent to 6.2 mg/kg bw/day) for rats based on reduction in body weight gain.

36.6.4.4 Observation in humans

A 15% hydrochloric acid solution was used in a pickling process at a zinc galvanising plant in the Netherlands (Remijn et al. 1982). An atmospheric concentration of 1.8 to 12.4 mg/m^3 (geometric mean) was observed at six sites within the plant with the workers exposed to a hydrochloric acid concentration above 7 mg/m^3 for 27% of their work (employment term unknown). Erosion in more than one incisor was observed in 34/38 workers examined.

36.6.4.5 Summary of repeat dose toxicity

In repeated dose toxicity studies, local irritation effects were observed at 10 ppm and above in a guideline sub-chronic inhalation study. The NOAEC for systemic toxicity (reduction in body weight gain) was 20 ppm. The only available oral study was a poorly conducted nine

week dietary study. A NOAEL of 625 mmol/kg diet (equivalent to 870 to 1160 mg/kg bw/day) was determined based on mortalities, decreased body weight and food consumption and changes to blood pH and femur length observed in all groups fed 937 mmol/kg and above.

36.6.5 *Genotoxicity*

Negative results for mutagenicity are available from an Ames test, a mitotic recombination test using *S. cerevisiae* (D4)(Isquith et al. 1988; Litton Bionetics Inc. 1978**)** and an *E. coli* reverse mutation assay (Demerec et al. 1951). The chemical did not produce growth inhibition in *E. coli* (W3110, P3078) (Isquith et al. 1988; Litton Bionetics Inc. 1978**)** or *B. subtilis* (McCarroll et al. 1981b) repair deficient strains. A DNA damage and repair assay in *E. coli,* showed positive results but these were judged to be unrelated to DNA damage (McCarroll et al. 1981a).

At high concentrations, the chemical was clastogenic to Chinese hamster ovary cells with and without metabolic activation in two *in vitro* chromosome aberration tests (equivalent to OECD TG 473) (Morita et al.1989; Brusick 1986). Positive results were also found at cytotoxic conditions (<pH 6.3) in a mammalian cell gene mutation assay using Mouse lymphoma L5178Y cells (Cifone et al. 1987). In a chromosome aberration test, sister chromatid exchange assay or mammalian cell gene mutation assay using Fischer L5178Y mouse-lymphoma cells obtained negative results at dose levels less than 1.6 µL/mL (Isquith et al. 1988; Litton Bionetics Inc. 1978).

The OECD (2005) concluded that positive results obtained in the non-bacterial systems could be considered an artefact due to low pH of the test media. Hydrochloric acid is not considered to be genotoxic.

36.6.6 *Carcinogenicity*

For carcinogenicity, no pre-neoplastic or neoplastic nasal lesions were observed in a 128-week inhalation study (six hours/day, five days/week) with Sprague-Dawley male rats at 10 ppm hydrogen chloride gas (Sellakumar 1985). A negative result was also obtained in an 84-week study of comparable design using the same dose levels (Albert 1982). In a poorly conducted dermal carcinogenicity study in mice administered 3 to 5% hydrochloric acid for 25 to 46 weeks, no incidence of malignant tumour was observed (Narat 1925).

Several case-control studies of US industry-based workers have been conducted. No association was found between exposure to hydrogen chloride and lung cancer (Bond et al. 1986; Bond et al. 1991; Siemiatycki 1991), intracranial neoplasms (Bond 1983) and renal cancer (Bond 1985). ln a study of 1165 male workers employed in 1940 to 1964 in three US steel-pickling operations for at least six months (Beaumont et al. 1987), a subset of 189 workers had been exposed to mists of acids other than sulfuric, which were primarily of hydrochloric acid. An excess risk for lung cancer was seen but the effect of confounding factors such as exposure to other acids or lifestyle factors such as smoking could not be excluded.

After review of the epidemiological studies, the IARC concluded that there is inadequate evidence for carcinogenicity of hydrochloric acid in humans and in experimental animals. Hydrochloric acid was subsequently classified as Group 3 (not classifiable as to its carcinogenicity to humans) (IARC 1992).

36.6.7 *Reproductive toxicity*

36.6.7.1 Fertility

No data for hydrochloric acid were available.

In a well -conducted, inhalation repeat dose study of hydrogen chloride in rodents that examined reproductive organs, no exposure-related effects were found in testis, epididymis, prostate, seminal vesicle; ovary, uterus, oviduct, mammary glands (CIIT 1984).

In a reproductive/developmental study, groups of female Wistar rats were exposed to hydrogen chloride gas at 450 mg/m^3 for one hour either 12 days prior to mating or on day nine of gestation (Pavlova 1976). Offspring were examined for growth and viability after birth and also underwent pulmonary, hepatic and renal tests at two to three months of age. The authors reported that the exposure was lethal to one-third of the dams, and functional disorders of the lungs, kidneys and liver were observed in surviving dams and offspring. In addition, treatment altered the oestrus cycles. Postnatal mortality was increased in the litters of dams exposed during pregnancy (31.9% versus 5.6%). However, due to the lack of methodology details and limited reporting of results, the OECD (2005) considered that no reliable conclusions could be drawn on the potential reproductive toxicity of hydrogen chloride.

36.6.7.2 Developmental toxicity

The only study available was the combined reproduction/developmental study of Pavlova (1976). In rats mated 12 to 16 days post-exposure and killed on day 21 of pregnancy, fewer live foetuses, a decrease in foetal weight, and an increase in relative lung weights of the foetuses were observed.

36.6.7.3 Summary of reproductive toxicity

For hydrogen chloride gas, a combined reproductive/developmental inhalation toxicity study showing adverse effects to dams and offspring at high dose levels was judged to be unreliable. In addition to this, no effects on the gonads were observed in a 90-day inhalation study up to 50 ppm.

36.6.8 *Other health effects*

No additional health effects were identified.

36.7 Health hazard summary

36.7.1 *Critical health effects*

Hydrochloric acid has demonstrated acute oral toxicity, corrosive effects to the skin and eye, and irritant effects to the respiratory system. Hydrochloric acid is not a skin sensitiser based on the available studies.

Only limited information on the repeated oral toxicity of hydrochloric acid is available. However, as the component ions are normal constituents of the human body (particularly the stomach), only localised effects are expected. No systemic effects from repeated exposures are expected. In rats, inhalation exposure to hydrogen chloride gas (50 ppm) for 90 days was associated with histopathological changes in the respiratory tract and decreased body weight gain. Based on the reduction in body weight gain, the NOAEC of 20 ppm (equivalent to 6.2 mg/kg bw/day) is used in this risk assessment for hydrochloric acid.

The chemical is not genotoxic. No evidence of treatment-related carcinogenicity was observed in animal studies performed by inhalation or dermal administration. In humans, no association between hydrogen chloride exposure and tumour incidence was observed.

No reliable studies were identified regarding specific toxicity to reproduction and development in animals after exposure to hydrochloric acid/hydrogen chloride. Because protons and chloride ions are normal constituents in the body fluids, low concentrations of

hydrochloric acid/hydrogen chloride would not be expected to cause adverse reproductive effects to animals. This conclusion is supported by the 90-day inhalation study where no effects on the gonads of rodents were observed.

36.7.2 *Hazard classification*

This hazard assessment confirms the existing classification under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A36.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A36.3 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* Classification
Irritation / Corrosivity	Causes severe skin burns and eye damage – Cat. 1B (H314) May cause respiratory irritation – Specific target organ toxicity, single exposure - Cat. 3 (H335)

* *Globally Harmonised System (UNECE 2009)*

36.8 References

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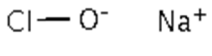
A37 Sodium hypochlorite

CAS No.	CAS Name
7681-52-9	Hypochlorous acid, sodium salt (1:1)

37.1 Chemical identity

The identity information was obtained from ChemID*plus* (2012), Agency for Toxic Substances and Disease Registry (ATSDR) (2010) and O'Neil (2001). A description of the chemical identity is provided in Table A37.1.

Table A37.1 Chemical identity

	Sodium hypochlorite
Synonyms	Sodium hypochlorite Sodium chloride oxide Sodium oxychloride Antiformin Chlorox Modified Dakin's solution
Appearance and odour	Solid sodium hypochlorite ($NaOCl.5H_2O$) is highly unstable and not commercially used. Solutions containing 5 to 15% sodium hypochlorite in water are colourless or slightly greenish-yellow with a chlorine-like odour.
Structural formula	
Molecular formula	ClO.Na
Molecular weight	74.44
SMILES notation	$Cl[O^-].[Na^+]$

37.2 Physical properties

The following physical properties information was obtained from the ATSDR (2010) and European Union Risk Assessment Report (EU RAR) (2007). The physical properties provided in

Table A37.2 are valid for an aqueous solution with a content of 15% (w/w) 'available chlorine'. Available chlorine is a metric of the oxidising strength of a solution and is equal to the amount of molecular chlorine that when added to water would produce a solution with equivalent oxidising power. For the practical conversion of units, the per cent weight of sodium hypochlorite can be assumed to approximate the per cent weight of available chlorine (EU RAR 2007).

Table A37.2 Physical properties

Property	Value
Melting point	-6 °C to -30 °C
Boiling point	96-120 °C (decomposes)
Density – kg/m^3	1.23 x 10^3 (25 °C)
Vapour pressure	1.74–2.0 kPa (20 °C)
Water solubility	293 g/L (0 °C)
Partition coefficient (log K_{ow})	-3.42 (calculated)

37.3 Current regulatory controls

Hereinafter the document refers to hypochlorous acid, sodium salt (1:1) as sodium hypochlorite, one of the synonyms of the chemical.

37.3.1 *Hazard classification for occupational health and safety*

Sodium hypochlorite is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) with the following risk phrases (Safe Work Australia 2013):

- C (Corrosive); R34 (Causes burns), R31 (Contact with acids liberates toxic gas)

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures. The risk phrases for this chemical are:

- Conc ≥10%: C; R34, R31
- 5% ≤Conc <10%: X_i; R36/38 (Irritating to eyes and skin), R31.

37.3.2 *Occupational exposure standards*

37.3.2.1 Australia

No specific exposure standards in Australia were available.

37.3.2.2 International

The following exposure standards were identified for the chemical (Galleria Chemica 2013):

- Short Term Exposure Limit (STEL)
  - 2 mg/m^3 [US, American Industrial Hygiene Association].
- Minimal Risk Level (MRL) for hazardous substances
  - 2 mg/kg/day [US, ATSDR].

37.3.3 *Australian food standards*

Sodium hypochlorite is listed in the Australia New Zealand Food Standards Code – Schedule 18 - Processing Aids – S18.05 Permitted processing aids for water (section 1.137) with a maximum permitted level of 5 mg/kg (available chlorine).

The chemical is also listed in Schedule 18 – Processing Aids – S18.06 Permitted bleaching, washing and peeling agents – various foods (section 1.138) with a maximum permitted level of 1.0 mg/kg (available chlorine) (Food Standards Australia New Zealand 2013).

37.3.4 *Australian drinking water guidelines*

Sodium hypochlorite is endorsed by the National Health and Medical Research Council (NHMRC) for use as a drinking water treatment chemical, with a guideline value of 3 mg/L (available chlorine) listed in the Australian Drinking Water Guidelines (NHMRC 2011).

37.3.5 *Additional controls*

37.3.5.1 Australia

Sodium hypochlorite is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedule 5 and Schedule 6 with the following entries:

Schedule 5:

'Chlorinating compounds containing 20 per cent or less of available chlorine, except:

a) when separately specified in these Schedules;

b) sodium hypochlorite preparations with a pH of less than 11.5;

c) liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

d) liquid preparations containing less than 2 per cent of available chlorine; or

e) other preparations containing 4 per cent or less of available chlorine.'

Schedule 6:

'Chlorinating compounds except:

a) when included in Schedule 5;

b) when separately specified in these Schedules;

c) sodium hypochlorite preparations with a pH of less than 11.5;

d) in liquid preparations containing not less than per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

e) in liquid preparations containing less than 2 per cent of available chlorine; or

f) in other preparations containing 4 per cent or less of available chlorine.'

Sodium hypochlorite is included in the Australian Dangerous Goods Code Edition 7 (ADG7) (National Transport Commission 2007), with an entry for hypochlorite solution (UN No. 1791) listed as corrosive, in Class 8. The ADG7 contains detailed provisions for the packaging, transport and marking of containers in Class 8.

37.3.5.2 International

The chemical is listed as a hazardous substance under Section 311(B)(2)(a) of the *Clean Water Act* (United States Environmental Protection Agency (US EPA) 2011), and under Section 102(a) of the *Comprehensive Environmental Response, Compensation, and Liability Act* (CERCLA), commonly known in the US as Superfund (US EPA 2012).

Hypochlorites (as metabolites of chlorine in water) are listed in the World Health Organization (WHO) Guidelines for Drinking Water Quality (WHO 2011) with a guideline value of 5 mg/L (available chlorine).

Sodium hypochlorite is currently regulated under the *Hazardous Products Act* Ingredient Disclosure List (SOR/88-64) (Canadian Department of Justice 2013) with the maximum authorised concentration of 1%.

37.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

37.5 Health hazard characterisation

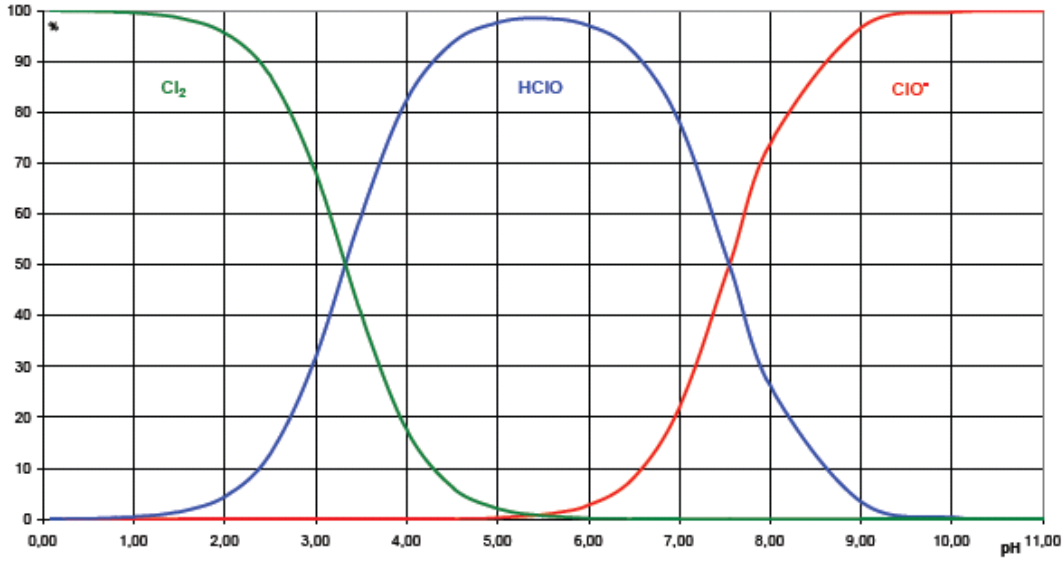
Information on sodium hypochlorite was sourced primarily from the ATSDR (2010) and the EU RAR (2007). Additional sources of hazard information for the chemical include the International Program on Chemical Safety (IPCS) (2012), US EPA (1999) and the International Agency for Research on Cancer (IARC) (1991). Unless noted, references to individual studies below are taken from these reviews.

37.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

Sodium hypochlorite solutions contain three species of chlorine in equilibrium; gaseous chlorine (Cl_2), hypochlorous acid (HClO) and the hypochlorite anion (ClO^-). Their concentration is a function of the pH of the solution (Figure A37.2). The pH of commercial solutions of sodium hypochlorite is adjusted using up to 1% sodium hydroxide and can range from pH 9 to pH 13; as such, the species present are the hypochlorite anion (ClO^-) and hypochlorous acid (HClO), with the former predominating. The toxicological relevance of each species is dependent on the buffering capacity and pH conditions prevailing in the different body tissues and organs.

Sodium is a normal constituent of the blood and between 3.0 and 6.0 g of sodium is taken up via eating food every day (Fodor et al. 1999). The influence of the sodium ion on toxicity is therefore expected to be negligible, with toxicokinetics and dynamics mainly influenced by the hypochlorite anion and protons.



Source: Solvay Chemicals International (2012)

Figure A37.2 Equilibrium of chlorine species in solution

37.5.1.1 Oral absorption

Sodium hypochlorite is corrosive.

Limited data were available regarding the oral absorption of hypochlorite ions in animals. A single dose of radiolabelled hypochlorous acid (^{36}Cl) administered to fasted rats was rapidly absorbed into the bloodstream, peaking in 2 to 4 hours, with a half-life of 2.2 hrs (Abdel-Rahman et al. 1983).

For the purposes of risk assessment, 100% oral absorption in humans is assumed.

37.5.1.2 Dermal absorption

No data were available regarding absorption of the chemical after dermal exposure to sodium hypochlorite. Dermal studies in humans and animals have focused exclusively on effects to the skin and therefore no systemic effects have been described that provide indirect evidence of absorption. However, there is potential for hypochlorite ions to be absorbed through the skin as corrosive substances will damage the skin surface and may therefore enhance penetration (European Union (EU) 2003).

For the purposes of risk assessment, given the corrosivity of the chemical as well as its low molecular weight, 100% dermal absorption in humans is assumed.

37.5.1.3 Inhalation absorption

No data for sodium hypochlorite aerosols were available. Human studies showed that greater than 95% of a bolus dose of chlorine gas (0.5 to 3 ppm), inhaled through the mouth or the nose, is absorbed by the upper respiratory tract and none reaches the lungs (Nodelman and Ultman 1999a, 1999b). Chlorine is a strong oxidiser and forms hydrochloric and hypochlorous acids in water. Because of the high water content of the epithelial lining fluid and the local concentration of chloride and pH, the hydrolysis reaction of chlorine has a large equilibrium constant, such that the concentration of chlorine in the form of hypochlorite is 120 000 times that of chlorine gas (Nodelman and Ultman 1999a). This explains the quantitative absorption of the inhaled chlorine in the upper airways. As the molecular weight

of the chemical is low, for the purposes of risk assessment 100% inhalation absorption of sodium hypochlorite in humans is assumed.

37.5.1.4 Distribution

In rats, 96 hours after the administration of a single gavage dose of approximately three mg/kg of ^{36}C-labelled hypochlorous acid, the labelled acid was highest in plasma followed by bone marrow, testes, skin, kidneys, lungs, duodenum, stomach, spleen, thyroid, thymus and liver (Abdel-Rahman et al. 1983). The lowest concentrations remained in the carcass and fat (Abdel-Rahman et al. 1983).

37.5.1.5 Metabolism

Hypochlorous acid is very reactive and reacts with proteins, amino acids, and unsaturated lipids to form chlorinated compounds, whereas the reaction with carbohydrates yields oxidation products. Scully et al. (1986) reported that chlorination of the stomach from rats resulted in the production of N-chloramines, tentatively identified as N-chloroalanine, N-chloroglycine, and N-chlorophenylalanine. Chemicals, including chloroform and dichloroacetonitrile, were shown to form *in vivo* in the stomach of rats following oral administration of sodium hypochlorite (Mink et al. 1983).

In a study in which rats received a single gavage dose of radiolabelled hypochlorous acid, 96 hours after dosing, 81% of radioactivity detected in plasma was due to ^{36}chloride ion (Abdel-Rahman et al. 1983).

Hyperchloraemic metabolic acidosis, possibly due to the formation of hypochlorous acid and chlorine in the low pH gastric environment, was reported in a human female who drank a bleach solution containing 10% sodium hypochlorite (Ward and Routledge 1988) and in a female who ingested a 5.25% bleach solution (Ross and Spiller 1999). Hypernatraemia and decreased blood pressure were also observed in the former case. These systemic effects may suggest the absorption and distribution of sodium hypochlorite and hypochlorous acid, although it is also possible that they are secondary to tissue damage caused by localised corrosive action of the bleach.

37.5.1.6 Excretion

The excretion of ^{36}Cl was studied in rats following administration of a single gavage dose of approximately 2.6 mg/kg bw of radiolabelled hypochlorous acid (Abdel-Rahman et al. 1983). Over a four-day period, 36% and 15% of the administered radioactivity had been recovered (primarily as the chloride ion) in the urine and faeces, respectively. No radioactivity was recovered in expired air.

37.5.1.7 Summary of toxicokinetics

Sodium hypochlorite in solution forms hypochlorite ions, hypochlorous acid and chlorine, which are strong oxidants. Animal studies have shown that due to its high reactivity, ingested hypochlorous acid is not enzymatically metabolised but is readily (bio)transformed through direct reactions with organic compounds, resulting in the formation of potentially harmful by-products. These chlorinated by-products are ultimately converted primarily to chloride in the blood and eliminated in the urine and faeces. Human data show that absorption of hypochlorite occurs after ingestion, although it is possible that the observed systemic effects were secondary to localised reactions.

37.5.2 *Acute toxicity*

37.5.2.1 Oral

The acute toxicity of sodium hypochlorite (5 to 13% available chlorine) is summarised in Table A37.3 (ATSDR 2010; EU RAR 2007).

Acute oral median lethal dose (LD50) values from studies with rats were between 5000 mg/kg bw to 13 000 mg/kg bw (Racioppi et al. 1994; Kaestner 1981) and 5800 mg/kg bw to 6800 mg/kg bw for mice (Momma 1986). Clinical signs in the mice included behavioural changes and gastrointestinal irritation.

Table A37.3 Sodium hypochlorite: summary of acute oral studies

Species	Solution (% available chlorine)	LD50 (mg/kg bw, solution)	LD50 (mg/kg bw, available chlorine)	Reference
Rat	5.25	13 000	683	Racioppi et al. (1994)
Rat	13	5000	650	Racioppi et al. (1994)
Rat (m)	12.5	8830	1100	Kaestner (1981)
Mouse (m) Mouse (f)	10	6800 5800	680 580	Momma (1986)

m = male; f = female

37.5.2.2 Dermal

Acute dermal toxicity was reported to be >2000 mg/kg bw for a 5.25% available chlorine solution, however no further details were provided (EU RAR 2007).

37.5.2.3 Inhalation

Inhalation studies of chlorine gas in animals are available but are not included here as gaseous chlorine can only be released from a sodium hypochlorite solution on mixing with strong acids. The anion, ClO^- will not volatilise from aqueous solutions.

37.5.2.4 Observation in humans

Sodium hypochlorite can burn the lips, tongue, throat and stomach. Symptoms may include nausea, vomiting, shock or collapse, gastrointestinal discomfort and unconsciousness (National Institute for Occupational Safety and Health (NIOSH) 1999).

The available information on the health effects of hypochlorous acid or sodium hypochlorite in humans is derived almost exclusively from cases of ingestion of chlorine bleach. While ingestion of small amounts of chlorine bleach may only cause oesophageal irritation, strong solutions can cause severe damage to the upper gastrointestinal tract and even death. A review of 129 cases of sodium hypochlorite solution (5.25%) ingestion by children seen at a United States (US) hospital reported that no severe complications were observed and only two cases exhibited any evidence of oesophageal injury (Pike et al. 1963). These data were comparable to observations on 160 patients admitted to another US hospital due to ingestion of household bleach, where five showed oesophageal burns but only two developed oesophageal stricture (French et al. 1970). Another review stated the lethal dose of sodium

hypochlorite in adults to be approximately 200 mL of a solution containing 3 to 6% chlorine (Racioppi et al. 1994); however, the survival of patients who swallowed from 0.5 L to 1 L of a 5 to 10% hypochlorite solution has also been reported (Strange et al. 1951; Ward and Routledge 1988). A 66-year-old female died of cardiac arrest 4.5 hours after ingesting an unknown quantity of bleach. Autopsy revealed oesophageal and gastric mucosal erosions, perforations at the gastro-oesophageal junction, and extensive necrosis of adjacent soft tissue (Ross and Spiller 1999).

37.5.2.5 Summary of acute toxicity

The acute toxicity of sodium hypochlorite solutions, (concentrations up to 13%) by the oral route in animals is low, with limited data also indicating a low level of toxicity by the dermal route at a concentration of 5.25%. From case reports of accidental ingestion of domestic sodium hypochlorite bleaches, it can be concluded that sodium hypochlorite is of low acute oral toxicity in humans and the effects vary from moderate to severe damage of the gastrointestinal tract. The effects are due to the corrosive effect of the chemical.

37.5.3 *Irritation / Corrosivity*

37.5.3.1 Skin irritation

Sodium hypochlorite at concentrations of up to 5.25% available chlorine was at most slightly irritating to rabbit and guinea pig skin (Osterberg et al.1977; Nixon et al. 1975). At concentrations of 12.5 to 12.7% available chlorine, the hypochlorite was considered to be moderately to severely irritating in rabbits; however, a non-standard 24-hour exposure time was used (Duprat et al. 1974; Colgate-Palmolive 1985). In a poorly described dermal irritancy/corrosion test in rabbits, sodium hypochlorite solution (0.24, 2.4, 4.2 and 6% available chlorine) showed slight irritation effects at the lowest concentration, moderate irritation at intermediate concentrations and corrosive effects at the highest concentration tested (Loden et al. 1985).

The chemical was corrosive to the skin in animal studies at high concentrations.

37.5.3.2 Eye irritation

The eye irritation potential of sodium hypochlorite was tested in several studies in rabbits and monkeys, a summary of which has been published (EU RAR 2007). Generally, at concentrations of up to 5.25%, the chemical was observed to be slightly to moderately irritating. At concentrations ranging from 12.5% to 15% the solutions produced severely irritating or corrosive effects to the eye. Few details were reported in an old study where the eye irritation potential of 5.5% sodium hypochlorite was compared in rabbits and monkeys. The irritant response was much greater in rabbits (recovery between day 7 and day 35) than in monkeys (recovery at day 2) (Buehler and Newmann 1964).

Overall, at high concentrations, the chemical is corrosive to the eyes of animals in the reported studies.

37.5.3.3 Respiratory irritation

The respiratory irritation potential of sodium hypochlorite has been assessed in mice and has been compared to that of chlorine. Mice were exposed to sodium hypochlorite aerosols at atmospheric concentrations of 9.2, 5.7 or 2.6 ppm, expressed as chlorine (Lewis 1990). The exposure concentration causing a 50% reduction in the respiratory rate (RD_{50}) was estimated to be 4.11 ppm indicating that the aerosol was a respiratory irritant. A concurrent test with chlorine resulted in an RD_{50} value of 5.7 ppm, suggesting that the chlorine content is responsible for the aerosol irritancy. The precise mechanism by which this might occur is not known, but the assumption is that products of the reaction of chlorine with water are able to

interact with components from cells in the respiratory epithelium. At low concentrations, only sensory receptors may be affected, triggering only changes in respiratory dynamics, but higher concentrations produce tissue damage due to disruption of cellular components (Morris 2005).

Aerosolised sodium hypochlorite, or the associated chlorine, act as a respiratory irritant.

37.5.3.4 Observation in humans

Slight skin irritation or local burns were reported in a two-year survey of accidental exposure to hypochlorite containing products. Of 38 skin contacts, 18 cases (47%) led to some skin effects (Instituto Nacional de Toxicologia 2002).

Application of a 2% sodium hypochlorite solution in a 48-hour patch test was found to cause weak to moderate irritation in 15/69 dermatitis patients (Habets et al. 1986) and 5 to 5.25% sodium hypochlorite was severely irritating to intact human skin under the same conditions (Nixon et al. 1975).

Rapidly reversible eye irritation was reported in a two-year survey of accidental exposure to hypochlorite containing products. Of 526 eye contacts, 218 cases (41.5%) led to some irritation (Instituto Nacional de Toxicologia 2002).

In two cases where Clorox (containing 5.25% sodium hypochlorite) was accidentally splashed into the eyes, a burning sensation and slight damage to the cornea was reported. Prompt rinsing of the eyes with water led to complete recovery within 48 hours (Grant et al. 1974 cited in BIBRA 1990).

37.5.3.5 Summary of Irritation / Corrosivity

Overall, patch tests in humans indicate that skin irritation occurs in some subjects from exposure to hypochlorite solutions at concentrations of 2% and above. Case reports indicate a corrosive potential for the chemical, although animal data were inconclusive with respect to severity of reaction. Eye irritation was also noted in domestic accident data; however, there was no consequential serious or long-term damage reported.

37.5.4 *Sensitisation*

37.5.4.1 Skin sensitisation

There was no evidence of delayed contact hypersensitivity in a Buehler Test with 8% sodium hypochlorite in guinea pigs. Similarly, 4.5% sodium hypochlorite was negative when presented in two different surfactants in separate studies (EU RAR 2007).

37.5.4.2 Respiratory sensitisation

No data were available.

37.5.4.3 Observation in humans

Repeated insult patch tests conducted on healthy human volunteers with hypochlorite formulations have shown no evidence of potential allergic contact dermatitis. In tests performed with 0.034% and 0.076% hypochlorite on 86 and 90 volunteers respectively, one subject in the latter study gave some evidence of skin sensitisation which was potentially attributable to another test article patched at an adjacent site (EU RAR 2007).

Two females with diagnosed dermatitis showed a positive reaction to 0.1–2% sodium hypochlorite patched in different dilutions together with additional reactions to other standard allergens (Habets et al. 1986). In a control study, 69 patients (randomly selected with

suspect allergic contact dermatitis) patched with 2% hypochlorite showed no reaction indicating an allergic response.

Inclusion of 0.5% sodium hypochlorite in a series of routine patch tests involving 225 patients in total showed one positive response that could be directly attributed to sodium hypochlorite (Osmundsen et al. 1978).

Of 40 females with suspected allergic hand dermatitis, 38 gave a negative response to sodium hypochlorite in a standard patch test (van Joost et al. 1987). Two showed sensitivity to sodium hypochlorite but this was concomitant with a nickel allergy in the first case and with Kathon allergy in the second case. Therefore the two cases cannot be clearly interpreted as a positive sensitisation reaction to hypochlorite.

37.5.4.4 Summary of sensitisation

Standard sensitisation tests indicate that there is no potential for skin sensitisation from hypochlorite in animals. Similarly, repeat insult patch tests in healthy humans indicate that hypochlorite does not induce contact sensitisation. The few isolated cases of allergic contact sensitisation reported from dermatology practices are generally inconclusive and rare in view of the extensive use of hypochlorite in the market-place.

Overall, based on the reliable animal and human study data, as well as on the scarcity of alleged sensitisation cases reported from the clinic, it is unlikely that sodium hypochlorite poses a skin sensitisation hazard.

37.5.5 *Repeat dose toxicity*

37.5.5.1 Oral

Rodent studies on the repeat dose oral toxicity of sodium hypochlorite were summarised from EU RAR (2007) and ATSDR (2010) and presented in Table A37.4. The Lowest Observed Adverse Effect Level (LOAEL), No Observed Adverse Effect Level (NOAEL) and Klimisch scores (Klimisch et al. 1997) (1 = reliable without restriction; 2 = reliable with restriction; 3 = not reliable) are indicated for each study.

Table A37.4 Repeat oral toxicity studies with sodium hypochlorite

Species	Treatment	Results*	Remarks	Reference (Klimisch rating)
Fischer 344 rats	Drinking water, 13 weeks 0, 0.05, 0.1, 0.2, 0.4%	LOAEL = 0.2% [84 mg/kg bw/day (f); 50 mg/kg bw/day (m)] NOAEL = 0.1% [44 mg/kg bw/day (f); 26 mg/kg bw/day (m)]	At 0.2% and above, reduced body weight gain and reductions of up to 66% in water consumption. At the top dose, reduced absolute organ weights (not specified).	Furukawa et al. (1980) (2)
Fischer 344 rats	Drinking water, 13 weeks 0, 0.025, 0.05, 0.1, 0.2, 0.4%	LOAEL = 0.2% (estimated 152 mg/kg bw/day) NOAEL = 0.1% (estimated 76 mg/kg bw/day)	At the top dose, reduced absolute organ weights (M: lung, liver, spleen; F: lung, heart, brain). At 0.2% and above, reduced body weight gain and blood	Hasegawa et al. (1986) (3)

Species	Treatment	Results*	Remarks	Reference (Klimisch rating)
			changes. Water and food consumption was not reported.	
SD rats	Drinking water, 90 days M: 0, 8.3, 16.7 mg/kg bw/day F: 0, 12.4, 24.9 mg/kg bw/day	No LOAEL or NOAEL established	No significant adverse effects seen at the top dose in either sex	Daniel et al. (1990) (2)
Fischer 344 rats	Drinking water, 104 weeks M: 0, 33, 67 mg/kg bw/day F: 0, 67, 133 mg/kg bw/day	LOAEL = 67 mg/kg bw/day (f) No LOAEL or NOAEL (males)	At low and high dose, reduced final body weight for females only. Higher water consumption in males in 2nd year of study is inconsistent with other studies.	Hasegawa (1986) (2)
Fischer 344 rats	Drinking water, 2 yrs 0, 70, 140, 275 mg/L (M: 0, 4.2, 7.3, 13.6 mg/kg bw/day F: 0, 4.2 , 7.8, 14.4 mg/kg bw/day)	No LOAEL or NOAEL established	No significant adverse effects seen at the top dose in either sex. Reduction in water consumption at the top dose due to taste aversion.	NTP (1992) (1)
B6C3F1 mice	Drinking water, 103 weeks 0, 477, 954 mg/L (M: 0, 33, 55 mg/kg bw/day F: 0, 27, 52 mg/kg bw/day)	LOAEL = 33 mg/kg bw/day (m); 27 mg/kg bw/day (f)	Dose-related reduction in body weight gain in treated groups but no further details provided.	Kurokawa et al. (1986) (2)
B6C3F1 mice	Drinking water, 2 years 0, 70, 140, 275 mg/L (M: 0, 7.4, 14, 24 mg/kg bw/day F: 0, 7.6, 14.2, 24.2 mg/kg bw/day)	No LOAEL or NOAEL established	No significant adverse effects seen at the top dose in either sex.	NTP (1992) (1)

** Doses expressed as available chlorine are based on default bodyweight and consumption values (EU RAR 2007); m = male; f = female.*

No systemic effects were observed in four chronic repeated-dose oral studies in rodents. The critical study for determining the effects of repeated exposure to the chemical was a two-year carcinogenicity study in rats (NTP 1992) as it was the best conducted study available. The only treatment-related effect was a reduction in water consumption at the highest dose level of 13.6 to 14.4 chlorine/kg bw/day and therefore no LOAEL or NOAEL was derived.

37.5.5.2 Dermal

In briefly described guinea pig studies, no effects were observed after exposure of guinea pigs to 0.125% sodium hypochlorite solution for up to eight weeks (Wohlab and Wozniak 1982) while epidermal hyperplasia was observed following 14 days exposure, eight hours/day to 0.1% sodium hypochlorite solution (Cotter et al. 1985).

In a dermal carcinogenicity study, no treatment-related effects were observed in mice treated twice weekly for 51 weeks with a 1% sodium hypochlorite solution (Kurokawa 1984).

37.5.5.3 Inhalation

No repeat dose inhalation studies are available on sodium hypochlorite aerosol. A chlorine gas study in monkeys (Klonne et al. 1987) was not considered as suitable for providing surrogate data for the quantitation of the potential effects of the sodium hypochlorite aerosol as gaseous chlorine will only be released from a sodium hypochlorite solution on mixing with strong acids.

37.5.5.4 Observation in humans

A child who sucked clothing that had been heavily bleached with sodium hypochlorite solutions experienced intermittent vomiting, stomach pains and inflammation of the lungs (Loeb and King 1974). A further case reported the use of 500 mL of a 1% sodium hypochlorite solution as a wound dressing, 2 to 3 times a day for 1 to 2 weeks. Effects included hypernatraemia due to poor kidney function, along with the patient's inability to complain of thirst or to drink (Thorp et al. 1987).

Several epidemiological studies of the effects of the consumption of chlorinated drinking water on the health of the general population have been reported. No causal link between any long term health effect, including increased cancer risk, and consumption of the drinking water was established in these studies (IARC 1991).

37.5.5.5 Summary of repeat dose toxicity

NOAELs could not be established from reliable 90 day oral studies in rats. None reported effects that could be attributed directly to sodium hypochlorite or only reported effects that were considered of unknown toxicological significance. A reduction in water intake, attributable to taste aversion, is a plausible explanation for the reductions in weight gain and sporadic changes in organ weights observed. Slight local irritant effects have been observed in guinea pigs following dermal exposure to a 0.1% sodium hypochlorite solution, and no systemic effects following dermal exposure of mice to 1% sodium hypochlorite.

37.5.6 *Genotoxicity*

Sodium hypochlorite has been studied in several mutagenicity assays, both *in vitro* and *in vivo* as summarised in Table A37.5 from the EU RAR (2007). It was noted that there are deficiencies in the conduct and / or reporting of most of the studies.

Table A37.5 Mutagenicity tests with sodium hypochlorite

Test	Type*	Results	Reference (Klimisch rating)
In vitro: bacteria	Ames/ *S.typhimurium* (*S. typh*.)	Positive TA1530 (non-standard test) Negative TA 1535, TA1538	Wlodkowski and Rosenkranz (1975) (3)
	Ames/*S.typh*.	Positive TA100 (+S9) Negative TA98	Kawachi et al. (1980) (2)
	Ames/*S.typh.*	Positive TA100 (+S9)	Ishidate et al. (1981); Ishidate et al. (1984) (2)
	Ames/*S.typh*.	Negative TA97, TA102 (±S9)	Fujita and Sasaki (1987) (2)
	Ames/*S.typh*. SOS Chromotest	Negative TA 100, TA 98 TA 102 (-S9) Negative	Le Curieux et al. (1993) (2)
	Pol. A/*E. Coli*	Positive	Rosenkranz (1973) (3)
	Rec. A/*Bacillus subtilis*	Negative (±S9)	Kawachi et al. (1980) (3)
	SOS Chromotest	Negative	Klimm et al. (1989) (3)
In vitro: mammalian cells	CA/CHL cells	Positive (-S9)	Ishidate et al. (1984) (2)
	CA/CHL cells	Positive (+S9)	Matsouka et al. (1979) (2)
	CA/HEF cells	Negative	Sasaki et al. (1980) (2)
	SCE/HEF Cells	Positive	Sasaki et al. (1980) (2)
	CAA HL	Negative	Shaw (1970) (3)
In vivo	MN/Mouse BM	Negative	Meier et al. (1985) (2)
	CA/Mouse BM	Negative	Meier et al. (1985) (2)
	MN/Mouse BM	Negative	Hayashi et al. (1988) (1)
	DNA adduct/rat kidney	Negative	Kasai et al. (1987) (2)

** CA chromosome aberration, MN micronucleus, SCE sister chromatid exchange*

The positive results produced in bacterial assays and the induction of chromosome aberrations and sister chromatid exchanges (SCE) in mammalian cells suggest that sodium hypochlorite may exert an *in vitro* mutagenic activity. In contrast, sodium hypochlorite was without effect in four animal studies, including a well-conducted mouse micronucleus assay, suggesting that sodium hypochlorite is not mutagenic *in vivo* under the conditions tested. Overall, the available data indicate that sodium hypochlorite is not likely to be genotoxic.

37.5.7 *Carcinogenicity*

The potential carcinogenicity of sodium hypochlorite has been examined in F344 rats (Kurokawa et al. 1986; Hasegawa et al. 1986; NTP 1992) and in B6C3F1 mice (Kurokawa et

al. 1986; NTP 1992) by long-term oral administration in drinking water (study outlines presented in Table A37.4). In one rat study (NTP 1992), there was a slight increased incidence in leukaemia in female rats considered by peer reviewers to be equivocal evidence of carcinogenicity based on a lack of a clear dose response relationship and a relatively low incidence in the concurrent controls. Similarly, an increase in lymphomas/leukaemias was seen in female Sprague-Dawley rats in a two-year drinking water study (Soffritti et al. 1997) with a lack of dose dependence and unusually low incidence of leukaemia in the control group.

The co-carcinogenic properties of hypochlorite have been examined in female Sencar mice following initiation with dimethylbenzanthracene (Kurokawa et al. 1984) and in NMRI mice with benzo-pyrene (Pfeiffer 1978). There was no carcinogenic effect due to topical application of sodium hypochlorite solution at different concentrations and no promoting effect of hypochlorite with either initiator.

Overall, the available rodent studies are not sufficient to indicate a clear relationship between the oral administration of sodium hypochlorite and cancer. Equivocal evidence is reported in two studies (NTP 1992; Soffritti et al. 1997) for leukaemia in female rats, but there is no other evidence reported in three other good quality studies. The available data show no evidence of carcinogenicity of sodium hypochlorite in mice by the dermal route of exposure.

Several epidemiology studies are available to evaluate the carcinogenicity of chlorinated drinking water, but they have deficiencies including the variability in water quality across regions, and the contribution of ill-defined chemical species present in water supplies and the derived reaction products. IARC (1991) reviewed the available studies and noted that, while some reported a correlation between a higher risk of cancer of the bladder and the long-term consumption of chlorinated drinking water, the methodological inadequacies and many confounding variables made interpretation of the data difficult. They concluded that chlorinated drinking water and hypochlorite salts are not classifiable as to their carcinogenicity to humans (Group 3). Similarly, more recent ecological and case-control studies reviewed by the International Programme on Chemical Safety (IPCS) (2000) include some that report small relative risks for colon and bladder cancer incidence for populations consuming chlorinated drinking water. Overall, they are equivocal or insufficient to establish a causal relationship, considering their quality and completeness.

In summary, the only studies available are related to chlorinated drinking water for which the epidemiological data were not sufficient to provide adequate evidence for linking the use of chlorinated drinking water to an increased cancer risk in humans.

37.5.8 *Reproductive toxicity*

37.5.8.1 Fertility

In a sperm head abnormality test, sodium hypochlorite (pH 8.5) was administered orally to B6C3F1 mice at doses of 0, 1.6, 4 and 8 mg chlorine/kg bw/day (Meier et al. 1985). A small increase in abnormalities was noted in the hypochlorite (pH 8.5) mid and high dose groups however these were independent of dose and only the mid dose group fell outside the highly variable background incidence of abnormalities. In contrast, no effect was seen in mice treated with hypochlorous acid (pH 6.5) in a separate test at the same doses. These results are inconsistent since the hypochlorite is expected to be converted to the hypochlorous acid by exposure to the acid pH of the stomach.

In a well-conducted single generation study, hypochlorous acid was administered by gavage to Long-Evans rats at doses of 0, 1, 2 and 5 mg chlorine/kg bw/day prior to and during mating, gestation and lactation (Carlton et al. 1986). Exposure to the chemical (at similar doses and ten-fold longer treatment duration than the Meier study described above) did not

affect fertility or the appearance of the reproductive organs, and did not induce sperm abnormalities. It was concluded that a LOAEL and NOAEL could not be defined for this study.

37.5.8.2 Developmental toxicity

Female Sprague-Dawley rats were exposed to 0, 0.1, 1, or 10 mg chlorine/kg bw/day (as hypochlorous acid) in drinking water for 2.5 months before mating and continuing throughout pregnancy until gestation day 20 (Abdel-Rahman et al. 1982). There were no significant effects on foetal viability or on foetal body weight; however, skeletal anomalies were increased at 1 and 10 mg/kg bw/day and total soft tissue defects at 10 mg/kg bw/day relative to controls. However, the reported incidence of foetal anomalies in the control group as higher than in the low-dose group, together with the absence of experimental detail (maternal body weight and water consumption data), limits the significance that can be attached to these findings.

No indication of toxic developmental effects was seen in the Carlton (1986) study described above in the 'Fertility' section. Litter size, perinatal mortality, pup growth, neonatal weight, eye opening and other developmental landmarks did not differ between control and treated groups. A developmental NOAEL was not identified.

37.5.8.3 Observation in humans

The EU RAR (2007) reviewed several exploratory epidemiological studies assessing possible adverse developmental outcomes associated with the consumption of chlorinated water. The results of these studies were difficult to interpret due to the inherent limitations of study design and interference by confounding factors, but overall there was no evidence available to suggest that the chemical would adversely affect fertility or development.

37.5.9 *Other health effects*

No additional health effects were identified.

37.6 Health hazard summary

37.6.1 *Critical health effects*

Sodium hypochlorite demonstrates low acute toxicity. It is corrosive to the skin, eyes and the gastrointestinal tract. Based on human and animal data, sodium hypochlorite concentrations over 5% are irritating to the skin and eye, while concentrations over 10% are corrosive. Aerosolised sodium hypochlorite is a respiratory irritant. The chemical is not a skin sensitiser.

No systemic effects in animals are associated with repeated exposure to sodium hypochlorite at the tested dose levels. The critical study is a two-year drinking water study in rats, where no adverse effects were seen at a top dose of 13.6 to 14.2 mg chlorine/kg bw/day (NTP 1992).

The available data, overall, indicate that it is not genotoxic. There is inadequate evidence for the carcinogenicity of sodium hypochlorite in animals and sodium hypochlorite is not considered to cause fertility or developmental effects.

Overall, the main critical effect to human health of sodium hypochlorite is its corrosivity.

37.6.2 *Hazard classification*

This hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A37.6. These NICNAS recommendations do not consider physical or environmental hazards.

Table A37.6 Hazard classification recommended by NICNAS to Safe Work Australia

Effect	GHS* Classification
Skin corrosion/irritation	Causes severe skin burns and eye damage – Cat. 1B (H314) May cause respiratory irritation – Specific target organ toxicity, single exposure - Cat. 3 (H335)

* *Globally Harmonised System (UNECE 2009)*

37.7 References

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A38 Hydrogen peroxide

CAS No.	CAS Name
7722-84-1	Hydrogen peroxide (H_2O_2)

38.1 Chemical identity

The identity information was obtained from ChemID*plus* (2012) and O'Neill (2001). A description of the chemical identity is provided in Table A38.1.

Table A38.1 Chemical identity

	Hydrogen peroxide
Synonyms	Dihydrogen dioxide Hydrogen dioxide Hydrogen oxide Hydroperoxide Peroxide Hioxyl
Appearance and odour	Colourless liquid with a slightly sharp odour
Structural formula	HO - OH
Molecular formula	H_2O_2
Molecular weight	34.014
SMILES notation	OO

38.2 Physical properties

The information on physical properties was obtained from O'Neill (2001), the European Chemicals Bureau (ECB) (2003) and the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013) and is provided in Table A38.2.

Table A38.2 Physical properties

Property	**Value**
Melting point	-0.43 °C
Boiling point	152 °C (decomposition)
Density – kg/m^3	1.4425 x 10^{-3} (25 °C)
Vapour pressure	0.3 kPa (25 °C)
Water solubility	miscible
Partition coefficient (log K_{ow})	-1.57

38.3 Current regulatory controls

38.3.1 *Hazard classification for occupational health and safety*

Hydrogen peroxide is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) with the following risk phrases (Safe Work Australia 2013):

- C (Corrosive); R35 (Causes serious burns)
- X_n (Harmful); R20/22 (Harmful by inhalation and if swallowed).

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures. The risk phrases for this chemical are:

- Conc ≥70%: C; R35, R20/22
- 50% ≤Conc <70%: C; R20/22, R34 (Causes burns)
- 35% ≤Conc <50%: X_n; R22 (Harmful if swallowed), R37/38 (Irritating to respiratory system and skin), R41 (Risk of serious eye damage)
- 8% ≤Conc <35%: X_n; R22, R41
- 5% ≤Conc <8%: X_i; R36 (Irritating to eyes).

38.3.2 *Occupational exposure standards*

38.3.2.1 Australia

The following exposure standard was identified (Safe Work Australia 2013):

Time Weighted Average (TWA): 1.4 mg/m^3 (1 ppm)

38.3.2.2 International

These exposure standards were identified for hydrogen peroxide (Galleria Chemica 2013).

TWA:

- 1.4 mg/m^3 (1 ppm) [Austria, Belgium, Denmark, Finland, France, Iceland, Korea, New Zealand, Norway, Peru, United Kingdom, US].

Short Term Exposure Limit (STEL):

- 2 to 3 ppm (2.8 to 4.2 mg/m^3) [Finland, Sweden, United Kingdom].

38.3.3 *Australian food standards*

Hydrogen peroxide is listed in the Australia New Zealand Food Standards Code – Standard 1.3.3 - Processing Aids – Permitted processing aids used in packaged water and in water used as an ingredient in other foods, as a bleaching, washing and peeling agent to treat all foods and other miscellaneous uses. The maximum permitted level (MPL) of residual hydrogen peroxide in the final food for the above permitted uses is 5 mg/kg (Food Standards Australia New Zealand 2013).

38.3.4 *Australian drinking water guidelines*

The chemical is endorsed as a drinking water treatment chemical as listed in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

38.3.5 *Additional controls*

38.3.5.1 Australia

The chemical is listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedules 5 and 6 with the following entries:

Schedule 5:

'Hydrogen peroxide (excluding its salts and derivatives):

a) *in hair dye preparations containing 12 per cent or less of hydrogen peroxide except in hair dyes containing 6 per cent or less of hydrogen peroxide; or*

b) *in other preparations containing 6 per cent (20 volume) or less of hydrogen peroxide except in preparations containing 3 per cent (10 volume) or less of hydrogen peroxide.'*

Schedule 6:

'Hydrogen peroxide (excluding its salts and derivatives) except:

a) *when included in Schedule 5;*

b) *in hair dye preparations containing 6 per cent (20 volume) or less of hydrogen peroxide; or*

c) *in other preparations containing 3 per cent (10 volume) or less of hydrogen peroxide.'*

38.3.5.2 International

Hydrogen peroxide is listed by the United States Food and Drug Administration (US FDA) as a direct food substance affirmed as Generally Recognised as Safe (21 CFR 184.1366) and as acceptable to treat food as an antimicrobial agent, bleaching agent, oxidising agent or for the removal of sulfur dioxide (US FDA 2013).

Hydrogen peroxide is currently regulated in the European Union (EU) under Regulation (EC) No 1223/2009 in Annex III, part 1 with a limit of 0.1% of hydrogen peroxide (or equivalent for substances that release hydrogen peroxide) in oral hygiene products, 12% in hair products, 4% in skin products and 2% in nail-hardening products (European Commission 2013).

The chemical is classified as a hazardous substance, acutely toxic (oral), harmful to human target organs and systems (oral, inhalation), and corrosive to dermal and ocular tissue under the Hazardous Substances and New Organisms (HSNO) Act of the Environmental Protection Authority New Zealand (EPA NZ) (2012).

38.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

38.5 Health hazard characterisation

The available European scientific opinion on hydrogen peroxide in oral hygiene and tooth whitening products (Scientific Committee on Consumer Products (SCCP) 2007) and a EU Risk Assessment Report for hydrogen peroxide (ECB 2003) were the main sources of information on the chemical. Additional sources of hazard information for the chemical include the REACH dossier for hydrogen peroxide (REACH 2013), the European Chemistry Industry Ecology and Toxicology Centre (ECETOC) (1992) and the International Agency for Research on Cancer (IARC) (1999).

Unless noted, references to individual studies below are taken from these reviews.

38.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

Hydrogen peroxide is an endogenous metabolite in aerobic cells generated during cell respiration, and by oxidative stress and patho-physiological reaction, such as those involving activated phagocytes (Chance et al. 1979).

38.5.1.1 Oral absorption

Limited data were available for hydrogen peroxide. The small molecular weight and lack of charge facilitate the movement of hydrogen peroxide across biological membranes.

Administration of hydrogen peroxide solutions to body cavities lined by mucous membranes resulted in increased oxygen content of the draining venous blood and, if the amounts of hydrogen peroxide were sufficiently high, formation of oxygen bubbles (ECB 2003). In cats, sublingual application of 9% or 19% ^{18}O-labeled hydrogen peroxide resulted in rapid absorption and transport of the decomposition product ($^{18}O_2$) through arterial blood to the lungs (Ludewig 1965). Within 34 minutes, one-third of the labelled oxygen administered was detected in expired air with no increase in ^{18}O-carbon dioxide detected. In dogs, the perfusion of the large intestine with hydrogen peroxide solutions raised the oxygen saturation of blood in the portal vein; however, no attempt was made to determine if decomposition occurred before or after absorption (Urschel 1967).

In human case reports, accidental ingestion of 35% hydrogen peroxide resulted in brain injury presumed to be due to cerebral oxygen embolism (Christensen et al. 1992; Giberson et al. 1989; Sherman et al. 1994). In another case, a child died after ingestion of a 3% hydrogen peroxide solution (estimated dose of 600 mg/kg bw) (Cina et al. 1994).

For the purposes of risk assessment, 100% oral absorption in humans is assumed.

38.5.1.2 Dermal absorption

Limited data were available for hydrogen peroxide.

Topically applied hydrogen peroxide can penetrate the epidermis (or mucous membranes) followed by rapid spontaneous or enzyme catalysed decomposition to oxygen and water in the underlying tissue (Hauschild et al. 1958).

After the application of 5 to 30% solutions of hydrogen peroxide on rat skin *in vivo*, the chemical is localised in the epidermis within a few minutes. By contrast, with human skin *in vitro*, the chemical was detectable in the dermis only after the application of high concentrations for several hours, or after pre-treatment with hydroxylamine (an inhibitor of

catalase). The uptake of the peroxide was trans-epidermal and not via the 'preformed pathways' of skin appendages (Ludewig1964 as cited in ECB 2003).

For the purposes of risk assessment, 100% dermal absorption in humans is assumed.

38.5.1.3 Inhalation absorption

Rabbits exposed to 1 to 6% hydrogen peroxide aerosol by inhalation showed oxygen-supersaturated arterial blood levels equivalent to oxygen administration at three atmospheres (Urschel 1967 as cited in ECB 2003). When this dose was increased, small bubbles began to appear in the samples. The 1% aerosol, which was least irritating, provided as high arterial oxygen levels as the higher hydrogen peroxide concentrations.

For the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

38.5.1.4 Distribution

No data were available for hydrogen peroxide.

Both animal studies and human case reports indicate that hydrogen peroxide passes the absorption surface rapidly entering the adjacent tissues and blood vessels where it is degraded, liberating oxygen bubbles (ECB 2003). While the bubbles are distributed in the circulation and give rise to lethal pulmonary and systemic embolic effects (ECB 2003), at high concentrations of hydrogen peroxide the bubbles obstruct blood flow and prevent some hydrogen peroxide from entering the general circulation and exerting systemic effects (Dieter 1988).

38.5.1.5 Metabolism

There are two main hydrogen peroxide metabolising enzymes, catalase and glutathione peroxidase, which control the hydrogen peroxide concentration in various tissues (ECB 2003). Catalase, (present at a wide range of concentrations in most mammalian cells and efficient in degrading large amounts of the chemical) catalyses the decomposition of hydrogen peroxide to form water and molecular oxygen. Glutathione peroxidase (more efficient at lower hydrogen peroxide concentrations) reduces hydrogen peroxide to water with consequent formation of oxidised glutathione. In the body, hydrogen peroxide may also undergo copper and iron-catalysed reactions (the Haber-Weiss and Fenton reactions) to produce the highly reactive hydroxyl radicals, which are capable of oxidising biomolecules in close proximity. Hydroxyl radical formation therefore mediates the cellular toxicity of hydrogen peroxide through lipid peroxidation, enzyme inactivation and DNA damage.

38.5.1.6 Excretion

Only limited data were available for hydrogen peroxide.

As discussed in 'Oral absorption' (Section A38.5.1.1), in cats dosed sublingually with ^{18}O-labeled hydrogen peroxide, one-third of the labelled oxygen was eliminated by exhalation within the first hour (Ludewig 1965).

38.5.2 *Acute toxicity*

The acute toxicity of hydrogen peroxide is summarised in

Table A38.3 (ECB 2003).The LD50 is the acute median lethal dose and LC50 is the acute median lethal concentration of the chemical.

Table A38.3 Hydrogen peroxide: summary of acute lethality studies

Route	Species	Substance	Results	Reference
Oral	Rat (m,f)	9.6% H_2O_2	LD50 = 1568 mg/kg	Ito et al. (1976)
	Rat	10% H_2O_2	LD50 >5000 mg/kg	FMC Corporation (1990a)
	Rat (m,f)	35% H_2O_2	LD50 = 1232 mg/kg	FMC Corporation (1983a)
	Rat (m,f)	60% H_2O_2	LD50 = 837 mg/kg	Mitsubishi (1981)
	Rat (m)	70% H_2O_2	LD50 = 75 mg/kg	FMC Corporation (1979a)
	Rat (m,f)	70% H_2O_2	LD50 = 805 mg/kg	Du Pont (1996)
Dermal	Rabbit	35% H_2O_2	LD50 >2000 mg/kg	FMC Corporation (1983b)
	Rabbit	70% H_2O_2	LD50 = 9200 mg/kg	FMC Corporation (1979b)
	Rabbit	90% H_2O_2	LD50 = ~ 700 mg/kg	Hrubetz et al. (1951)
	Rat	H_2O_2	LD50 = 4060 mg/kg	Kondrashov (1977)
	Rat	90% H_2O_2	LD50= ~ 5000 mg/kg	Hrubetz et al. (1951)
Inhalation	Rat (m,f)	Vapour from 50% H_2O_2	LC50 >170 mg/m^3 (4-h whole-body exposure)	FMC Corporation (1990b)
	Rat	Vapour from 90% H_2O_2	LC50 >427 mg/m^3 (4-h or 8-h whole-body exposure)	Comstock et al. (1954) Oberst et al. (1954)
	Rat	H_2O_2 vapour, no details	LC50= 2000 mg/m^3 (4-h whole-body exposure)	Kondrashov (1977)

m = male; f = female

38.5.2.1 Oral

The LD50 values in rats ranged from approximately 800 mg/kg bw for 70% hydrogen peroxide (Du Pont 1996) to more than 5000 mg/kg bw for 10% hydrogen peroxide (FMC 1990a), although Ito et al. (1976) found the dilute substance (9.6%) more toxic with an LD50 of 1568 mg/kg bw. In the Du Pont (1996) study, conducted in accordance with the Organisation for Economic Co-Operation and Development (OECD) Test Guideline (TG) 401, clinical signs of toxicity were observed in all dose groups and included lethargy, immobility, irregular respiration and hunched posture. Gross changes of the tongue, oesophagus, stomach and duodenum, and adhesions in the peritoneal cavity were noted in decedent rats. At all dose levels degenerative ulceration and regenerative hyperplasia of the pyloric antrum of the stomach were found (Du Pont 1996).

Hydrogen peroxide has moderate acute toxicity by the oral route.

38.5.2.2 Dermal

The available acute dermal toxicity studies are generally poorly described. Dermal LD50 values for concentrated hydrogen peroxide solutions (90%) have a wide range (700 to 5000 mg/kg bw) depending on the species - the rat being a resistant species, and the

rabbit a sensitive species (Hrubetz et al. 1951). For 70% hydrogen peroxide solution, the dermal LD50 in rabbits is reported to be 9200 mg/kg bw (FMC Corporation 1979b). In a reliable study in rabbits, 35% hydrogen peroxide solution under occlusive dressing for 24 hours did not result in deaths of any animals at a dose of 2000 mg/kg bw. All animals displayed significant dermal effects, with a small number reported to show lacrimation and nasal discharge (FMC Corporation 1983b). An LD50 of 4060 mg/kg bw in rats was calculated in a poorly reported study that probably tested a concentrated hydrogen peroxide solution (Kondrashov 1977).

Hydrogen peroxide is therefore generally regarded as being of low toxicity by the dermal route.

38.5.2.3 Inhalation

In an acute inhalation toxicity study, conducted in accordance with a method equivalent to OECD TG 403, rats were exposed (whole-body) for four hours to 170 mg/m^3 of hydrogen peroxide which was the maximum attainable vapour concentration from a 50% solution (FMC Corporation 1990b). There were no deaths and signs of toxicity were limited to nasal discharge and a transient decrease in body weight.

Rats were exposed (whole-body) to the vapour of hydrogen peroxide in two studies to concentrations ranging from 338 to 427 mg/m^3 for 4 or 8 hours (Comstock et al. 1954; Oberst et al. 1954). No deaths were reported but pathological examination revealed congestion in the trachea and lungs. Localised areas of pulmonary oedema and alveolar emphysema were present in the lungs in addition to severe congestion. In another poorly reported study, whole-body exposure of rats to hydrogen peroxide vapour for four hours gave an LD50 value of 2000 mg/m^3, with the primary cause of death in the animals attributable to gas embolism (Kondrashov 1977).

In two aerosol studies in mice, exposure durations ranged from five minutes to two hours. Half of the mice died after a 10 to 15 minute exposure at 12 000 to 13 000 mg/m^3 of aerosol generated from 90% hydrogen peroxide (Punte et al. 1953), and in two-hour nose-only exposures, doses ranging from 920 to 2000 mg/m^3 (generated from a 70% solution) were lethal to some mice (Solvay Duphar 1995a). In the latter study, clinical signs in the decedents, such as discolouration of the skin of the head and tongue, subcutaneous emphysema and haemorrhages, red lymph nodes and diffuse red lungs were attributed to the bleaching and corrosive nature of the test substance.

Hydrogen peroxide is moderately toxic to animals by the inhalation route.

38.5.2.4 Observation in humans

Mortality has been observed in humans following accidental ingestion of hydrogen peroxide. A two-year-old male ingested 113 to 170 g of 35% hydrogen peroxide (dose estimated at approximately 3800 mg/kg bw) (Christensen et al. 1992). Investigation showed gas in the heart and portal venous system together with severe haemorrhagic gastritis without perforation. After death on day 4, autopsy showed marked diffuse cerebral oedema. In a second case, a 16-month-old male died 10 hours after ingesting approximately 230 g of 3% hydrogen peroxide solution (dose estimated at 600 mg/kg bw) (Cina et al. 1994). On post-mortem examination there was frothy blood in the right ventricle and the portal venous system. The gastric mucosa was red and the brain was oedematous. Histopathology showed oedema in the lungs, diffuse interstitial emphysema and gas emboli within the pulmonary vasculature and gastrointestinal lymphatics. Clear vacuoles were also found within the spleen, kidney and myocardium.

Non-lethal poisoning has been reported in adults. Cerebral infarction, attributed to gas embolisation of the cerebral vasculature, was reported in an 84-year-old male who ingested

30 mL of 35% hydrogen peroxide (dose estimated at approximately 150 mg/kg bw) (Sherman et al. 1994) and multiple brain embolisms occurred in a 63-year-old male who ingested 120 mL of 35% solution (dose estimated at approximately 600 mg/kg bw) (Ijichi et al. 1997).

38.5.3 *Irritation / Corrosivity*

38.5.3.1 Skin irritation

The application of 3 to 8% hydrogen peroxide solutions to rabbit skin elicited mild reactions after 24-hour occluded exposure (Du Pont 1972a, 1973, 1974). In studies conducted in accordance with OECD TG 404, a hydrogen peroxide solution of 10% was only slightly irritating (FMC Corporation 1990a), while solutions at 50% and higher concentrations were severely irritating and corrosive (FMC Corporation 1990b, 1989).

In a study in rabbits, conducted according to US Environmental Protection Agency (EPA) Guideline PB82-232984, 35% hydrogen peroxide was applied under occlusion for four hours (FMC Corporation 1983c). Slight to moderate erythema and / or oedema was observed in all rabbits at 4 and 24 hours; at 48 and 72 hours there were slight erythema and brown areas that developed into desquamation on day six which persisted in 2/6 animals until at least day 14. Hydrogen peroxide was found to be a moderate skin irritant under the conditions of the test.

In Draize tests in rabbits, 50% hydrogen peroxide caused delayed corrosive effects after a one or four-hour exposure (Du Pont 1994). Similar effects were observed after a three-minute exposure to a 70% solution.

Hydrogen peroxide is corrosive to rabbit skin at 50%, is moderately irritating at 35% and only slightly irritating at 10%.

38.5.3.2 Observation in humans (skin irritation)

Of 25 cases of dermal exposure to hydrogen peroxide reported to the Utah Poison Control Center over a three-year period, the most common clinical findings were paresthesias (60%), whiteness (56%), and blistering (16%) generally as mild and transient effects (Dickson and Caravati 1994).

The irritancy potential of the chemical was investigated in 32 volunteers by exposing one hand to hydrogen peroxide vapour in a chamber (Kondrashov 1977). Increasing the time over which the skin was exposed to the vapour from five minutes to four hours decreased the irritation threshold from 180 mg/m^3 to 20 mg/m^3.

38.5.3.3 Eye irritation

Three Draize tests in rabbits, conducted in accordance with OECD TG 405, showed that solutions containing 5%, 8% and 10% hydrogen peroxide exhibited the mild to highly irritating potential of the chemical (FMC Corporation 1987a, 1987b and 1985, respectively).

In an ocular irritation study in rabbits, conducted in accordance with OECD TG 405, a 6% hydrogen peroxide solution produced moderate corneal irritation (Sarver et al. 1996). All animals developed slight corneal opacity, moderate iritis, mild or severe conjuctival redness and chemosis, with most exhibiting copious blood-tinged discharge. Blanching of the conjuctiva and conjuctival haemorrhaging with corneal vascularisation were observed in one rabbit. The eyes of 2/3 rabbits were clinically normal by 48 or 72 hours.

In a series of eye irritancy studies, conducted in accordance with the method described in the US *Federal Hazardous Substances Act* using 8, 10 or 12% hydrogen peroxide, both 10%

and 12% solutions produced generalised, severe injury in rabbit eyes (Du Pont 1972b). Penetrating corneal injury, iritis and conjunctivitis were observed. At the lowest concentration, only mild conjunctivitis was noted.

Hydrogen peroxide is corrosive to rabbit eyes.

38.5.3.4 Observation in humans (eye irritation)

Of 26 cases of ocular exposure to hydrogen peroxide reported to the Utah Poison Control Center over a three-year period, the most common clinical findings included burning (65%), redness (50%), and blurry vision (19%), generally as mild and transient effects (Dickson and Caravati 1994).

In 10 volunteers, the threshold of detection for irritation was approximately 0.1% and less than 0.03% when hydrogen peroxide was administered as drops directly to the eye or via contact lenses, respectively (McNally 1990). In another ocular study in eight volunteers, the threshold of irritation (as measured by subjective discomfort and conjunctival hyperaemia) was 0.02% when hydrogen peroxide was administered in a hydrogel contact lens (Paugh et al. 1988). When used as an intraocular antibacterial agent, 5% hydrogen peroxide caused cloudiness in the cornea, severe pain and inflammation (Chalmers 1989). A female who had inadvertently stored a contact lens in a 3% hydrogen peroxide disinfectant solution experienced hyperaemia, tearing, and eyelid spasm (Knopf 1984).

38.5.3.5 Respiratory irritation

The respiratory irritation potential of hydrogen peroxide has been assessed in the mouse. Animals were exposed to aerosols generated from 70% hydrogen peroxide at atmospheric concentrations of 300, 616, 1135, or 1856 mg/m^3 (Solvay Duphar 1995b). The RD_{50} value, the exposure concentration causing a 50% reduction in the respiratory rate, was estimated to be 665 mg/m^3, indicating that the aerosol was a respiratory irritant.

38.5.3.6 Observation in humans (respiratory irritation)

In 32 volunteers, the threshold of detection for irritation was 10 mg/m^3 (independent of exposure time from fiveminutes to four hours) when hydrogen peroxide vapour was inhaled through the nose using a face mask (Kondrashov 1977). In two occupational exposure cases, seven dairy workers exposed to approximately 12 mg/m^3 of hydrogen peroxide vapour (and possibly briefly to 41 mg/m^3), experienced eye and throat irritation (Kaelin et al. 1988). Slight nasal irritation was observed in factory workers involved in vessel filling at a hydrogen peroxide production facility after one hour exposure to a maximum concentration of 3.5 mg/m^3 (CEFIC 1996). A recent study exposed 11 volunteers to 0, 0.5, or 2.2 ppm hydrogen peroxide vapour for two hours. The vapour was slightly irritating at the high dose (Ernstgard et al. 2012).

Hydrogen peroxide is a respiratory irritant based on these studies.

38.5.4 *Sensitisation*

38.5.4.1 Skin sensitisation

There was no evidence of delayed contact hypersensitivity to 0.1% or 3% hydrogen peroxide in 10 guinea pigs tested using a modified Magnusson-Kligman procedure (Du Pont 1953).

Test solutions were re-applied six times over a two-week period prior to a challenge to evaluate sensitisation.

Hydrogen peroxide is not a skin sensitiser based on this non-guideline study.

38.5.4.2 Respiratory sensitisation

No data were available for hydrogen peroxide.

38.5.4.3 Observation in humans

A case report described positive patch tests in two females who had been exposed to hydrogen peroxide as an ingredient in commercial hair dyes (Aguire et al. 1994). Both females tested positively to 3% hydrogen peroxide and other ingredients in the dyes. It was reported that 156 other hairdressers patch-tested with the hairdressers' series of chemicals were all negative to 3% hydrogen peroxide.

During 1991 to 1997, 130 patients (mainly hairdressers) were patch-tested at the Finnish Institute of Occupational Health because of suspected occupational dermatitis (Kanerva et al. 1998). No allergic patch test reactions to hydrogen peroxide were observed. Of the 10 806 cases of allergic dermatoses reported to the Finnish Register of Occupational Diseases during 1975 to 1997, none were caused by hydrogen peroxide (Kanerva et al. 1998). No positive reactions were recorded in 59 patients (suspected of having eczema caused by hairdressing compounds) who were patch-tested with 3% hydrogen peroxide at the Dermatology Department of the University Central Hospital in Turku, Finland during 1995 to 1996 (Kanerva et al. 1998).

Despite two reported positive patch tests in humans, based on the lack of reports of skin sensitisation during widespread occupational and consumer use of hydrogen peroxide, it can be concluded that the chemical does not cause sensitisation.

38.5.5 *Repeat dose toxicity*

38.5.5.1 Oral

Animal data on repeat dose toxicity of hydrogen peroxide are summarised from the ECB (2003) and SCCP (2007) and are presented in Table A38.4. The Lowest Observed Adverse Effect Level (LOAEL) and No Observed Adverse Effect Level (NOAEL) are indicated for each study.

Table A38.4 Repeat oral toxicity studies with hydrogen peroxide

Substance	Species, method, duration and doses	Results	Remarks	Reference
5% H_2O_2	Wistar rats, male Gavage, 12 weeks 0, 56.2, 168.7, or 506 mg/kg bw/day)	LOAEL = 56.2 mg/kg bw/day NOAEL not established	At the top dose, decreased body weight gain and food consumption, haematological and clinical chemistry effects and gastric mucosal erosion. At the medium dose, haematological and clinical chemistry effects. At the low dose, decreased liver enzyme (S-GOT).	Ito et al. (1976)
0.06-6% H_2O_2	Wistar rats, male Gavage, 100 days 0, 6, 10, 20, 30, or 60 mg/kg bw/day	LOAEL = 30 mg/kg bw/day NOAEL = 20 mg/kg bw/day	At the top dose, decreased body weight gain and transient increase in spleen weight, decreased haematological and clinical chemistry values, including plasma catalase. At 30 mg/kg bw/day, decreased plasma catalase.	Kawasaki et al. (1969)
0.15-2.4% H_2O_2	Fisher 344 rats Drinking water, 10 weeks 0, 0.15, 0.3, 0.6, 1.2, or 2.4% (males: 0, 75, 150, 300, 600 or 1200 mg/kg bw/day) (females: 0, 86, 172, 344, 688, or 1376 mg/kg bw/day)	LOAEL = 75 mg/kg bw/day (males); 86 mg/kg bw/day (females) NOAEL not established	At the top dose, increased mortality, reduced bodyweight gain, gastric erosions and ulcers. At all lower doses, reduced bodyweight gain.	Takayama (1980)
100-3000 ppm H_2O_2	C57BL/6N mice (catalase deficient) Drinking water, 90 days; 42 days recovery 0, 100, 300, 1000, or 3000 ppm (male: 26, 76, 239, or 547 mg/kg bw/day female: 37, 103, 328, or 785 mg/kg bw/day)	LOAEL = 76 mg/kg bw/day (males); 103 mg/kg bw/day (females) NOAEL = 26 mg/kg bw/day (males); 37 mg/kg bw/day (females)	At the top dose, reduced bodyweight gain, food and water consumption (males), decreased blood protein and globulin (males). Duodenal mucosal hyperplasia that resolved during recovery. At the 300 and 1000 ppm doses, reduced food and water consumption (females). Duodenal mucosal hyperplasia that resolved during recovery.	Weiner et al. (1998)

Substance	Species, method, duration and doses	Results	Remarks	Reference
0.15% H_2O_2	dd strain mice, male Drinking water, 35 weeks 0, 0.15% (est. 0, or 150 mg/kg bw/day)	LOAEL = 150 mg/kg bw/day	Changes visible in all organs examined (liver, kidney, spleen, stomach and small intestine). Hyperplastic changes of gastric mucosa and hypertrophy of lymphoid tissue of the small intestine wall. Necrosis and inflammation of tissue structure in stomach wall Hydropic degeneration of liver and epithelium of the kidney tubule. Necrotic foci in the liver.	Aoki and Tani (1972)

There are several rodent studies available to characterise the repeat dose toxicity of hydrogen peroxide by the oral route. Decreased body weight gain was a typical finding, as were decrements in erythrocyte count, haematocrit, plasma protein concentration, and plasma catalase. Localised effects, including changes to the gastric and duodenal mucosa, were considered to be irritant effects of the chemical. In a reliable 90-day drinking water study in mice, a NOAEL of 100 ppm (corresponding to 26 and 37 mg/kg bw/day for males and females, respectively) was found based on dose-related reductions in food and water consumption, and on the observation of duodenal mucosal hyperplasia (Weiner et al. 1998). In a 100-day gavage study in rats, a significant decrease in the level of plasma catalase was observed at termination in the 30 and 60 mg/kg bw/day groups (Kawasaki et al. 1969). Therefore, for the purposes of risk assessment, a NOAEL for decreased catalase levels of 20 mg/kg bw/day was derived based on significant effects at doses of 30 mg/kg bw/day.

38.5.5.2 Dermal

In a poorly reported and unconventional study, rats with shaved skin were exposed (whole-body) to hydrogen peroxide vapour at 0.1 to 10.1 mg/m^3 for five hours/day over four months (Kondrashov 1977). The Lowest Observed Effect Concentration (LOEC) for vapours on the rat skin was reported to be 1 mg/m^3, with a No Observed Effect Concentration (NOEC) of 0.1 mg/m^3 based on histoenzymological staining of the epidermis sections that showed an increase in the activity of four tissue enzyme levels. In addition, a significant dysfunction of the horny layer of the skin was reported, although no further details were available.

38.5.5.3 Inhalation

In a range-finding study, conducted in accordance with OECD TG 412, Alpk:APfSD rats were exposed to hydrogen peroxide vapour at 2.9, 14.6, or 33 mg/m^3 for five days/week over a period of 28 days (CEFIC 2002). Clinical signs demonstrating respiratory tract irritation seen at the mid and top doses included necrosis and inflammation of the epithelium in the anterior regions of the nasal cavity. Mononuclear cell infiltration in the larynx was also seen at the top dose. Perivascular neutrophil infiltration and haemorrhage in the lungs of some animals was not dose-related. A No Observed Adverse Effect Concentration (NOAEC) of 2.9 mg/m^3 was derived for the localised irritation effects at 14.6 mg/m^3.

38.5.5.4 Observation in humans

A case report described a milk packaging machine operator who developed progressive dyspnoea and nodular infiltrates of the lungs after exposure to hydrogen peroxide vapour over a three year period for 2 to 5 days/week (Kaelin et al. 1988). Air measurements of peroxide of the day's exposure were approximately 12 mg/m^3, with transient elevations up to 41 mg/m^3. At work he (and six others) had noticed eye and throat irritation and gradual bleaching of the hair. Pulmonary function testing was consistent with interstitial lung disease and subsequent biopsy revealed alveolar collapse, thickening of the alveolar walls and interstitial infiltration by mononuclear cells. Upon withdrawal from the occupational exposure, the patient improved progressively with treatment. The authors attributed the clinical condition to the high hydrogen peroxide exposure, although heavy smoking may have been a contributing factor.

Six workers exposed to hydrogen peroxide vapours for up to three years in fruit juice packaging operations complained of irritation in the eyes and airways, headaches, temporary loss of olfaction, skin symptoms, and blanching of hair (Riihimäki et al. 2002). Peak exposures up to 11 mg/m^3 (eight-hour TWA 2 to 3 mg/m^3) of peroxide in air were measured in the breathing zone of the individuals, with those who handled peroxide-treated cartons reporting a burning and prickling of fingers, drying of the hands and face, and decrease of skin elasticity. Three machine operators exhibited recurring bronchitis-sinusitis, coincident with a 10-month period of high vapour concentrations, with two other patients presenting with bronchoconstriction and asthma symptoms. As the study did not include specific lung examinations, possible chronic lung changes caused by peroxide could not be evaluated, however, all patients monitored regained good health after the exposures were reduced. A LOAEL of 2 mg/m^3 (eight-hour TWA) for respiratory effects was derived.

38.5.6 *Genotoxicity*

The ECB (2003) investigated the available *in vitro* and *in vivo* data on the mutagenic effects of hydrogen peroxide.

Under *in vitro* conditions, hydrogen peroxide showed induction in the number of revertants for most of the gene mutation assays conducted in bacteria, with the increases primarily observed in strains sensitive to oxygen radicals. In mammalian cells, positive results were generally recorded in numerous assays validated to detect gene mutations, DNA damage and repair, unscheduled DNA synthesis, sister chromatid exchange, and chromosomal aberrations. The responses observed were modified by the presence of peroxide degrading enzymes (i.e. catalase), the extent of formation of hydroxyl radicals (via the Fenton reaction), and the cells' repair abilities.

In reference to *in vivo* genotoxicity, positive results were seen in two, non-guideline, host-mediated assays. In one, the mutagenicity observed in *Salmonella* indicator bacteria inoculated intraperitoneally (i.p.) in mice prior to gavage administration of 0.3% hydrogen peroxide, suggested that the chemical had been absorbed and made direct contact with the bacteria (Keck et al. 1980). In the second assay, i.p. injections of hydrogen peroxide in mice which had previously received inoculated tumour cells (showing a low level of catalase activity) i.p., resulted in chromosomal aberrations as a direct, local effect of hydrogen peroxide on the tumour cells (Schöneich 1967). In contrast to the host-mediated assays, negative results for the chemical were obtained in four erythrocyte micronucleus tests administered to mice (via oral and i.p. routes) at doses up to 1000 mg/kg bw (Keck et al. 1980; Liarskii et al.,1983; Du Pont 1995; CEFIC 1995). The absence of chromosomal abnormalities in the bone marrow of these mice may be explained by decomposition of the hydrogen peroxide in the gut or peritoneum prior to absorption and / or the high catalase activity of red blood cells which can decompose the chemical after absorption.

An unscheduled DNA synthesis (UDS) study in rats, conducted in accordance with OECD TG 486, with concentrations up to 50 mg/kg bw, showed that the chemical was unable to induce UDS (CEFIC 1997).

As a pre-screen for carcinogenicity, hydrogen peroxide 0.2 to 3.2% solutions were applied to the skin of Sencar mice twice-weekly for four weeks (Society for Plastic Industry 1997). There was no indication of induced DNA damage, mutations, epidermal hyperplasia or dermal cellularity changes.

A single dose of 3% hydrogen peroxide did not induce germ cell damage in male *Drospophila* larvae in a sex-linked recessive lethal test (Di Paolo 1952).

Overall, hydrogen peroxide is capable of acting as a genotoxicant *in vitro* through reaction of hydroxyl radicals in direct contact with target DNA. In general, the addition of exogenous metabolic activators (including catalase) reduces or abolishes the mutagenicity. Most available *in vivo* studies are not in support of a significant mutagenicity for hydrogen peroxide, which may, in part, be due to the reduced bioavailability of the chemical to exert a systemic effect.

38.5.7 *Carcinogenicity*

Fischer 344 rats were exposed to the chemical in drinking water at 0, 0.3, or 0.6% for 78 weeks, followed by a six-month recovery phase (Ishikawa and Takayama 1984). Body weight was decreased by 10% in the high dose group. At the end of the study (104 weeks), there was no evidence of carcinogenicity, however, the quality of the study is unclear as it was not reported in detail.

Catalase deficient C57BL/6J mice were given 0, 0.1, or 0.4% hydrogen peroxide in drinking water (estimated doses of 300 and 1200 mg/kg bw/day) for 100 weeks (Ito et al. 1981a, 1981b). There was a dose-dependent incidence of erosion and ulcer in the glandular stomach, as well as single or multiple duodenal nodules which were classified into hyperplasia, adenoma or carcinoma by their histopathological appearance. Localised duodenal carcinomas were found only in treated mice (5% in high dose, 1% in low dose and none among the controls) with invasion of these carcinomas into the muscular layer and small vessels, but no metastatic tumours were evident.

In a limited follow up to the previous study, the effect of hydrogen peroxide on the stomach and duodenum was studied in three mouse strains (Ito et al. 1982). C57BL/6N, DBA/2N, BALB/cAnN mice were provided 0, 0.1, or 0.4% hydrogen peroxide in drinking water for variable time periods of up to 740 days. After 140 days of treatment, the chemical was replaced with distilled water for 10 to 30 days. In C57BL mice, gastric lesions seen in the forestomach of mice exposed for at least 60 days mostly regressed and even disappeared after the cessation of treatment. Among mice given 0, 0.1 and 0.4% hydrogen peroxide for 420 days to 740 days, 0%, 1% and 5%, respectively, developed duodenal cancer though they did not show any distant metastases.

Four strains of mice – C3H/HeN (high catalase activity), C57BL/6N (low catalase activity), their F1 hybrid: B6C3F1 and C3H/Csb (low catalase activity) – were given 0.4% hydrogen peroxide as drinking water for six to seven months (Ito et al. 1984). The incidence of duodenal tumours (defined as hyperplasia or neoplasia) and the mean number of tumours per mouse were, respectively:

- 11.1% and 0.11 in C3H/HeN mice
- 31.8% and 0.36 in B6C3F1 mice
- 100% and 3.91 in C57BL/6N mice

- 91.7% and 2.63 in C3H/Csb mice.

There was a strong negative correlation between the incidence of duodenal tumours and catalase activities in duodenal mucosa, blood and liver among the different strains of mice.

As one part of a skin tumour promotion study, female Sencar mice were used to test the complete carcinogenic activity of hydrogen peroxide (Klein-Szanto and Slaga 1982). Mice received twice-weekly topical applications of hydrogen peroxide (15%) for 25 weeks. No squamous-cell carcinoma was found when these animals were observed for up to 50 weeks. No increase in the incidence of skin tumours were found in mice treated dermally for 51 weeks with 5% hydrogen peroxide (Kurokawa et al. 1984) or for 56 weeks with 3% hydrogen peroxide following initiation with 9,10-dimethyl-1,2-benzanthracene (DMBA) (Bock et al. 1975).

As one part of an oral tumour promotion study, rats given 1% hydrogen peroxide in drinking water for 32 weeks did not show carcinogenic or promotion activity, but the incidence of squamous cell papillomas in the forestomach was significantly increased (Takahashi et al. 1986). Similarly, rats given near lethal doses (1.5%) of hydrogen peroxide in drinking water for 21 weeks did not develop carcinomas in the gastrointestinal tract (Hirota and Yokoyama 1981).

In an oral cavity tumour promotion study, 30% hydrogen peroxide was painted onto one buccal pouch of hamsters twice weekly for 22 weeks. Although chronic inflammation, hyperchromatic cells and dysplasia were noted, there were no tumours found (Weitzman et al. 1986).

Overall, although hydrogen peroxide has a weak potential to induce a local carcinogenic effect in the duodenum of sensitive mouse strains, it is notable that the lesions showed a marked tendency to regress or disappear after the cessation of treatment. Based on these studies, the International Agency for Research on Cancer (IARC) concluded that there is limited evidence in experimental animals for the carcinogenicity of hydrogen peroxide. It also concluded that there is inadequate evidence in humans for carcinogenicity of the chemical, and as such hydrogen peroxide is not classifiable as to its carcinogenicity to humans (Group 3) (IARC 1999).

38.5.8 *Reproductive toxicity*

38.5.8.1 Fertility

There were only non-guideline studies available that were poorly designed and / or inadequately reported.

In a male reproductive toxicity study, rats were given 0.33 or 1% hydrogen peroxide in drinking water; there were no controls (Wales et al. 1959). All female mice mated to treated males became pregnant within a few days and in each case, healthy young were born in litters of normal size. The concentration, morphology and motility of the spermatozoa after three weeks of treatment appeared normal. Similarly, there were no detectable abnormalities in the sperm of three albino rabbits given 0.33, 1, or 3% hydrogen peroxide in drinking water for six weeks.

Three weanling female rats were given 0.45% hydrogen peroxide in drinking water for five months prior to mating with untreated males (Hankin 1958). Normal litters were produced suggesting that long-term treatment with the chemical did not appear to affect reproduction in female rats.

Male and female rats were administered hydrogen peroxide daily by gavage at doses (not specified) of 1/10-1/5 LD50 for 45 days (Antonova 1974). At the top dose, females showed

changes in the oestrus cycle and males showed reduced mobility of spermatozoa without effects on the weight of the testes. In a second experiment, male and female rats were gavaged with 0.005, 0.05, 0.5, 5, and 50 mg hydrogen peroxide/kg bw/day for six months before mating. Variations seen in the oestrous cycle in females were not dose-dependent. Reduced mobility of spermatozoa in males was observed at the top dose, with no changes in the morphology and weight of the testes. Among the high dose females, only 3/9 produced litters, compared to 7/9 in the control group, and both litter size and body weight gain of the offspring was reduced.

Overall, the data available are insufficient to allow evaluation of reproductive toxicity.

38.5.8.2 Developmental toxicity

Foetotoxic effects (including decreased bodyweight, skeletal hypoplasias, haemorrhaging of organs and increased mortality) were seen in the only developmental toxicity study available in which pregnant Wistar rats were fed on a powdered feed mixed with up to 10% hydrogen peroxide (Moriyama et al. 1982). There are major deficiencies in study design, including test substance stability, diet palatability, dose uncertainty and small group sizes. The investigators proposed that the deleterious effect was due to the breakdown of essential nutrients in food by hydrogen peroxide. The poor study design and reporting limit the significance that can be attached to these findings.

Hydrogen peroxide has also been tested for embryotoxicity using the three-day chicken embryo air chamber method (Korhonen et al. 1984). The total effective (ED_{50}) dose (including all deaths and malformations) was 2.7 mmol hydrogen peroxide/egg, indicating that the chemical was relatively ineffective in causing malformations and exhibited a low potency of embryotoxicity. The relevance of this *in vitro* result to toxicity in mammalian species is uncertain (ECETOC 1992).

Overall, the only developmental toxicity study available for the chemical was judged as inadequate for evaluation.

38.5.9 *Other health effects*

No additional health effects were identified.

38.6 Health hazard summary

38.6.1 *Critical health effects*

Hydrogen peroxide demonstrates moderate acute toxicity by the oral and inhalation routes and low acute toxicity by the dermal route. The chemical is corrosive to the skin and eyes and is a respiratory irritant. Based on animal data, concentrations of greater than 35% are irritating to the skin, while a concentration of 50% is corrosive. Hydrogen peroxide is not a skin sensitiser.

Repeated oral exposures to the chemical produced localised inflammation of the gastric mucosa accompanied by erosion, ulceration and hyperplasia. Adverse systemic effects included decreased bodyweight gain, haematological changes and changes in blood and organ enzyme levels. The most appropriate NOAEL for risk assessment of hydrogen peroxide, determined from the 100-day gavage study in rats of Kawasaki et al. (1969), is 30 mg/kg bw/day based on systemic effects at the LOAEL of 60 mg/kg bw/day.

While the chemical is genotoxic in a variety of *in vitro* test systems, available studies do not provide evidence of a significant mutagenicity under *in vivo* conditions. Although hydrogen peroxide has the potential to induce localised carcinomas in the duodenum of sensitive mice,

regression after cessation of treatment and lack of an effect in another species suggest currently that the carcinogenicity of the chemical is not practically significant.

Reliable data on reproductive and developmental toxicity are not available.

38.6.2 *Hazard classification*

The hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004).

The substance is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A38.5.These NICNAS recommendations do not consider physical or environmental hazards.

Table A38.5 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Acute toxicity	Harmful if swallowed – Cat. 4 (H302) Harmful if inhaled – Cat. 4 (H332)
Irritation / Corrosivity	Causes severe skin burns and eye damage - Cat 1A (H314) May cause respiratory irritation – Specific target organ toxicity, single exposure - Cat.3 (H335)

* *Globally Harmonised System (UNECE 2009)*

38.7 References

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A39 Ammonium persulfate, Sodium persulfate

CAS No.	CAS Name
7727-54-0	Peroxydisulfuric acid (((HO)S(O)$_2$)2O$_2$), ammonium salt (1:2)
7775-27-1	Peroxydisulfuric acid (((HO)S(O)$_2$)2O$_2$), sodium salt (1:2)

39.1 Justification of group assessment

Ammonium and sodium persulfate are closely related chemicals and are assessed as a group in this report.The justification for inclusion of members within the persulfate category is supported by common features which include:

- similarity of chemical structure – a common dianion consisting of two sulfate groups connected via a peroxo bridge resulting in a peroxodisulfate dianion. The chemicals differ only by the cationic portion of the salt
- similarity of physico-chemical properties – molecular weight, melting point, density, water solubility and oxidising properties
- similarity of mammalian toxicity – acute toxicity, irritation, sensitisation, repeated dose toxicity (local effects), genotoxicity.

Accordingly, data gaps for each persulfate can be filled by read-across (refer to Table A39.1). In this assessment, read-across is a technique used to predict endpoint information for the untested persulfate salt by using data (for the same endpoint) from the tested persulfate salt as both are considered to possess common features.The overall data were adequate to conduct a hazard assessment. The similar toxicological effects identified in the acute oral, dermal and inhalation studies support the applicability of the read-across approach.

Table A39.1 Summary of available toxicity end-point data

	Peroxydisulfuric acid (((HO)S(O)$_2$)2O$_2$), ammonium salt (1:2) (CAS No. 7727-54-0)	**Peroxydisulfuric acid (((HO)S(O)$_2$)2O$_2$), sodium salt (1:2) (CAS No. 7775-27-1)**
Acute oral toxicity	✓	✓
Acute dermal toxicity	✓	✓
Acute inhalation toxicity	✓	✓
Skin irritation	✓	✓
Eye irritation	✓	✓
Respiratory irritation	×	✓
Skin sensitisation	✓	✓
Respiratory sensitisation	✓	✓

	Peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), ammonium salt (1:2) (CAS No. 7727-54-0)	**Peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), sodium salt (1:2) (CAS No. 7775-27-1)**
Repeat dose toxicity (oral)	✓	✓
Repeat dose toxicity (dermal)	×	×
Repeat dose toxicity (inhalation)	✓	×
Genotoxicity	✓	✓
Carcinogenicity	✓	×
Reproductive and developmental toxicity	✓	×

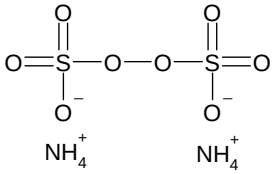
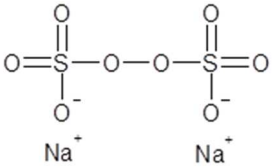
✓*Existing data point;* × *Missing data point*

39.2 Chemical identity

The identity information was obtained from ChemID*plus* (2012), the Organisation for Economic Co-operation and Development (OECD) (2005) and O'Neil (2001).

A description of the chemical identity is provided in Table A39.2. The salts are more commonly known as the diammonium and disodium salts rather than the ammonium salt (1:2) and sodium salt (1:2).

Table A39.2 Chemical Identity

	Peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), diammonium salt	**Peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), disodium salt**
Synonyms	Ammonium persulfate; Diammonium persulfate; Ammonium peroxodisulfate Ammonium peroxodisulfate	Sodium persulfate; Disodium persulfate; Sodium peroxydisulfate; Disodium peroxodisulfate
Appearance and odour	Yellow-white plate-like or prismatic (monoclinic) crystals or white granular powder. Odourless.	White, crystalline powder.
Structural formula		
Molecular formula	H8N2O8S2	Na2O8 S2
Molecular weight	228.20	238.13
SMILES	S(OOS(=O)(=O)[O-])(=O)(=O)[O-].[NH4+].[	S(OOS(=O)(=O)[O-])(=O)(=O)[O-].[Na+].

	Peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), diammonium salt	**Peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), disodium salt**
Synonyms	Ammonium persulfate; Diammonium persulfate; Ammonium peroxodisulfate Ammonium peroxodisulfate	Sodium persulfate; Disodium persulfate; Sodium peroxydisulfate; Disodium peroxodisulfate
notation	NH4+]	[Na+]

39.3 Physical properties

The following physical properties information was obtained from the OECD (2005), Cosmetic Ingredient Review (CIR) (2001) and O'Neil (2001). A description of the physical properties is provided in Table A39.3.

Table A39.3 Physical properties

Property	**Peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), diammonium salt**	**Peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), disodium salt**
Melting point	120 °C (decomposes)	>180 °C (decomposes)
Boiling point	Not applicable	Not applicable
Density – kg/m^3	1.982×10^3 (20 °C)	2.6×10^3 (20 °C)
Vapour pressure	Not applicable	Not applicable
Water solubility	559 g/L (20 °C)	549 g/L (20 °C)
Partition coefficient (log Kow)	Not applicable	Not applicable

39.4 Current regulatory controls

The document from now on refers to peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), diammonium salt (CAS No. 7727-54-0) as 'ammonium persulfate', one of the synonyms of the chemical. Similarly, peroxydisulfuric acid ($(HO)S(O)_2)2O_2$), disodium salt (CAS No. 7775-27-1) will be refered to as 'sodium persulfate'.

39.4.1 *Hazard classification for occupational health and safety*

Ammonium and sodium persulfate are both classified as hazardous for human health in the Hazardous Substances Information System (HSIS) with the following risk phrases (Safe Work Australia 2013):

- X_n(Harmful); R22 (Harmful if swallowed)
- X_i (Irritant); R36/37/38 (Irritating to eyes, respiratory system and skin), R42/43 (May cause sensitisation by inhalation and skin contact).

Mixtures containing ammonium and sodium persulfates are classified as hazardous based on the concentration (Conc) of the chemicals in the mixtures with following risk phrases:

- Conc ≥25%: X_n: R22, R42/43, R36/37/38
- 20% ≤Conc <25%: X_n: R42/43, R36/37/38
- 1% ≤Conc <20%: X_n: R42/43.

39.4.2 *Occupational exposure standards*

39.4.2.1 Australia

The same specific exposure standard is listed for ammonium persulfate and sodium persulfate (Safe Work Australia 2013):

- Time Weighted Average (TWA) of 0.01 mg/m^3.

39.4.2.2 International

The following exposure standards were identified for persulfate salts (Galleria Chemica 2013; RTECS 2012).

TWA:

- 0.1 mg/m^3 [Belgium, Canada, Ireland, Italy, Portugal, Spain, US,]
- 2 mg/m^3 [Denmark, Iceland, Norway].

39.4.3 *Australian food standards*

Sodium persulfate is listed in the Australia New Zealand Food Standards Code – Schedule 18 -Processing Aids – S18.06 Permitted bleaching, washing and peeling agents and in water used as an ingredient in other foods (section 1.138): all foods under Good Manufacturing Practice (GMP) conditions (Food Standards Australia New Zealand 2013).

Ammonium persulfate is listed in Schedule 18–Processing Aids- S18.08 Permitted processing aids—Miscellaneous purposes (section 1.140): Yeast washing agent under GMP conditions (Food Standards Australia New Zealand 2013).

39.4.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the substances in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

39.4.5 *Additional controls*

39.4.5.1 Australia

Ammonium persulfate and sodium persulfate are listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedule 6 (Poison) with the following entries:

Schedule 6:

'Ammonium persulfate:

a) in hair preparations.'

Schedule 6:

'Sodium persulfate:

a) in hair preparations; or

b) in products for the treatment of water for swimming pools and spas.'

39.4.5.2 International

Both substances are listed by the United States Food and Drug Administration (US FDA) (2012) under 21CFR 176-170a as 'Indirect Food Additives- Substances for Use Only as Components of Paper and Paperboard - Components of paper and paperboard in contact with aqueous and fatty foods' with no restrictions.

Persulfate compounds are currently regulated under the Canadian Department of Justice (2013), *Hazardous Products Act*, Ingredient Disclosure List (SOR/88-64) with the maximum authorised concentration of 0.1%.

39.5 Use

The use of the substances in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

39.6 Health hazard characterisation

Information on ammonium and sodium persulfate was sourced primarily from the Organisation for Economic Co-operation and Development (OECD) (2005) and the NICNAS Priority Existing Chemical Assessment Report No. 18 (NICNAS 2001). Additional sources of hazard information for the chemicals include the Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Report on Cosmetovigilance in the Netherlands (de Wit-Bos et al. 2012) and the Final Report on the Safety Assessment of Ammonium, Potassium, and Sodium Persulfate (CIR 2001). Unless noted, references to individual studies below are taken from these reviews.

39.6.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

Information on the kinetics, metabolism or distribution of the substances was sourced from the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier for the ammonium salt (REACH 2013). Persulfate salts rapidly dissociate in water to remove the respective cation (ammonium, sodium) from the anionic persulfate. The influence of the cations on toxicity is expected to be negligible with toxicokinetics and dynamics mainly influenced by the persulfate anion (OECD 2005).

39.6.1.1 Oral absorption

No data were available.

Ingested sodium ions will be readily taken up in the gastrointestinal tract and will enter the body's electrolyte pool (REACH 2013). The sulfate ion is poorly absorbed from the gastrointestinal tract, especially when administered in large doses such that the capacity of specialised transport processes for this ion in the intestines is exceeded (REACH 2013).

39.6.1.2 Dermal absorption

No data were available. In general, salts do not penetrate the skin and dermal absorption is not expected (REACH 2013).

39.6.1.3 Inhalation absorption

No data were available.

39.6.1.4 Distribution

No data were available.

Once absorbed, the sodium ions will be rapidly distributed throughout the body. The ammonium ions will be either directly excreted or incorporated into larger molecules and widely distributed (REACH 2013). Some sulfate ion is required for the synthesis of sulfur-containing macromolecules.

39.6.1.5 Metabolism

No data were available.

Sodium ions are not further degraded. Ammonium ions will be anabolised by enzymic mechanisms to form nitrogen containing polymers such as proteins and nucleic acids (REACH 2013).

Based on the *in vitro* chemistry of persulfates, the persulfate anion is expected to decompose under *in vivo* conditions to form hydrogen peroxide and sulfate ion radicals (REACH 2013). Hydrogen peroxide will be rapidly metabolised to oxygen and water by catalase and peroxidase enzymes in mammalian tissues and there is practically no potential for bioaccumulation (OECD 2005).

39.6.1.6 Excretion

No data were available.

Physiological studies have demonstrated that sodium and ammonium ions are mainly excreted in the urine (REACH 2013). Inorganic sulfate is also eliminated from the body almost entirely by renal excretion (i.e. without biotransformation) (REACH 2013).

39.6.1.7 Summary of toxicokinetics

Ammonium and sodium persulfates rapidly hydrolyse upon contact with water to form the corresponding cations (ammonium, sodium) and persulfate anion. The persulfate anion, independent of the cation, undergoes further decomposition upon contact with water to form sulfate species and hydrogen peroxide which is detoxified. All degradation products are physiologically essential to organisms with bioaccumulation of the compounds unlikely in view of the rapid degradation and high water solubility.

39.6.2 *Acute toxicity*

The acute toxicities of ammonium persulfate and sodium persulfate are summarised in Table A39.4 and Table A39.5, respectively (NICNAS 2001; OECD 2005). LD50 is the acute median lethal dose and LC50 is the acute median lethal concentration of the substance.

Table A39.4 Summary of acute lethality studies of ammonium persulfate

Route	Species	Results	Reference
Oral	Rat (m)	LD50 = 820 mg/kg	Smyth et al. (1969)
	Rat (f)	LD50 = 495 mg/kg	FMC Corporation (1991a)
	Rat (m)	LD50 = 600 mg/kg	FMC Corporation (1979a)
	Rat (m) Rat (f)	LD50 = 742 mg/kg LD50 = 700 mg/kg	FMC Corporation (2001)
Dermal	Rat	LD50 >2000 mg/kg	FMC Corporation (1991b)
	Rabbit (m)	LD50 >10 000 mg/kg	FMC Corporation (1979a)
Inhalation	Rat	LC50 >2.95 mg/L (4 hr exposure, 97% dust particles <10 μm)	FMC Corporation (1987a)
	Rat (m)	LC50 = 520 mg/L (1 hr exposure)	FMC Corporation (1979a)

m = male; f = female

Table A39.5 Summary of acute lethality studies of sodium persulfate

Route	Species	Results	Reference
Oral	Rat (m)	LD50 = 930 mg/kg	Degussa (1979)
	Rat (f)	LD50 = 920 mg/kg	Degussa (1979)
	Rat (m)	LD50 = 895 mg/kg	FMC Corporation (1979c)
Dermal	Rabbit (m)	LD50 >10 000 mg/kg	FMC Corporation (1979c)
Inhalation	Rat	LC50 >5.10 mg/L (4 hr exposure)	FMC Corporation (1995)
	Rat	LC50 >21.6 mg/L 17 – 19% dust particles <5 μm (4 hr exposure)	FMC Corporation (1987b)
	Rat (m)	LC50 >191.7 mg/L 50% aq. suspension (1 hr exposure)	FMC Corporation (1979b)

m = male; f = female

39.6.2.1 Oral

Acute oral LD50 values from studies with rats for the substances were between 495 mg/kg bw to 700 mg/kg bw in females and from 600 mg/kg bw to 820 mg/kg bw in males for ammonium persulfate (Smyth et al. 1969; FMC Corporation 1979a, 1991a, 2001) and 895 mg/kg bw to 930 mg/kg bw for sodium persulfate (Degussa 1979; FMC Corporation 1979c). Clinical signs were ocular and oral discharge, irregular breathing and loss of muscle control.

39.6.2.2 Dermal

Acute dermal LD50 in rats (FMC Corporation 1991b) and rabbits were all greater than the highest treatment level of 10 000 mg/kg bw for both salts in rabbits (FMC Corporation 1979a, 1979c). Ocular and nasal discharge and slight irritation were reported among the exposed animals in the acute dermal toxicity studies.

39.6.2.3 Inhalation

Guideline inhalation studies in rats using ammonium and sodium persulfates indicated a LC50 value greater than the maximum attainable concentration of 2.95 mg/L and 5.10 mg/L respectively. After exposure animals exhibited dyspnoea, respiratory distress and increased nasal, ocular and oral secretions (FMC Corporation 1987a, 1995). Older less reliable studies with both salts also indicate a low toxicity by the inhalation route (OECD 2005).

39.6.2.4 Observation in humans

No data were available.

39.6.2.5 Summary of acute toxicity

The results of the acute toxicity tests on ammonium and sodium persulfates by all routes of exposure in several good quality animal studies are indicative of similar toxicity for the two salts and further support the persulfate category justification. Both salts have low acute toxicity by dermal and inhalation routes and effects observed appear to be due to local action.

39.6.3 *Irritation / Corrosivity*

39.6.3.1 Skin irritation

Ammonium persulfate was not irritating to the rabbit skin in a study performed according to OECD Test Guideline (TG) 404 (FMC Corporation 1988). An older, unpublished study on ammonium persulfate did not show irritation when it was tested in rabbits, using the Draize Scoring method (FMC Corporation 1979a). Similarly, three brief study reports submitted by industry on sodium persulfate showed at most a slight skin irritant potential in rabbits (FMC Corporation 1979c, 1979d, 1980).

The chemicals are non-irritating to the skin in animal studies.

39.6.3.2 Eye irritation

The eye irritation potential of ammonium persulfate was tested in several studies in rabbits, summaries of which have been published (CIR 2001). In one study, ammonium persulfate was stated not to be irritating and in a second study, rabbits exhibited slight to mild conjunctivitis and iritis. In a third study, severe conjunctival redness, chemosis and discharge were observed, which disappeared within 72 hours although corneal opacity persisted longer than 72 hours. The investigators concluded that ammonium persulfate is slightly irritating to the eye.

In a single unpublished study, sodium persulfate was instilled into the eyes of eight rabbits. Eyes were scored by the Draize method at 24, 48 and 72 hours. Only slight conjunctivitis was noted at 48 hours (FMC Corporation 1979c).

Overall, the chemicals are non-irritating to slightly irritating to the eyes of animals.

39.6.3.3 Respiratory irritation

No data were available for ammonium persulfate.

Groups of male ND4 Swiss Webster mice were exposed, head-only, to sodium persulfate dust for 30 minutes at concentrations of 0.26 to 3.22 mg/L (FMC Corporation 1994). Mortality was observed in all except the lowest exposure group during the seven day post-exposure period with clinical signs that included ocular and nasal discharge and decreased respiratory rate. Abnormal gait and whole body tremors were observed in animals exposed to the highest concentration of dust. The concentration of dust which produced a 50% decrease in respiratory rate (RD_{50}) was 2.25 mg/L, which indicated that sodium persulfate was a slight sensory irritant.

39.6.3.4 Observation in humans

Standard patch tests have shown that 5% ammonium persulfate is irritant to humans (Calnan and Shuster 1963; Cronin 1980) although a separate study found 1/20 people exhibited an equivocal response when tested with 5% to 10% ammonium persulfate (Forck 1968). Application of 17.5% solution of the persulfate salts under an occlusive wrap for four hours was found to cause irritation in 8/46 subjects (Jordan 1998 cited in CIR 2001).

One case of corneal burns from potassium persulfate was reported and irritant effects of persulfates are reported to include pain in the eyes with conjunctivitis (BIBRA International 1997). Two cases of irritant reactions to hair bleach containing ammonium persulfate have been described, involving erythema of the scalp and forehead developing over several hours followed by weeping and crusting (Cronin 1980; Fisher and Dooms-Goossens 1976). Skin rashes appearing within one month of beginning work in a factory manufacturing ammonium and potassium persulfates occurred in 20% to 70% of new employees (White et al. 1982).

Overall, patch tests in humans (supported by case reports) indicate that irritation occurs in some subjects from exposure to persulfate solutions at concentrations greater than 5%.

39.6.4 *Sensitisation*

39.6.4.1 Skin sensitisation

There was evidence of delayed contact hypersensitivity in two maximisation tests (OECD TG 406) with ammonium and sodium persulfate in guinea pigs (CIR 2001; BG Chemie 1996; BIBRA International 1997). All test animals reacted positively following challenge by intradermal injection of 0.1% ammonium persulfate and 80% of animals were positive following dermal challenge with 1% ammonium persulfate 14 days later. The corresponding figures for sodium persulfate were 90% test animals positive following a (non-standard) intra-cutaneous challenge and 60% test animals positive following topical challenge.

Sodium persulfate was not sensitising when applied to the skin of guinea pigs in an unpublished Buehler Test conducted to guideline standards (FMC 1990b).

In a murine Local Lymph Node Assay (LLNA), investigators concluded that both ammonium and sodium persulfate were moderate to strong sensitisers with EC3 values (the effective concentration required to produce a three-fold increase in stimulation index) calculated to be 1.9% and 0.9% respectively (Cruz et al. 2009 cited in HSDB 2013). The EC3 value is an estimate of the concentration of a sensitiser required to generate a threefold stimulation of proliferation in draining lymph nodes

39.6.4.2 Respiratory sensitisation

Ammonium persulfate has been tested in an animal model of occupational lung disease, namely, airway responsiveness to acetylcholine in rabbits. Airway hyper-responsiveness (AHR) is regarded as an initial step in the development of obstructive lung disease (Vandenplas et al. 1996). Ammonium persulfate at approximately 50 mg/m^3 for four hours induced AHR (Mensing et al. 1995).

39.6.4.3 Observation in humans

NICNAS (2001), CIR (2001), OECD (2005), and de Wit-Bos et al. (2012) evaluated the available clinical skin sensitisation data comprising experimental studies, case reports, multiple case studies and epidemiological studies including those summarised in Table A39.6.

Table A39.6 Human skin sensitisation studies with persulfate salts

Study type	Salt	Cohort	Result	Reference
Repeated insult patch test	Sodium	Human	Not sensitising at 5000 ppm in water	FMC Corporation (1996)
Patch test	Ammonium, sodium	Human	Not sensitising under occluded and non- occluded wraps as a 17.5% aqueous solution	Jordan 1998 cited in CIR 2001
Patch test	Sodium	Human	Sensitising in 19% (5/26) at 0.5% solution under occlusion and 12% (3/26) at re-challenge at 0.001% or 0.25%	E.I. Dupont de Nemours and Co. (1992)
Patch test	Ammonium	Human (hairdressers)	3 case studies with 7 of 9 positive	Fisher and Dooms-Goossens (1976)
Patch test	Sodium	Human (hairdressers)	Positive in case study via dermal (and inhalation) routes (n=2)	Pepys et al. (1976)
Patch test	Ammonium	Human (hairdressers)	Case control 12/49 positive (1/69 controls)	Kellett and Beck (1985)
Skin prick test, patch test, lung function	Ammonium	Human (hairdressers)	Case control study; allergic rhinitis in 1.6% (6/355), contact dermatitis in 0.5% (2/355) and occupational asthma in 0.8% (3/355). 6.5% (7/107) of hairdressers gave positive skin prick tests and 1.85% (1/54) gave positive patch tests.	Leino et al. (1998)
Skin prick test	Ammonium	Human (hairdressers)	Positive in case study (n=1 for each reference)	Veien et al. (2001); Reiffers et al. (1974)
Epi-cutaneous	Ammonium, sodium	Human (workers)	3/3 workers gave positive results	Bauer and Fruhmann

Study type	Salt	Cohort	Result	Reference
test				(1979)

There are strong indications that both ammonium and sodium persulfate are linked to a variety of skin complaints in occupationally exposed human subjects indicative of sensitisation. In general, persulfates are associated with immediate and delayed contact hypersensitivity, contact urticaria, eczema, dermatoses and rashes (White et al. 1982).

Occupational asthma, rhinitis, bronchitis and decreased lung function has been widely reported in hairdressers from bleaching powders and industrial workers exposed to persulfate salts. Several large occupational studies were reviewed in CIR (2001) and NICNAS (2001).

39.6.4.4 Summary of sensitisation

Skin sensitisation (for ammonium and sodium persulfate) and respiratory sensitisation (for ammonium persulfate) has been demonstrated in experimental animals. The results from human studies indicate that both the persulfates are capable of inducing skin and respiratory tract sensitisation in occupationally exposed individuals.

39.6.5 *Repeat dose toxicity*

39.6.5.1 Oral

Three rat studies on repeat dose oral toxicity of ammonium and sodium persulfate were summarised from NICNAS (2001) and OECD (2005) and presented in Table A39.7. The Lowest Observed Adverse Effect Concentration (LOAEC), No Observed Adverse Effect Concentration (NOAEC) and Klimisch scores (Klimisch et al. 1997) (1 = reliable without restriction; 2 = reliable with restriction; and 3 = not reliable) are indicated for each study.

Table A39.7 Repeated dose toxicity in rats

Test Substance	Treatment	Results	Remarks	Reference (Klimisch score)
Ammonium	28 day, diet (males only)	LOAEC=600 ppm (82 mg/kg bw/day) NOAEC=300 ppm (41 mg/kg bw/day)	0, 100, 300, 600 ppm. Decreased relative adrenal weight at the top dose.	FMC Corporation (1979a) (2)
Ammonium	7 day, inhalation	LOAEC=4 mg/m^3 NOAEC=1 mg/m^3	Aerosolised 0, 1, 4, 9, 17 and 20 mg/m^3. Reduction in body weight gain and indications of pulmonary oedema and / or inflammation at ≥4 mg/m^3.	Last et al. (1982) (2)
Ammonium	90 day, inhalation	LOAEC=25 mg/m^3 NOAEC=10 mg/m^3	Dust: 0, 5, 10 and 25 mg/m^3. Elevated lung weights, clinical signs and depressed body weights at top dose. All effects reversible during recovery period. NOEL=5 mg/m^3: Sporadic rales, increased respiration at ≥10 mg/m^3.	FMC (1998) (1)
Sodium	28 day, diet (males	NOAEC=1 000 ppm	0, 100, 316, 1000 ppm. No effects and no macroscopic findings at	FMC

Test Substance	Treatment	Results	Remarks	Reference (Klimisch score)
	only)	(137 mg/kg bw/day)	the top dose.	(1979c) (2)
Sodium	90 day, diet	LOAEC=3000 ppm (200- 250 mg/kg bw/day)	0, 300, 3000 and 1000 ppm for 7 weeks raised to 5000 ppm for final 6 weeks. Local effects on the gastrointestinal tract (epithelial necrosis and atrophy) at 13 weeks and decreased body weight at 3000 ppm.	FMC (1979e) (2)

Twenty-eight-day repeated- dose oral (dietary) toxicity studies in rats were conducted on both chemicals. NOAELs for sodium and ammonium salts were 41 mg/kg bw/day and the top dose of 137 mg/kg bw/day, respectively (FMC Corporation 1979a, 1979c).

In addition, a 90-day study in rats using sodium persulfate in diet (FMC Corporation 1979e) showed decreases in body weight at the two high dose levels. Based on this and pathological findings (limited to the 3000 ppm group only) consisting of effects on the gastrointestinal tract epithelial lining, a LOAEL of 3000 ppm was established for local effects.

39.6.5.2 Dermal

No data were available.

39.6.5.3 Inhalation

Two repeated dose inhalation studies in rats dosed with ammonium persulfate are summarised in Table A39.7. A well-conducted 90-day inhalation study of ammonium persulfate revealed evidence of inflammation of the airways, reduced body weight gain, rales, increased respiratory rate and increased lung weights at the LOAEL of 25 mg/m^3 (FMC 1998). A NOAEL of 5 mg/m^3 was identified by the OECD (2005) based on sporadic rales and respiratory effects seen (in females only) at the NOAEL of 10.3 mg/m^3.

39.6.5.4 Observation in humans

Pulmonary function tests conducted on employees of a persulfate production facility indicated no adverse effects on pulmonary function at workplace levels, measured at 0.5 mg/m^3 (FMC Corporation 1992). Follow-up of these same employees indicated that exposure at 0.5 mg/m^3 had no long-term effects on pulmonary function (Greaves 1997).

39.6.5.5 Summary of repeat dose toxicity

Ammonium and sodium persulfates produced lesions at the site of contact via the oral and inhalation routes of exposure. The findings were gastrointestinal lesions in the sub-chronic dietary study of sodium persulfate (FMC Corporation 1979e), with a LOAEL of 3000 ppm identified. Inflammatory lesions of the bronchi and trachea and adverse respiratory effects were observed during an inhalation study of ammonium persulfate and a NOAEC of 10.3 mg/m^3 was established (FMC Corporation 1998).

Although studies of each were limited in number, there were no differences in effects between the two chemicals.

39.6.6 *Genotoxicity*

Negative results for mutagenicity are available from Ames tests in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 for sodium persulfate (FMC Corporation 1990a) and *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2 uvrA (Shimizu 1985) or *S. typhimurium* strains TA97 or TA102 (Ishidate 1984) for ammonium persulfate . An *in vitro* unscheduled DNA synthesis test was also negative for sodium persulfate (FMC Corporation 1990d). Similarly, ammonium persulfate was not clastogenic to Chinese hamster fibroblasts in the absence of metabolic activation in a chromosome aberration test (Ishidate et al. 1988).

Sodium persulfate was negative in two *in vivo* genotoxicity studies. Doses of sodium persulfate up to 338 mg/kg injected into mice intraperitoneally did not increase the incidence of micronuclei in erythrocytes (FMC Corporation 1990c). Sodium persulfate was found to be non-genotoxic when tested up to 820 mg/kg in an *in vivo*/*in vitro* unscheduled DNA synthesis test in rats (FMC Corporation 1991c).

Sodium and ammonium persulfates are not genotoxic.

39.6.7 *Carcinogenicity*

In a non-guideline dermal study, female SENCAR mice were exposed twice weekly to 0.2 mL of a 200 mg/mL solution of ammonium persulfate for 51 weeks (Kurokawa et al. 1984). The investigators concluded that ammonium persulfate is neither a tumour promoter nor a complete carcinogen when applied to the skin.

39.6.8 *Reproductive toxicity*

39.6.8.1 Fertility

In a well-conducted fertility/developmental study (OECD TG 421), groups of rats (12 per sex per group) were administered ammonium persulfate in the diet at doses of 0, 40, 100 and 250 mg/kg bw/day (Weaver 2004). Animals were dosed prior to and during mating, gestation and following gestation until lactation day four. In the parental generation there were no treatment-related clinical signs, effects on body and organ weights or gross lesions. There were no significant adverse effects on the gonads and a normal progression of spermatogenesis, although a non-significant decrease in pregnancy rates was reported at ≥100 mg/kg bw/day. On this basis, it was concluded that the NOAEL for fertility indices and reproductive performance was the top dose of 250 mg/kg bw/day.

39.6.8.2 Developmental toxicity

The fertility/developmental study for ammonium persulfate (described above) was the only report available (Weaver 2004). There were no treatment-related clinical signs, mortality or necropsy findings among pups with live birth and viability indices similar across all groups. There was a slight transient depression in mean pup body weight however it was not considered adverse. The developmental toxicity NOAEL determined was the high dose of 250 mg/kg bw/day.

39.6.9 *Other health effects*

No additional health effects were identified.

39.7 Health hazard summary

39.7.1 *Critical health effects*

Ammonium and sodium persulfates have very similar physical/chemical properties. In addition, available animal and human studies indicate that these chemicals also have similar toxicological properties. Accordingly, the chemicals form an appropriate chemical category for assessment of human health.

Although the chemicals are harmful by the oral route, this potential for acute toxicity was generally not demonstrated via the dermal or inhalation routes. The chemicals were non-irritating to slightly irritating to eyes and respiratory system and not a skin irritant in animal studies, whilst studies in humans indicate that the chemicals can cause irritation.

The chemicals are capable of inducing skin and respiratory sensitisation in animals and these are also the major chronic effects observed in humans. Mouse LLNA results for ammonium and sodium persulfate suggest that the chemicals are moderate to strong sensitisers.

For ammonium persulfate the most sensitive endpoint was effects on the respiratory system with a NOAEC of 10.3 mg/m^3 (equivalent to (2.1 mg/kg bw/day) in a 90-day inhalation study (FMC Corporation 1998). Local effects, including respiratory tract inflammation, increased lung weight and rales were observed in rats at the LOAEC of 25 mg/m^3. A systemic effect observed at this concentration was decreased body weight, which may be a consequence of adverse local effects on the respiratory tract rather than as a direct action of the oxidising chemical. An older, 28-day repeat oral dose study provided a much larger NOAEL of 41 mg/kg bw/day, based on decreased relative adrenal weight at the top dose (FMC Corporation 1979a). However, as this study was not well documented and is also potentially confounded by local irritant effects arising from the oxidising chemical, the more conservative NOAEL of 2.1 mg/kg bw/day is appropriate.

A 90-day study in rats using sodium persulfate in diet (FMC Corporation 1979e) showed decreases in body weight at the two high dose levels. Based on this and pathological findings (limited to the 3000 ppm group only) consisting of effects on the gastrointestinal tract epithelial lining, a LOAEL of 3000 ppm was established. The next dose of 1000 mg/kg bw/day was changed to 5000 mg/kg bw/day midway through the experiment and a NOAEL could not be established in the study.

The chemicals were not genotoxic or shown to cause tumour induction or promotion in a mouse skin model.

Repeated oral exposures to ammonium persulfate provided evidence that persulfates are not reproductive or developmental toxicants.

Overall, the main critical effects to human health are sensitisation and irritancy.

39.7.2 *Hazard classification*

This hazard assessment confirms the existing classification for both chemicals under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004).

The chemicals are recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A39.8. These NICNAS recommendations do not consider physical or environmental hazards.

Table A39.8 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification (CAS No. 7727-54-0)	**GHS* classification (CAS No. 7775-27-1)**
Acute toxicity	Harmful if swallowed – Cat. 4 (H302)	Harmful if swallowed – Cat. 4 (H302)
Irritation / Corrosivity	Causes serious eye irritation – Cat. 2A (H319) May cause respiratory irritation – Specific target organ toxicity, single exposure - Cat. 3 (H335) Causes skin irritation – Cat. 2 (H315)	Causes serious eye irritation – Cat. 2A (H319) May cause respiratory irritation – Specific target organ toxicity, single exposure - Cat. 3 (H335) Causes skin irritation – Cat. 2 (H315)
Sensitisation	May cause an allergic skin reaction – Cat.1 (H317) May cause allergy or asthma symptoms or breathing difficulties if inhaled – Cat.1 (H334)	May cause an allergic skin reaction – Cat.1 (H317) May cause allergy or asthma symptoms or breathing difficulties if inhaled – Cat.1 (H334)

**Globally Harmonised System (UNECE 2009)*

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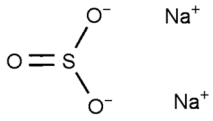
A40 Sodium sulfite

CAS No.	CAS Name
7757-83-7	Sulfurous acid, sodium salt (1:2)

40.1 Chemical identity

The information on chemical identity was obtained from ChemID*plus* (2012) and the Hazardous Substances Data Bank (HSDB) (2013). Details are provided in Table A40.1.

Table A40.1 Chemical identity

	Sodium sulfite
Synonyms	Sodium sulfite Sulfurous acid, sodium salt (1:2) Disodium sulfite
Structural formula	
Molecular formula	Na_2SO_3
Molecular weight	126.04
Appearance and odour	Odourless white crystals or powder
SMILES notation	O=S(O{-}.[Na]{+})O{-}.[Na]{+}

40.2 Physical properties

The physical properties of the chemical are presented in Table A40.2. The information was obtained from the Organisation for Economic Co-operation and Development (OECD) (2009).

Table A40.2 Physical properties

Property	**Value**
Melting point	Decomposes at 150 °C
Density	2633 kg/m^3 at 15.4 °C
Water solubility	125.4 g/L at 0 °C 283 g/L at 80 °C
Partition coefficient n-octanol/water (log K_{ow})	- 4

40.3 Current regulatory controls

The document from now on refers to sulfurous acid, sodium salt (1:2) (CAS No. 7757-83-7) as 'sodium sulfite', one of the synonyms of the chemical.

40.3.1 *Hazard classification for occupational health and safety*

The chemical is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

40.3.2 *Occupational exposure standards*

40.3.2.1 Australia

No specific exposure standards were available.

40.3.2.2 International

No specific exposure standards were available.

40.3.3 *Australian food standards*

The chemical is listed in Standard 1.3.3 of the Australia New Zealand Food Standards Code as permitted processing aid in packaged water and water used as an ingredient in other foods under conditions of Good Manufacturing Practice (GMP), and as a dough conditioner at a maximum permitted level of 60 mg/kg (Food Standards Australia New Zealand 2013).

40.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

40.3.5 *Additional controls*

40.3.5.1 Australia

The substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

40.3.5.2 International

Inorganic sulfites and bisulfites are currently regulated in the European Union (EU) Cosmetic Directive 76/768/EEC with maximum authorised concentrations of 0.67% expressed as free sulfur dioxide (SO_2) in oxidative hair dye products, 6.7% expressed as free SO_2 in hair straightening products, 0.45% expressed as free SO_2 in self-tanning products for the face, 0.4% expressed as free SO_2 in other self-tanning products, and 0.2% expressed as free SO_2 in preservatives (EC 2010).

Sodium sulfite is listed in the United States Food and Drug Administration (US FDA) as a food substance generally recognised as safe when used in accordance with GMP, with restricted use in meats, in foods as a source of vitamin B1, in fruits or vegetables intended to be served/sold raw to consumers, or in food presented to consumers as fresh (US FDA 1999).

40.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

40.5 Health hazard characterisation

The information on health hazards is obtained from OECD (2009), the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) Opinion on inorganic sulfites and bisulfites (SCCNFP 2003), and the Cosmetic Ingredient Review (CIR) of seven sulfite compounds (CIR 2003). Unless otherwise noted, references to individual studies below are taken from this review.

40.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

40.5.1.1 Oral absorption

No data were available.

The distribution and metabolism studies showed that sodium sulfite is absorbed in the gastrointestinal tract and widely distributed in the organs (Sections A40.5.1.4 and A40.5.1.5).

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

40.5.1.2 Dermal absorption

No data were available.

For the purposes of risk assessment, 100% dermal absorption in humans is assumed.

40.5.1.3 Inhalation absorption

No data were available.

The acute inhalation toxicity and respiratory irritation studies showed that sodium sulfite is absorbed in the respiratory system (Sections A40.5.2.3 and A40.5.3.3).

For the purposes of risk assessment, 100% inhalation absorption in humans is therefore assumed.

40.5.1.4 Distribution

Holtzman rats were administered $Na_2{}^{35}SO_3$ plus cold $NaHSO_3$, equivalent to 50 mg/kg bw/day SO_2, by gavage for 14 days (Gibson and Strong 1974). ^{35}S radioactivity levels in the tissues were recorded after 2, 7, and 14 days of exposure. At all observation periods, the highest relative sulfite levels were reported in the stomach, skin and hair, intestine, kidney and the carcass. Lower sulfite levels were also found in the lung, spleen, reproductive organs, heart, liver, and brain. The sulfite levels relative to the applied dose decreased as duration of exposure increased, from 6.05% after two days to 0.7% after 14 days.

Fischer 344 rats were administered ^{35}S-labelled sodium sulfite by bronchioalveolar lavage. ^{35}S radioactivity levels were reported in pulmonary arteries, arterioles, and the walls of conducting airways and pleura after 48 and 72 hours (Dahl et al. 1981).

40.5.1.5 Metabolism

The OECD (2009) reviewed several metabolism studies and concluded that there are three sodium sulfite metabolism pathways: the enzymatic oxidation of sulfite (SO_3^{2-}) to sulfate (SO_4^{2-}); the formation of S-sulfonates; and the formation of sulfite-derived radicals.

The primary metabolic route is the oxidation of the sulfite to sulfate by the sulfite oxidase enzyme. Multiple studies reported high tissue activities in the liver, kidney, and heart in rats, mice, rabbits, and rhesus monkeys, and lower tissue levels in spleen, brain, testes and lung (Beck et al. 1983; Gunison et al. 1977; MacLeod et al. 1961; Tejnorova 1978). The capacity of human liver and lung for sulfite oxidation was estimated to be 70 000 and 500 mg/day of sodium sulfite, respectively, based on *in vitro* sulfite oxidase activities (Beck-Speier et al. 1985). The highest levels of sulfite oxidase activity have been reported in rat liver (Beck et al. 1983; Beck-Speier et al. 1985*;* Gunnison et al. 1977; Gunnison 1981; Tejnorova 1978).

Metabolism studies also reported that a constant fraction of sulfite is metabolised in the liver with a finite amount of sulfite surviving the first pass through the organ and entering into systemic circulation (Gunnison 1981*;* Gunnison and Jacobsen 1987). A metabolic disorder of the enzyme, known as sulfite oxidase deficiency, is known to exist in humans (Johnson and Rajagopalan 1976; Mudd et al. 1967; Shih et al. 1977).

Sulfite as a strong nucleophile reacts with biomolecules by substitution at electrophilic positions (Neta and Huie 1985; Petering 1977). S-sulfonates are thus formed by sulfitolysis of the disulfide bonds in proteins or in free cysteine (Gunnison and Benton 1971; Gunnison and Farruggella 1979; Gunnison and Palmes 1973, 1978; Wever 1985). S-sulfonates of plasma constituents have reported half-lives of 1 to 4 days (Gunnison et al. 1973, 1978). *In vitro* treatment of lung cells showed decreased glutathione disulfide levels and increased glutathione and glutathione S-sulfonate levels (Keller and Menzel 1989).

Formation of sulfite-derived radicals were reported in *in vitro* studies, with generation of sulfur trioxide anion radical SO_3^-, peroxyl radicals, or sulfate anion radical SO_4^- (Chamulitrat 1998, 1999; Constantin et al. 1994; Ito and Kawanishi 1991; Mottley et al. 1982a, 1982b; Mottley and Mason 1988, 1989; Neta and Huie 1985; Shi and Dalal 1990; Shi and Mao 1994; Sun et al. 1992). *In vitro* studies also demonstrated the generation of sulfur dioxide anion radical SO_2^- from the cytochrome P-450-dependent one-electron reduction of sulfite (Mottley et al. 1985).

40.5.1.6 Excretion

A series of excretion studies were evaluated in rats, mice, and monkeys by Gibson and Strong (1973). Holtzman rats received 50 mg/kg bw SO_2 in drinking water for a maximum of 14 hours. Within 24 hours, 74 to 79% and 4 to 17% of ^{35}S-activity levels were found in the urine and faeces, respectively. The ^{35}S-activity levels in the carcass were 9 to 21% after 24 hours, 4 to 7% after 48 hours, 2% after one week, and 1% after two weeks.

In albino mice given 50 mg/kg bw SO_2 in drinking water, 80 and 15% of the ^{35}S-activity levels were found in the urine and faeces, respectively. The ^{35}S-activity levels in mice carcass were 3% after 24 hours and 2% after 48 hours.

In rhesus monkeys administered 50 mg/kg bw SO_2 by gavage, excretion was nearly complete within 48 to 72 hours of administration with the primary route being the urine.

40.6 Acute toxicity

40.6.1.1 Oral

Animal data on acute oral toxicity of sodium sulfite are summarised from OECD (2009) and SCCNFP (2003) and presented in Table A40.3. In addition, the Klimisch scores (Klimisch et al. 1997) (1 = reliable without restrictions; 2 = reliable with restrictions; 3 = not reliable; and 4 = not assignable) for each study are indicated where available. The acute oral median lethal dose (LD50) is indicated for each study.

Table A40.3 Acute oral toxicity studies with sodium sulfite

Species **Doses**	**LD50 (mg/kg bw)**	**Effects**	**Reference** **(Klimisch score)**
Male Wistar rats 3550, 4440, 5550, 6940, or 8670 mg/kg bw	5680	Decreased spontaneous activity, taking neck to the floor, twitching of hind legs, walking with body rubbing the floor, induced seizure, and hyper secretions.	Yamada et al. (1979) (2)
Wistar rats 2000, 2500, 2800, 3100, or 5000 mg/kg bw	3930 (males) 3560 (females)	Decreased bodyweight, sedation, spasms, and rough hair.	Loser (1982a, 1982b) (Klimisch score not assigned in SCCNFP (2003))
Male rats (strain not specified) 3100, 3500, 4000, 5000, or 5800 mg/kg bw	3560	Poor general condition, decreased bodyweight, sedation, piloerection, and convulsions. No abnormalities in pathology.	Bomhard et al. (1982) (2)
ddYS mice Doses not specified	900-920 (males) 820-903 (females)	No other information available.	Kobayashi et al. (1976) (2)
Rabbits (strain not specified) Doses not specified	600-700	No other information available.	Rost and Franz (1913) (3)

The studies show that sodium sulfite has low acute oral toxicity in rats and moderate acute oral toxicity in mice and rabbits.

40.6.1.2 Dermal

No data were available.

40.6.1.3 Inhalation

No data were available to determine the acute median lethal concentration (LC50) of the chemical.

In two similar studies testing the depression of respiratory rate, mice (strain not specified) were exposed to sodium sulfite aerosol dissolved in 50% distilled water and 50% polyethylene glycol in an exposure chamber for 10 minutes. The concentrations were 73, 189, 592, or 1603 mg/m^3 (Alarie et al. 1973) and 246, 435, 917, or 1834 mg/m^3 (Wakisaka 1976). The respiratory rate of exposed mice was similar to controls in both the studies.

Rabbits (strain not specified) were exposed to sodium sulfite aerosol for one hour at concentrations of 0.42, 0.62, 1.56, 1.89, 2.29, or 3.07 mg/m^3 (Chen and Schlesinger 1983) The particles had a mass median aerodynamic diameter (MMAD) of 0.3 µm. The mucociliary clearance of the particles was accelerated at concentrations of 1.89 mg/m^3 and higher, which the authors concluded as an irritant effect of the sulfite anion.

Groups of male Hartley guinea pigs were exposed to sodium sulfite aerosol for one hour in two separate experiments: head-only exposure, at concentrations of 0, 0.474, 0.669, or 0.973 mg/m^3; and whole body exposure at concentrations of 0, 0.204, 0.395, or 1.152 mg/m^3 (Chen et al. 1987). The particles had a MMAD of 0.36 µm. In the first experiment, the effects were decreased dynamic compliance in all treated animals, increased mean frequency of breaths and decreased tidal volume at the mid and top concentrations, and increased lung resistance at the top concentration. All the effects, except lung resistance, were partially or fully reversible in the post-observation period. In the second experiment, decreased lung volumes and increased wet lung to bodyweight ratio were observed at all treatment doses.

40.6.1.4 Observation in humans

No data were available for sodium sulfite.

Ingesting sulfites may cause irritation of the human stomach, due to liberation of SO_2, producing sulfurous acid (HSDB 2013). In some asthmatic individuals, adverse reactions such as bronchospasm, angioedema, urticaria, nausea, abdominal cramping and / or diarrhoea were reported following ingestion of food containing sulfites (Grotheer et al. 2005).

40.6.2 *Irritation / Corrosivity*

40.6.2.1 Skin irritation

In a study conducted in accordance with OECD Technical Guideline (TG) 404, semi-occlusive application of 500 mg sodium sulfite to clipped intact skin of male New Zealand White rabbits produced no signs of irritation (Bomhard et al. 1982).

Thirty-eight per cent sodium sulfite solution, applied by semi-occlusive patches to the shaved skin of male New Zealand albino rabbits, was not irritating based on the conditions of the test conducted in accordance with OECD TG 404 (Suberg 1983a, 1983b).

The chemical is not a skin irritant in rabbits.

40.6.2.2 Eye irritation

Three eye irritation tests, all conducted in accordance with OECD TG 405, were available.

There were no signs of irritation after a 24-hour instillation of 100 mg of the chemical (concentration not specified) in to the eyes of male New Zealand rabbits (Bomhard et al. 1982).

A 38% sodium sulfite and sodium bisulfite solution was instilled into the conjunctival sac of New Zealand White rabbits. No effects were seen on the cornea and iris. Slight erythema and oedema were observed at the 24 hour observation period only and was considered reversible (Suberg 1983a, 1983b).

In another study, a 38% solution of sodium sulfite (without crystal water) and sodium bisulfite was instilled in the eyes of male Vienna White rabbits. Slight, at observation day 8, to severe, at observation day 15, changes in the cornea and iris were reported. Slight to moderate conjunctival effects, such as erythema and oedema, were also reported up to the end of the observation periods. Based on the persistency of effects, the chemicals were considered severe eye irritants (Kirsch and Grundler 1981; Kirsch and Kieczka 1984).

The chemical is a severe eye irritant in rabbits.

40.6.2.3 Respiratory irritation

Effects on respiratory system are described in the Acute Inhalation Toxicity section. There were no effects on respiratory rates in mice treated sodium sulfite aerosol for 10 minutes at concentrations up to 1603 mg/m^3 (Alarie et al. 1973) or 1834 mg/m^3 (Wakisaka 1976). In guinea pigs exposed to the aerosolised chemical for one hour, bronchoconstriction was observed at concentrations of 0.204 mg/m^3 and higher (Chen et al. 1987).

Respiratory tract irritation was observed in guinea pigs at ≥0.204 mg/m^3 while no respiratory effects were seen in mice at concentrations up to 1834 mg/m^3.

40.6.2.4 Observation in humans

No data were available.

40.6.3 *Sensitisation*

40.6.3.1 Skin sensitisation

No data were available.

Sulfites (including sulfite, bisulfite and metabisulfite), which are used widely in cosmetic products, are rarely contact allergens and were not found to be potent primary sensitisers (CIR 2003).

The chemical is not a skin sensitiser.

40.6.3.2 Respiratory sensitisation

No data were available.

40.6.3.3 Observation in humans

Pharmaceutical creams containing sodium sulfite (0.2 to 2% in aqueous solution or 0.2 to 5% in petrolatum) as an antioxidant were applied to six individuals. The patch tests showed positive reactions, such as eczema on the face and groin and vesicular papular dermatitis on the face and chest, and the chemical was identified as the cause for dermatitis for five of the six individuals (Garcia-Bravo et al. 1989; Lodi et al. 1993; Vissers-Croughs et al. 1988).

Delayed hypersensitivity was reported in 25 of 1762 eczema patients patch tested with 1% sodium sulfite in petrolatum (Petersen and Menné 1992). Two out of 2894 eczematous patients were positive in a patch test of 1% sodium sulfite in petrolatum (Vena et al. 1994).

40.6.4 *Repeat dose toxicity*

40.6.4.1 Oral

Wistar rats were administered anhydrous sodium sulfite daily for three months at dietary doses of 0, 620, 1670, or 3230 mg/kg bw/day for males, and 0, 650, 1190, or

3070 mg/kg bw/day for females (Taniguchi et al. 1981). At the top dose in males, effects were 9.8% decrease in bodyweight gain, increased relative testis and brain weights, and increased blood urea nitrogen. No treatment-related effects were reported in the females.

The NOAEL is 1670 mg/kg bw/day based on systemic effects at the LOAEL of 3230 mg/kg bw/day.

40.6.4.2 Dermal

No data were available.

40.6.4.3 Inhalation

In a study specifically examining lung response parameters, male Sprague-Dawley rats were exposed to 0, 0.1, 1, 5, or 15 mg/m^3 dry sodium sulfite particles in filtered air for 23.5 hours/day for three consecutive days (Last et al. 1980; Last 1989). The MMAD of the aerosol particles was 0.83 to 1.15 µm. At 15 mg/m^3, effects reported were increased glycoprotein secretion and tracheal epithelium irritation. At concentrations of 1 mg/m^3 and higher, a dose-dependent increase of wet to dry weight ratio of lungs, indicative of mild pulmonary oedema, was observed. The No Observed Adverse Effect Concentration (NOAEC) is 0.1 mg/m^3 based on lung responses at the Lowest Observed Adverse Effect Concentration (LOAEC) of 1 mg/m^3.

Beagle dogs were exposed to 1 mg/m^3 sodium metabisulfite aerosols for 290 days. The dose equivalent in terms of the S(IV) particles was 0.3 mg/m^3 (CIR 2003). The MMAD of the aerosol particles was 0.63 µm. Severe epithelial changes were observed with hyperplastic foci in the respiratory region of the nasal cavity. An increase in the non-ciliated cell numbers in the membranous portion of the trachea of the animals was also observed. No other effects were reported.

40.6.4.4 Observation in humans

No data were available.

40.6.5 *Genotoxicity*

In vitro data on genotoxicity of sodium sulfite are summarised from OECD (2009) and SCCNFP (2003), and presented in Table A40.4.

Table A40.4 *In vitro* genotoxicity studies with sodium sulfite

Test	Results	Reference
Reverse mutation test in *Salmonella typhimurium* (modified OECD TG 471)	Negative with and without activation	Hoffman and Engelhardt (1989a)
Reverse mutation test in *S. typhimurium* (modified OECD TG 471)	Negative with and without activation	Hoffman and Engelhardt (1989b)
Reverse mutation test in *S. typhimurium* (modified OECD TG 471)	Negative with and without activation	Hoffman and Engelhardt (1989c)
Reverse mutation test in *S. typhimurium*	Negative with and without activation	Litton Bionetics (1975)
Reverse mutation test in *S. typhimurium*	Negative with and	Fujita and Sasaki

Test	Results	Reference
	without activation	(1987)
Reverse mutation test in *S. typhimurium*	Negative with activation	Ishidate et al. (1984)
Gene mutation test in *Saccharomyces cerevisiae*	Negative with and without activation	Litton Bionetics (1975)
Gene mutation test in mouse lymphoma cells	Negative without activation	Reed and Jones (1996)
Chromosome aberration test in Chinese hamster fibroblasts	Negative without activation	Ishidate et al. (1984)
DNA damage and repair assay	Negative with and without activation	De Flora et al. (1984a, 1984b)

DNA – deoxyribonucleic acid

No *in vivo* genotoxicity data for the chemical were available.

Sodium sulfite is not considered to be genotoxic based on the available data.

40.6.6 *Carcinogenicity*

No data were available for sodium sulfite.

The International Agency for Research on Cancer (IARC) reported that sulfites, bisulfites, and metabisulfites are not classifiable as to their carcinogenicity to humans (IARC 1997).

40.6.7 *Reproductive toxicity*

40.6.7.1 Fertility

In a previously described dietary study by Taniguchi et al. (1981) (refer to Repeat Oral Dose Toxicity), increased relative testes weights of Wistar rats was reported at 3230 mg/kg bw/day. No histopathological changes were observed in the testes. There was no indication of male fertility impairment.

Sodium sulfite is not considered to be toxic to fertility.

40.6.7.2 Developmental toxicity

Pregnant Wistar rats were fed diets containing 0, 0.32, 0.63, 1.25, 2.5, or 5% sodium sulfite heptahydrate on gestational days 8 to 20 (Itami et al. 1989). The doses were equivalent to 0, 150, 300, 550, 1050, or 1650 mg/kg bw/day sodium sulfite. Dams showed decreased food consumption and bodyweight gain at 1650 mg/kg bw/day. Foetal bodyweight was reduced at all doses except the female offspring of the 1050 mg/kg bw/day group. There were no significant increases in malformations, skeletal variations, or delayed ossification. The NOAEL for maternal toxicity is 1050 mg/kg bw/day. A NOAEL for developmental toxicity could not be established in this study.

Sodium sulfite is not considered to be a developmental toxicant.

40.6.8 *Other health effects*

No data were available.

40.7 Health hazard summary

40.7.1 *Critical health effects*

Sodium sulfite has low acute oral toxicity in rats, is not a skin irritant, is a severe eye irritant, and is not a skin sensitiser.

The critical health effect of the chemical is severe eye irritation. Irritation of the human stomach from sodium sulfite ingestion is possible from the liberation of SO_2 in highly acidic environments.

A NOAEL of 1670 mg/kg bw/day was established from repeated exposures to the chemical, with systemic effects reported at the LOAEL of 3230 mg/kg bw/day.

The most appropriate NOAEL for risk assessment, determined from the developmental toxicity study by Itami et al. (1989), is 1050 mg/kg bw/day based on maternal systemic toxicity at the LOAEL of 1650 mg/kg bw/day.

The chemical is neither genotoxic, carcinogenic, nor a reproductive toxicant.

40.7.2 *Hazard classification*

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A40.5. These NICNAS recommendations do not consider physical or environmental hazards.

Table A40.5 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation / Corrosivity	Risk of serious damage to eyes (X_i; R41)	Causes serious eye damage – Cat. 1 (H318)

[a] *Approved Criteria for Classifying Hazardous Substances (NOHSC 2004)*

[b] *Globally Harmonised System (UNECE 2009)*

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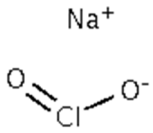
A41 Sodium chlorite

CAS No.	CAS Name
7758-19-2	Chlorous acid, sodium salt (1:1)

41.1 Chemical identity

Details of the chemical identity obtained from ChemID*plus* (2012) and Hazardous Substances Data Bank (HSDB) (2013) are provided in Table A41.1.

Table A41.1 Chemical Identity

	Sodium chlorite
Synonyms	Sodium chlorite
Structural formula	
Molecular formula	$ClHO_2.Na$
Molecular weight	90.44
Appearance and odour	White crystals or crystalline powder
SMILES notation	O=ClO{-}.[Na]{+}

41.2 Physical properties

For the purposes of this assessment, the chemical will be referred to using the synonym sodium chlorite. The physical properties of sodium chlorite were obtained from the Organisation for Economic Co-operation and Development (OECD) (2009) and are provided in Table A41.2.

Table A41.2 Physical properties

Property	**Value**
Melting point	234 °C[1]
Boiling point	Decomposes at >170 °C[1]
Density	2.43 g/cm^3 at 20 °C
Vapour pressure	1.1 x 10^{-4} kPa at 25 °C
Water solubility	572 g/L at 20 °C
Partition coefficient n-octanol/water (log Kow)	-2.7 at 21 °C

[1] *Due to substance instability, obtaining data for 100% pure test substance was not possible.*

41.3 Current regulatory controls

The document from now on refers to chlorous acid, sodium salt (1:1) as 'sodium chlorite', one of the synonyms of the chemical.

41.3.1 *Hazard classification for occupational health and safety*

Sodium chlorite is not classified as hazardous for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

41.3.2 *Occupational exposure standards*

41.3.2.1 Australia

There is no specific exposure standard for sodium chlorite. However, the permissible exposure limits for dusts apply:

- Time Weighted Average (TWA): 10 mg/m^3 measured as inspirable dust.

41.3.2.2 International

There are no specific exposure standards for sodium chlorite. However, the following exposure standards for particulates are identified (Galleria Chemica 2013).

TWA:

- 10 mg/m^3 [Canada, Ireland, Spain]
- 5 mg/m^3 [US]
- 1 mg/m^3 [Latvia].

41.3.3 *Australian food standards*

Sodium chlorite has the following listings in the Australia New Zealand Food Standards Code – Standard 1.3.3 Processing Aids (Food Standards Australia and New Zealand 2013):

- As a permitted bleaching agent, washing and peeling agent (maximum level 1 mg/kg available chlorine)
- As a permitted processing aid with miscellaneous functions (anti-microbial agent for meat, fish, fruit and vegetables; maximum level is the limit of determination for chlorite, chlorate, chlorous acid and chlorine dioxide).

41.3.4 *Australian drinking water guidelines*

The National Health and Medical Research Council (NHMRC) Australian Drinking Water Guidelines lists chlorite under microbial, chemical and physical characteristics as a by-product of chlorine dioxide disinfection. The guideline value for chlorite based on health considerations is 0.8 mg/L (NHMRC 2011).

41.3.5 *Additional controls*

41.3.5.1 Australia

Chlorinating compounds (which would include sodium chlorite) are listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014) in Schedule 5 and Schedule 6 with the following entries:

Schedule 5:

'Chlorinating compounds containing 20 per cent or less of available chlorine, except:

a) when separately specified in these Schedules;

b) sodium hypochlorite preparations with a pH of less than 11.5;

c) liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

d) liquid preparations containing less than 2 per cent of available chlorine; or

e) other preparations containing 4 per cent or less of available chlorine.'

Schedule 6:

'Chlorinating compounds except:

a) when included in Schedule 5;

b) when separately specified in these Schedules;

c) sodium hypochlorite preparations with a pH of less than 11.5;

d) in liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements:

WARNING – Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products

e) in liquid preparations containing less than 2 per cent of available chlorine; or

f) in other preparations containing 4 per cent or less of available chlorine.'

Sodium chlorite is also included in the Australian Dangerous Goods Code Edition 7 (ADG7) (National Transport Commission 2007), with UN Number 1496. It is listed as a Class 5.1 'oxidising substance',Packing Group II. The ADG7 contains detailed provisions for the packaging, transport and marking of containers in Class 5.1.

41.3.5.2 International

Sodium chlorite is listed on the United States Food and Drug Administration (US FDA) Food Additives Status List as a miscellaneous additive. It is listed as a food starch modifier with a maximum limit of 0.5% (US FDA 2013).

The US Environmental Protection Agency (EPA) has also set a maximum contaminant level for chlorite in drinking water of 1 mg/L (Agency for Toxic Substances and Disease Registry (ATSDR) 2004b).

No additional international restrictions were identified.

41.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

41.5 Health hazard characterisation

The following information on health hazards is obtained from US EPA (2000), ATSDR (2004a), OECD (2009) and a registration dossier on sodium chlorite submitted by industry under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013) program.

41.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

41.5.1.1 Oral absorption

Chlorite (and therefore sodium chlorite) is rapidly absorbed following oral administration. A well-conducted study in rats where radiolabelled chlorite ($^{36}ClO_2^-$) was administered via gavage reported peaks in plasma ^{36}Cl two hours after dosing (Abdel-Rahman et al. 1982, 1985). The rate constant and half-life of absorption were 0.198/hour and 3.5 hours, respectively. Based on reports in this study of 87% and 13% of the initial dose of $^{36}ClO_2^-$ being found in urine and faeces respectively, it can be assumed that oral absorption is at least 87%. It is not known to what extent faecal excretion reflects absorption preceding enterohepatic circulation.

For human risk assessment purposes, an oral absorption of 100% is assumed.

41.5.1.2 Dermal absorption

Only limited data were available for dermal absorption of sodium chlorite. Dermal absorption of ^{36}Cl was measured in rats following 10 daily applications of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed (Scatina et al. 1984). Maximal levels of plasma ^{36}Cl were reached after 72 hours. The absorption rate constant and half-life were 0.0314/hour and 22.1 hours, respectively.

Acute dermal toxicity data (see below) indicate that sodium chlorite is absorbed through the skin. Significant differences in the acute median lethal dose (LD50) values in different dermal toxicity studies were attributed to differences in dermal absorption, possibly related to the level of skin destruction observed with different preparations.

An *in vitro* dermal absorption test conducted in 2008 to OECD Test Guideline (TG) 428 reported absorptions through human skin of 9.7% and 5.1% with high dose and low dose sodium chlorite respectively. In human skin samples, thinning of the stratum corneum and partial disruption of the epidermis were observed (REACH 2013).

For human risk assessment purposes, a dermal absorption of 10% is assumed.

41.5.1.3 Inhalation absorption

No data were available for absorption following inhalation.

For the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

41.5.1.4 Distribution

Oral administration of sodium chlorite results in widespread distribution of ionic species in body fluids. Following oral administration of radiolabelled chlorite ($^{36}ClO_2^-$), the highest concentrations of ^{36}Cl were found in whole blood, followed by packed cells, plasma, stomach and lungs. There was no apparent bioaccumulation of the tracer in any of the major organs (Abdel-Rahman et al. 1982, 1985).

No detailed data were available for distribution following dermal absorption. Dermal absorption of ^{36}Cl measured in rats following 10 daily applications of Alcide resulted in maximal levels in plasma after 72 hours (Scatina et al. 1984).

No data were available for distribution following inhalation absorption.

41.5.1.5 Metabolism

Following oral administration of radiolabelled chlorite ($^{36}ClO_2^-$) in rats, 87% and 13% of the initial dose of $^{36}ClO_2^-$ was found in urine and faeces respectively. Of the fraction found in urine, 84% of the total radioactivity found in the urine was in the form of chloride ion ($^{36}Cl^-$) with the remainder being present as the chlorite ion ($^{36}ClO_2^-$) (Abdel-Rahman et al. 1982, 1985).

41.5.1.6 Excretion

Following oral administration of radiolabelled chlorite ($^{36}ClO_2^-$) in rats, 87% and 13% of the initial dose of $^{36}ClO_2^-$ was found in urine and faeces respectively. No ^{36}Cl species were found in expired air. The elimination rate constant and elimination half-life from plasma of $^{36}ClO_2^-$ were 0.0197/hour and approximately 35 hours respectively (Abdel-Rahman et al. 1982, 1985).

41.5.2 *Acute toxicity*

41.5.2.1 Oral

An acute oral toxicity study in rats similar to OECD TG 401 derived an LD50 for oral sodium chlorite of 284 mg/kg bw. At doses of 250 mg/kg bw and above, the main clinical signs were prostration and cyanosis (Atochem 1984). A further study using only two dose levels of sodium chlorite reported an LD50 of between 250 and 500 mg/kg bw (Atochem 1985a).

41.5.2.2 Dermal

A dermal toxicity study administered various doses of an aqueous slurry (80%) of sodium chlorite powder under semi-occlusive dressings over 10% of the body surface area of rabbits for 24 hours (Degussa Corporation 1984a). Animals were observed for clinical signs after dosing immediately, at one and four hours and once daily for 14 days. Dosing areas were observed for erythema and oedema on days 1, 3, 7, 10 and 14 after dosing. Slight depression and dose-related dermal irritation consisting of skin thickening, epidermal scaling, necrosis and sloughing were noted in all animals. The study reported a dermal LD50 of 134 mg/kg bw.

A similar study in rabbits administered a single dose of 31% sodium chlorite solution under semi-occlusive dressings (Atochem US Inc. 1985b). Mild skin irritation was observed but no deaths or signs of systemic toxicity were reported. The LD50 was >2000 mg/kg bw.

The difference in the LD50 values reported from these studies was attributed to different forms and concentrations of sodium chlorite which induced different levels of irritation and systemic absorption.

41.5.2.3 Inhalation

No data were available.

41.5.2.4 Observation in humans

A multi-phase study in which male volunteers were exposed initially to a single oral dose of chlorite reported no adverse effects at the highest dose tested (0.034 mg/kg bw) (Lubbers et al. 1982, 1984a).

41.5.3 *Irritation / Corrosivity*

41.5.3.1 Skin irritation

In a skin irritation study, 0.5 g sodium chlorite powder (80% pure) was applied to three male and three female New Zealand White rabbits under occlusive dressing for four hours (REACH 2013). Dermal responses were assessed at 30 to 60 minutes and at daily intervals until 21 days after application. Irritation consisted of erythema (Grades 1 through 3) in all sites at 30 to 60 minutes and 24 hours after dosing, persisting through day seven at two sites. Oedema (Grade 1) was observed at one site at 30 to 60 minutes and at two sites at 48 hours. Other dermal effects included blanching, thickening, necrosis, sloughing, and blackened areas.

In a skin irritation study in rabbits conducted in accordance with OECD TG 404, a 34.5% solution of sodium chlorite was applied for four hours under semi-occlusive dressings (Elf Atochem SA 1994). One of three animals displayed very slight erythema and dryness of the skin. The sodium chlorite solution was considered non-irritating according to EU classification criteria.

In another skin irritation study in rabbits, a single dose of 31.5% sodium chlorite solution was applied to intact and abraded skin under semi-occlusive dressings for 24 hours. The study concluded that sodium chlorite was mildly irritating according to EU classification criteria (Atochem 1985b).

Application to abraded skin and prolonged exposures (24 hours compared to 4 hours) in the second study could explain the observed irritation not seen in the first study.

41.5.3.2 Eye irritation

In an eye irritation study, a 31.5% sodium chlorite solution was applied to the eyes of rabbits (Atochem 1985c). All but 3 of 9 animals showed corneal opacity not reversed by rinsing 30 seconds after instillation. All animals showed iris damage similarly not reversed by rinsing. All animals also exhibited moderate to severe redness and chemosis not abolished by rinsing. All but one animal exhibited superficial corneal vascularisation and transient cases of haemorrhaging and adhesion of conjunctivae to cornea were also seen. Sodium chlorite was concluded to be a severe eye irritant according to the EU classification criteria.

41.5.3.3 Respiratory irritation

No data were available.

41.5.3.4 Observation in humans

No data were available.

41.5.4 *Sensitisation*

41.5.4.1 Skin sensitisation

A guinea pig maximisation test conducted according to OECD TG 406 reported no clinical signs and no cutaneous reactions upon challenge application of 1% sodium chlorite in normal saline (CEFIC sodium chlorite sector group 2002). Induction applications were conducted using 5% sodium chlorite in normal saline. Sodium chlorite was concluded not to be a skin sensitiser.

41.5.4.2 Respiratory sensitisation

No data were available.

41.5.4.3 Observation in humans

No data were available.

41.5.5 *Repeat dose toxicity*

41.5.5.1 Oral

In a study used by the World Health Organization (WHO) to establish a drinking water guideline for chlorite in 1993, rats were administered sodium chlorite at doses of 0, 10, 50, 100, 250 and 500 mg/L (equivalent to 0, 1, 5, 10, 25 and 50 mg/kg bw/day) via drinking water for 30, 60 or 90 days (Heffernan et al. 1979). After 30 days, haematological parameters were depressed indicating slight anaemia at 10 and 25 mg/kg bw/day. These were correcting at 60 days and returned to near normal levels by 90 days. Decreases in erythrocyte glutathione levels were observed at 5 mg/kg bw/day and above, but given the magnitude of variations normally seen in mammals, the toxicological significance of these changes was uncertain. The No Observed Adverse Effect Level (NOAEL) established from this study was 5 mg/kg bw/day.

In a 14-day range finding study conducted to OECD TG 407, rats were administered sodium chlorite daily by gavage at doses of 0, 25, 50, 100 or 200 mg/kg bw day (CMA 1992a; Harrington et al. 1995a). At 200 mg/kg bw/day, 3 of 10 animals died. At 100 mg/kg bw/day, changes in haematological parameters were seen and body weight gains were reduced. At 50 mg/kg bw/day, body weights in males were reduced and at both 25 and 50 mg/kg bw/day haematocrits were slightly reduced.

A follow-up 90-day study was performed in which rats were administered sodium chlorite daily by gavage at doses of 0, 10, 25 or 80 mg/kg bw day (CMA 1992b; Harrington et al. 1995a). At 80 mg/kg bw/day, four of 30 animals died and surviving animals displayed hypoactivity, piloerection and hunched posture. At 25 mg/kg bw/day, one of 30 animals died. Increased salivation was observed at both doses. Treatment-related haematological changes consisting of reduced erythrocyte counts, reduced associated erythrocyte parameters and morphological changes in erythrocytes were observed at 80 mg/kg bw/day. These were accompanied by increases in absolute and relative spleen weights, histopathological abnormalities in the spleen and evidence of irritation of the gastric mucosa. At 25 mg/kg bw/day, minor clinical signs and occasional histopathological abnormalities in the stomach mucosa were seen. There were no haematological changes considered treatment-related at this dose. A NOAEL was established at 10 mg/kg bw/day.

Data on repeat dose toxicity were also available from a two-generation reproductive toxicity study in rats conducted to OECD TG 416 (Chlorine Dioxide Panel of the Chemical Manufacturers Association 1996; Gill et al. 2000). This study was used by the WHO to revise an earlier drinking water quality guideline for chlorite and chlorate (WHO 2005). A NOAEL of 35 ppm (approximately 3.9 mg/kg bw/day) was derived based on decreased liver weights in two generations. Details of this study are available under Reproductive Toxicity.

Repeated dose toxicity studies have also been performed in mice. Mice were treated for 30 days with doses equivalent to 0, 0.19, 1.9 and 19 mg/kg bw/day sodium chlorite in drinking water (Moore and Calabrese 1980). Slight changes in haematological parameters suggestive of effects on erythrocyte cell membranes were seen at 19 mg/kg bw/day. A NOAEL of 1.9 mg/kg bw day was established.

Similarly, in more limited studies, mice were administered sodium chlorite in drinking water at doses up to approximately 17 mg/kg bw/day for 30, 90 or 180 days. No effects on water consumption, body weight gain, kidney weights or kidney histology were seen (Connor et al. 1985). Also, no dose-related immunomodulatory effects were seen in a study of immunotoxicity in mice receiving sodium chlorite in drinking water at levels up to 30 mg/L for 28 days (Karrow et al. 2001).

In conclusion, several rodent studies of 30 to 90 days' duration have reported haemotoxicity from repeated doses of sodium chlorite. A guideline 90-day repeated dose toxicity study in rats reported reduced erythrocyte counts, reduced associated erythrocyte parameters and morphological changes in erythrocytes at 80 mg/kg bw/day. At lower doses, minor clinical signs and occasional histopathological abnormalities in the stomach mucosa were seen. A NOAEL for repeated dose oral toxicity was established from this 90-day study at 10 mg/kg bw/day.

41.5.5.2 Dermal

No data were available.

41.5.5.3 Inhalation

No reliable data were available.

41.5.5.4 Observation in humans

In a follow-up to an acute study, 10 male volunteers were exposed to chlorite in drinking water (equivalent to 0.036 mg/kg bw/day) for 12 weeks (Lubbers et al. 1982, 1984b). No treatment-related changes in general health, vital signs, haematology, clinical chemistry or serum T3 or T4 were detected. An additional study with three volunteers deficient in glucose-6-phosphate dehydrogenase (important in erythrocyte metabolism) also reported no treatment-related changes (Lubbers et al. 1984c).

41.5.6 *Genotoxicity*

Data from *in vivo* genotoxicity testing for sodium chlorite are available. However, no reliable *in vitro* genotoxicity testing for sodium chlorite are available. There are *in vitro* tests available for chlorine dioxide. Chlorite (and chlorate) ions are produced following dissolution of chlorine dioxide in aqueous media. Therefore, *in vitro* tests from chlorine dioxide are regarded as relevant to sodium chlorite.

Table A41.3 summarises available genotoxicity testing for sodium chlorite (*in vivo* data) and chlorine dioxide (*in vitro* data) (adapted from OECD 2009).

Table A41.3 Genotoxicity data for sodium chlorite and chlorine dioxide

Test	Species	Result	Reference
***In vitro* – sodium chlorite**			
No reliable tests	-	-	-
***In vitro* – chlorine dioxide**			
Chromosomal aberration (US EPA OTS guideline)	Chinese hamster ovary (CHO) cells	Positive	Scopas Technology Company 1986a
Gene mutation (EPA OTS guideline)	Mouse lymphoma L5178Y cells	Ambiguous	Scopas Technology Company 1986b
Cell transformation (EPA OTS guideline)	BALB/3T3 cells	Negative	Scopas Technology Company 1986c
***In vivo* – sodium chlorite**			
Bone marrow chromosomal aberrations (two studies) (US EPA guideline)	Mouse	Negative	Meier et al. 1985
Micronucleus (US EPA guideline)	Mouse	Negative	Meier et al. 1985
Sperm head abnormality (US EPA guideline)	Mouse	Negative	Meier et al. 1985

All *in vivo* testing for sodium chlorite was negative. Testing *in vivo* for chlorine dioxide was overall inconclusive.

Additional *in vivo* genotoxicity testing for chlorine dioxide in mice was all negative (data not shown).

Across all available studies, data suggest that sodium chlorite (and chlorine dioxide) have low genotoxic potential.

41.5.7 *Carcinogenicity*

In an oral carcinogenicity study designed to be conducted in a similar fashion to OECD TG 451, groups of 50 male and female rats were exposed to sodium chlorite in drinking water at concentrations of 0, 300 or 600 mg/L (estimated to be 0, 18 or 32 mg/kg bw/day for males and 0, 28 or 41 mg/kg bw/day for females) for 85 weeks (Shimoyama et al. 1985). The original study envisaged an exposure period of 104 weeks, but was stopped at 85 weeks due to infections in all groups. At this time there were no significant changes in organ weights or haematological and clinical chemistry findings between groups. Tumours developed in the testis, uterus, pituitary gland, thyroid gland (males) and adrenal gland (males) of both treatment and control rats. However, the incidences of tumours and non-neoplastic lesions in the three groups were not significantly different. There were no findings suggestive of a carcinogenic effect for sodium chlorite.

In another oral carcinogenicity study conducted in a similar fashion to OECD TG 451, groups of 50 male and 50 female B6C3F1 mice were exposed to sodium chlorite in drinking water at concentrations of 0, 250 or 500 mg/L (estimated to be 0, 36 and 71 mg/kg bw/day) for 80 weeks (Kurokawa et al. 1986; Yokose et al. 1987). After 85 weeks, surviving animals were killed and histopathological examinations were performed. Although tumours developed

in a variety of organs in all animals including controls, the only significant change was an increase in lung adenomas in top dose males: 5/43 (12%) in treated group, compared to 0/35 (0%) in the control group. Based on an absence of dose-related increases in the incidence of lung adenomas and the lack of increased incidence of lung adenocarcinomas, the authors concluded that sodium chlorite had no carcinogenic potential.

No studies were available for carcinogenicity testing via the dermal or inhalational routes.

41.5.8 *Reproductive toxicity*

41.5.8.1 Fertility

In a series of studies on fertility and sperm parameters, male Sprague-Dawley rats (12/group) were exposed to sodium chlorite via drinking water for 56 days prior to breeding and throughout a 10-day breeding period (Carlton et al. 1987). Females (24/group) were exposed for 14 days prior to mating, throughout a 10-day mating period, gestation and lactation until weaning (day 21 of lactation). Doses were 0, 1, 10 or 100 mg/L (equivalent to 0, 0.1, 1 and 10 mg/kg bw/day). Males were evaluated for sperm parameters and reproductive tract histopathology following the breeding period. Females were exposed throughout gestation and lactation. Most dams and pups were killed at weaning while some selected pups were observed up to day 40. There was no effect on mating, pregnancy, litter size or survival of neonates or on the weight of the testis or epididymis. No significant alterations in sperm count, percentage of sperm mobility or percentage of abnormal sperm were observed. A trend towards decreased sperm mean progressive movement was observed in the 100 mg/L group, but the velocity was not significantly different from controls. In F1 males and females from dams exposed to 100 mg/L, significant decreases in serum T3 and T4 were observed on post-natal days 21 and 40.

In a second experiment to further investigate effects of sodium chlorite on sperm parameters, groups of male rats were exposed to 0, 100 or 500 mg/L of sodium chlorite in drinking water (equivalent to 10 and 50 mg/kg bw/day) for 72 to 76 days (Carlton et al. 1987). No significant alterations in sperm counts, percentage of sperm mobility or mean progressive movement were reported. However, there was a trend towards decreased progressive movement in both treated groups. Also, a significant increase in the percentage of abnormal sperm morphology was observed for adult males at 100 or 500 mg/L.

In a third experiment to confirm reproductive effects observed previously, groups of male rats were exposed to 0, 10 or 100 mg/L of sodium chlorite in drinking water. No effects were detected at 1 and 10 mg/L. However, confirming the results from the second experiment, a significant increase in abnormal sperm was observed at 100 mg/L (Carlton et al. 1987). Overall, a NOAEL of 10 mg/L (equivalent to 1 mg/kg bw/day) was identified in these studies based on abnormal sperm morphology.

In a two-generation reproduction study in rats conducted according to OECD TG 416 (Gill et al. 2000), groups of 30 male and 30 female Sprague-Dawley rats were administered sodium chlorite via drinking water at doses of 0, 35, 70 or 300 ppm (approximately 0, 4, 7.6 or 28.2 mg/kg bw/day for males and 0, 3.9, 8 and 38.7 mg/kg bw/day for females) (Chlorine Dioxide Panel of the Chemical Manufacturers Association 1996; Gill et al. 2000). Dosing was conducted in the parental F0 generation commencing 10 weeks prior to mating, until weaning of the F2 generation. Males were exposed through mating and then sacrificed. Females were exposed through mating, pregnancy and lactation and were sacrificed following weaning of litters. F1 pups were continued on the same treatment regime as the parents. At 14 weeks they were mated to produce the F2 generation.

Reductions in food and water consumption and body weight gain were observed for all generations, attributed to unpalatability of the formulated drinking water.

At 35 and 70 ppm, minor reductions in several haematological parameters were observed in F1 female pups. These appeared within the range of historical control data and were not regarded as toxicologically significant. At 70 ppm, a reduction in liver weight was also observed in F0 females and F1 males and females. A slight decrease in the maximum response to auditory startle stimulus was also observed in F2 pups.

At 300 ppm, reductions in haematological parameters were seen in F1 male and female pups and adults. Reduced liver weights were seen in F0 adult males, F1 adult males and females and F1 pups. Reduced thymus and spleen weights were also seen in both generations. A slight decrease in absolute brain weight was seen in F1 male pups at post-natal day (PND) 11 but not at PND 25. In F2 pups at this dose, there was a slightly lowered incidence of normal righting reflexes and a slight decrease in the maximum response to auditory startle stimulus. Reduced pup body weight at birth and during lactation in F1 and F2 generations were also observed. Delays in preputial separation and vaginal openings were reported for F1 pups.

Despite systemic toxicity, the authors reported no treatment-related changes to oestrous cyclicity, sperm motility, sperm morphology, or mating, fertility or gestational indices. Also, there were no treatment-related changes in number of pups born, sex ratios, live birth index or pup survival indices. There were no treatment-related changes in serum T3 or T4 in F1 pups or F1 adults. On the basis of historical data, delays in preputial separation and vaginal openings reported for F1 pups were attributed to reduced body weight rather than a direct treatment-related effect. Similarly, slight decreases in brain weight in male pups were consistent with decreased body weight.

The toxicological significance of decreases in auditory startle stimulus response at 70 and 300 ppm was unclear. The magnitude of responses was small compared to known neuroactive chemicals, dose response to the stimulus was weak, there was a lack of corroborative evidence from neuropathology or other test of motor function or arousal, and the decreases in response were not replicated upon later examination of the same animals at PND 60 (Gill et al. 2000).

A NOAEL of 35 ppm (approximately 3.9 mg/kg bw/day) with a LOAEL at 70 ppm (approximately 7.6 mg/kg bw/day) were derived based on decreased liver weights.

41.5.8.2 Developmental toxicity

In a rabbit study conducted to national guidelines (US EPA OPPTS), sodium chlorite was administered via drinking water to groups of 16 pregnant New Zealand White rabbits at doses of 0, 200, 600 or 1200 mg/L during days 7 to 19 of gestation (Chlorine Dioxide Panel of the Chemical Manufacturers Association 1990; Harrington et al. 1995b). At 600 and 1200 mg/L, dose-related reductions in water consumption (due to palatability problems), food consumption and body weight gain were observed. No treatment-related abnormalities were observed at maternal necropsy.

Marginal, non-dose related reductions in foetal weights were seen at 600 and 1200 mg/L, with a slightly increased incidence of incomplete ossification of some bones. The external and visceral abnormalities observed in the foetuses were regarded as spontaneous and non-treatment related and typical for the strain of rabbit. Pre and post-implantation losses were within expected ranges and other reproductive parameters were similar in all groups. At 200 ppm, there were no maternal or foetal effects. Sodium chlorite was not considered to be teratogenic or a selective developmental toxicant. The NOAEL for both maternal and embryotoxicity was 200 mg/L (approximately 53.1 mg/kg bw/day).

In a limited study in Sprague-Dawley rats, groups of 6 to 9 female animals were administered sodium chlorite at 0, 1 or 10 mg chlorite ion/L) via drinking water for 2.5 months prior to mating with unexposed males and during the mating period and gestation until day 20 of

pregnancy (Suh et al. 1983). Slight decreases in maternal weight gain were observed at both dose levels. There were no foetal observations or malformations regarded as of toxicological significance.

In another limited study in Sprague Dawley rats, groups of 10 pregnant females were given 0, 0.1, 0.5 or 2% sodium chlorite in drinking water (corresponding to 0, 110, 540 or 700 mg/kg bw/day) from day 8 to day 15 of gestation (Couri et al. 1982). A dose-related decrease in food and water consumption probably due to palatability problems was observed. Haemotoxicity was observed additionally at the highest dose.

Foetal toxicity included a significant decrease in crown-rump distance in all treatment groups. At the highest dose, a decrease in the number of live foetuses associated with a significant increase in foetal resorption was observed. No malformations were observed in any group. In addition, no differences were observed in the post-natal growth of selected pups at any dose. The NOAEL for maternal toxicity was 0.1% (110 mg/kg bw/day) and the NOAEL for embryotoxicity was 0.5% (540 mg/kg bw/day).

Overall, data indicate that sodium chlorite is not a developmental toxicant at doses below those associated with maternal toxicity.

41.5.9 *Other health effects*

No other health effects were identified.

41.6 Health hazard summary

41.6.1 *Critical health effects*

Animal studies with sodium chlorite showed moderate acute toxicity following oral administration. The LD50 was 284 mg/kg bw. Acute dermal toxicity studies showed dependencies on the form and concentration of sodium chlorite. For a concentrated slurry (80%), the LD50 was 134 mg/kg bw. In contrast, no deaths were observed for a 31% solution. The LD50 was >2000 mg/kg bw.

Sodium chlorite solutions (31 to 34%) induced no or only mild skin irritation but induced severe eye irritation. Sodium chlorite tested as a powder (80%) induced severe skin reactions including blanching, thickening, necrosis, sloughing, and blackened areas. Sodium chlorite as a concentrated slurry (80%) tested for acute dermal toxicity also induced severe skin reactions and necrosis which appeared to enhance systemic uptake. Sodium chlorite was shown not to be a skin sensitiser.

Repeated dose toxicity studies in rats and mice commonly revealed haematological changes with oral sodium chlorite exposures. A guideline 90-day repeated dose toxicity study in rats reported reduced erythrocyte counts, reduced associated erythrocyte parameters and morphological changes in erythrocytes at 80 mg/kg bw/day. At lower doses, minor clinical signs and occasional histopathological abnormalities in the stomach mucosa were seen. A NOAEL for repeated dose oral toxicity was established from this study at 10 mg/kg bw/day.

Across available *in vivo* and *in vitro* studies, data suggest that sodium chlorite has low genotoxic potential.

Oral studies in rats and mice concluded that sodium chlorite has no carcinogenic potential. From a reliable study in mice conducted to OECD TG 451, a NOAEL for carcinogenicity was established at 71 mg/kg bw/day.

A guideline two-generation reproductive toxicity study in rats also reported haemotoxicity, as well as hepatotoxicity and slight neurobehavioural changes at doses below those associated

with no effects in repeated dose studies. The study reported no effects on fertility or development. A previous series of studies on fertility and sperm parameters reported effects on sperm morphology and serum T3 and T4 in pups but in the absence of effects on mating, pregnancy, litter sizes, offspring survival, or testis or epididymis weights. These effects on sperm morphology and serum T3 and T4 levels in pups were not replicated in the two-generation study. Accordingly, a NOAEL for hepatotoxicity was established from this two-generation study at 3.9 mg/kg bw/day. The LOAEL was approximately 7.6 mg/kg bw/day.

Sodium chlorite was not considered to be teratogenic or a selective developmental toxicant. A reliable developmental toxicity study in rabbits conducted to national test guidelines established a NOAEL for both maternal and embryotoxicity at 200 mg/L (approximately 53.1 mg/kg bw/day).

41.6.2 *Hazard classification*

Sodium chlorite is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004).

Sodium chlorite is also recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A41.4. These NICNAS recommendations do not consider physical or environmental hazards.

Table A41.4 Hazard classification recommended by NICNAS to Safe Work Australia

Effect	Approved Criteria (HSIS)[a]	GHS[b] classification
Acute toxicity	Harmful if swallowed (X_n; R22) Toxic in contact with skin (X_n; R24)	Toxic if swallowed – Cat. 3 (H301) Fatal in contact with skin – Cat 2 (H310)
Irritation / Corrosivity	Causes burns (C; R34) Risk of serious damage to eyes (X_i; R41)	Causes severe skin burns and eye damage – Cat 1B (H314) Causes serious eye damage – Cat 1 (H318)
Repeated dose toxicity	Danger of serious damage to health by prolonged exposure if swallowed (T; R48/22)	May cause damage to organs through prolonged or repeated exposure via the oral route – Cat 2 (H373)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

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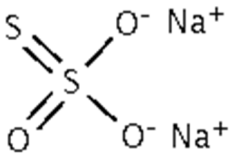
A42 Sodium thiosulfate

CAS No.	CAS Name
7772-98-7	Thiosulfuric acid ($H_2S_2O_3$), sodium salt (1:2)

42.1 Chemical identity

The identity information was obtained from ChemID*plus* (2012) and O'Neil (2001). A description of the chemical identity is provided in Table A42.1.

Table A42.1 Chemical identity

	Sodium thiosulfate
Synonyms	Sodium thiosulfate Sodium hyposulfite Chlorine Control Chlorine Cure Declor-It Disodium thiosulfate S-Hydril Sodium oxide sulfide ($Na_2S_2O_3$)
Structural formula	
Molecular formula	$H_2O_3S_2.2Na$
Molecular weight	158.13
Appearance and odour	Powder or colourless monoclinic crystals.
SMILES notation	S(=O)(=S)([O-])[O-].[Na+].[Na+]

42.2 Physical properties

The following information was obtained from the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013), O'Neil (2001) and World Health Organisation (WHO) (2006) provided in Table A42.2.

Table A42.2 Physical properties

Property	**Value**
Melting point	48 °C
Density – kg/m^3	1.67 x 10^3 (20 °C)
Vapour pressure	negligible

Property	Value
Water solubility	764 g/L (25 °C)
Partition coefficient (log K_{ow})	-4.35 (calculated)

42.3 Current regulatory controls

The document from now on refers to thiosulfuric acid ($H_2S_2O_3$), sodium salt (1:2) as sodium thiosulfate, one of the synonyms of the chemical .

42.3.1 *Hazard classification for occupational health and safety*

Sodium thiosulfate is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

42.3.2 *Occupational exposure standards*

42.3.2.1 Australia

No specific exposure standards were available.

42.3.2.2 International

No specific exposure standards were available.

42.3.3 *Australian food standards*

No Australian food standards were identified (Food Standards Australia New Zealand 2012).

42.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

42.3.5 *Additional controls*

42.3.5.1 Australia

The substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

42.3.5.2 International

Sodium thiosulfate is listed by the United States Food and Drug Administration (US FDA) as a food substance generally recognised as safe when used in accordance with good manufacturing practice (GMP), with restricted use in alcoholic beverages and table salt as a formulation aid and reducing agent (US FDA 1999).

The chemical is classified as a hazardous substance, irritating to the skin and eye, and as a contact sensitiser under the Hazardous Substances and New Organisms (HSNO) Act of the Environmental Protection Authority New Zealand (EPA NZ) (2012).

42.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

42.5 Health hazard characterisation

The information on health hazards was sourced primarily from the REACH Dossier for sodium thiosulfate (REACH 2013).

Only limited toxicity data were available for sodium thiosulfate. Reliable data for potassium thiosulfate (CAS No. 10294-66-3) and / or ammonium thiosulfate (CAS No. 7783-18-8), both analogues of the sodium compound, were available for the majority of the acute toxicity endpoints. All of the thiosulfates have similar chemical properties. In addition, once the three salts enter the body, they will dissociate directly into the thiosulfate anion and the corresponding cations, i.e. sodium, ammonium and potassium. The toxicity of the chemicals is mainly attributable to the thiosulfate ion. Thus, the use of data for the other salts, as analogues for sodium thiosulfate, is appropriate to read across for the endpoints where no data were available for the sodium salt (Table A42.3).

In addition, as thiosulfate is a sulfur (VI) oxyanion, the chemical may be appropriately grouped with other compounds that in solution undergo pH-dependent equilibration reactions between sulfur dioxide, sulfurous acid, bisulfite ion, and sulfite ion (Green 1976). This is because thiosulfate hydrolyses to sulfur dioxide and elemental sulfur under acidic conditions, and elemental sulfur in turn is oxidised to sulfate. Such compounds include various sulfites, bisulfites, and metabisulfites; a group approach for food additives comprising sulfur dioxide equivalents arising from six of these compounds together with sodium thiosulfate has been adopted by the WHO on this basis (WHO 1999). Accordingly, the data gaps for sodium thiosulfate may also be read across from chronic toxicity data available for sodium metabisulfite as a representative compound in this group (Table A42.3).

Table A42.3 Summary of available toxicity endpoint data

	Sodium thiosulfate (CAS No. 7772-98-7)	**Ammonium thiosulfate (CAS No. 7783-18-8)**	**Potassium thiosulfate (CAS No. 10294-66-3)**	**Sodium metabisulfite (CAS No. 7681-57-4)**
Acute oral toxicity	✓	✓	✓	✓
Acute dermal toxicity	×	✓	✓	✓
Acute inhalation toxicity	×	✓	✓	×
Skin irritation	×	✓	×	✓
Eye irritation	×	✓	×	✓
Respiratory irritation	×	×	×	×
Skin sensitisation	×	✓	×	×
Respiratory sensitisation	×	×	×	×

	Sodium thiosulfate (CAS No. 7772-98-7)	**Ammonium thiosulfate (CAS No. 7783-18-8)**	**Potassium thiosulfate (CAS No. 10294-66-3)**	**Sodium metabisulfite (CAS No. 7681-57-4)**
Repeat dose toxicity (oral)	×	✓	×	✓
Repeat dose toxicity (dermal)	×	×	×	×
Repeat dose toxicity (inhalation)	×	×	×	×
Genotoxicity *in vitro*	✓	✓	×	✓
Genotoxicity *in vivo*	✓	✓	×	✓
Carcinogenicity	×	×	×	✓
Reproductive toxicity (fertility)	×	×	×	✓
Reproductive toxicity (development)	✓	×	×	✓

✓Existing data point; × Missing data point;

Additional sources of hazard information for the chemical include the Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set Initial Assessment Report (SIAR) for ammonium compounds (OECD 2008), sodium dithionite (OECD 2006) and disodium disulphite (OECD 2004). Unless noted, references to individual studies below are taken from these reviews.

42.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

Thiosulfate is a normal constituent of human body fluids and a metabolite of normal dietary constituents (OECD 2007).

In solution, the chemical will undergo pH-dependent equilibration reactions between sulfur dioxide, sulfurous acid, bisulfite ion, and sulfite ion. At normal physiological pH values and concentrations of greater than 1 M, the equilibrium is between approximately equal proportions of sulfite and bisulfite while at the lower pH of the stomach of fasting humans, the equilibrium is essentially between bisulfite ion and free sulfur dioxide (Green 1976).

42.5.1.1 Oral absorption

Only limited data were available for the chemical. It was reported that sodium thiosulfate was poorly absorbed from the bowel (Gosselin et al. 1976); however, studies have shown that sulfite is readily absorbed from the digestive tract of rats (Gibson and Strong 1973). Moreover, as thiosulfate will convert to sulfur dioxide equivalents in the acidic environment of the stomach as mentioned, the reported poor absorption of thiosulfate from the bowel is not relevant to human exposures involving ingestion of the chemical.

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

42.5.1.2 Dermal absorption

No data were available.

For the purposes of risk assessment, 100% dermal absorption in humans is assumed.

42.5.1.3 Inhalation absorption

No data were available.

The acute inhalation toxicity and respiratory irritation studies for other thiosulfates showed that they are absorbed in the respiratory system (see Sections A42.5.2.3 and A42.5.3.3).

For the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

42.5.1.4 Distribution

Only limited data were available for sodium thiosulfate. It was reported that thiosulfate ion distributes itself in extracellular fluid (Gosselin et al. 1976).

In rats that were orally administered radiolabelled sodium sulphite, the highest relative sulfite levels were reported in the stomach, skin and hair, intestine, kidney and the carcass with lower levels also found in the lung, spleen, reproductive organs, heart, liver, and brain (Gibson and Strong 1974).

In rats administered ^{35}S-labelled sodium sulfite by bronchioalveolar lavage, the radioactivity levels were reported in pulmonary arteries, arterioles, and the walls of conducting airways and pleura after 48 and 72 hours (Dahl et al. 1981).

It is assumed that the distribution of sodium thiosulfate will be similar to that of sodium sulphite.

42.5.1.5 Metabolism

Only limited data were available for sodium thiosulfate. Thiosulfate is eliminated mainly unchanged by renal excretion, but a certain amount is enzymatically oxidised in the liver to sulfate. This latter fraction increases as the dose of thiosulfate decreases (WHO 1983).

42.5.1.6 Excretion

The thiosulfate ion is a normal constituent of the blood and, when in excess, is excreted via the urine (OECD 2006).

42.5.2 *Acute toxicity*

42.5.2.1 Oral

In a briefly reported study, the acute oral median lethal dose (LD50) in rats was >5000 mg/kg bw (Registry of Toxic Effects of Chemical Substances (RTECS) 2013).

Supporting oral toxicity data were available for other thiosulfates, with studies reporting LD50 values in rats of 1950 to 3824 mg/kg bw for the ammonium salt, >2000 mg/kg bw for the calcium salt and >2500 mg/kg bw for the potassium salt (REACH 2013; OECD 2008).

42.5.2.2 Dermal

No data were available for sodium thiosulfate.

Acute dermal toxicity tests with potassium and ammonium thiosulfate, conducted in accordance with OECD Test Guideline (TG) 402, were used to read across to sodium thiosulfate for this endpoint (REACH 2013). The acute dermal toxicity dose was reported to be >2000 and >1000 mg/kg bw for the potassium and ammonium salt respectively.

42.5.2.3 Inhalation

No information was available for sodium thiosulfate but data available from ammonium and potassium thiosulfate studies were used to read across to sodium thiosulfate.

An acute inhalation toxicity test with potassium thiosulfate, conducted in accordance with OECD TG 403, reported the acute median lethal concentration (LC50) to be >2.60 mg/L (REACH 2013). The OECD (2008) reported the LC50 for ammonium thiosulfate as >2260 mg/m^3 in rats and >1800 mg/m^3 in mice with no signs of toxicity. In another study, rats exposed to 80, 150, or 300 mg/m^3 ammonium thiosulfate showed a decrease in serum calcium levels, an increase in oxygen consumption, and changes in cardiovascular function at all dose levels (OECD 2008).

42.5.2.4 Observation in humans

No data were available for sodium thiosulfate, although Gosselin et al. (1976) reported that the chemical was remarkably inert *in vivo* except for its activity as an osmotic cathartic. Humans given 1 to 2 g ammonium thiosulfate over an undisclosed period showed no overt toxic effects (OECD 2007).

42.5.2.5 Summary of acute toxicity

The acute toxicity of sodium thiosulfate by the oral route in rats is low based on a briefly reported study for the chemical and supported by data on potassium and ammonium compounds. Sodium thiosulfate also has a low level of toxicity by the dermal and inhalation routes based on data available for the potassium and ammonium compounds.

42.5.3 *Irritation / Corrosivity*

42.5.3.1 Skin irritation

No data were available for sodium thiosulfate.

Skin irritation tests with ammonium thiosulfate were used to read across to sodium thiosulfate for this endpoint. In an unpublished study, an unreported amount of an ammonium thiosulfate solution applied to the skin of rabbits produced no erythema, oedema or any dermal effects (REACH 2013). In a study conducted in accordance with OECD TG 404, 75% ammonium thiosulfate was not irritating to rabbit skin after four hours of exposure (OECD 2008). Rats given a series of 20 four-hour applications of 45% ammonium thiosulfate to the skin of the tail and back showed no dermal irritation (OECD 2007).

42.5.3.2 Eye irritation

No data were available for sodium thiosulfate.

Data from two eye irritation tests with ammonium thiosulfate, conducted in accordance with OECD TG 405, are used to read across to sodium thiosulfate. In a 1988 study, the effects observed included conjunctival redness (grade 1) and chemosis (grade 2) which persisted for less than 24 hours (REACH 2013). Ammonium thiosulfate (75%) was not irritating to the rabbit eye in a study conducted according to OECD TG 405 (OECD 2008).

42.5.3.3 Respiratory irritation

The respiratory irritation potential of sodium thiosulfate has not been assessed in animals and no data were available from analogues.

42.5.3.4 Observation in humans

Under acidic conditions, sodium thiosulfate may liberate sulfur dioxide (SO_2), which is known to induce respiratory irritation in humans (Klaassen 2001).

42.5.3.5 Summary of Irritation / Corrosivity

The chemical is unlikely to be a skin or eye irritant based on data available for ammonium thiosulfate. No conclusion can be made on the respiratory irritancy potential of sodium thiosulfate.

42.5.4 *Sensitisation*

42.5.4.1 Skin sensitisation

No data were available for the chemical.

Results from a Local Lymph Node Assay, conducted with ammonium thiosulfate in accordance with OECD TG 429, were used to read across to sodium thiosulfate (REACH 2013). Treatment with ammonium thiosulfate at concentrations of 10%, 25% or 50% did not result in increased values for lymph node cell count or in lymph node weight; therefore, the chemical was judged to be non-sensitising.

Sulfites, which are used widely in cosmetic products, are rarely contact allergens and were not found to be potent primary sensitisers (CIR 2003).

42.5.4.2 Respiratory sensitisation

No data were available for sodium thiosulfate or other analogue chemicals.

42.5.4.3 Observation in humans

Under acidic conditions, sodium thiosulfate (and sulfites in general) may liberate SO_2 which is known to induce bronchospasm in disposed humans (Klaassen 2001).

Sodium metabisulfite is unlikely to induce respiratory sensitisation in humans, but may enhance symptoms of asthma in sensitive individuals. Humans exposed to this chemical may experience effects such as urticaria, oedema, rhinitis and nasal congestion (OECD 2004). A clinical study reported that only 14 of 980 eczematous patients were positive in a patch test with sodium metabisulfite (Angelini et al. 1997).

The US FDA estimated that up to 1% of the population is sensitive to sulfites. This sensitivity can cause a wide range of reactions ranging from mild to severe dermatological, pulmonary, gastrointestinal, or cardiovascular symptoms (Grotheer et al. 2005).

42.5.4.4 Summary of sensitisation

The chemical is unlikely to be a skin sensitiser based on data available for ammonium thiosulfate. Human data suggest that sulfites (or other SO_2 liberating chemicals such as

thiosulfates) are generally not likely to be skin or respiratory sensitisers, except in sensitive individuals.

42.5.5 *Repeat dose toxicity*

42.5.5.1 Oral

No data were available for the chemical.

Oral exposure of rats to 300 mg/kg bw/day ammonium thiosulfate by gavage over 45 to 90 days resulted in growth reduction, increased levels of acid and alkaline phosphatase, effects on calcium and cardiovascular changes (OECD 2008). Only limited information and no data on controls were available.

REACH (2013) included a three-generation dietary study (study description provided in the fertility section) for sodium metabisulfite (as a sulphite analogue) which is used to read across to sodium thiosulfate (Til et al. 1972). There was no systemic toxicity at the highest tested dose. The predominant effect was the induction of stomach lesions due to the local irritation, characterised by forestomach and glandular stomach hyperplasia and inflammation at 450 mg/kg bw/day and above. On this basis, a No Observed Adverse Effect Level (NOAEL) for local effects of 217 mg/kg bw/day (or 70 mg/kg bw/day of SO_2 equivalents) was established. This NOAEL was the equivalent of 180 mg sodium thiosulfate/kg bw/day.

42.5.5.2 Dermal

No data were available for the chemical.

In a poorly reported study, dermal exposure of rats to a 45% ammonium thiosulfate solution for 20 days was reported to decrease blood catalase concentration (OECD 2008).

42.5.5.3 Inhalation

No repeat dose inhalation studies are available on sodium thiosulfate.

In a poorly reported repeat dose inhalation study with rats, exposure to 26.8 mg/m^3 ammonium thiosulfate for two or four months resulted in systemic effects such as growth reduction, increased levels of acid and alkaline phosphatase, haematological and central nervous system (CNS) effects, and cardiovascular changes (OECD 2008).

42.5.5.4 Observation in humans

Sodium thiosulfate is used in humans to lessen some of the side effects of cisplatin (an anti-cancer therapeutic) and it is also used in the emergency treatment of cyanide poisoning. Sodium thiosulfate is assumed to be intrinsically non-toxic (IPCS/CEC 1993).

The Food and Agriculture Organization (FAO)/WHO Joint Expert Committee on Food Additives used the NOAEL of 70 mg SO_2 equivalents/kg bw/day (derived from the 104-week, three-generation rat study for sodium metabisulfite previously described) to set a group acceptable daily intake (ADI) of 0 to 0.7 mg SO_2/kg bw/day for sodium thiosulfate, nine sulphites, metabisulfites and sulfur dioxide (WHO 1999).

42.5.5.5 Summary of repeat dose toxicity

Sodium thiosulfate was not tested for its repeated dose toxicity and therefore toxicity data for ammonium thiosulfate and sodium metabisulfite were used for the evaluation of this endpoint.

The systemic effects observed after repeat dose dermal and inhalation exposure of rats to ammonium thiosulfate were poorly documented. For sodium metabisulfite, an oral NOAEL of 217 mg/kg bw/day (70 mg SO_2 equivalents/kg bw/day) was obtained for local gastrointestinal toxicity in rats with no systemic toxicity at 942 mg/kg bw/day.

The latter result appears to be sufficiently representative also for the assessment of sodium thiosulfate.

42.5.6 *Genotoxicity*

Sodium thiosulfate pentahydrate, which is equivalent to the anhydrous chemical in aqueous solution, tested negative (with and without metabolic activation) in a bacterial reverse mutation assay (OECD TG 471) with *Salmonella typhimurium* (REACH 2013). There was no evidence of chromosomal damage in a bone marrow assay in rats and mice following single oral doses of 50 to 5000 mg/kg bw of sodium thiosulfate (Litton Bionetics 1973).

Supporting data were available for ammonium thiosulfate. In an Ames test conducted according to OECD TG 471, ammonium thiosulfate was not mutagenic with and without metabolic activation (Wagner 2001). It also did not induce chromosomal aberrations with and without metabolic activation in Chinese Hamster Ovary cells (OECD TG 473) (Gudi 2001).

Sodium thiosulfate is not mutagenic under the conditions tested.

42.5.7 *Carcinogenicity*

No data were available for sodium thiosulfate and therefore toxicity data for sodium metabisulfite were used for the evaluation of this endpoint.

Sodium metabisulfite was not carcinogenic in rats when tested by oral administration with up to 2% concentration for 104 weeks (Til et al. 1972). The International Agency for Research on Cancer (IARC) reported that sulfites, bisulfites, and metabisulfites are not classifiable as to their carcinogenicity to humans (IARC 1997).

42.5.8 *Reproductive toxicity*

42.5.8.1 Fertility

No data were available for sodium thiosulfate.

Data from a previously described repeated oral toxicity study and from a three-generation reproductive toxicity study with sodium metabisulfite, conducted in accordance with OECD TG 422, were used to read across to sodium thiosulfate (REACH 2013). Sodium metabisulfite was fed to rats for 30 to 104 weeks at 0, 0.125, 0.25, 0.5, 1.0, or 2.0% in the diet (equivalent to 0, 48, 106, 217, 450, or 942 mg/kg bw/day) (Til et al. 1972). There were no treatment-related effects on mating performance, fertility, and the gonads over a period of two years at 942 mg/kg bw/day, the highest dose tested.

No Lowest Observed Adverse Effect Level (LOAEL) or NOAEL could be established for parental or fertility effects.

Sodium thiosulfate is not toxic to fertility based on data available for sodium metabisulfite.

42.5.8.2 Developmental toxicity

Four well documented prenatal developmental toxicity studies, conducted according to OECD TG 414, were available for sodium thiosulfate (Til et al. 1972). There was no evidence of either maternal or developmental toxicity observed in rats, guinea pigs, mice or rabbits administered up to 400, 400, 550 and 580 mg/kg bw/day respectively, by gavage, for 5 to 13

days through gestation. No LOAEL or NOAEL could be established for maternal or developmental effects.

Sodium thiosulfate is not a developmental toxicant under the conditions of the studies.

42.5.9 *Other health effects*

No additional health effects were identified.

42.6 Health hazard summary

42.6.1 *Critical health effects*

Sodium thiosulfate demonstrates low acute oral toxicity. Based on data available for ammonium thiosulfate and potassium thiosulfate, the chemical has low acute toxicity by dermal and inhalation routes, is not irritating to the skin or eye, and is not a skin sensitiser. Irritation of the human stomach from sodium thiosulfate ingestion is possible from the liberation of SO_2 in highly acidic environments.

The most appropriate NOAEL for risk assessment, determined from the 104-week, combined repeat dose and reproductive study on sodium metabisulfite by Til et al. (1972), is 217 mg/kg bw/day (70 mg/kg bw/day of SO_2 equivalents) for local gastrointestinal effects. This NOAEL was the equivalent of 180 mg sodium thiosulfate/kg bw/day and will be applied to the chemical under assessment. No NOAEL was established for systemic effects.

The chemical is not genotoxic or a developmental toxicant and, based on data for sodium metabisulfite, is not a carcinogen or toxic to fertility.

42.6.2 *Hazard classification*

The chemical is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) and is not recommended by NICNAS to Safe Work Australia for classification as hazardous under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004). Classification for physical or environmental hazards has not been considered.

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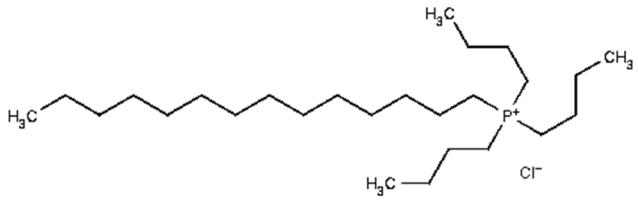
A43 Tributyltetradecyl phosphonium chloride

CAS No.	CAS Name
81741-28-8	Phosphonium, tributyltetradecyl-, chloride (1:1)

43.1 Chemical identity

Details of the chemical identity are provided in Table A43.1. The information was obtained from ChemID*plus* (2012) and Cytec (2008).

Table A43.1 Chemical identity

	Tributyltetradecyl phosphonium chloride (TTPC)
Synonyms	Tributyltetradecylphosphonium chloride Tri-N-butyl tetradecyl phosphonium chloride Tributyltetradecylphosphine chloride TTPC Bellacide 350 Belclene 350 BE-9 Cyphos IL 167
Structural formula	
Molecular formula	$C_{26}H_{56}P.Cl$
Molecular weight	435.15
Appearance and odour	Solid
SMILES notation	C(CCCCCCCCCCCCC)P{+}(.Cl{-})(CCCC)(CCCC)CCCC

43.2 Physical properties

The physical properties of the chemical are presented in Table A43.2. The information was obtained from Cytec (2008) and the United States Environmental Protection Agency (US EPA) Estimation Programs Interface (EPI) Suite (2012a) and the US EPA (2012b).

Table A43.2 Physical properties

Property	Value
Melting point	45 °C
Boiling point	439 °C (estimated)
Density	No data
Vapour pressure	1.04 x 10^{-8} kPa at 25 °C (estimated)
Water solubility	Soluble
Partition coefficient n-octanol/water (log K_{ow})	6.48 (estimated)

43.3 Current regulatory controls

The document from now on refers to Phosphonium, tributyltetradecyl-, chloride (1:1) (CAS No. 81741-28-8) as 'TTPC', one of the synonyms of the chemical.

43.3.1 *Hazard classification for occupational health and safety*

The chemical is not listed in the Hazardous Substance Information System (HSIS) (Safe Work Australia 2013).

43.3.2 *Occupational exposure standards*

43.3.2.1 Australia

No specific exposure standards were available.

43.3.2.2 International

No specific exposure standards were available.

43.3.3 *Australian food standards*

No Australian food standards were identified (Food Standards Australia New Zealand 2013).

43.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011)

43.3.5 *Additional controls*

43.3.5.1 Australia

The chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

The chemical is included in the Australian Dangerous Goods Code Edition 7 (ADG7) (National Transport Commission 2007), with a general entry for UN Number 2922, corrosive liquid, toxic, N.O.S. (contains Tributyl Tetradecyl Phosphonium Chloride) listed in Class 8 (Corrosive substances) with subsidiary risk Division 6.1 (Toxic substances). The ADG7 contains detailed provisions for the packaging, transport and marking of containers in Class 8 and Division 6.1.

43.3.5.2 International

The chemical is included on the List of Toxic Substances in Schedule 1 of the Canadian Environmental Protection Act (CEPA), 1999 (CEPA 2005).

TTPC is classified as a hazardous substance, corrosive to dermal and ocular tissue, under the Hazardous Substances and New Organisms (HSNO) Act of the Environmental Protection Authority New Zealand (EPA NZ) (EPA NZ 2012).

43.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

43.5 Health hazard characterisation

Limited information on health hazards of TTPC was obtained from data submitted by Cytec Industries Inc. to the US EPA under the Toxic Substances Control Act (TSCA) Section 8(E) (US EPA 2012b).

A search of structurally similar chemicals was conducted using the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Application Toolbox (OECD 2013) and the US EPA Analog Identification Methodology (AIM) (US EPA 2012c).

Six analogue chemicals of TTPC were identified using profiling within the OECD Toolbox; however, published data were only available for three of these analogue chemicals.

TTPC, tributylhexadecylphosphonium bromide (THPB), tetrabutyl phosphonium chloride (TBPC) and tetrabutyl phosphonium bromide (TBPB) have similar molecular weights (435, 507, 294 and 339, respectively), are used as biocides and are composed of four alkyl chains attached to a functional phosphonium group that is quaternary in nature. In addition, once the three chemicals enter the body, they will dissociate into the tetraalkylphosphonium cation and halide anion. The molecular weight of the cation is even more similar, namely 400, 427, 259 and 259, for TTP^+, THP^+, TBP^+ and TBP^+, respectively. The toxicity of the chemicals is attributable to the tetraalkylphosphonium cation. Therefore, the use of data for THPB and TBPC, as analogues for TTPC, is appropriate to read across for the endpoints where no data were available for TTPC (Table A43.3).

Studies for the analogue chemical, THPB (Phosphonium, tributylhexadecyl -, bromide, CAS No. 14937-45-2, MW 507.65, $C_{28}H_{60}BrP$) were used, based on similarity of carbon chain lengths, where data were not available for endpoints of TTPC (i.e. acute oral toxicity, skin irritation and eye irritation). The information on these endpoints is from studies submitted by Monsanto Co. to the US EPA under TSCA Section 8(E) (US EPA 1992d).

Data for TBPC (Phosphonium, tetrabutyl-, chloride, CAS No. 2304-30-5, MW 294.88, $C_{16}H_{36}ClP$), an analogue of TTPC with the same counter ion but of shorter carbon chain, were also used where data were not available for endpoints of TTPC (i.e. acute oral and dermal toxicity, skin and eye irritation and skin sensitisation). The information on these endpoints was obtained from Dunn et al. (1982) and from data submitted by Allied Chemical Corp. and Cincinnati Milacron Chemicals Inc. to the US EPA under TSCA Section 8(E) (US EPA 1978, 1979).

Data for TBPB (Phosphonium, tetrabutyl-, bromide, CAS No. 3115-68-2, MW 339.33, $C_{16}H_{36}BrP$), an analogue of TTPC with a different halide counter ion and of shorter carbon chain length equivalent to TBPC, were also used where data were not available for endpoints

of TTPC (i.e. acute oral and dermal toxicity, eye irritation and genotoxicity). The information on these endpoints is obtained from Dunn et al. (1982) and from data submitted by Allied Signal Inc. and American Cyanamid Inc. to the US EPA under TSCA Section 8(E) (US EPA 1992a, 1992b, 1992c, 1992e).

No data were available for repeated dose toxicity, reproductive toxicity or carcinogenicity.

The chemicals in relation to which data have been used to inform the hazard assessment for TTPC are summarised according to toxicological endpoints inTable A43.3.

Table A43.3 Summary of available toxicity endpoint data

	Tributyltetradecyl phosphonium chloride (TTPC) (CAS No. 81741-28-8)	**Tributylhexadecyl phosphonium bromide (THBP) (CAS No. 14937-45-2)**	**Tetrabutyl phosphonium chloride (TBPC) (CAS No. 2304-30-5)**	**Tetrabutyl phosphonium bromide (TBPB) (CAS No. 3115-68-2)**
Acute oral toxicity	×	✓	✓	✓
Acute dermal toxicity	×	✓	✓	✓
Acute inhalation toxicity	✓	×	×	×
Skin irritation	×	✓	✓	×
Eye irritation	×	✓	✓	✓
Respiratory irritation	×	×	×	×
Skin sensitisation	×	×	✓	×
Respiratory sensitisation	×	×	×	×
Repeat dose toxicity (oral)	×	×	×	×
Repeat dose toxicity (dermal)	×	×	×	×
Repeat dose toxicity (inhalation)	×	×	×	×
Genotoxicity	×	×	×	✓
Carcinogenicity	×	×	×	×
Reproductive toxicity (fertility)	×	×	×	×
Reproductive toxicity (development)	×	×	×	×

✓Existing data point; × Missing data point

43.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

43.5.1.1 Oral absorption

No data were available for the chemical.

Effects observed in acute oral toxicity studies for the analogues THPB, TBPC and TBPB indicate that TTPC is likely to be absorbed in the gastrointestinal tract (see Section A43.5.2.1).

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

43.5.1.2 Dermal absorption

No data were available for the chemical.

Severe systemic effects observed following acute dermal exposure studies for the analogues THPB, TBPC and TBPB indicate that TTPC is absorbed through the skin (see Section A43.5.2.2).

For the purposes of risk assessment, 100% dermal absorption in humans is therefore assumed.

43.5.1.3 Inhalation absorption

No data were available for the chemical.

Effects observed in the acute inhalation toxicity study indicate that TTPC is absorbed through the respiratory system (see Section A43.5.2.3).

For the purposes of risk assessment, 100% inhalation absorption in humans is therefore assumed.

43.5.1.4 Distribution

No data were available.

Intestinal and hepatic changes seen after respiratory exposure are suggestive of extensive distribution (see Section A43.5.2.3).

43.5.1.5 Metabolism

No data were available.

43.5.1.6 Excretion

No data were available.

43.5.2 *Acute toxicity*

43.5.2.1 Oral

No data were available for TTPC. However, briefly reported acute oral toxicity tests with THPB, TBPC and TBPB were used to read across to TTPC for this endpoint.

Rats were given 15% THPB in corn oil by gavage of doses up to 316 mg/kg bw. The acute oral median lethal dose (LD50) was 249 mg/kg bw (US EPA 1992d).

Studies with TBPC reported an LD50 of 916 and 325 mg/kg bw in rats and rabbits, respectively (Dunn et al. 1982). In rats, major signs of toxicity included depression of the nervous system as manifested by a decrease in spontaneous activity and reactivity,

staggering gait and loss of righting reflex. At necropsy there was evidence of haemorrhaging in the lungs and mottling of the kidney and liver (US EPA 1978).

An acute oral toxicity study with TBPB, conducted in accordance with US EPA Title 40 Code of Federal Regulation (CFR) Part 160, reported the LD50 was 583 mg/kg bw (US EPA 1992c). Clinical signs included tremors, convulsions and red discharge around the eyes and nose. Necropsy of deceased rats showed liquid filled stomachs and intestines, opaque caecums and red colouration of lungs, livers, intestines and kidneys.

The acute toxicity of TTPC by the oral route is likely to be moderate based on the results of studies available for the three analogues.

43.5.2.2 Dermal

No information was available for TTPC but data were available for the analogues TBPC and TBPB.

Pure (>98%) TBPC applied to rabbit skin at dose levels of 100, 200, 300, or 400 mg/kg bw produced weight loss, ataxia, hypotonia, laboured breathing, cyanosis, and convulsion (Dunn et al. 1982; US EPA 1978). The study, conducted in accordance with the CFR, Title 16, No. 1500.40, reported an acute dermal LD50 of 225 mg/kg bw in male rabbits. The LD50 of TBPC (mixed at concentrations from 11.9% to 66.8% with ethylene carbonate) was 600 and 500 mg/kg bw in males and females, respectively.

TBPC (90%) applied to rabbit skin at dose levels of 19.4, 57.6, 90, or 193.5 mg/kg bw produced localised effects in addition to emaciation, diarrhoea, red nasal discharge and depression. The study, conducted in accordance with the CFR, Title 16, No. 1500.40, reported an acute dermal LD50 of 109 mg/kg bw (US EPA 1979).

In a well-conducted dermal toxicity test in rabbits with TBPB, the LD50 was 200 mg/kg bw (US EPA 1992b). Gross lesions at necropsy included mottled and tan livers, liquid-filled stomachs, yellow or gas-filled intestines and red colouration of the lungs, thymuses, kidneys and tracheas.

The acute toxicity of TTPC by the dermal route in rabbits is likely to be moderate based on the consistent results of studies for the analogues TBPC and TBPB.

43.5.2.3 Inhalation

An inhalation study (EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS) 870.1300) in rats exposed nose-only to TTPC (particle size 1.7 to 2.1 µm) reported hypoactivity, gasping, irregular respiration, red nasal discharge, ano-genital staining and abdominal distension at 0.05 mg/L (US EPA 2012b). Six of the 10 animals died within three days of a four-hour exposure. Gross necropsy revealed red coloured lungs, distension of stomach and / or intestines and / or mottled liver. The single exposure acute inhalation LC50 for this study was identified as <0.05 mg/L.

This study shows that TTPC is highly toxic by the inhalation route in rats.

43.5.2.4 Observation in humans

No data were available.

43.5.3 *Irritation / Corrosivity*

43.5.3.1 Skin irritation

No information was available for TTPC but data were available for the analogues THPB and TBPC.

Occluded topical application of THPB as a finely ground powder to shaved intact skin of three rabbits was used (US EPA 1992d). The contact period was 24 hours with observations made from 1 hour to 7 days after application. The hygroscopic chemical produced moderate erythema with slight to moderate oedema within one hour resulting in a primary irritation index (PII) of 5.0/8.0. After 24 hours, there was marked swelling, redness and necrotic tissue present and the PII was 8.0/8.0. The study concluded that THPB is corrosive to the skin when applied as a powder.

In a primary dermal irritation test in rabbits (CFR 16, No. 1500.42) 0.5 g TBPC was applied to the skin of rabbits for 24 hours (Dunn et al. 1982). Severe erythema, oedema, necrosis and death in 3/6 animals were reported with a PII of 7.18/8.0 determined for the surviving animals. Similar results were obtained using the chemical sourced from two different suppliers (US EPA 1978). The chemical was found to be a severe skin irritant or corrosive under the conditions of the tests.

Overall, the effects observed with the analogues THPB and TBPC, albeit after a 24-hour exposure period compared with the four-hour exposure specified by the equivalent OECD Test Guideline (TG), demonstrate the likely corrosive potential of TTPC to the skin.

43.5.3.2 Eye irritation

No information was available for TTPC but data were available for the analogues THPB, TBPC and TBPB.

A 50% aqueous dilution of THPB was applied to the conjunctival sac of a rabbit with an exposure of 2-seconds before rinsing (US EPA 1992d). Similarly, a second and third animal were exposed for 4-seconds and 24-hours respectively. Irritation was evaluated using the Draize criteria at 1, 24, 48, 72, 120, 160, and 240 hours. All of the treated eyes showed severe to maximal irritation (including opacity, iritis, conjunctivitis and chemosis) from 1 to 24 hours, with the severity of irritation persisting for 48 hours to 240 hours. The chemical was found to be corrosive to the eye under the conditions of the test.

Instillation of a TBPC solution in rabbit eyes produced corneal opacity, conjunctival hyperaemia and necrosis, chemosis and discharge that generally persisted for at least 72 hours after dosing (US EPA 1978).

In an ocular irritation study with TBPB, conducted in accordance with OECD TG issued in 1981 and US EPA Good Laboratory Practice regulations (40 CFR Part 160, 40 CFR Part 792), instillation of 0.1 mL of the compound produced moderate to severe corneal injury (US EPA 1992a). All rabbits developed iritis, conjunctival irritation, ocular discharge and severe necrosis with most exhibiting conjunctival haemorrhage or a bloody conjunctival discharge.

The effects observed in all tests with the analogues THPB, TBPC and TBPB demonstrate the likely corrosive potential of TTPC to the eyes.

43.5.3.3 Respiratory irritation

In an inhalation study with TTPC in rats, a red nasal discharge and facial staining was noted (US EPA 2012b). While the information in the study is limited based on the analogues being

corrosive to the skin it is likely that the chemicals are also irritant to the respiratory mucosa. TTPC is therefore likely to be respiratory irritant.

43.5.3.4 Observation in humans

No data were available.

43.5.4 *Sensitisation*

43.5.4.1 Skin sensitisation

No data were available for TTPC.

TBPC at 0.1% concentration in normal saline solution was determined as not sensitising to the skin following dermal applications (undisclosed induction and one challenge treatment) in guinea pigs (US EPA 1978).

TBPC is not a skin sensitiser in guinea pigs and therefore a sensitisation potential for TTPC is not expected.

43.5.4.2 Respiratory sensitisation

No data were available.

43.5.4.3 Observation in humans

No data were available.

43.5.5 *Repeat dose toxicity*

43.5.5.1 Oral

No data were available.

43.5.5.2 Dermal

No data were available.

43.5.5.3 Inhalation

No data were available.

43.5.5.4 Observation in humans

No data were available.

43.5.6 *Genotoxicity*

No data were available for TTPC.

A brief report for TBPB noted that the chemical tested negative in an Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration test and a cell transformation test using Hamster Embryo Cells (HEC) although further details were not provided (Dunn et al. 1982). Therefore, TBPB is not mutagenic under the conditions tested and, on the basis of this limited evidence; it is assumed that TTPC is not genotoxic.

43.5.7 *Carcinogenicity*

No data were available.

43.5.8 *Reproductive toxicity*

No data were available.

43.5.9 *Other health effects*

No data were available.

43.6 Health hazard summary

43.6.1 *Critical health effects*

TTPC demonstrates high acute toxicity by the inhalation route. Based on read across data available from THPB, TBPC and TBPB, the chemical has moderate acute toxicity by oral and dermal routes and is corrosive to the skin and eye and is a respiratory irritant. Data available for TBPC and TBPB indicate that the chemical is not a skin sensitiser or genotoxic, respectively.

No repeat dose, carcinogenicity or reproductive toxicity data were available for the chemical or suitable analogues. Chronic exposure may be considered as inappropriate given the nature of TTPC and analogues as direct acting corrosives mediating severe adverse effects at the site of contact.

In conclusion, the critical health effect of TTPC is its acute inhalation toxicity.

43.6.2 *Hazard classification*

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC), 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in A43.4. These NICNAS recommendations do not consider physical or environmental hazards.

Table A43.4 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful if swallowed (X_n; R22) Toxic in contact with skin (T; R24) Very toxic by inhalation (T^+; R26)	Harmful if swallowed – Cat. 4 (H302) Toxic in contact with skin – Cat. 3 (H311) Fatal if inhaled (V) – Cat. 2 (H330)
Irritation/ Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage – Cat. 2B (H314)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

43.7 References

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A44 Cellulase, Hemicellulase, Enzyme

CAS No.	CAS Name
9012-54-8	Cellulase
9025-56-3	Hemicellulase
Confidential Business Information (CBI)	Enzyme

Three enzymes were assessed in a group. Confidentiality from public disclosure was claimed for the name and Chemical Abstracts Service (CAS) number of one of the enzymes. Therefore in this publicly available version of the hazard assessment report, the enzyme is listed by a generic name and its CAS Number has been omitted. Data on this enzyme subject to commercial-in-confidence claims were provided to NICNAS and a detailed hazard assessment of the enzyme has been conducted.

A summary of the assessment findings is presented below.

44.1 Justification for group assessment

The enzymes being considered in this group are all of biological origin; however, the substrates of the three enzymes differ. As compounds of biological origin, cellulase, hemicellulase and 'enzyme' are considered as substances of unknown or variable composition, complex reaction products or biological materials (UVCB). All these enzymes, as used in commerce, are produced by microorganisms and, because they are poorly purified, are likely to contain in addition to the enzyme after which they are named, varying amounts of other enzymes produced by the microorganism.

Cellulase (CAS No. 9012-54-8, Enzyme Commission (EC) 3.2.1.4) refers to a group of enzymes that cleave the beta-1,4-glycosidic bonds in cellulose. Hemicellulase (CAS No. 9025-56-3, EC 3.2.1) refers to an undefined mixture of glycolytic enzymes (generally containing β-xylanase, β-xylosidase, α-aribinofuranosidase and mannanase as active principles) that may also be classified under the term 'cellulase'. However, while cellulase (CAS No. 9012-54-8) will hydrolyse cellulose (which contains only anhydrous glucose) the hemicellulase group (CAS No. 9025-56-3) has greater substrate specificity for the heteropolymer hemicellulose which contains many different sugar monomers such as xylan, glucuronoxylan, arabinoxylan, glucomannan, and xyloglucan.

As they are related UVCBs, the enzymes are assessed as a group in this report. The justification for grouping is supported by common features which include:

- similarity of chemical structure – regardless of their substrate specificity, all enzymes are proteins, i.e. polymers of natural amino acids linked by peptide bonds in an essentially globular three-dimensional structure.
- similarity of function – specifically a common hydrolytic activity toward biopolymers.
- similarity of physico-chemical properties – molecular weight range, density, water solubility and partition coefficient.

Accordingly, data gaps against most endpoints for each enzyme can be filled by read across (refer to Table A44.1). The overall data were adequate to conduct a hazard assessment.

Table A44.1 Summary of available toxicity endpoint data

	Cellulase (CAS No. 9012-54-8)	**Hemicellulase (CAS No. 9025-56-3)**	**Enzyme (CAS No. CBI)**
Acute oral toxicity	✓	×	✓
Acute dermal toxicity	✓	×	×
Acute inhalation toxicity	✓	×	✓
Skin irritation	✓	×	✓
Eye irritation	✓	×	✓
Respiratory irritation	×	×	×
Skin sensitisation	✓	×	×
Respiratory sensitisation	✓	✓	×
Repeat dose toxicity (oral)	✓	×	✓
Repeat dose toxicity (dermal)	×	×	×
Repeat dose toxicity (inhalation)	×	×	×
Genotoxicity *in vitro*	✓	×	✓
Genotoxicity *in vivo*)	✓	×	×
Carcinogenicity	×	×	×
Reproductive toxicity (fertility)	×	×	×
Reproductive toxicity (development)	✓	×	×

✓Existing data point; × Missing data point

44.2 Chemical identity

The identity information was obtained from Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013a, 2013b), ChemID*plus* (2012) and Human and Environmental Risk Assessment (HERA) on ingredients of household cleaning products (2005). A description of the chemical identity is provided in

Table A44.2.

Table A44.2 Chemical identity

	Cellulase	**Hemicellulase**	**Enzyme**
Synonyms	β-(1,4) Glucanase Endo-1,4-β-D-glucanase β-1,4-endoglucan hydrolase	Albazyme 10 Amano 90 Bioamylase V Cartazyme MP	

	Cellulase	Hemicellulase	Enzyme
	Celluase A Celluclast Cellulosin AP Endoglucanase D Alkaline cellulase Carboxymethyl cellulase Cellulase A3 Celludextrinase Avicelase Optimash TBG Pancellase SS Endoglucanase	Fermizyme HS 2000 Gammanase GBW-12CD Gemmicellulase Macerozyme A Novozyme 348 Pentopan Pulpzyme Sumizyme X Validase DP 374 Veron HE, ST Xylavomarin	
Structural formula	Not applicable	Not applicable	Not applicable
Molecular formula	Not applicable	Not applicable	Not applicable
Molecular weight	13 000 - 252 000	No data	<200 000
Appearance and odour	Powder	Off-white to tan powder (or brown liquid) with sweet organic odour	Powder (or brown liquid)
SMILES notation	Not applicable	Not applicable	Not applicable

44.3 Physical properties

The following information on physical properties was obtained from REACH (2013a, 2013b) and HERA (2005) and is provided in Table A44.3.

Table A44.3 Physical properties

Property	Cellulase, Hemicellulase, Enzyme
Melting point	Not applicable
Boiling point	Not applicable
Density – kg/m^3	1.33-1.42 x 10^3 (20 °C)
Vapour pressure	<1 x 10^{-9} kPa (25 °C)
Water solubility (g/L)	100-800 (20 °C)
Partition coefficient (log K_{ow})	-2.95 to -3.1

44.4 Current regulatory controls

44.4.1 *Hazard classification for occupational health and safety*

Cellulase is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) with the following risk phrases (Safe Work Australia 2013):

- X_n(Harmful); R42 (May cause sensitisation by inhalation)

Mixtures containing the enzyme are classified as hazardous based on the concentration (Conc) of the enzyme in the mixtures. The risk phrases for this enzyme are:

- Conc ≥1%: X_n: R42

Hemicellulase and enzyme are not listed on the HSIS.

44.4.2 *Occupational exposure standards*

44.4.2.1 Australia

No specific exposure standards were available.

44.4.2.2 International

No exposure standards were available.

44.4.3 *Australian food standards*

Cellulase is listed in the Australia New Zealand Food Standards Code – Standard 1.3.3 – Processing Aids. It is listed under permitted enzymes of microbial origin: in the course of manufacture of any food provided the enzyme is derived from corresponding specified microbial sources (Food Standards Australia New Zealand 2013).

Hemicellulase endo-1,3-β-xylanase (EC 3.2.1.32), Hemicellulase endo-1,4- β-xylanase or xylanase (EC 3.2.1.8) is similarly listed.

Enzyme is not listed.

44.4.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the enzymes in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

44.4.5 *Additional controls*

44.4.5.1 Australia

The enzymes are not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

44.4.5.2 International

Cellulase enzyme preparation derived from a non-pathogenic, non-toxicogenic strain of *Trichoderma longibrachiatum* is listed by the United States Food and Drug Administration (US FDA) as a food substance generally recognised as safe when used in accordance with good manufacturing practice (GMP), with restricted use in food as an enzyme to break-down

cellulose (US FDA 1999). Similarly, hemicellulase from *Aspergillus aculeatus* is authorised for the treatment of wine and juice to facilitate the separation of juice from the fruit.

44.5 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

44.6 Health hazard characterisation

Information was sourced primarily from HERA on ingredients of household cleaning products (α-amylase, cellulases and lipases) (HERA 2005), the REACH dossiers for cellulase (REACH 2013a) and enzyme (REACH 2013b) as well as a safety evaluation of an alkaline cellulase (Greenough et al. 1991). Reviews published on the toxicology of enzymes used in cleaning products by Basketter et al. (2012) and the Enzymes REACH Consortium (ERC) (2010) were also used to provide additional data.

Published studies were the primary source of respiratory sensitisation data for cellulase and hemicellulase.

44.6.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the chemical in humans or laboratory animals.

44.6.1.1 Oral absorption

No data were available for the enzymes.

Microorganisms that produce hemicellulases are found in the digestive tract of humans and higher animals. Oral exposure to the enzymes will lead to breakdown of the enzymes into small peptides and amino acids as for any other ingested protein (HERA 2005). Apart from pre-systemic enzymatic degradation of the enzymes, the other reason for their low oral bioavailability is the poor penetration of the intestinal membrane (Mahato et al. 2003). For the purpose of human risk assessment, 0% oral absorption is assumed.

44.6.1.2 Dermal absorption

No data were available.

Absorption across intact skin is expected to be precluded by the large molecular size of the proteins (Basketter et al. 2012; HERA 2005). Therefore 0% dermal absorption is assumed.

44.6.1.3 Inhalation absorption

No data were available.

In general, proteins with molecular weights between 6 000 and 50 000 Daltons are relatively resistant to most peptidases present in the lung and have good bioavailability following inhalation (Patton et al. 2004). For the purpose of risk assessment, 100% inhalation absorption is therefore assumed.

44.6.1.4 Distribution

No data were available.

Enzymes are hydrophilic in nature and no bioaccumulation will occur after absorption. Absorbed proteins are rapidly degraded to amino acids and are carried in circulating blood to the liver. The amino acids are distributed to different tissues, where they form a series of amino acid pools (McGraw Hill 2005).

44.6.1.5 Metabolism

No data were available.

As the different organs require protein synthesis for energy and tissue production, they are supplied by pools of amino acids that are stored in tissues. Amino acids that are in excess of the body's needs are converted by liver enzymes into keto acids and urea. Keto acids may be used as sources of energy, converted into glucose, or converted to and stored as fat (Mosby's medical dictionary 2009).

44.6.1.6 Excretion

No data were available.

Metabolised protein is excreted from the body as urea through the sweat and in the urine.

44.6.2 *Acute toxicity*

44.6.2.1 Oral

An acute oral toxicity test with cellulase (batch PPC 4795) in rats, conducted in accordance with the Organisation for Economic Co-Operation and Development (OECD) Test Guideline (TG) 401, reported the acute median lethal dose (LD50) to be >2880 mg Total Organic Solids (TOS)/kg bw (REACH 2013a). No clinical signs were observed, the overall body weight gain during the study was considered to be normal and the post-mortem inspection revealed no abnormalities.

Acute oral LD50 values from studies with rats and mice for alkaline cellulase SP 227 (from the fungus *Humicola insolens*, batch PPC 1317) were >10 000 mg/kg bw and 8000 mg/kg bw respectively (Agger 1982a, 1982b). No clinical signs were observed in the rats; however, the mice showed decreased motor activity and diarrhoea.

Rats were given a 50% solution of enzyme by gavage at a dose of 3320 mg Total Protein (TP)/kg bw in a well-conducted acute oral toxicity test (REACH 2013b). Clinical signs were limited to temporary piloerection and the LD50 was >3320 mg TP/kg bw.

Both cellulase and enzyme were of low toxicity which is consistent with their hydrolysis in the stomach and consequent unavailability for absorption. Hence, hemicellulase is also expected to be of low toxicity.

44.6.2.2 Dermal

No data were available.

44.6.2.3 Inhalation

An acute inhalation toxicity test with cellulase (batch PPC 3425), conducted in accordance with OECD TG 403, reported the acute median lethal concentration (LC50) to be >4.44 mg TOS/L (REACH 2013a).

A well-conducted inhalation study in rats using alkaline cellulase SP 227 (batch PPC 1317) indicated a LC50 value greater than the maximum attainable concentration of 3.48 mg/L over the four-hour period (Greenough and McDonald 1984).

Rats were exposed nose-only to a droplet aerosol of enzyme at a concentration of 0.426 mg TOS/L in an acute inhalation study (REACH 2013b). The mass median aerodynamic diameter and the percentage of particles of <7 µm of enzyme were 2.9 µm and 87%, respectively. The LC50 was >0.426 mg TOS/L.

44.6.2.4 Observation in humans

No data were available.

44.6.2.5 Summary of acute toxicity

The results of the acute toxicity tests for cellulase and enzyme in good quality animal studies indicate low acute toxicity by oral and inhalation routes. Although no studies were found for hemicellulase, it is similarly considered likely to be of low acute toxicity.

44.6.3 *Irritation / Corrosivity*

44.6.3.1 Skin irritation

Alkaline cellulase SP 227 (batch PPC 1317) was not irritating to rabbit skin under occlusion in a study performed according to US 16CFR 1500.41 (Stavnsbjerg 1983, 1984a). A second test preparation (batch PPC 1247) was judged as a mild irritant on the basis of 3 of 6 rabbits having very slight oedema at the dosing site approximately one hour after patch removal. The investigator noted that the irritation potential was dependent on the amount of protease contamination in the test preparation.

In a study conducted according to OECD TG 404, cellulase induced slight erythema in one rabbit at the 24 and 48 hour observation points following the four-hour exposure period. This effect was fully reversed by 72 hours (REACH 2013a).

Enzyme produced no dermal reaction in rabbits after a single, semi-occluded application in a skin irritation study conducted according to OECD TG 404 (REACH 2013b).

Overall, cellulase and enzyme were non-irritating to the skin under the conditions of the studies. These data support the conclusion that hemicellulase is unlikely to be a skin irritant.

44.6.3.2 Eye irritation

Alkaline cellulase SP 227 (batch PPC 1317) was non-irritating to the rabbit eye in a study performed according to 16CFR 1500.42 (Agger 1982c; Stavnsbjerg 1984b). A second test preparation (batch PPC 1247) induced mild conjunctival reddening that was present in 1 of 6 rabbits at seven days post application. The investigators noted that the irritation potential is dependent on the amount of active protease contamination in the test preparation.

Cellulase produced no ocular irritation to the rabbit eye in a study conducted according to OECD TG 405 (REACH 2013a).

In an eye irritation test in rabbits, conducted in accordance with OECD TG 405, an unspecified concentration of enzyme was instilled into the eyes (REACH 2013b). At the one-hour reading, slight conjunctival effects in the form of redness, chemosis and discharge were present (score 1 for all parameters) in all rabbits. In two animals this effect had disappeared at the 24-hour observation point. Slight redness, without any swelling of the conjunctivae or any discharge, remained in one rabbit at 24 hours; however, all effects had cleared completely at the following 48-hour observation.

Overall, cellulase and enzyme are non-irritating to the eyes of rabbits in the reported studies. No data were available for hemicellulase; however, on the basis of the results presented here it is considered unlikely to have an irritant potential.

44.6.3.3 Respiratory irritation

No data were available.

There is no evidence that industrial enzymes, with the possible exception of proteases, can potentiate respiratory irritation (Basketter et al. 2012).

44.6.3.4 Observation in humans

No data were available.

44.6.4 *Sensitisation*

44.6.4.1 Skin sensitisation

A negative result was demonstrated in a Buehler test in guinea pigs with alkaline cellulase SP 227(Cuthbert and D´Arcy-Burt 1984).

44.6.4.2 Respiratory sensitisation

No animal data were available.

44.6.4.3 Observation in humans

A review by Basketter et al. (2008) concluded that enzymes should not be considered skin sensitisers. The lack of skin sensitising potential is substantiated by evidence from human experimental data and in-use human studies (including those with atopic individuals) performed with detergents containing enzymes (ERC 2010).

The respiratory sensitisation studies summarised from primary sources and presented in Table A44.4 include the known health effects of cellulase and hemicellulase on humans. While systematic studies of the effects of these UVCBs are lacking, a substantial body of evidence is available from case reports and epidemiological studies relating to respiratory pathologies.

Table A44.4 Human sensitisation studies with cellulase and hemicellulase

Study type	UVCB	Cohort	Result	Reference
SPT, RAST, BPT	Cellulase	Enzyme factory worker	Case report of pharyngeal oedema, rhinitis and asthma. Positive SPT, RAST and BPT to cellulase.	Hytönen et al. (1994)
SPT	Cellulase	Grain worker	Case report of rhinitis and contact urticaria. Positive SPT to cellulase, negative to 11 other enzymes.	Kanerva et al. (1998)
SPT, BPT	Cellulase	Baker	Case report of asthma and rhinitis. SPT positive to cellulase; BPT vs cellulase n.d.	Merget et al. (2001)
RAST, BPT	Hemicell-ulase	Bakers	Asthma, rhinitis and / or conjuctivitis (n=140). 8% (11/140) RAST and BPT positive to hemicellulase.	Bauer et al. (1988)

Study type	UVCB	Cohort	Result	Reference
SPT, BPT	Cellulase	Bakers	Asthma and rhinitis or rhinoconjuctivitis (n=5). 4/5 SPT positive to cellulase, 4/5 BPT positive.	Quirce et al. (1992)
SPT	Cellulase	Bakers	Allergic rhinitis in 16.7% (25/150), 8% (2/25) positive to cellulase.	Vanhanen et al. (1996)
SPT	Cellulase	Enzyme research lab workers	Rhinorrhea and cough in 3.2% (3/94). 67% (2/3) positive to cellulase.	Vanhanen et al. (1997)
SPT	Cellulase	Enzyme and yeast production workers	Rhinorrhea and / or cough and / or conjunctivitis in 11.4% (9/79). 67% (6/9) positive to cellulase	Vanhanen et al. (1997)
SPT, BPT	Cellulase	Enzyme production and lab workers	Asthma or rhinitis (n=11). 91% (10/11) SPT positive to cellulase. 63.6% (7/11) BPT positive to cellulase.	Vanhanen et al. (2000)
SPT, BPT	Cellulase	Pharmaceut-ical packing workers	Asthma, rhinorrhea, cough (n=2). 2/2 SPT positive to cellulase, negative to other allergens. 2/2 BPT positive to cellulase.	Losada et al. (1986)
SPT, BPT	Cellulase	Detergent production workers	Asthma (n=3). 2/3 SPT positive, 1/3 BPT positive to cellulase.	Brant et al. (2004)

SPT – skin prick test; BPT – bronchial provocation test; RAST – radioallergosorbent test; n.d. – not done

Skin sensitisation by cellulase has not been demonstrated in experimental animals. Cellulases, including those described as hemicellulase, have been shown by specific skin and bronchial challenge tests to cause occupational asthma via dust exposure in the baking, detergent, pharmaceutical and enzyme production industries. Enzyme is also likely to be a respiratory sensitiser based on data available for cellulase and hemicellulase. A recent review of enzymes in cleaning products concluded that it was reasonable to assume that the majority of industrial enzymes possess the intrinsic potential to act as respiratory sensitisers (Basketter et al. 2012).

44.6.5 *Repeat dose toxicity*

44.6.5.1 Oral

Aqueous cellulase SP 227 (batch PPC 1317) was administered by gavage to rats for 28 days at doses of 0, 300, 1000, and 3000 mg/kg bw/day (Husband and Wood 1983). No treatment related clinical signs were seen although there was a slight dose-related increase in body-weight gain (less than 10%) in the males at the top dose. A No Observed Adverse Effect Level (NOAEL) was not established in this study.

In a subsequent 13-week study (Perry et al. 1990), rats were fed diets formulated with cellulase SP 227 (batch PPC 2809) at 0, 120, 600, and 3000 mg/kg bw/day. An increase in serum alkaline phosphatase at 600 mg/kg bw/day and above was considered to be an adaptive response in the absence of any gross pathologies or histopathological lesions. There was a 10 to 20% reduction in body-weight gain in both sexes at the top dose which was accompanied by a reduction in food consumption likely related to poor palatability of the

test substance. As this effect was unrelated to the toxicity of the enzyme, a NOAEL was not established.

Rats administered by gavage 0, 100, 300, and 1000 TOS mg/kg bw/day β-glucanase (produced from *Trichoderma reesei*) for 13 weeks (OECD TG 408) did not show any systemic, behavioural or pathological effects. A NOAEL was not established in this well-conducted study (REACH 2013a).

Enzyme was administered by gavage to rats for 90 days (OECD TG 408) at doses of 0, 7.5, 37.5, and 75 mg TP/kg bw/day. No treatment-related clinical signs were seen at any dose and therefore a NOAEL could not be established (REACH 2013b).

Overall, cellulase and enzyme were well tolerated by repeated oral exposure, and this is consistent with the enzymes not being orally available due to their digestion in the stomach. Therefore hemicellulase is also expected to have a low potential for toxicity after repeated oral administration.

44.6.5.2 Dermal

No data were available.

44.6.5.3 Inhalation

No data were available.

44.6.5.4 Observation in humans

No data were available.

44.6.6 *Genotoxicity*

A negative result for mutagenicity was available from a reverse mutation assay in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 for alkaline cellulase SP 227 (batch PPC 1317) with and without metabolic activation at up to 10 mg/mL in liquid culture (Pedersen 1984). Similarly, cellulase (as β-glucanase, Optimash BG from *Trichoderma reesei*), was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2uvrA (OECD TG 471) with and without metabolic activation at up to 5000 µg/plate (REACH 2013a).

Enzyme was not mutagenic in a reverse mutation assay in *Salmonella typhimurium* TA 98, TA 100, TA 1535 and TA 1537 and *Escherichia coli* WP2uvrA (REACH 2013b). Enzyme was tested, with and without metabolic activation, at doses of up to 5 mg/L in liquid culture in a modified ‘treat and plate’ variant of OECD TG 471.

There was no increase in mutation frequency of cellulase (lot no. E21003SU3421Z1) and enzyme at 6100 µg TOS/mL and up to 5000 µg TP/mL, respectively, in two separate *in vitro* cytogenetic tests using human lymphocytes (OECD TG 473) both in the presence and absence of metabolic activation (REACH 2013a, 2013b).

Alkaline cellulase SP 227 (batch PPC 1317) was not clastogenic in rats in an *in vivo* bone marrow cell assay at doses up to 3.0 g/kg bw/day for five days (Asquith 1983).

Overall, cellulase and enzyme are not genotoxic and it is therefore considered unlikely that hemicellulase would act as a mutagen. Proteins are in general not genotoxic as there is no mechanism by which their primary amino acid structure can be mutagenic (Basketter et al. 2012).

44.6.7 *Carcinogenicity*

There were no experimental studies on the carcinogenic potential of cellulase, hemicellulase or enzyme available. Carcinogenicity is not expected for enzymes in general since it has been demonstrated that the systemic bioavailability for enzymes is likely to be low and toxicologically insignificant (ERC 2010). Additionally, there have been no public reports that enzymes possess carcinogenic properties (HERA 2005).

44.6.8 *Reproductive toxicity*

44.6.8.1 Fertility

No data were available.

44.6.8.2 Developmental toxicity

Rats were fed alkaline cellulase SP 227 (batch PPC 2809) in the diet at 0, 120, 680, and 3000 mg/kg bw/day during days 6 to 16 of gestation (McCay and Barton 1990). There was no evidence of treatment-related maternal, embryo, or foetal toxicity (including malformation) at any of the doses tested and therefore a NOAEL could not be established.

Data from 26 unpublished fertility and developmental toxicity studies in rodents, dogs and rabbits did not identify any evidence for reproductive toxicity of enzymes (ERC 2010).

This lack of developmental toxicity through the oral route is also consistent with the expected lack of oral availability of the enzymes due to their digestion in the stomach.

44.7 Health hazard summary

44.7.1 *Critical health effects*

Only limited data were available for hemicellulase but it is expected that its toxicity profile will be very similar to that of the related UVCBs, cellulase and enzyme.

Cellulase and enzyme demonstrate low acute oral and inhalation toxicity and are not irritating to the skin or eye. Limited animal data indicate that cellulase is not a skin sensitiser, however both cellulase and hemicellulase are capable of inducing respiratory sensitisation in humans who are occupationally exposed. Similarly, it is expected that enzyme is also a respiratory sensitiser.

An appropriate NOAEL or Lowest Observed Adverse Effect Level (LOAEL) could not be established for the enzymes. Cellulase has low repeat oral dose toxicity. The critical study is a 13-week dietary study in rats, where no adverse effects were seen at a top dose of 3000 mg/kg bw/day. There were no signs of systemic toxicity in a 90-day gavage study of enzyme in rats at the highest dose tested of 75 mg/kg bw/day.

Cellulase and enzyme are not genotoxic and the former is not a developmental toxicant. Similarly, hemicellulase is not considered a genotoxin or developmental toxicant.

The carcinogenic potential of the three UVCBs is unknown but carcinogenicity is not expected for enzyme preparations in general.

Overall, the main critical effect to human health is respiratory sensitisation.

44.7.2 *Hazard classification*

This hazard assessment confirms the existing classification for cellulase under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004).

Cellulase is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A44.5. These NICNAS recommendations do not consider physical or environmental hazards.

Table A44.5 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Sensitisation	May cause allergy or asthma symptoms or breathing difficulties if inhaled – Cat.1 (H334)

* *Globally Harmonised System (UNECE 2009)*

Hemicellulase and enzyme are recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) and the adopted GHS (UNECE 2009) as shown in Table A44.6. These recommendations do not consider physical or environmental hazards.

Table A44.6 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Sensitisation	May cause sensitisation by inhalation (X_i; R42)	May cause allergy or asthma symptoms or breathing difficulties if inhaled – Cat.1 (H334)

[a] *Approved Criteria for Classifying Hazardous Substances (NOHSC 2004);* [b] *Globally Harmonised System (UNECE 2009)*

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A45 Alkanes, C12-26 branched and linear

CAS No.	CAS Name
90622-53-0	Alkanes, C12-26-branched and linear

45.1 Chemical identity

Alkanes, C12–26-branched and linear (CAS No. 90622-53-0) is considered as a substance of unknown or variable composition, complex reaction products or biological materials (UVCB), . A search of SciFinder (2013) indicated that the Chemical Abstracts Service (CAS) Registry Number for this substance has the name as 'Unspecified' with Alkanes, C12–26-branched and linear listed as another name associated with the CAS Number. The Conservation of Clean Air and Water in Europe (CONCAWE) (2012) indicated that the substance is a petroleum product.

Identity information was obtained from Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013a). Details are provided in Table A45.1.

Table A45.1 Substance identity

	Alkanes, (C=12–26)-branched and linear
Synonyms	Alkanes, (C=12–26)-branched and linear
Appearance and odour	Clear to yellowish liquid with a diesel odour

45.2 Physical properties

The physical properties of the substance are presented in Table A45.2. The information was obtained from REACH (2013a).

Table A45.2 Physical properties

Property	**Value**
Pour point	-40 °C to 6 °C
Boiling point	172-379 °C
Density	800-900 kg/m^3
Vapour pressure	0.4 kPa at 40 °C
Flash point	>56 °C

45.3 Current regulatory controls

The document from now on refers to alkanes, C12–26-branched and linear as either 'alkanes, C12–26-branched and linear', or 'the substance'.

45.3.1 *Hazard classification for occupational health and safety*

The substance is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) with the following risk phrase:

- Carc. Cat. (Carcinogen Category) 2; R45 (May cause cancer)

Mixtures containing the substance are classified as hazardous with the following risk phrase based on the concentration (Conc) of the substance in the mixtures. The risk phrase for this substance is:

- Conc ≥0.1%: T (Toxic); R45 (May cause cancer)

45.3.2 *Occupational exposure standards*

45.3.2.1 Australia

No specific exposure standards were available.

45.3.2.2 International

No specific exposure standards were available.

45.3.3 *Australian food standards*

No Australian food standards were identified.

45.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this substance in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

45.3.5 *Additional controls*

45.3.5.1 Australia

The substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

45.3.5.2 International

The substance is currently regulated in the European Union (EU) Cosmetic Directive 76/768/EEC in Annex II (List of substances which must not form part of the composition of cosmetic products) (EC 2010). The substance is also included in Annex VI (List of substances which are carcinogenic, mutagenic, or toxic for reproduction) of the European Classification, Labelling and Packaging (CLP) Regulation of substances and mixtures (European Chemicals Agency (ECHA) 2012). The substance is classified under the adopted *Globally Harmonised System of Classification* (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as Carcinogen, Cat 1B (Carc cat 2) in Annex VI of the European Classification, Labelling and Packaging (CLP) Regulation, with an appended note (Note N) that states *'The classification as a carcinogen need not apply if the full refining history is known and it can be shown that the substance from which it is produced is not a carcinogen.'*

The substance is included in the Canadian Cosmetic Ingredient Hotlist (Health Canada 2013).

45.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

45.5 Health hazard characterisation

The information on health hazards is obtained from REACH (2013a, 2013b and 2013c). Unless otherwise noted, references to individual studies below are taken from these reviews.

The European Union Council (EUC) adopted the grouping of petroleum substances as developed by CONCAWE. The grouping was established based on the refinery processing history of the substances (CONCAWE 2012). Petroleum substances listed in the European Inventory of Existing Commercial Chemical Substances (EINECS) were categorised into groups and subgroups to facilitate the evaluation of hazard data, as indicated in the EUC Regulation EEC No. 793/93 of 23 March 1993 (EUC 1993). The grouping was established based on the similar manufacturing process for each group/subgroup. In addition, the Regulation stated that hazard information for one substance in each specific group/subgroup can be submitted for hazard assessment purposes for all the substances in that group/subgroup (EUC 1993) on the presumption that the hazards are similar across all the substances in each category (Comber and Simpson 2006; CONCAWE 2012).

The substance belongs to the group 'Other Gas Oils'. Substances in this group are derived from crude petroleum, with carbon numbers ranging from C_9 to C_{36}, and are composed of the following hydrocarbon types:

- aromatics
- alkylated aromatics
- mixed aromatic cycloalkanes
- straight and branched alkanes and alkenes
- cycloalkanes and cycloalkenes.

The typical boiling range of the group is from 150°C to 400°C (CONCAWE 2012). The CONCAWE grouping process is similar to the Petroleum Sector Stream Approach by the Canadian Government, wherein 160 petroleum substances identified as priorities through Canada's chemical categorisation process are assessed by a sectoral approach based on the production and uses of the substances (Government of Canada 2013).

No specific toxicity data were available for alkanes, C12-26-branched and linear. Information from two other UVCB substances was used to read across for the substance. The two substances are Hydrodesulfurised middle petroleum distillates (Distillates, petroleum, hydrodesulfurised middle (CAS No. 64742-80-9)) and Hydrotreated middle petroleum distillates (Distillates, petroleum, hydrotreated middle (CAS No. 64742-46-7)) (REACH 2013a).

The United States Environmental Protection Agency (US EPA) Substance Registry Services (SRS) (US EPA 2013) defined the two substances as follows:

- Hydrodesulfurised middle petroleum distillates:

  'a complex combination of hydrocarbons obtained from a petroleum stock by treating with hydrogen to convert organic sulfur to hydrogen sulfide which is removed. It consists of hydrocarbons having carbon numbers predominantly in the range of C11 through C25 and boiling in the range of approximately 205°C to 400°C (401°F to 752°F)'

Source: US EPA (2013)

- Hydrotreated middle petroleum distillates:

  'a complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C11 through C25 and boiling in the range of approximately 205°C to 400°C (401°F to 752°F)'

  Source: US EPA (2013)

Alkanes, C12-26-branched and linear, hydrodesulfurised middle petroleum distillates, and hydrotreated middle petroleum distillates all belong to the same petroleum group, Other Gas Oils, with the three substances expected to possess similar properties (CONCAWE 2012; EUC 1993). All the category members of the Other Gas Oils group are classified similarly in HSIS (Safe Work Australia 2013) and in the EU Harmonised CLP Regulation (Annex VI of Regulation (EC) No. 1272/2008) as Carcinogenic Category 1B (Category 2 carcinogens), unless information is available on the refining history demonstrating that the substances produced from refining are not carcinogenic.

Information available for the substance, hydrodesulfurised middle petroleum distillates, and hydrotreated middle petroleum distillates is presented in Table A45.3. No toxicity data were available for alkanes, C12-26-branched and linear and therefore data available for hydrodesulfurised middle petroleum distillates and hydrotreated middle petroleum distillates are used to read-across to the various endpoints for alkanes, C12-26-branched and linear. Read-across is a technique used here to predict endpoint information for the untested alkanes, C12-26-branched and linear by using data (from the same endpoint) from the two tested middle petroleum distillates which are considered to possess similar properties.

Table A45.3 Summary of available toxicity endpoint data

	Alkanes, C12-26-branched and linear (CAS No. 90622-53-0)	**Hydrodesulfurised middle petroleum distillates (CAS No. 64742-80-9)**	**Hydrotreated middle petroleum distillates (CAS No. 64742-46-7)**
Acute oral toxicity	×	✓	×
Acute dermal toxicity	×	✓	×
Acute inhalation toxicity	×	✓	×
Skin irritation	×	✓	×
Eye irritation	×	✓	×
Respiratory irritation	×	×	×
Skin sensitisation	×	✓	×
Respiratory sensitisation	×	×	×
Repeat dose toxicity (oral)	×	×	×
Repeat dose toxicity (dermal)	×	✓	×
Repeat dose toxicity (inhalation)	×	✓	×
Genotoxicity	×	✓	×
Carcinogenicity	×	×	✓

	Alkanes, C12-26-branched and linear (CAS No. 90622-53-0)	Hydrodesulfurised middle petroleum distillates (CAS No. 64742-80-9)	Hydrotreated middle petroleum distillates (CAS No. 64742-46-7)
Reproductive toxicity	×	×	×

✓*Existing data point;* ×*Missing data point*

45.5.1 *Toxicokinetics*

This section covers the absorption, distribution, metabolism and excretion of the substance in humans or laboratory animals.

45.5.1.1 Oral absorption

No data were available.

For the purposes of risk assessment, 100% oral absorption in humans is assumed.

45.5.1.2 Dermal absorption

No data were available.

For the purposes of risk assessment, 100% dermal absorption in humans is assumed.

45.5.1.3 Inhalation absorption

No data were available.

For the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

45.5.1.4 Distribution

No data were available.

45.5.1.5 Metabolism

No data were available.

45.5.1.6 Excretion

No data were available.

45.5.2 *Acute toxicity*

45.5.2.1 Oral

No data were available for alkanes, C12-26-branched and linear.

Two studies, conducted similarly to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, were available for hydrodesulfurised middle petroleum distillates.

In the first study, hydrodesulfurised middle petroleum distillates was administered by gavage to Sprague-Dawley rats at a single dose of 5000 mg/kg bw (REACH 2013a). Clinical signs included hypoactivity, urine-stained abdomen, and oily-looking hair. Necropsy results included mildly enlarged cervical lymph nodes, distended stomach, moderately dilated renal

pelvis, and alopecia in the stomach region. The reported acute oral median lethal dose (LD50) was >5000 mg/kg bw.

In the second study, hydrodesulfurised middle petroleum distillates was administered by gavage to Sprague-Dawley rats at a single dose of 5000 mg/kg bw (REACH 2013a). Clinical signs included diarrhoea, yellow stained anal-genital region, ptosis, opacity in one or both eyes, and inflammation of the salivary and ophthalmic glands. Necropsy results included red exudate and severe corneal ulcerations. The reported LD50 was >5000 mg/kg bw.

The studies show that hydrodesulfurised middle petroleum distillates have low acute oral toxicity in rats and reading across the data to alkanes, C12-26-branched and linear, indicates low acute oral toxicity for this substance.

45.5.2.2 Dermal

No data were available for alkanes, C12-26-branched and linear.

Two studies conducted similarly to OECD TG 402 were available for hydrodesulfurised middle petroleum distillates.

In the first study, hydrodesulfurised middle petroleum distillates was applied occlusively to the shaved skin of New Zealand White rabbits at a single dose of 2000 mg/kg bw (REACH 2013a). Three out of eight animals showed mild crusting, redness, or both at the site of application. Increased body-weight was noted in all of the animals throughout the study. The reported acute dermal LD50 was >2000 mg/kg bw.

In the second study, hydrodesulfurised middle petroleum distillates was applied occlusively to the unshaved skin of New Zealand White rabbits at a single dose of 2000 mg/kg bw (REACH 2013a). No clinical signs or toxicity were observed. Increased body-weight was noted in all of the animals throughout the study. Dermal irritation ranging from slight to moderate erythema was observed along with oedema, atonia, desquamation, or fissuring. The reported acute dermal LD50 was >2000 mg/kg bw.

Based on reading across the data available for hydrodesulfurised middle petroleum distillates, alkanes, C12-26-branched and linear has low acute dermal toxicity in rabbits.

45.5.2.3 Inhalation

No data were available for alkanes, C12-26-branched and linear.

In a study conducted similarly to OECD TG 403, Sprague-Dawley rats were exposed to hydrodesulfurised middle petroleum distillates in a whole-body exposure chamber for four hours (REACH 2013a). The concentrations were 0, 3.5, 3.6, 4.0, 6.9, or 7.3 mg/L. Clinical signs included dyspnoea, gasping, matted fur, nasal discharge, eyes matted shut, alopecia, open sores, and scabs. There was a dose-related increase in macroscopic congestion of the lungs in all treated animals. The reported acute inhalation median lethal concentration (LD50) was 4.6 mg/L.

Based on read-across the data available for hydrodesulfurised middle petroleum distillates, alkanes, C12-26-branched and linear has low acute inhalation toxicity in rabbits.

45.5.2.4 Observation in humans

No data were available.

45.5.3 *Irritation / Corrosivity*

45.5.3.1 Skin irritation

No data were available for alkanes, C12-26-branched and linear.

Two studies conducted similarly to OECD TG 404 were available for hydrodesulfurised middle petroleum distillates.

In the first study, hydrodesulfurised middle petroleum distillates was applied occlusively to the shaved back skin of male New Zealand White rabbits (REACH 2013a, 2013b). Based on the Draize scoring at 24 and 72 hours, the mean erythema and oedema scores were 1.9 and 2.25, respectively. No information on reversibility or individual animal score data were provided. Hydrodesulfurised middle petroleum distillates was found to be mildly irritating in this test.

In the second study, hydrodesulfurised middle petroleum distillates was applied occlusively to the shaved back skin of male New Zealand White rabbits (REACH 2013a, 2013b). Based on the Draize scoring at 24 and 72 hours, the mean erythema and oedema scores were 2.75 and 3.1, respectively. The effects were fully reversible within 14 days. The individual animal scores were not provided. Hydrodesulfurised middle petroleum distillates was found to be irritating in this test.

Based on reading across the data available for hydrodesulfurised middle petroleum distillates alkanes, C12-26-branched and linear has skin irritant effects.

45.5.3.2 Eye irritation

No data were available for alkanes, C12-26-branched and linear.

Two studies conducted similar to OECD TG 405 were available for hydrodesulfurised middle petroleum distillates.

In the first study, 0.1 mL of the undiluted hydrodesulfurised middle petroleum distillates was instilled into New Zealand White rabbit eyes (REACH 2013a, 2013b). Moderate irritation was observed, with a mean overall eye irritation Draize score of 1.0 at 24 hours that resolved fully within 48 hours. The individual irritation scores were not provided. Hydrodesulfurised middle petroleum distillates was found to be not irritating in this test.

In the second study, 0.1 mL of undiluted hydrodesulfurised middle petroleum distillates was instilled into New Zealand White rabbit eyes (REACH 2013a, 2013b). The maximum primary irritation score was 2.7 at 1 hour and 2.0 at 24 hours, with the effects fully reversible within 48 hours. The individual irritation scores were not provided. Hydrodesulfurised middle petroleum distillates was found to be not irritating in this test.

Alkanes, C12-26-branched and linear is not irritating to rabbit eyes, based on read-across the data available for hydrodesulfurised middle petroleum distillates.

45.5.3.3 Respiratory irritation

No data were available.

45.5.3.4 Observation in humans

No data were available.

45.5.4 *Sensitisation*

45.5.4.1 Skin sensitisation

No data were available for alkanes, C12-26-branched and linear.

Two studies conducted similar to OECD TG 406 were available for hydrodesulfurised middle petroleum distillates.

Hydrodesulfurised middle petroleum distillates, undiluted during induction and 10% in paraffin oil during challenge phase, was found to be not skin sensitising in male Hartley guinea pigs (REACH 2013a, 2013b). In another study, hydrodesulfurised middle petroleum distillates, 25% in paraffin oil during induction and 10% in paraffin oil during challenge phase, was reported as not skin sensitising in male Hartley guinea pigs (REACH 2013a, 2013b).

Alkanes, C12-26-branched and linear is not sensitising to guinea pig skin, based on reading across the data available for hydrodesulfurised middle petroleum distillates.

45.5.4.2 Respiratory sensitisation

No data were available.

45.5.4.3 Observation in humans

No data were available.

45.5.5 *Repeat dose toxicity*

45.5.5.1 Oral

No data were available.

45.5.5.2 Dermal

No data were available for alkanes, C12-26-branched and linear.

Two similar studies conducted in a manner comparable to OECD TG 410 utilised the same application conditions. Hydrodesulfurised middle petroleum distillates was applied to the dorsal trunk of New Zealand White rabbits for six hours/day, five days/week, for four weeks at doses of 0, 200, 1000, or 2000 mg/kg bw/day (REACH 2013a, 2013b).

In the first study, 20% mortality was observed at the top dose on the second day of treatment. At unspecified doses, two animals were sacrificed on days 13 and 16 due to severe dermal reactions. Clinical signs and gross pathology revealed flaking skin, thin appearance, lesion or injury to treated area, scab on treated area, and discharge. There was a dose-related increase in frequency of clinical signs (significance not stated). Histopathology, conducted on the control and top dose groups only, reported moderate to severe acanthotic dermatitis, minimal to severe hyperkeratosis, and presence of skin lesions. The Draize scoring for dermal irritation was conducted for erythema and oedema. The severity of irritation increased in a dose-dependent manner, with the highest mean irritation score of 6.9 in males at the top dose and the lowest mean irritation score of 1.9 in females at the low dose. No other treatment-related effects were observed. The study reported a No Observed Adverse Effect Level (NOAEL) of 1000 mg/kg bw/day based on local irritation at the top dose (REACH 2013a and 2013b).

In the second study, one male died in each of the control and top dose groups but the deaths were not considered to be treatment-related. Clinical signs included flaking skin, cracking skin, scabs, discharge, and thin appearance. Microscopic evaluation, conducted in the

control and top dose groups only, showed moderate to severe acanthotic dermatitis and hyperkeratosis in the top dose animals. The Draize scores reported the highest mean irritation score of 5.2 in males at the top dose and the lowest mean irritation score of 0.7 in females at the low dose. The irritation score of the control group was 0. The study reported a NOAEL of 1000 mg/kg bw/day for local effects based on severe irritation at the top dose (REACH 2013a, 2013b).

Repeated dermal exposure to hydrodesulfurised middle petroleum distillates was consistently associated with dermatitis and hyperkeratosis at all doses. The NOAEL is 1000 mg/kg bw/day for local effects from two similar studies. This NOAEL will be applied to alkanes, C12-26-branched and linear.

45.5.5.3 Inhalation

No data were available for alkanes, C12-26-branched and linear.

Two similar studies conducted comparable to OECD TG 412 utilised the same application conditions. Sprague-Dawley rats were exposed by dynamic whole-body exposure to hydrodesulfurised middle petroleum distillates at a concentration of 24 mg/m^3 (first study), or 23 mg/m^3 (second study) for six hours/day, five days/week, for four weeks (REACH 2013a, 2013b). Control groups were established for both studies.

In the first study, there were no treatment-related effects in mortality, clinical signs, bodyweight, clinical chemistry, or gross and histologic pathology. The effects of treatment were 30% decrease in leukocyte count in both sexes, and increased organ weights (i.e. 9% in kidney, 14% in liver, and 8% in testes) (REACH 2013a, 2013b).

In the second study, there were no treatment-related effects in mortality, clinical signs, bodyweight, clinical chemistry, haematology, or gross and histologic pathology. The effects of treatment in male rats were 9% increase in kidney weight, 14% increase in liver weight, 8% increase in testis weight, and 9% decrease in brain to bodyweight ratio. In female rats, 9% increase in liver weight and 7% increase in lung weight were reported (REACH 2013a, 2013b).

45.5.5.4 Observation in humans

No data were available.

45.5.6 *Genotoxicity*

No data were available for alkanes, C12-26-branched and linear.

In vitro and *in vivo* data on genotoxicity of hydrodesulfurised middle petroleum distillates are summarised from REACH (2013a, 2013b) and presented in Table A45.4 and Table A45.5.

Table A45.4 *In vitro* genotoxicity studies with hydrodesulfurised middle petroleum distillates

Test	Results	Reference
Reverse mutation test in *Salmonella typhimurium* TA 98 strain only (similar to OECD TG 471); Metabolic activation not tested.	Weakly positive without activation	1988-1991 study in REACH (2013a)
Reverse mutation test in *S. typhimurium* TA 98 strain only (non-guideline)	Negative with and without activation	1994 study in REACH (2013a)

Test	Results	Reference
Gene mutation test in mouse lymphoma cells (similar to OECD TG 476)	Weakly positive with and without activation	1986 study in REACH (2013a)
Gene mutation test in mouse lymphoma cells (similar to OECD TG 476)	Positive with activation; Negative without activation	1987 study in REACH (2013a)
Gene mutation test in mouse lymphoma cells (similar to OECD TG 476)	Negative with and without activation	1987 study in REACH (2013a)
Gene mutation test in mouse lymphoma cells (similar to OECD TG 476)	Weakly positive with activation; Negative without activation	1984 study in REACH (2013a)
Gene mutation test in mouse lymphoma cells (similar to OECD TG 476)	Equivocal with and without activation	1985 study in REACH (2013a)
Chromosome aberration test in Chinese hamster ovary cells (similar to OECD TG 479)	Equivocal with activation; Negative without activation	1988 study in REACH (2013a)

Table A45.5 *In vivo* genotoxicity studies with hydrodesulfurised middle petroleum distillates

Test	Results	Reference
Sprague-Dawley rat chromosome aberration test in bone marrow cells with intraperitoneal administration of 300, 1000, or 3000 mg/kg bw/day (similar to OECD TG 475)	Negative	1985 study in REACH (2013a)
Sprague-Dawley rat chromosome aberration test in bone marrow cells with intraperitoneal administration of 300, 1000, or 3000 mg/kg bw/day (similar to OECD TG 475)	Negative	1984 study in REACH (2013a)
CD-1 mice micronucleus test in bone marrow cells with administration of 1000, 2500, or 5000 mg/kg bw/day by gavage (non-guideline)	Negative	1994 study in REACH (2013a)

Alkanes, C12-26-branched and linear is considered to be not genotoxic, based on reading across the data available for hydrodesulfurised middle petroleum distillates.

45.5.7 *Carcinogenicity*

No data were available for alkanes, C12-26-branched and linear.

Information is available for hydrotreated middle petroleum distillates (REACH 2013a, 2013c). In a 104-week carcinogenicity study conducted similarly to OECD TG 451, 0, 28.5, 50, or 100% hydrotreated middle petroleum distillates, test material labelled as MD6, in mineral oil vehicle was applied in the dorsal area of male C3H mice for 104 weeks. MD6 contained 1.3% of 3 to 7 ring polycyclic aromatic compounds. A positive control of 5% solution of heavy clarified oil in mineral oil vehicle was included. All the animals were examined for clinical signs, mortality, bodyweight gain/loss, gross pathology, and neoplastic histopathology.

There were no treatment-related effects on body-weight gain. Slightly higher mortality was observed in the positive control group (statistical significance not specified) and at the mid and top doses (statistical significance not specified). Dose-dependent dermal irritation was observed in all the treated animals. The irritation scores for the treated animals were 0.02, 0.09, and 2.0 at 28.5, 50, and 100%, respectively. Dermal irritation was also seen in the negative control group (irritation score = 0.06) and positive control group (irritation score = 0.73). No tumours were seen in the negative control group. The positive control group showed 73 squamous cell carcinomas, 88 papillomas, and 3 kerato-acanthomas. The treated animals showed the following tumours: a single squamous cell carcinoma at the low dose; no

tumours at the mid dose; a single squamous cell carcinoma and a single basal cell carcinoma at the top dose. Hydrotreated middle petroleum distillates was not carcinogenic in this test (REACH 2013a, 2013c).

Based on the limited carcinogenicity studies available for the CONCAWE grouping Other Gas Oils, the result for hydrotreated middle petroleum distillates will be used to read across to alkanes, C12-26-branched and linear.

45.5.8 *Reproductive toxicity*

45.5.8.1 Fertility

No data were available.

In the REACH Dossier for the substance (REACH 2013a), information is available for a test material labelled as VDF gas oil but the characterisation of the test material was not provided. Whether this test material can be used as a suitable analogue for alkanes, C12-26-branched and linear cannot be established from the insufficient information.

45.5.8.2 Developmental toxicity

No data were available.

45.5.9 *Other health effects*

No data were available.

45.6 Health hazard summary

45.6.1 *Critical health effects*

Based on reading across data available for hydrodesulfurised middle petroleum distillates, Alkanes, C12-26-branched and linear has low acute oral, dermal and inhalation toxicity, has skin irritant effects, and is not an eye irritant or a skin sensitiser.

A NOAEL was not established for systemic toxicity at a dose of up to 2000 mg/kg bw/day from 28-day rabbit studies (REACH 2013a, 2013b) available for hydrodesulfurised middle petroleum distillates. This will be applied to the substance.

The substance is neither genotoxic, based on reading across data available for hydrodesulfurised middle petroleum distillates, nor carcinogenic, based on reading across data available for hydrotreated middle petroleum distillates.

45.6.2 *Hazard classification*

Under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004), the existing hazard classification of the substance is Category 2 carcinogen (Substances that should be regarded as if they are carcinogenic to man). Two notes were appended to this classification as follows:

- Note N*:*

  'The classification as a carcinogen need not apply if the full refining history is known and it can be shown that the substance from which it is produced is not a carcinogen.'

Source: NOHSC (2004)

- Note H:

  'The classification and label shown for this substance applies to the dangerous property(ies) indicated by the Risk Phrase(s) in combination with the category(ies) of danger shown. The manufacturers, distributors and importers of this substance shall be obliged to carry out an investigation to make themselves aware of the relevant and accessible data which exists for all other properties to classify and label the substance. The final label shall follow the requirements of section 7 of Annex VI of directive 67/548/EEC.'

  Source: NOHSC (2004)

Although the data available for the analogues of the substance do not support this classification, the limited information on the full refining history of the substance or its analogues is not sufficient for NICNAS to recommend removal of the current HSIS classification to Safe Work Australia.

The equivalent classification and labelling under the adopted GHS (UNECE 2009) is shown in Table A45.6. This NICNAS recommendation does not consider physical or environmental hazards.

Table A45.6 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Carcinogenicity	May cause cancer – Carc. 1B (H350)

** Globally Harmonised System (UNECE 2009)*

45.7 References

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A46 2-Ethylhexanol heavies

CAS No.	Chemical Name
CBI	2-Ethylhexanol heavies

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) Number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to NICNAS and a detailed hazard assessment of the chemical has been conducted.

A summary of the assessment findings are presented below.

46.1 Chemical identity

The identity information was obtained from a European Commission (EC) dossier (EC 2013). A description of the chemical identity is provided in Table A46.1.

Table A46.1 Chemical identity

	2-Ethylhexanol heavies
Molecular weight	<200
Appearance and odour	Clear, colourless liquid with a sweet odour

46.2 Physical properties

The following physical properties information provided in Table A46.2 was obtained from EC (2013).

Table A46.2 Physical properties

Property	Value
Melting point	<-50 °C
Boiling point	<200 °C
Density	<1000 kg/m^3 (20 °C)
Vapour pressure	<0.1 kPa (20 °C)
Water solubility	<10 g/L (20 °C)
Partition coefficient (log K_{ow})	3-4 (25 °C)
Flash point	<100 °C

46.3 Current regulatory controls

The document from now on refers to 2-Ethylhexanol heavies as 'the chemical'.

46.3.1 *Hazard classification for occupational health and safety*

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

46.3.2 *Occupational exposure standards*

46.3.2.1 Australia

No specific exposure standards were available.

46.3.2.2 International

The following occupational exposure standards were identified (Galleria Chemica 2013).

Time Weighted Average (TWA):

- 110 mg/m³ [Switzerland]
- 160 mg/m³ [Poland]
- 270 mg/m³ [Austria].

Short Term Exposure Limit (STEL):

- 110 mg/m³ [Switzerland]
- 320 mg/m³ [Poland]
- 540 mg/m³ [Austria].

46.3.3 *Australian food standards*

No Australian food standards were identified.

46.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

46.3.5 *Additional controls*

46.3.5.1 Australia

The chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

46.3.5.2 International

The chemical is currently regulated under the Canadian Department of Justice (2013), Hazardous Products Act, Ingredient Disclosure List (SOR/88-64) with the maximum authorised concentration of 1%.

46.4 Use

The use of the chemical in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

46.5 Health hazard characterisation

The information on health hazards was sourced primarily from a Joint European Community Food Additive (JECFA) monograph (World Health Organisation (WHO) 2013), an IUCLID dataset (EC 2013) and a Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier (REACH 2013). Unless otherwise noted, references to individual studies below are taken from these reviews.

46.5.1 *Toxicokinetics*

Toxicokinetic studies on the ^{14}C-labeled chemical in rats found the oral absorption to be 76% within four days.

In rats exposed dermally to the ^{14}C-labeled chemical, absorption of approximately 5% of the administered dose was observed. An *in vitro* dermal study conducted with full thickness rat skin and human stratum corneum showed that rat skin is more permeable to the chemical than human skin.

For the purposes of risk assessment, 100% oral, 10% dermal, and 100% inhalation absorption in humans is therefore assumed from the available absorption data of the chemical in animals.

46.5.2 *Acute toxicity*

46.5.2.1 Oral

The chemical was shown to have low acute oral toxicity with a median lethal dose (LD50) of 2053 to 6400 mg/kg bw in four studies conducted in rats.

46.5.2.2 Dermal

The chemical was shown to have low acute dermal toxicity (LD50 >3000 mg/kg bw) in a rat study conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 402. Briefly described studies in rabbits reported LD50s of 1986 mg/kg bw and >2600 mg/kg bw.

The chemical is of low acute toxicity by the dermal route in rats and rabbits.

46.5.2.3 Inhalation

A four-hour inhalation study in rats (equivalent or similar to OECD TG 403) reported moderate toxicity with a median lethal concentration (LC50) of 0.89 to 5 mg/L for the chemical.

46.5.3 *Irritation / Corrosivity*

46.5.3.1 Skin irritation

In a study conducted in accordance with OECD TG 404, the undiluted chemical was corrosive to the skin of rabbits.

46.5.3.2 Eye irritation

In two studies, severe iritis and wide-spread corneal opacity was reported in rabbits after the undiluted chemical was applied to the conjunctival sac. The chemical was found to be a severe eye irritant under the conditions of the tests.

46.5.3.3 Observation in humans

An irritation study in 15 volunteers using inhalation exposure to the chemical vapour reported sensory irritation at concentrations >10 ppm.

46.5.4 *Sensitisation*

No animal data were available.

The chemical is not considered to be a skin sensitiser based on the result of a human repeat insult patch test conducted with a 4% solution of the chemical under occlusive dressing.

46.5.5 *Repeat dose toxicity*

46.5.5.1 Oral

A two-year gavage study in rats at doses of 0, 50, 150, or 500 mg/kg bw/day gave a No Observed Adverse Effect Level (NOAEL) of 50 mg/kg bw/day. From the mid dose, there were consistent increases in relative organ weights, in particular, the brain, kidney, forestomach and liver. There was also reduced body-weight gain and, at the top dose, bronchopneumonia and increased mortality (females).

46.5.5.2 Dermal

In a nine-day dermal repeated dose study, rats were exposed to the chemical at either 417 or 834 mg/kg bw/day. The Lowest Observed Adverse Effect Level (LOAEL) for systemic toxicity in females was 417 mg/kg bw/day based on increased triglycerides at this dose while there were no effects in males at either dose.

46.5.5.3 Inhalation

In a 90-day inhalation toxicity study in rats, conducted in accordance with OECD TG 413, no treatment-related effects were noted following exposures of up to 120 ppm (638.4 mg/m^3) of the chemical.

46.5.5.4 Observation in humans

No data were available.

46.5.6 *Genotoxicity*

The chemical was not mutagenic (with and without metabolic activation) in five Ames tests. Similarly, the chemical did not increase mutation frequency in mouse lymphoma cells, was not clastogenic to Chinese hamster ovary (CHO) cells and did not induce unscheduled DNA synthesis (UDS) in rat hepatocytes.

In vivo studies in rodents showed negative results for genotoxicity in an erythrocyte micronucleus test, a cytogenetic assay, and a dominant lethal assay.

46.5.7 *Carcinogenicity*

Histopathological investigations in oral gavage studies showed no evidence of carcinogenicity in Fischer 344 rats administered doses of up to 500 mg/kg bw/day for two years, or B6C3F1 mice administered doses of up to 750 mg/kg bw/day for 18 months.

46.5.8 *Reproductive toxicity*

46.5.8.1 Fertility

An increase in testes weight was reported at a dose level of 500 mg/kg bw/day in a two-year oral carcinogenicity study in rats. Testes effects (interstitial oedema and reduced spermiogenesis) were also induced in a 16-day dermal study at a dose of 1660 mg/kg bw/day.

The chemical is expected to cause effects on fertility at high dose levels.

46.5.8.2 Developmental toxicity

Reliable developmental studies are available for rats (oral, dermal, inhalation) and mice (oral). Foetotoxic effects were only observed in rats treated by the oral route at doses of at least 650 mg/kg bw/day and included skeletal variations and retardations in the presence of only slight maternal toxicity. The NOAEL for developmental toxicity was 130 mg/kg bw/day.

46.5.9 *Other health effects*

No data were available.

46.6 Health hazard summary

46.6.1 *Critical health effects*

The chemical has low acute oral and dermal toxicity but can be considered moderately toxic by inhalation. It is corrosive to the skin and eye but is not expected to be a skin sensitiser.

Repeated oral exposures to the chemical produced adverse effects on several organs, in particular the kidney, stomach and liver. The most appropriate NOAEL for systemic effects is 50 mg/kg bw/day based on reduced body-weight gain and increases in relative organ weights from a two-year oral carcinogenicity study.

The chemical is not genotoxic or carcinogenic based on the available data but did induce effects on fertility (testes) at high dose levels. In an oral developmental toxicity study, a NOAEL of 130 mg/kg bw/day was determined based on foetotoxicity (reduced foetal body weights and increased skeletal malformations) noted in the absence of signs of marked maternal toxicity.

46.6.2 *Hazard classification*

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A46.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A46.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful by inhalation (X_n; R20)	Harmful if inhaled – Cat. 4 (H332)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage – Cat. 1 (H314)
Reproductive and developmental toxicity	Repr. Cat 3 – Possible risk of harm to the unborn child (X_n; R63)	Suspected of damaging the unborn child – Cat. 2 (H361d)

a Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); b Globally Harmonised System (UNECE 2009)

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A47 Quaternary amine, Amine salt

CAS No.	Chemical Name
CBI	Quaternary amine
CBI	Amine salt

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical names and Chemical Abstracts Service (CAS) numbers of these chemicals. Therefore in this publicly available version of the hazard assessment report, the chemicals are listed by a generic name and their CAS Numbers have been omitted. Data on these chemicals subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and detailed hazard assessments of the chemicals have been conducted.

A summary of the assessment findings is presented below.

47.1 Justification for group assessment

The category assessed in this report consists of the above two chemicals. The justification for inclusion of members within the category is supported by common features which include:

- similarity of chemical structure and functional groups – composed of a functional amine group with all three hydrogen atoms replaced by the same organic substituent
- similarity of mode of action (MOA) – the amine salt will dissociate into the parent amine and the salt once it enters the body with toxicity due to the parent amine.

The available data show that the parent amine is associated with local signs of gastrointestinal irritation and systemic toxicity. The known acute toxicity effects are generally related to the alkaline properties of the parent amine.

The European Food Safety Authority (EFSA) indicated that the amine salt can be considered as a variant of the quaternary amine.

Information available for the chemicals is presented in Table A47.1. Accordingly, the data gaps for the amine salt can be filled by read across from the data of the parent amine for some endpoints.

Table A47.1 Summary of available toxicity endpoint data

Toxicity endpoint	Quaternary amine	Amine salt
Acute oral toxicity	✓	✓
Acute dermal toxicity	✓	×
Acute inhalation toxicity	✓	×
Skin irritation	✓	✓
Eye irritation	✓	✓
Respiratory irritation	✓	×

Toxicity endpoint	Quaternary amine	Amine salt
Skin sensitisation	×	×
Respiratory sensitisation	×	×
Repeat dose toxicity (oral)	✓	✓
Repeat dose toxicity (dermal)	×	×
Repeat dose toxicity (inhalation)	✓	×
Genotoxicity	✓	×
Carcinogenicity	×	×
Reproductive toxicity	✓	✓

✓Existing data point; × Missing data point

47.2 Chemical identity

The information on chemical identity was obtained from the International Programme on Chemical Safety (IPCS)(2013) and Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013). Details are provided in Table A48.2.

Table A48.2 Chemical identity

	Quaternary amine	Amine salt
Molecular weight	<100	<100
Appearance and odour	Colourless, compressed liquefied gas (neat); Aqueous solution at 40% concentration with pungent odour	White monoclinic crystals with ammoniacal odour

47.3 Physical properties

The physical properties of the chemicals are presented in Table A48.3. The information was obtained from an Organisation of Economic Co-operation and Development (OECD) report (OECD 2013) and REACH (2013).

Table A48.3 Physical properties

Property	Value	
	Quaternary amine	Amine salt
Melting point	<-100 °C	<300 °C
Boiling point	<10 °C at 101.3 kPa	>200 °C
Density	<1000 kg/m^3 at 20 °C	>1000 kg/m^3 at 20 °C
Vapour pressure	<2 kPa at 20 °C	<1 kPa at 25 °C (estimated)
Water solubility	<500 g/L at 19 °C	<1000 g/L at 20 °C and pH 4.7-4.8
Partition coefficient n-octanol/water (log K_{ow})	0.2-0.3 at 25 °C	-2 to -3 (estimated)

47.4 Current regulatory controls

47.4.1 *Hazard classification for occupational health and safety*

The quaternary amine is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) with the following risk phrases (Safe Work Australia 2013):

- X_n (Harmful); R20/22 (Harmful by inhalation and if swallowed)
- C (Corrosive); R34 (Causes burns)

Mixtures containing the quaternary amine are classified as hazardous with the following risk phrases based on the concentration (Conc) of the chemical in the mixtures. The risk phrases for different concentration ranges are:

- Conc ≥15%: C; R34/R20/22
- 10% ≤Conc <15% C; R34
- 5% ≤Conc <10% X_i (Irritant); R36/37/38 (Irritating to eyes, respiratory system and skin).

The amine salt is not listed in the HSIS (Safe Work Australia 2013).

47.4.2 *Occupational exposure standards*

47.4.2.1 Australia

The following occupational exposure standards were identified (Safe Work Australia 2013).

Quaternary amine:

- Time Weighted Average (TWA) of 10 ppm (24 mg/m^3)
- Short-Term Exposure Limit (STEL) of 15 ppm (36 mg/m^3).

No specific exposure standards were available for the amine salt.

47.4.2.2 International

The following exposure standards were identified (Galleria Chemica 2013).

Quaternary amine:

TWA:

- 5 ppm (12 mg/m^3) [Belgium, Denmark, Finland, Iceland]
- 10 ppm (24 to 25 mg/m^3) [France, Korea, New Zealand, Norway]
- 12.3 mg/m^3 [Hungary].

STEL:

- 15 ppm (36 to 37 mg/m^3) [Belgium, Finland, Korea, New Zealand]
- 36.9 mg/m^3 [Hungary].

No specific exposure standards were available for the amine salt.

47.4.3 *Australian food standards*

No Australian food standards were identified.

47.4.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the chemicals in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

47.4.5 *Additional controls*

47.4.5.1 Australia

The chemicals are not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

47.4.5.2 International

No international restrictions were identified.

47.5 Use

The use of the chemicals in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

47.6 Health hazard characterisation

The information on health hazards was obtained from OECD report.

47.6.1 *Toxicokinetics*

No data were available for quaternary amine or the amine salt.

Due to the low molecular weight (<100 Da) of the chemicals dermal absorption may occur. Acute toxicity studies in animals describe systemic effects following administration of quaternary amine by oral, dermal and inhalation routes. This indicates that quaternary amine is absorbed in the gastrointestinal tract, through the skin and in the respiratory system.

For the purposes of risk assessment for the chemicals, 100% absorption via the oral, dermal and inhalation routes in humans is therefore assumed.

47.6.2 *Acute toxicity*

47.6.2.1 Oral

Three acute oral toxicity studies in rats were available for the chemicals. All the studies were similar to the OECD Test Guideline (TG) 401.

Quaternary amine was shown to have low-moderate acute oral toxicity (median lethal dose (LD50) of 766 mg/kg bw and 397 to 820 mg/kg bw) in two studies while the amine salt has low acute toxicity (LD50 2000 mg/kg bw) in a single study.

47.6.2.2 Dermal

Quaternary amine was shown to have low acute toxicity based on an occlusive dermal test. Although no data were available for the amine salt, its toxicity is also expected to be low based on the data for the parent amine.

47.6.2.3 Inhalation

Three acute inhalation toxicity studies in rats were available for quaternary amine. All the studies were similar to the OECD TG 403 and quaternary amine was shown to have low-moderate acute inhalation toxicity (four-hour median lethal concentration (LC50) >5.9 mg/L and 8.5 mg/L; one-hour LC50 19.1 mg/L). Although no data were available for the amine salt, its toxicity is also expected to be low based on the data for the parent amine.

47.6.3 *Irritation / Corrosivity*

47.6.3.1 Skin irritation

In two separate studies, the undiluted quaternary amine was found to be corrosive to the skin of rabbits. In a study comparable with OECD TG 404, the amine salt, in an aqueous solution of 60 to 65% was irritating to the skin of rabbits.

47.6.3.2 Eye irritation

Quaternary amine was corrosive to the eyes in a single study in rabbits. In a study comparable with OECD TG 405, the amine salt in a solution of 60 to 65% was irritating to the cornea and conjunctivae.

47.6.3.3 Respiratory irritation

Whole-body vapour exposure to a dose of 5.91 mg/L quaternary amine was conducted in rats in a study similar to OECD TG 403. Clinical signs of respiratory irritation, such as gasping and nasal secretion, were reported. No data were available for the amine salt.

Quaternary amine is a respiratory tract irritant in rats. The amine salt is also likely to be a respiratory tract irritant based on the data for the parent amine.

47.6.3.4 Observation in humans

Concentrated aqueous quaternary amine was reported as corrosive to human skin and eyes according to an American Conference of Governmental Industrial Hygienists (ACGIH) report. No data were available for the amine salt.

47.6.4 *Sensitisation*

No data were available.

The OECD concluded that a group of chemicals with similar structure to quaternary amine and amine salt were not sensitising to skin from guinea pig maximisation and Buehler tests, and in mouse local lymph node assays.

47.6.5 *Repeat dose toxicity*

47.6.5.1 Oral

A combined repeated dose/reproduction/developmental toxicity test (OECD TG 422) in rats at doses of 0, 8, 40, or 200 mg quaternary amine /kg bw/day gave a No Observed Adverse Effect Level (NOAEL) of 40 mg/kg bw/day. In this gavage study, there was mortality at the top dose as well as inflammatory changes in the stomach and intestinal tract, and squamous hyperplasia and oedema in the submucosa. Males had decreased body-weight gain, and changes in plasma protein concentrations.

In a 90-day feeding study in male rats, the amine salt was administered at equivalent doses of 0, 25, 50, 100, 190, or 380 mg/kg bw/day of the parent amine. Decreased body-weight gain was observed at the top two dose groups. At the highest dose, effects included reduced seminal vesicle size, reduced number of secretory granules and changes in the prostate. The NOAEL for this study was 100 mg/kg bw/day.

Repeated gavage administration of quaternary amine showed local effects in the gastrointestinal tract at 200 mg/kg bw/day while dietary administration of the amine salt did not induce any local effects.

47.6.5.2 Dermal

No data were available.

47.6.5.3 Inhalation

In a 14-day inhalation study, similar to OECD TG 412, male rats were exposed (nose only) to quaternary amine at doses of 0.18, 0.58, or 1.8 mg/L. At the mid and top doses, dose-related haematological and clinical chemistry changes were seen. Pathological examination showed irritation of the nasal cavity and turbinates together with tracheal and lung effects. The Lowest Observed Adverse Effect Concentration (LOAEC) for this study was 0.18 mg/L.

A 7-month inhalation study in rats at doses of 0.025 or 0.075 mg/L quaternary amine gave a LOAEC of 0.025 mg/L. At both doses there were bronchial changes and haemorrhage of the lung, liver, kidneys and spleen together with morphological variations in these organs.

No data were available for the amine salt.

Repeated inhalation of quaternary amine showed effects in the respiratory tract with a minimum LOAEC of 0.025 mg/L. Exposure to amine salt dust is likely to produce similar effects.

47.6.6 *Genotoxicity*

Quaternary amine was negative in two Ames tests both in the presence and absence of metabolic activation. Quaternary amine did not induce gene mutations or chromosomal aberrations in Chinese hamster ovary cells both in the presence and absence of metabolic activation. There are no *in vivo* data available for quaternary amine although *in vivo* micronucleus tests for other similar amines reported negative results.

No *in vitro* or *in vivo* data were available for the amine salt.

Quaternary amine is not considered to be genotoxic and amine salt is not considered to be genotoxic based on data for the parent amine.

47.6.7 *Carcinogenicity*

No data were available.

47.6.8 *Reproductive toxicity*

47.6.8.1 Fertility

In a previously described repeated dose/reproduction/developmental toxicity study (refer to Repeat Oral Dose Toxicity), there were no effects on the reproductive organs or reproductive performance of the rats administered quaternary amine by gavage. The NOAEL for fertility effects was 200 mg/kg bw/day.

In a mouse study, intraperitoneal administration of a solution of amine salt from gestation days 1 to 17 at doses up to 295 mg/kg bw/day resulted in deaths in the dams at the highest dose. No other details provided. The NOAEL for maternal toxicity was 150 mg/kg bw/day.

The chemicals have no demonstrated fertility effects in rodents.

47.6.8.2 Developmental toxicity

There were no effects on the viability of the delivered pups, sex ratio, bodyweight and gross development in the combined repeated dose/reproduction/developmental toxicity study previously described. The NOAEL for parental toxicity was 40 mg/kg bw/day based on systemic effects at the LOAEL of 200 mg/kg bw/day. No data were available for the amine salt.

Quaternary amine has no developmental effects in rats. Similarly, the amine salt has no developmental effects based on the available data.

47.7 Health hazard summary

47.7.1 *Critical health effects*

Quaternary amine has low to moderate acute oral and inhalation toxicity and low acute dermal toxicity, is corrosive to the skin and eyes, and is a respiratory tract irritant.

Amine salt has low acute oral toxicity and is a skin and eye irritant. Based on the supporting data for quaternary amine, amine salt has low acute dermal toxicity, low to moderate acute inhalation toxicity, and is a respiratory tract irritant. Based on data available for amines of similar structure, both chemicals are not expected to be skin sensitisers.

The most appropriate NOAEL for risk assessment of quaternary amine, determined from the combined repeated dose toxicity study with reproduction/developmental toxicity testing, is 40 mg/kg bw/day based on local effects in the gastrointestinal tract and systemic effects at the LOAEL of 200 mg/kg bw/day. The most appropriate NOAEL for risk assessment of amine salt, determined from the 90-day dietary study, is 100 mg/kg bw/day based on systemic effects at the LOAEL of 190 mg/kg bw/day.

Quaternary amine is not genotoxic or carcinogenic, and is not a reproductive toxicant. Amine salt, based on data for quaternary amine, is not genotoxic or carcinogenic, and is not a reproductive toxicant.

47.7.2 *Hazard classification*

The hazard assessment for quaternary amine confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004).

The equivalent classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) is shown in Table A48.4. These NICNAS recommendations do not consider physical or environmental hazards.

Table A48.4 Hazard classification recommended by NICNAS to Safe Work Australia

	GHS* classification
Acute toxicity	Harmful if inhaled – Cat. 4 (H332), C ≥15% Harmful if swallowed – Cat. 4 (H302), C ≥15%
Irritation / Corrosivity	Causes severe skin burns and eye damage – Cat. 1B (H314), C ≥10% Causes serious eye irritation – Cat. 2 (H319), 5% ≤C <10% May cause respiratory irritation – Specific target organ toxicity, single exposure – Cat. 3(H335), 5% ≤C <10% Causes skin irritation – Cat. 2 (H315), 5% ≤C <10%

** Globally Harmonised System (UNECE 2009)*

Amine salt is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (NOHSC 2004) and the adopted (GHS) (UNECE 2009) as shown in Table A48.5. These NICNAS recommendations do not consider physical or environmental hazards.

Table A48.5 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful by inhalation (X_n; R37)	Harmful if inhaled – Cat. 4 (H332)
Irritation / Corrosivity	Irritating to skin (X_i; R38) Irritating to eyes (X_i; R36) Irritating to respiratory system (X_i; R37)	Causes skin irritation – Cat. 2 (H315) Causes eye irritation – Cat. 2B (H320) May cause respiratory irritation – Specific target organ toxicity, single exposure - Cat. 3 (H335)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

47.8 References

ACGIH Documentation of the TLV's and BEI's with other worldwide occupational exposure values. American Conference of Governmental Industrial Hygienists CD-ROM Cincinnati, OH.

EFSA Conclusion on the peer review of the pesticide risk assessment of the active substance. European Food Safety Authority Journal.

Galleria Chemica (2013). Accessed August 2013 at http://jr.chemwatch.net/galleria/

IPCS International Chemical Safety Card: Chemical and 40% aqueous solution, International Programme on Chemical Safety, World Health Organization. Accessed on 1 August 2013 at http://www.inchem.org/

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Safe Work Australia (2013) Hazardous Substances Information System. http://hsis.safeworkaustralia.gov.au/HazardousSubstance. Accessed 1 August 2013

TGA (2014) Poisons Standard 2014. Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Therapeutic Goods Administration.

UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe, New York and Geneva. Accessed in June 2013 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

A48 Ester alcohol

CAS No.	Chemical Name
CBI	Ester alcohol

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemical has been conducted.

A summary of the assessment findings is presented below.

48.1 Chemical identity

The information on chemical identity was obtained from an Organisation for Economic Co-operation and Development (OECD) report. Details are provided in Table A48.1.

Table A48.1 Chemical identity

	Ester alcohol
Molecular weight	<300
Appearance and odour	Colourless liquid with slight odour

48.2 Physical properties

The physical properties of the chemical are presented in Table A48.2. The information was obtained from the OECD.

Table A48.2 Physical properties

Property	Value
Melting point	<0 °C
Boiling point	<300 °C
Density	<1000 kg/m^3 at 20 °C
Vapour pressure	<1 x 10^{-2} kPa
Water solubility	<1 g/L at 18-22 °C
Partition coefficient n-octanol/water (log K_{ow})	3-4 at 25 °C

48.3 Current regulatory controls

The document from now on refers to ester alcohol as either ‘ester alcohol’ or ‘the chemical’.

48.3.1 *Hazard classification for occupational health and safety*

The chemical is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

48.3.2 *Occupational exposure standards*

48.3.2.1 Australia

No specific exposure standards were available.

48.3.2.2 International

No specific exposure standards were available.

48.3.3 *Australian food standards*

No Australian food standards were identified.

48.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

48.3.5 *Additional controls*

48.3.5.1 Australia

The substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

48.3.5.2 International

No international restrictions were identified.

48.4 Use

The use of the chemical in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

48.5 Health hazard characterisation

The information on health hazards was obtained from the OECD and the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier (REACH 2013).

48.5.1 *Toxicokinetics*

No data were available for the chemical.

Based on its low molecular weight, water solubility and vapour pressure, the chemical is expected to be absorbed in the gastrointestinal tract and in the skin.

For the purposes of risk assessment for the chemical, 100% absorption via the oral, dermal and inhalation routes in humans is assumed.

48.5.2 *Acute toxicity*

48.5.2.1 Oral

The chemical was shown to have low acute oral toxicity in four rat studies.

48.5.2.2 Dermal

The chemical was shown to have low acute dermal toxicity based on occluded tests in guinea pigs and rabbits.

48.5.2.3 Inhalation

No mortality or abnormality was reported in rats exposed (whole-body) to the chemical at a concentration of 8730 mg/m^3 for six hours.

48.5.3 *Irritation / Corrosivity*

48.5.3.1 Skin irritation

The undiluted chemical was found to be slightly irritating to skin of rabbits and guinea pigs.

48.5.3.2 Eye irritation

In an eye irritation test in rabbits, conducted in accordance with OECD Test Guideline (TG) 405, the undiluted chemical caused minimal ocular irritation. Two other studies reported corneal opacity (without inflammation of the iris) and slight to moderate erythema. Overall, the studies show that the chemical is slightly irritating to rabbit eyes.

48.5.4 *Sensitisation*

The chemical, at concentrations ranging from 1% to 100%, was not found to be sensitising in three reliable guinea pig maximisation tests.

48.5.5 *Repeat dose toxicity*

48.5.5.1 Oral

In a 51-day oral (gavage) combined repeated dose/reproduction/developmental study in rats, the chemical was administered at doses of 0 to 1000 mg/kg bw/day. Kidney lesions seen in male rats at the mid and top dose groups were consistent with α2μ-globulin nephropathy which is considered not relevant to humans. In addition, increased absolute and relative liver weights seen in males at all doses were regarded as associated with metabolic activation rather than a direct effect of the chemical. No systemic effects were observed in females and neither a Lowest Observed Adverse Effect Level (LOAEL) or a No Observed Adverse Effect Level (NOAEL) could be established.

48.5.5.2 Dermal

No systemic effects were reported in an 11-day study where the undiluted chemical was applied on the clipped skin of the backs of guinea pigs.

48.5.6 *Genotoxicity*

The chemical was negative in two Ames tests both in the presence and absence of metabolic activation. It was not clastogenic in mice in an *in vivo* mammalian erythrocyte micronucleus test.

48.5.7 *Carcinogenicity*

No data were available.

48.5.8 *Reproductive toxicity*

In a previously described combined repeated dose/reproduction/developmental study in rats, the chemical was not toxic to fertility or a developmental toxicant.

48.6 Health hazard summary

48.6.1 *Critical health effects*

The chemical has low acute oral, dermal and inhalation toxicity, is not a skin or eye irritant, and is not a skin sensitiser.

A NOAEL could not be established for systemic effects in the repeated dose toxicity studies. In the 51-day oral (gavage) study of the chemical in rats, no adverse effects were observed at the highest dose tested (1000 mg/kg bw/day).

The chemical is neither genotoxic nor a reproductive toxicant. No data were available to determine the carcinogenic potential of the chemical.

48.6.2 *Hazard classification*

The chemical is not recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009).

48.7 References

NHMRC (2011) Australian Drinking Water Guidelines 6 2011. National Health and Medical Research Council. Accessed in November 2013 at http://www.nhmrc.gov.au/guidelines/publications/eh52

NICNAS (2017a) Identification of chemicals associated with coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NICNAS (2017b) Human health hazards of chemicals used in coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

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Safe Work Australia (2013) Hazardous Substances Information System. Accessed November 2013 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

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UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe, New York and Geneva. Accessed in June 2013 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

A49 Ethoxylated fatty acid I, Ethoxylated fatty acid III

CAS No.	Chemical Name
CBI	Ethoxylated fatty acid I
CBI	Ethoxylated fatty acid III

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical names and Chemical Abstracts Service (CAS) Numbers of these chemicals. Therefore in this publicly available version of the hazard assessment report, the chemicals are listed by a generic name and their CAS Numbers have been omitted. Data on these chemicals subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemicals have been conducted.

A summary of the assessment findings is presented below.

49.1 Justification for group assessment

The ethoxylated fatty acid category assessed in this report consists of the above two chemicals. The justification for inclusion of members within the category is supported by common features which include similarity of:

- Chemical structure – composed of polyethylene glycols (ethylene oxide units) linked to saturated fatty acids.
- Function – specifically as non-ionic surfactants for domestic and industrial use.
- Toxicokinetics – both substances will metabolise in the body to form the parent fatty acids and ethylene oxy chains.

49.2 Chemical identity

Ethoxylated fatty acid I and ethoxylated fatty acid III are considered as substances of unknown or variable composition, complex reaction products or biological materials (UVCB), having a biological origin.

Information on substance identity was obtained from ChemID*plus* (2012). Details are provided in Table A49.1.

Table A49.1 Substance identity

	Ethoxylated fatty acid I	Ethoxylated fatty acid III
Appearance and odour	Yellow, wax-like solid	Yellowish solid, mild odour

49.3 Physical properties

The following physical properties information provided in Table A49.2 was obtained from Safety Data Sheets (SDS).

Table A49.2 Physical properties

Property	Value	
	Ethoxylated fatty acid I	**Ethoxylated fatty acid III**
Melting point	>10°C	No data
Boiling point	>100°C	No data
Bulk density	No data	>1000 kg/m^3
Water solubility	Soluble	Soluble
Partition coefficient n-octanol/water (log K_{ow})	No data	No data
Flash point	>50 °C	>100 °C

49.4 Current regulatory controls

The document from here on refers to ethoxylated fatty acid I and ethoxylated fatty acid III as 'EFA I' and 'EFA III' respectively. Collectively, the two substances are also referred to as 'substances'.

49.4.1 *Hazard classification for occupational health and safety*

The substances are not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

49.4.2 *Occupational exposure standards*

49.4.2.1 Australia

No specific exposure standards were available.

49.4.2.2 International

No specific exposure standards were available.

49.4.3 *Australian food standards*

No Australian food standards were identified.

49.4.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the substances in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

49.4.5 *Additional controls*

49.4.5.1 Australia

The substances are not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

49.4.5.2 International

EFA III is listed by the United States Food and Drug Administration (US FDA) as an inert pesticide ingredient for food use and is exempt from the requirement of a tolerance when used as an emulsifier (40 CFR part 180.910) (US FDA 2013).

49.5 Use

The use of the substances in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

49.6 Health hazard characterisation

Limited toxicity information is available on EFA I and EFA III.

A search of structurally similar chemicals was conducted using the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Application Toolbox (OECD 2013) and the US Environmental Protection Agency (US EPA) Analog Identification Methodology (AIM) (US EPA 2012).

Data were available for the structurally similar alcohol ethoxylate (AE) compounds. Based on the similarity of chemical structure, composition and biotransformation of the substances and the AE class with overlapping fatty alkyl chain lengths, the use of data for the latter is appropriate to read across for the endpoints where no data were available for the substances.

In addition, QSAR modelling was conducted on endpoints such as Sensitisation and Genotoxicity on specific chain lengths of the chemicals using the predictive modelling tool OASIS-TIMES.

Information on health hazards was sourced primarily from the Human and Environmental Risk Assessment (HERA) review of AE (HERA 2009).

49.6.1 *Toxicokinetics*

No information was available for EFA I or EFA III but data were available from AE studies that were used to read across to both substances.

Based on the observations for analogous AE compounds in animals and humans, 100% oral, 10% dermal, and 100% absorption of the substances in humans is assumed.

49.6.2 *Acute toxicity*

No acute toxicity information was available for EFA I or EFA III but data were available from AE studies that were used to read across to both substances.

Based on observations for analogue chemicals, EFA I and EFA III are considered likely to have low to moderate acute toxicity by the oral route and low acute toxicity by the inhalation and dermal routes.

49.6.3 *Irritation / Corrosivity*

No information was available for EFA I or EFA III but extensive data from analogue studies in animals were available that were used to read across to both substances. Accordingly, the substances are considered as potentially irritating to rabbit skin and severely irritating to the eye.

Human patch test results indicate the analogue chemicals to be, at most, mild skin irritants. Noting there is currently no accepted test method for human skin irritation, collectively these studies reinforce the observations in animals that the analogues are irritating to the skin.

49.6.4 *Sensitisation*

In a guinea pig maximisation test, it was concluded that EFA III was not a contact sensitiser (US EPA). Supporting data were available for a range of AEs where no evidence for skin sensitisation was reported in numerous Buehler studies and maximisation tests.

Two AEs were evaluated in a Human Repeated Insult Patch Test (HRIPT) at high concentrations. The evaluation of the skin after challenge revealed no evidence of skin sensitisation for either of the surfactants.

QSAR modelling using OASIS-TIMES predicted negative results for skin sensitisation.

EFA III is not a skin sensitiser in guinea pigs and a sensitisation potential for EFA I is unlikely.

49.6.5 *Repeat dose toxicity*

No information was found for EFA I or EFA III, however reliable AE data for repeated dose oral toxicity were available and considered appropriate to read across to both substances.

Growth retardation and organ weight changes were the most common observations in animals in all AE repeat dose studies. No Observed Adverse Effect Levels (NOAELs) of 50 to 700 mg/kg bw/day have been established in studies (of at least 90 days) with various AEs based mostly on changes in relative organ weights and liver hypertrophy. A NOAEL of 50 mg/kg bw/day was established in a good quality 90-day oral feeding study in Wistar rats at doses of 0, 15, 50, 150 and 500 mg/kg bw/day. Adverse effects included a reduction in mean body weights, increased liver and spleen weights accompanied by changes in clinical chemistry and haematological parameters.

The NOAEL of 50 mg/kg bw/day will be used for human risk assessment of the related EFA I and EFA III substances.

No reliable data for repeated exposure by inhalation or dermal routes were available for the substances or analogues.

49.6.6 *Genotoxicity*

No data were found for EFA I and EFA III however several well documented *in vitro* and *in vivo* genotoxicity assays for AEs were negative.

QSAR modelling using OASIS-TIMES predicted negative results for *in vitro* and *in vivo* genotoxicity.

Based on these results, it was concluded that there is no evidence that EFA I and EFA III are likely to be genotoxic.

49.6.7 *Carcinogenicity*

Based on the available analogue data for two chronic feeding studies in rats, EFA I and EFA III are not considered to be carcinogenic.

49.6.8 *Reproductive toxicity*

No information was found for EFA I and EFA III; however, reliable analogue data for reproductive toxicity were available.

AE analogues have no demonstrated fertility effects in rats and no developmental effects in rats and rabbits. EFA I and EFA III are not reproductive toxicants based on this supporting data.

49.7 Health hazard summary

49.7.1 *Critical health effects*

Very little information is available for EFA I and EFA III. For the purpose of hazard assessment, it is assumed that the effects observed in tests with the closely related AE analogues demonstrate the likely toxicological profile of both substances.

Based on data available for AEs, the substances have low to moderate acute oral toxicity and low dermal and inhalation toxicity. They cause skin irritation in animals and are a severe eye irritant. EFA III was not found to be a skin sensitiser and it is likely that EFA I is also not a skin sensitiser.

Reliable repeated dose oral studies indicated effects on body and organ weights in rats. A NOAEL of 50 mg/kg bw/d for systemic toxicity was determined in a 90-day study with an AE analogue based on reduced body-weight gain, increased liver and spleen weights, and changes to clinical chemistry and haematological parameters. This NOAEL will be used for human risk assessment of both substances.

The AEs are not genotoxic or carcinogenic, or reproductive toxicants. EFA I and EFA III, based on data for the AEs, are not genotoxic, carcinogenic, or reproductive toxicants.

49.7.2 *Hazard classification*

Based on the above studies, EFA I and EFA III are recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A49.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A49.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Acute toxicity	Harmful if swallowed (X_n; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation/ Corrosivity	Irritating to skin (X_i; R38) Risk of serious eye damage (X_i; R41)	Causes skin irritation – Cat. 2 (H315) Causes serious eye irritation – Cat. 1 (H318)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

49.8 References

ChemID*plus* (2012) Accessed in February 2014 at http://chem.sis.nlm.nih.gov/chemidplus/

HERA (2009) Human and Environmental Risk Assessment on ingredients of household cleaning products (alcohol ethoxylates). Version 2, September 2009. Accessed in January 2014 at: http://www.heraproject.com/files/38-F-Hera_Bridging_document_28.10.05.pdf

NHMRC (2011) Australian Drinking Water Guidelines 6 2011. National Health and Medical Research Council. http://www.nhmrc.gov.au/guidelines/publications/eh52

NICNAS (2017a) Identification of chemicals associated with coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NICNAS (2017b) Human health hazards of chemicals used in coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. National Occupational Health and Safety Commission.

OECD (2013) OECD QSAR Toolbox version 3.1. Organisation for Economic Co-operation and Development.

Safe Work Australia (2013) Hazardous Substances Information System. http://hsis.safeworkaustralia.gov.au/HazardousSubstance. Accessed in February 2014.

TGA (2014) Poisons Standard 2014. Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Therapeutic Goods Administration.

UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe, New York and Geneva. Accessed in June 2013 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

US EPA (2012) Analog Identification Methodology. United States Environmental Protection Agency.

US EPA Report on Skin Sensitizing Effects with Ethoxylated Fatty Acids in Guinea Pigs. United States Environmental Protection Agency, Office of Toxic Substances.

US FDA (2013) Pesticide Inert Ingredient Database InertFinder. Food Use tolerance information (40 CFR Part 180).

A50 Ethoxylated fatty acid II

CAS No.	Chemical Name
CBI	Ethoxylated fatty acid II

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemical has been conducted.

A summary of the assessment findings is presented below.

50.1 Chemical identity

Ethoxylated fatty acid II is considered as a substance of unknown or variable composition, complex reaction products or biological materials (UVCB), having a biological origin.

Information on substance identity was obtained from a safety assessment by a Cosmetic Ingredient Review (CIR) expert panel (CIR a). Details are provided in Table A50.1.

Table A50.1 Substance identity

	Ethoxylated fatty acid II
Appearance and odour	Light yellowish viscous liquid with a mild fatty odour

50.2 Physical properties

The physical properties of the substance are presented in Table A50.2. The information was obtained from the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013).

Table A50.2 Physical properties

Property	Value
Freezing point	<0 °C
Boiling point	>100 °C at 96.0 kPa >200 °C at 99.5 kPa
Bulk density	<1000 kg/m^3 at 23 °C >1000 kg/m^3 at 30 °C
Vapour pressure	<0.1 kPa at 20 °C
Water solubility	>10 g/L at 23 °C <100 g/L at 30 °C

Property	Value
Partition coefficient n-octanol/water (log K_{ow})	1-2 at 23°C and pH 5.69 0-1 at 30°C and pH 7
Flash point	>100 °C at 96.0 kPa >400 °C at 99.5 kPa

50.3 Current regulatory controls

The document from here on refers to ethoxylated fatty acid II as the 'substance'.

50.3.1 *Hazard classification for occupational health and safety*

The substance is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

50.3.2 *Occupational exposure standards*

50.3.2.1 Australia

No specific exposure standards were available.

50.3.2.2 International

No specific exposure standards were available.

50.3.3 *Australian food standards*

No Australian food standards were identified.

50.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the substance in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

50.3.5 *Additional controls*

50.3.5.1 Australia

The substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

50.3.5.2 International

No international restrictions were identified.

50.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

50.5 Health hazard characterisation

Information on health hazards was obtained from the CIR final report on the safety assessment of the substance (CIR a), a CIR amended safety assessment of the substance as used in cosmetics (CIR b), and the REACH Dossier for the substance (REACH 2013).

50.5.1 *Toxicokinetics*

No data were available for the substance.

For the purposes of risk assessment, 100% absorption via the oral, dermal and inhalation routes in humans is assumed.

50.5.2 *Acute toxicity*

The substance was shown to have low acute oral toxicity (median lethal dose (LD50) >2000 and >10 000 mg/kg bw) in two rat studies.

There were no data on the dermal and inhalation toxicity of the substance.

50.5.3 *Irritation / Corrosivity*

50.5.3.1 Skin irritation

In two studies, slight irritation was reported after application of the undiluted substance to the skin of rabbits. No irritation was observed after multiple applications of a microemulsion containing the substance to the skin of guinea pigs.

50.5.3.2 Eye irritation

The substance is slightly irritating at 50% in rabbit eyes but not irritating at 13% and 30%.

50.5.3.3 Observation in humans

Patch testing of a 30% aqueous solution of the substance on 20 individuals reported no signs of irritation after 48 hours.

50.5.4 *Sensitisation*

There was no evidence of sensitisation noted in two guinea pig tests.

Two cases of eczema were reported following patch testing of a cream containing up to 1% of the substance. A control group of 10 individuals showed negative reactions.

50.5.5 *Repeat dose toxicity*

There were no treatment-related effects from the dietary administration of the substance to rats and dogs at doses up to 5%. Effects on organ weights, haematology and clinical chemistry were observed from the drinking water administration of the substance to mice at 10%.

There were no data on the dermal and inhalation repeated dose toxicity of the substance.

50.5.6 *Genotoxicity*

The substance was negative in a dominant lethal test, two micronucleus tests in mice, and a spermatogonial test in Chinese hamsters. It was also negative in a chromosomal aberration assay using Chinese hamster ovary cells and sperm head abnormality assays in mice.

50.5.7 *Carcinogenicity*

Rats administered 10% substance by gavage over 26 weeks showed a minimal number of neoplasms in tissues including within the liver, pituitary gland, prostate, testis, pancreas, spleen, and adrenal gland. However, the normal range of occurrence of the tumours in the historical database was not reported.

No neoplastic response was seen in female mice after administration of a 2% solution of the substance in a lung adenoma assay.

Based on the available data, the substance is not considered to be carcinogenic.

50.5.8 *Reproductive toxicity*

There was no evidence of treatment-related developmental toxicity from the oral administration of the substance to mice at doses up to 11%.

50.5.9 *Other health effects*

50.5.9.1 Nephrotoxicity

Several nephrotoxicity studies of a drug with the substance as a vehicle were evaluated. Vasoconstriction, reduced renal blood flow and glomerular filtration rate were reported in an isolated perfused rat kidney model in rats. Development of crystals in the proximal tubules of rats (but not rabbits) was observed from intravenous administration.

50.6 Health hazard summary

50.6.1 *Critical health effects*

The substance has low acute oral toxicity, is a slight skin irritant, is not irritating to the eye at 30% but is a slight eye irritant at 50%. Based on slight irritation at 50%, the substance is likely to be an eye irritant at 100%. The substance is not a skin sensitiser.

A No Observed Adverse Effect Level (NOAEL) was not established in any of the repeat dose studies. The oral administration of the substance reported no significant effects at doses up to 5% (equivalent to 7143 mg/kg bw/day). The intravenous administration of the substance resulted in changes in lipid and lipoprotein values, and build-up of lipid in the spleen, lymph nodes, liver, and kidneys of dogs; while these effects were not observed in rabbits.

The substance was not genotoxic, carcinogenic, or a developmental toxicant.

50.6.2 *Hazard classification*

Although the substance is likely to be an eye irritant at 100%, data were insufficient to be able to classify for this endpoint. The substance is not recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009).

50.7 References

CIR (a) Cosmetic Ingredient Review Expert Panel Final report on the safety assessment of the substance.

CIR (b) Amended safety assessment of the substance as used in cosmetics. Cosmetic Ingredient Review Expert Panel.

NHMRC (2011) Australian Drinking Water Guidelines 6 2011. National Health and Medical Research Council. Accessed in September 2013 at http://www.nhmrc.gov.au/guidelines/publications/eh52

NICNAS (2017a) Identification of chemicals associated with coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NICNAS (2017b) Human health hazards of chemicals used in coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. National Occupational Health and Safety Commission.

REACH (2013) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier on the substance. Accessed 17 September 2013 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Safe Work Australia (2013) Hazardous Substances Information System. http://hsis.safeworkaustralia.gov.au/HazardousSubstance. Accessed 17 September 2013.

TGA (2014) Poisons Standard 2014. Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Therapeutic Goods Administration.

UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe, New York and Geneva. Accessed in June 2013 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

A51 Fatty acids ester

CAS No.	Chemical Name
CBI	Fatty acids ester

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) Number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemical has been conducted.

A summary of the assessment findings is presented below.

51.1 Chemical identity

Fatty acids ester is considered a substance of unknown or variable composition, complex reaction products or biological materials (UVCB), being a complex product of a chemical reaction. The substance is composed of a mixture of five fatty acid esters ranging in molecular weight from 200 to 400 Da (Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) 2013a).

The information on chemical identity was obtained from a report by NICNAS. Details are provided in Table A51.1.

Table A51.1 Chemical identity

	Fatty acids ester
Appearance	Clear, colourless to slightly yellow liquid

51.2 Physical properties

The following information on physical properties was obtained from REACH (2013a) and NICNAS and is provided in Table A51.2.

Table A51.2 Physical properties

Property	Value
Melting point	<0 °C
Boiling point	>300 °C
Density	<1000 kg/m^3 (20 °C)
Vapour pressure	<1 x 10-4 kPa (38 °C)
Water solubility	<0.01 g/L (20 °C)
Partition coefficient (log Kow)	>6
Flash point	>100 °C

51.3 Current regulatory controls

The document from here on refers to fatty acids ester as the 'substance'.

51.3.1 *Hazard classification for occupational health and safety*

The substance or its chemical constituents are not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

51.3.2 *Occupational exposure standards*

51.3.2.1 Australia

No specific exposure standards were available for the substance or the chemical constituents.

51.3.2.2 International

No specific exposure standards were available for the substance or the chemical constituents.

51.3.3 *Australian food standards*

No Australian food standards were identified for the substance or the chemical constituents.

51.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the substance or the chemical constituents in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

51.3.5 *Additional controls*

51.3.5.1 Australia

The substance or the chemical constituents are not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

51.3.5.2 International

No specific controls were available.

51.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

51.5 Health hazard characterisation

The information on health hazards of the substance was sourced primarily from a report by NICNAS and a dossier submission for the substance (REACH 2013a).

Information was also available on two of the five chemical constituents of the substance. The health hazards of Constituent 1 were sourced from an IUCLID dataset (European Commission (EC)) and a dossier submission for the chemical (REACH 2013b). For Constituent 2, a Cosmetics Ingredient Review (CIR) safety assessment and a dossier submission for the chemical (REACH 2013c) was available.

Information available for the substance, Constituent 1 and Constituent 2 is presented in Table A51.3. Accordingly, the data gaps for the substance are filled by reading across data available for Constituent 1 and Constituent 2. However, noting that the substance is fully synthetic rather than being derived from natural sources, the proportions of the two constituents in the substance are not known.

Table A51.3 Summary of available toxicity endpoint data

	Fatty acids ester	**Constituent 1**	**Constituent 2**
Acute oral toxicity	✓	✓	✓
Acute dermal toxicity	×	✓	✓
Acute inhalation toxicity	×	✓	×
Skin irritation	✓	✓	✓
Eye irritation	✓	✓	✓
Respiratory irritation	×	×	×
Skin sensitisation	✓	✓	✓
Respiratory sensitisation	×	×	×
Repeat dose toxicity (oral)	✓	✓	×
Repeat dose toxicity (dermal)	×	×	✓
Repeat dose toxicity (inhalation)	×	×	×
Genotoxicity *in vitro*	✓	✓	×
Genotoxicity *in vivo*	✓	✓	×
Carcinogenicity	×	×	×
Fertility toxicity	×	×	×
Developmental toxicity	×	×	✓

✓Existing data point; × Missing data point

51.5.1 *Toxicokinetics*

No data were available for the substance or chemical constituents.

For the purposes of risk assessment for the chemical, 100% absorption via the oral and inhalation routes in humans is assumed.

Based on the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Application Toolbox estimates, the dermal absorption of three constituents of the substance were calculated to be extremely low. It was also noted that the substance is highly hydrophobic (log K_{ow} >6). On this basis, 10% dermal absorption of the substance in humans is assumed.

51.5.2 *Acute toxicity*

51.5.2.1 Oral

The substance was shown to have low acute oral toxicity (median lethal dose (LD50) >2000 mg/kg bw) in a study conducted in rats. Supporting data were available for the chemical constituents, with LD50 values of >2000 mg/kg bw for Constituent 1 and >5000 mg/kg bw for Constituent 2.

51.5.2.2 Dermal

No data were available for the substance.

The dermal LD50 for Constituent 1 and Constituent 2 were reported to be >3000 mg/kg bw in rats and >8.1 g/kg bw in rabbits, respectively.

These data for the two constituent chemicals indicate a likely low acute toxicity for the substance by the dermal route.

51.5.2.3 Inhalation

No data were available for the substance.

An acute inhalation median lethal concentration (LC50) for Constituent 1 in rats of >230 mg/L indicates that the substance is not likely to be toxic via the inhalation route.

51.5.3 *Irritation / Corrosivity*

51.5.3.1 Skin irritation

In a study in rabbits, the undiluted substance caused, at most, slight irritation (erythema and oedema) to the skin with similar effects seen for Constituent 1 and Constituent 2 in separate studies.

Overall, the effects observed in these studies demonstrate the likely low irritancy potential of the substance to the skin.

51.5.3.2 Eye irritation

No data were available for the substance.

In a study in rabbits, undiluted Constituent 1 produced slight conjunctival redness. Similarly, in three separate studies, undiluted Constituent 2 was, at most, minimally irritating to the eye.

The substance is not an eye irritant based on rabbit data available for the two tested constituents.

51.5.3.3 Observation in humans

A primary irritation patch test conducted on 20 volunteers using a 24-hour occluded application at concentrations of 25%, 50% or 100% substance showed slight, transient erythema with the undiluted substance, with an apparent smaller incidence of moderate erythema and slight oedema.

51.5.4 *Sensitisation*

There was no evidence of sensitisation for the substance, Constituent 1 or Constituent 2 in separate guinea pig maximisation tests.

In a repeat insult patch test conducted in 20 volunteers, no dermal irritant effects were reported after daily 24-hour exposures to a 46% Constituent 1 formulation. The substance is not considered to be a skin sensitiser based on these studies.

51.5.5 *Repeat dose toxicity*

There were no treatment-related effects from the 28-day gavage administration of the substance, or Constituent 1, to rats at doses up to 1000 mg/kg bw/day.

Similarly, no systemic effects were observed in a six-week dermal study in rats exposed daily to Constituent 2 at a dose equivalent to 860 mg/kg bw/day.

51.5.6 *Genotoxicity*

The substance and Constituent 1 were negative in separate Ames tests both in the presence and absence of metabolic activation. The substance and Constituent 1 were not clastogenic in mice in separate *in vivo* erythrocyte micronucleus tests.

51.5.7 *Carcinogenicity*

No data were available for the substance or its constituents.

51.5.8 *Reproductive toxicity*

No data were available for the substance or pure constituents; however, a developmental toxicity study was available for a UVCB that comprised a ‘substantial variable degree’ of Constituent 2 in addition to a close structural analogue. In this study, female rats were administered the UVCB on gestation days 6 to 15 via oral gavage at doses up to 1000 mg/kg bw/day. No adverse substance-related effects were reported in dams or foetuses at any dose.

51.6 Health hazard summary

51.6.1 *Critical health effects*

Fatty acids ester demonstrates low acute oral toxicity. Based on data available for two constituents, the chemical also has low acute toxicity by dermal and inhalation routes. It is not irritating to the skin and is not a skin sensitiser. Data available for two constituents indicate that the substance is unlikely to be an eye irritant.

In an oral repeat dose toxicity test, the substance was well tolerated and a No Observed Adverse Effect Level (NOAEL) could not be established for local or systemic effects. No adverse effects were observed at the highest dose tested (1000 mg/kg bw/day) in the critical 28-day gavage study of the substance in rats. Similarly, a NOAEL could not be derived in repeat dose tests via the oral and dermal route for Constituent 1 and Constituent 2 respectively.

The chemical is not genotoxic and, based on test data for a related UVCB (which contained unspecified quantities of Constituent 2) is not likely to be a developmental toxicant. This is despite a metabolite of fatty acids ester being reported to cause developmental toxicity in rats. This indicates that toxicokinetic factors are limiting any health impacts of the metabolite.

51.6.2 *Hazard classification*

The substance is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) and is not recommended by NICNAS to Safe Work Australia for classification as hazardous under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and under the Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009). Classification for physical or environmental hazards has not been considered.

51.7 References

EC European Commission: European chemical Substances Information System (ESIS). IUCLID Dataset for constituent 1, European Chemicals Bureau. Accessed November 2013 at: http://esis.jrc.ec.europa.eu/

CIR Cosmetic Ingredient Review Expert Panel Final Report on the Safety Assessment of three chemicals.

NHMRC (2011) Australian Drinking Water Guidelines 6 2011. National Health and Medical Research Council. Accessed in November 2013 at http://www.nhmrc.gov.au/guidelines/publications/eh52

NICNAS Report for the substance. National Industrial Chemicals Notification and Assessment Scheme.

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NOHSC (2004) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. National Occupational Health and Safety Commission.

REACH (2013a) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier on the substance. Accessed November 2013 at: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

REACH (2013b) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier on constituent 2. Accessed November 2013 at: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

REACH (2013c) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier on constituent 3. Accessed November 2013 at: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Safe Work Australia (2013) Hazardous Substances Information System. http://hsis.safeworkaustralia.gov.au/HazardousSubstance. Accessed 28 May 2013.

TGA (2014) Poisons Standard 2014. Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Therapeutic Goods Administration.

UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe,

New York and Geneva. Accessed in June 2013 at
http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

A52 Inner salt of alkyl amines

CAS No.	Chemical Name
CBI	Inner salt of alkyl amines

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) Number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name (inner salt of alkyl amines) and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemical has been conducted.

A summary of the assessment findings is presented below.

52.1 Chemical identity

The information on chemical identity was obtained from a Cosmetic Ingredient Review (CIR) of the chemical and the United States Environmental Protection Agency (US EPA). Details are provided in Table A52.1.

Table A52.1 Chemical identity

	Inner salt of alkyl amines
Molecular weight	<400
Appearance and odour	Clear pale yellow liquid with a slight fatty odour

52.2 Physical properties

The physical properties of the chemical are presented in Table A52.2. The information was obtained from the US EPA.

Table A52.2 Physical properties

Property	Value
Boiling point	>300 °C
Vapour pressure	<1 x 10^{-10} kPa at 25 °C
Water solubility	Dispersible at 25 °C
Partition coefficient n-octanol/water (log K_{ow})	Not applicable

In addition, information for a cosmetic grade product (>60% water content) containing the chemical is available from the CIR and presented in Table A52.3.

Table A52.3 Additional physical properties

Property	Value
Boiling point	>100 °C
Density	>1000 kg/m^3 at unspecified temperature
Water solubility	>100 g/L at 25 °C

52.3 Current regulatory controls

52.3.1 *Hazard classification for occupational health and safety*

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

52.3.2 *Occupational exposure standards*

52.3.2.1 Australia

No specific exposure standards were available.

52.3.2.2 International

No specific exposure standards were available.

52.3.3 *Australian food standards*

No Australian food standards were identified.

52.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

52.3.5 *Additional controls*

52.3.5.1 Australia

The specific chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014); however it is a member of a category of compounds that are listed in Schedules 5 and 6.

52.3.5.2 International

No international restrictions were identified.

52.4 Use

The use of the chemical in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

52.5 Health hazard characterisation

The information on health hazards is obtained from the following comprehensive reviews of the chemical:

- CIR
- screening level hazard characterisation of chemicals by the US EPA
- from data submitted by the American Chemistry Council
- the Organisation for Economic Co-operation and Development (OECD) assessment of the chemical category.

52.5.1 *Toxicokinetics*

No data were available. However, due to the low molecular weight (<400 Da) of the chemical, dermal absorption may occur. Acute oral toxicity studies describe systemic effects following administration of 30% chemical indicating that it is absorbed in the gastrointestinal tract.

For the purposes of risk assessment for the chemical, 100% absorption via the oral, dermal and inhalation routes in humans is therefore assumed.

52.5.2 *Acute toxicity*

The chemical was shown to have low acute oral toxicity (LD50s 1500 to 2600 mg/kg bw) in four studies conducted in rats (US EPA) and (LD50s >1800 to 7970 mg /kg bw) in other studies conducted in rodents (CIR).

The chemical has low acute dermal toxicity in rats.

There were no data on the inhalation toxicity of the chemical.

52.5.3 *Irritation / Corrosivity*

52.5.3.1 Skin irritation

In several reliable studies, the chemical at a concentration of 30%, was found to be slightly irritating to the skin of rabbits (OECD).

52.5.3.2 Eye irritation

In 13 reliable studies, the chemical at concentrations of 2 to 80%, was shown to be a moderate to severe eye irritant in rabbits (OECD).

52.5.3.3 Observation in humans

A primary irritation patch test conducted on 10 volunteers using a daily occluded application at a concentration of 1.9% chemical in a soap formulation showed signs of irritation (CIR). In a separate study, the chemical was non-irritating at a concentration of 0.52% (CIR).

The chemical is a skin irritant in humans.

52.5.4 *Sensitisation*

52.5.4.1 Skin sensitisation

There was no evidence of delayed contact hypersensitivity to the chemical in guinea pigs at levels up to 10% but other tests showed that the chemical was a sensitiser at a concentration of 30% (CIR). A Local Lymph Node Assay (LLNA) with the chemical was positive for sensitisation but no other details were provided (CIR).

The chemical is not considered to be a skin sensitiser in animals.

52.5.4.2 Observation in humans

Five patch tests of 1% aqueous solution of the chemical reported up to 7.2% positive reaction (CIR). Six human repeat insult patch tests (HRIPT) showed no sensitisation effects at levels up to 6% of the chemical (CIR). Case studies of individuals already sensitised to the chemical showed reactions to 1% aqueous solution (CIR).

The chemical is not considered to be a skin sensitiser in humans.

52.5.5 *Repeat dose toxicity*

In a 90-day oral (gavage) study in rats, a 30% aqueous solution of the chemical was administered at 0, 250, 500, or 1000 mg/kg bw/day (US EPA). The No Observed Adverse Effect level (NOAEL) for local effects was 250 mg/kg bw/day (75 mg/kg bw/day for the chemical) based on forestomach effects such as submucosal oedema, squamous hyperplasia, and inflammatory cell infiltration in the mid and top-dose groups. A NOAEL for systemic effects was not established in this study.

The same local irritant effects in the forestomach were observed at a higher dose (1000 mg/kg bw/day) in two 28-day gavage studies in rats (US EPA).

52.5.6 *Genotoxicity*

The chemical was negative in five Ames tests both in the presence and absence of metabolic activation (US EPA). There was no significant increase in the mutation frequency of the chemical at 30.9% concentration in a mouse lymphoma assay with and without metabolic activation.

52.5.7 *Carcinogenicity*

There was no evidence of carcinogenicity in mice dermally administered a formulation containing 0.09% of the chemical for 20 months.

52.5.8 *Reproductive toxicity*

Rats were administered 0, 95, 286, or 950 mg/kg bw/day of the chemical by gavage on gestation days 5 to19 (US EPA). Maternal effects observed at mid and top-doses included decreased bodyweight gain and stomach changes (including ulceration); the NOAEL for maternal toxicity was 95 mg/kg bw/day based on these effects. Developmental effects, observed at the highest dose only, were embryotoxicity (increased number of resorptions, decreased number of viable foetuses, and decreased foetal bodyweight) however these were considered to be secondary to maternal toxicity.

The chemical is not considered to cause developmental effects.

52.6 Health hazard summary

52.6.1 *Critical health effects*

The chemical has low acute oral and dermal toxicity. The chemical is a skin irritant in humans at 1.9% concentration from cumulative skin irritation tests, and is an eye irritant in animals. The chemical is not a skin sensitiser.

A NOAEL could not be established for systemic effects in the repeated dose toxicity studies at the highest dose tested of 1000 mg/kg bw/day. The most appropriate NOAEL for local effects is 75 mg/kg bw/day based on forestomach effects from a 90-day oral study.

The chemical is not genotoxic or carcinogenic based on the available data. It caused local effects in the dams in a developmental study in rats. The developmental effects observed at the highest dose only were considered to be secondary to maternal toxicity (US EPA).

52.6.2 *Hazard classification*

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A52.4. These NICNAS recommendations do not consider physical or environmental hazards.

Table A52.4 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation / Corrosivity	Irritating to eyes (X_i; R36)	Causes serious eye irritation – Cat. 2A (H319)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

52.7 References

CIR Cosmetic Ingredient Review Expert Panel Final Report on the Safety Assessment of the chemical.

NHMRC (2011) Australian Drinking Water Guidelines 6 2011. National Health and Medical Research Council. Accessed in May 2013 at http://www.nhmrc.gov.au/guidelines/publications/eh52

NICNAS (2017a) Identification of chemicals associated with coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NICNAS (2017b) Human health hazards of chemicals used in coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. National Occupational Health and Safety Commission.

OECD SIDS Initial Assessment Report for chemical category. Organisation for Economic Co-operation and Development Existing Chemicals Database. Accessed in May 2013 at http://webnet.oecd.org/hpv/ui/Search.aspx

Safe Work Australia (2013) Hazardous Substances Information System. Accessed in May 2013 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

TGA (2014) Poisons Standard 2014. Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Therapeutic Goods Administration.

UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe, New York and Geneva. Accessed in June 2013 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

US EPA Screening-level hazard characterization: chemical category. United States Environmental Protection Agency Hazard Characterization Document. Accessed in June 2010 at http://www.epa.gov/

A53 Organic acid salt

CAS No.	Chemical Name
CBI	Organic acid salt

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) Number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name (organic acid salt) and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemical has been conducted. Detailed hazard assessments of chemicals notified to NICNAS as Confidential Business Information (CBI) were conducted.

A summary of the assessment findings is presented below.

53.1 Chemical identity

Details of the chemical identity were obtained from the web-based database ChemID*plus* (2012). The chemical has a molecular weight of <500 Da.

53.2 Justification for data read-across

No information on the physical properties or health hazards of this particular chemical was available from published literature. However, peer reviewed data for related chemicals were available in an Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) Initial Assessment Profile (SIAP) (OECD 2007a) and report (SIAR) (OECD 2007b) for the chemical category Alkyl Sulfates, Alkane Sulfonates and -Olefin Sulfonates. In the absence of data specific for the chemical, data will be read-across from these related chemicals. Read-across is a technique used here to predict endpoint information for the untested organic acid salt by using data (for the same endpoint) from other tested chemicals in the category described which are considered to possess similar properties.

In this assessment, read-across is justified on the basis that the most important common structural feature of this anionic surfactant category is the presence of a linear aliphatic hydrocarbon chain with a polar sulphate or sulphonate group, neutralised with a counter ion (i.e. Na^+, K^+, NH_4^+, or an alkanolamine cation). The hydrophobic hydrocarbon chain and polar sulphate or sulphonate groups confer surfactant properties, enabling commercial uses of these substances as anionic surfactants. Close structural similarities confer similar physico-chemical properties, structurally similar metabolic products and similar human health hazard profiles (OECD 2007a).

The alkyl sulphate subgroup contains chemical mixtures of homologues with various hydrophobic chain lengths and cations. Where available, data were read-across from alkyl sulphates of similar chain lengths and the same cation as the assessed chemical.

In addition, Quantitative Structure-Activity Relationship (QSAR) modelling was conducted on specific endpoints such as sensitisation and genotoxicity for one of the components of the chemical using the predictive modelling tool OASIS-TIMES.

53.3 Physical properties

Data on the physical properties of the chemical were not available. The following modelled data (using EPI Suite) were provided for a close analogue (OECD 2007b) and are presented in Table A53.1.

Table A53.1 Physical properties

Property	Value
Melting Point	<300 °C
Boiling Point	<700 °C
Density	Data not available
Vapour pressure	<1 x 10^{-15} kPa at 25 °C
Water solubility	<1 x 10^{-3} g/L at 25 °C
Partition coefficient n-octanol/water (log K_{ow})	Not applicable for surfactants
Flash point	Data not available

53.4 Current regulatory controls

53.4.1 *Hazard classification for occupational health and safety*

The chemical is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

53.4.2 *Occupational exposure standards*

53.4.2.1 Australia

No specific exposure standards were available.

53.4.2.2 International

No specific international exposure standards were available.

53.4.3 *Australian food standards*

No Australian food standards were identified.

53.4.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

53.4.5 *Additional controls*

53.4.5.1 Australia

No additional controls were identified.

53.4.5.2 International

No additional controls were identified.

53.5 Use

The use of the chemical in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

53.6 Health hazard characterisation

53.6.1 *Toxicokinetics*

For the purposes of risk assessment, based on the observations for analogous compounds in animals and humans, 100% oral and 1% dermal absorption of the chemical in humans is assumed (OECD 2007b). No data were available for inhalation absorption. For human risk assessment purposes, an inhalation absorption of 100% is therefore assumed.

53.6.2 *Acute toxicity*

Acute oral toxicity studies are available for a large number of alkyl sulphates in the anionic surfactant chemical category, with appropriate chain lengths. Overall, data indicate that that these chemicals have low acute oral toxicity with LD50 values >1100 mg/kg bw (OECD 2007b). Also, the acute toxicity does not appear to be significantly influenced by the type of counter ion. Based on these data, the chemical is considered to have low acute oral toxicity.

Available acute dermal toxicity data for appropriate chain length alkyl sulphates in the anionic surfactant chemical category showed no mortality in dermal toxicity studies at the highest doses tested (>500 mg/kg bw) (OECD 2007b). Based on these data, the chemical is considered to have low acute dermal toxicity.

There were no data on the inhalation toxicity of the chemical.

53.6.3 *Irritation / Corrosivity*

53.6.3.1 Skin irritation

Skin irritation studies have been performed with alkyl sulphates of various chain lengths and with various counter ions (OECD 2007a). In concentrated form, alkyl sulphates are corrosive to the skin with irritant properties not significantly influenced by the type of counter-ion. Based on these data, the undiluted chemical is considered to be corrosive. A human repeated patch test of an analogue alkyl sulphate at a concentration of 20% produced moderate irritation.

53.6.3.2 Eye irritation

Eye irritation studies have been performed in rabbits with alkyl sulphates of various chain lengths and with various counter ions (OECD 2007a). Overall, alkyl sulphates of appropriate chain lengths were moderately to severely irritating at concentrations ≥10%. Based on these data, the undiluted chemical is considered to be a severe eye irritant.

53.6.4 *Sensitisation*

Alkyl sulphates of various chain lengths were tested in a number of guinea pig maximisation and Buehler tests (OECD 2007b). Across these studies, alkyl sulphates were shown not to be sensitising.

Positive results were reported for some alkyl sulphates in the Local Lymph Node Assay (LLNA), however, the observed positive reactions were regarded as a non-antigen-specific proliferative stimulus induced by the irritating effect of the tested concentrations (up to 25%).

QSAR modelling using OASIS-TIMES predicted negative results for skin sensitisation.

Based on these data, the chemical is not considered to be a skin sensitiser.

Alkyl sulphates tested negative in several human repeat insult patch tests at concentrations of up to 4% (OECD 2007b).

53.6.5 *Repeat dose toxicity*

53.6.5.1 Oral

Repeat dose toxicity studies in rats via the oral route have been conducted on alkyl sulphates with appropriate chain lengths (OECD 2007b). Overall, the liver appeared to be the primary target organ, with increases in liver weight, histological evidence of cellular enlargement and altered clinical chemistry parameters observed across several studies. Gastrointestinal irritation was observed after gavage but not dietary administration.

For the class of alkyl sulphates, regarded as having a chain length most analogous to the assessed chemical, a well-conducted study 13 week rat dietary study reported, in addition to liver hypertrophy, increased serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) and decreased serum cholesterol commencing at 482 mg/kg bw/day (OECD 2007b). At lower doses, the only liver effects reported were histological evidence of liver hypertrophy and increased serum ALP. Doses higher than 482 mg/kg bw/day were associated with additional changes in clinical chemistry (decreases in serum total protein, cholesterol, triglycerides, AST) as well as histological changes in the liver. A No Observed Adverse Effect Level (NOAEL) of 230 mg/kg bw/day, based on liver effects, was established and will be used for human risk assessment of the related organic acid salt.

53.6.5.2 Dermal

Dermal repeated dose toxicity data for the class of alkyl sulphates established a NOAEL of 400 mg/kg bw/day based on organ weight changes reported in mice treated twice weekly for 3 or 13 weeks at up to 600 mg/kg bw/day (OECD 2007b). At 400 mg/kg bw/day, epidermal hyperplasia was observed and at ≥500 mg/kg bw/day, epidermal cytotoxicity (ulceration) as well as changes in organ weights were observed.

53.6.6 *Genotoxicity*

Overall, the results of genotoxicity testing *in vitro* and *in vivo* on a variety of alkyl sulphates, as well as QSAR predictions, do not suggest these chemicals possess genotoxic potential (OECD 2007b). Based on this information, the chemical is not considered to be genotoxic.

53.6.7 *Carcinogenicity*

Two oral carcinogenicity studies have been conducted on an analogous alkyl sulphate salt (OECD 2007b). In both studies, rats were dosed via diet with up to 1125 mg/kg bw/day of the analogue for two years. No increase in tumour incidence or changes in spontaneous tumour types were observed. Animals administered the highest dose showed decreased food and water intake as well as decreased growth rates. In these groups, the total number of tumours and total number of rats with tumours was decreased, probably related to a decreased caloric intake.

Dermal carcinogenicity studies were not available for alkyl sulphates. However, separate two-year dermal carcinogenicity studies have been conducted in rats and mice for α-olefin sulphonates (OECD 2007b). Neither study reported evidence of carcinogenicity.

Based on this information, the chemical is not considered to be a carcinogen.

53.6.8 *Reproductive toxicity*

53.6.8.1 Fertility

No impairment of epididymal spermatozoa was seen in male mice fed an alkyl sulphate salt at a dose of either 1% for two weeks or 0.1% for six weeks (OECD 2007b). A NOAEL of 1000 mg/kg bw/day was derived.

Oral repeated dose studies of 13 weeks duration with three classes of alkyl sulphate salts reported no adverse effects on reproductive organs (OECD 2007b). At very high doses (≥1000 mg/kg bw/day) increases in relative (but not absolute) testes weights were noted in several studies. However, this effect was attributed to decreased body fat and body weight and not considered adverse.

53.6.8.2 Developmental toxicity

Several studies were available in rats, mice and rabbits examining the developmental effects of alkyl sulphates administered over gestation days 6 to 15 via oral gavage (OECD 2007b). Across studies, developmental effects were seen only at doses that caused significant maternal toxicity (decreased food intake, anorexia, weight loss, and death at doses between 300 and 500 mg/kg bw for rats and at 300 mg/kg bw/day for mice and rabbits). The principal developmental effects were increased foetal loss and increased incidences of total litter losses. Increased incidences of skeletal variations were also reported in some studies (OECD 2007b).

On the basis of developmental effects only associated with maternal toxicity, no NOAELs for developmental toxicity were established.

53.7 Health hazard summary

53.7.1 *Critical health effects*

No health hazard data were available for the organic acid salt. However, data were available for the chemical category Alkyl Sulfates, Alkane Sulfonates and α-Olefin Sulfonates. On the basis of structural similarity, the data for this chemical group, and in particular alkyl sulphates

in this group with similar chain lengths to the assessed chemical, were read-across to the chemical.

The chemical is considered to be well absorbed via the oral route, and poorly absorbed by the dermal route. Data were unavailable regarding inhalation absorption, but alkyl sulphates are expected to be well absorbed also via this route.

Based on available studies of alkyl sulphates of similar chain length, the chemical is of low acute oral and dermal toxicity. In general, alkyl sulphates are corrosive to the skin in concentrated form and irritant properties appear not to be significantly influenced by the type of counter-ion. Accordingly, the chemical is considered to be corrosive to the skin.

A defined chain length class of alkyl sulphates at concentrations ≥10% were severe eye irritants, causing irreversible corneal effects. Irritant properties decreased with increasing alkyl chain length. Other classes of alkyl sulphates were moderately irritating to the eye at a concentration of 25% and still moderately irritating at 5%. The chemical is considered to be a severe eye irritant.

Alkyl sulphates are not regarded as skin sensitisers. Positive results in some LLNA were attributed to irritation and not allergic responses. The chemical is not considered to be a skin sensitiser.

In repeat dose toxicity studies of alkyl sulphates, the liver appeared to be the primary target organ, with increases in liver weight, cellular enlargement, and elevated levels of liver enzymes and changes in other clinical chemistry parameter observed consistently. For defined chain length alkyl sulphates, and by read-across to the chemical, a NOAEL for repeat dose toxicity was established at 230 mg/kg bw/day from a 13 week rat feeding study on an analogue alkyl sulphate. This NOAEL will be used for human health risk assessment.

Genotoxicity testing *in vitro* and *in vivo* did not suggest alkyl sulphates possess genotoxic potential. In addition, available oral studies for alkyl sulphates and dermal studies for appropriate α-olefin sulphonates did not report evidence of carcinogenicity. Similarly, the chemical is not considered a genotoxin or carcinogen.

Available studies do not show evidence of fertility or developmental toxic effects in the absence of maternal toxicity.

53.7.2 *Hazard classification*

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) under the Approved Criteria and adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A53.2. These NICNAS recommendations do not consider physical or environmental hazards.

Table A53.2 Hazard classification by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage – Cat. 1C (H314)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

53.8 References

ChemID*plus* (2012) Accessed in February 2014 at http://chem.sis.nlm.nih.gov/chemidplus/

NHMRC (2011) Australian Drinking Water Guidelines 6 2011. National Health and Medical Research Council. Accessed in February 2014 at http://www.nhmrc.gov.au/guidelines/publications/eh52

NICNAS (2017a) Identification of chemicals associated with coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NICNAS (2017b) Human health hazards of chemicals used in coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. National Occupational Health and Safety Commission.

OECD (2007a) SIDS Initial Assessment Profile for SIAM 25. Alkyl Sulfates, Alkane Sulfonates and α-Olefin Sulfonates.

OECD (2007b) SIDS Initial Assessment Report for SIAM 25. Alkyl Sulfates, Alkane Sulfonates and α-Olefin Sulfonates.

Safe Work Australia (2013) Hazardous Substances Information System (HSIS). Accessed in February 2014 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe, New York and Geneva. Accessed in June 2013 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

A54 Organic sulfate

CAS No.	Chemical Name
CBI	Organic sulfate

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) Number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemical has been conducted.

A summary of the assessment findings is presented below.

54.1 Chemical identity

The chemical belongs to a widely used class of anionic surfactants called alcohol ethoxysulphates. They are synthesised by the ethoxylation of alcohol followed by sulfation of the product and neutralisation to form sodium or ammonium salts. The basic structure of alcohol ethoxysulphates is $CH_3(CH_2)_nO(CH_2CH_2O)_mSO_3NH^+$, where n is the carbon chain length and m depicts the extent of ethoxylation of the alcohol ethoxysulphate (AES) molecule as the number of ethylene oxide units in the molecule (Human and Environmental Risk Assessment (HERA) 2003).

The identity information was obtained from HERA (2003). A description of the chemical identity is provided in Table A54.1.

Table A54.1 Chemical identity

	Organic sulfate
Molecular weight	>200
Appearance and odour	Clear pale yellow liquid with a characteristic odour

54.2 Physical properties

The physical properties of the substance are presented in Table A54.2. The information was obtained from HERA (2003).

Table A54.2 Physical properties

Property	Value
Boiling point	<100 °C
Bulk density	<1100 kg/m^3 at 20 °C
Vapour pressure	Not available
Water solubility	Soluble

Property	Value
Partition coefficient n-octanol/water (log K_{ow})	Not applicable as substance is a surfactant

54.3 Current regulatory controls

54.3.1 *Hazard classification for occupational health and safety*

The substance is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

54.3.2 *Occupational exposure standards*

54.3.2.1 Australia

No specific exposure standards were available.

54.3.2.2 International

No specific exposure standards were available.

54.3.3 *Australian food standards*

No Australian food standards were identified.

54.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the substance in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

54.3.5 *Additional controls*

54.3.5.1 Australia

The substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

54.3.5.2 International

No international restrictions were identified.

54.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports; Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

54.5 Health hazard characterisation

Toxicology information on the specific substance is not available. Toxicological information for alcohol ethoxysulphates (with appropriate carbon chain lengths, counter ions and numbers of ethoxy units) is available and is used to read-across for toxicity of the substance (HERA 2003; other confidential sources). Read-across is a technique used here to predict endpoint information for the untested organic sulfate by using data (for the same endpoint) from alcohol ethoxysulphates which are considered to possess similar properties.

54.5.1 *Toxicokinetics*

For the purposes of risk assessment, based on the observations for analogous compounds in animals and humans, 100% oral and 5% dermal absorption of the substance in humans is assumed (HERA 2003). No data were available for inhalation absorption. For human health risk assessment purposes, an inhalation absorption of 100% is therefore assumed.

54.5.2 *Acute toxicity*

Acute oral toxicity studies in rats are available for alcohol ethoxysulphates with appropriate chain lengths (HERA 2003). Overall, data indicate that that these chemicals have low acute oral toxicity with LD50 values >1700 mg/kg bw. Based on these data, the substance is considered to have low acute oral toxicity.

Available acute dermal toxicity data for appropriate chain length alcohol ethoxysulphates showed no mortality in dermal toxicity studies at the highest doses tested (≥2000 mg/kg bw) (HERA 2003). Based on these data, the substance is considered to have low acute dermal toxicity.

There are no data on the inhalation toxicity of the substance. A limited study of a related alcohol ethoxysulphate salt indicated no mortality at a high dose level (HERA 2003). Based on this result, the substance is considered to have low acute toxicity by the inhalation route.

54.5.3 *Irritation / Corrosivity*

Skin irritation studies have been conducted in rabbits to evaluate the potential for alcohol ethoxysulphates of various chain lengths to cause skin irritation (HERA 2003). Results indicated that alcohol ethoxysulphates at concentrations higher than 70% were moderately to severely irritating to rabbit skin. Based on these observations, the substance is considered as a severe skin irritant.

Various undiluted alcohol ethoxysulphates were determined to be severe eye irritants in rabbits causing extensive corneal damage, haemorrhage of the iris and maximal conjunctival irritation in tests done according to the Draize procedure (HERA 2003). Therefore the substance is also considered to be severely irritating to the eyes.

Primary irritation patch tests were conducted in human volunteers using 24-hour occluded application of alcohol ethoxysulphates at concentrations of 0.1% and 11.4% (HERA 2003). No skin effects were seen in any of the tests at the lower concentration but a mild skin irritant effect was noted at 11.4%.

54.5.4 *Sensitisation*

Several skin sensitisation studies were conducted for AES, according to both the Buehler method and the Magnusson-Kligman protocol (HERA 2003). From these studies, it is concluded that AES C10-16 ammonium salt does not have skin sensitisation potential.

Alcohol ethoxysulphates of various chain lengths were tested in a number of guinea pig maximisation and Buehler tests (HERA 2003). Across these studies, the chemicals were shown not to be sensitising. From these studies, it is concluded that the substance does not have a skin sensitisation potential.

Alcohol ethoxysulphates tested negative in two human repeat insult patch tests at concentrations of 0.0185% and 0.012%.

54.5.5 *Summary of acute toxicity*

Studies with some members of the alcohol ethoxysulphates class of chemicals indicated that the substance has low acute oral, dermal and inhalation toxicity. It is a severe skin and eye irritant. Information on the respiratory irritant potential is not available, however it is likely to be a respiratory irritant. The substance is considered to be non-sensitising to skin based on animal and human tests with other closely related alcohol ethoxysulphates.

54.5.6 *Repeat dose toxicity*

Several repeat oral toxicity studies with alcohol ethoxysulphates of appropriate chain lengths are reported (HERA 2003).

In two separate 90-day studies, alcohol ethoxysulphates were tested at dose levels of 0, 40, 200, 1000 and 5000 ppm. For one of the compounds at the top dose, total serum protein was increased (males) and liver, kidney and testes weights significantly increased (both sexes). Both ethoxysulphates increased kidney weight in males. These increases were not accompanied by histological, clinical, chemical or haematological changes and were therefore considered to be adaptive in nature and not a toxic effect of the compound by the authors. A No Observed Effect Level (NOEL) or No Observed Adverse Effect Level (NOAEL) was not indicated by the authors, but based on the available information and taking a conservative approach, the NOAEL is considered to be 1000 ppm (equivalent to 50 mg/kg/day).

In another 90-day gavage study with an alcohol ethoxysulphate, no systemic treatment-related effects were observed although local effects were seen in the forestomach including hyperplasia, submucosal oedema and chronic ulceration in the highest dose group. Since there is no human equivalent to the rat forestomach, these effects are not considered to be relevant to human health assessment and a NOAEL was not determined.

No systemic toxicity was noted in two separate two-year chronic feeding studies in rats in which an alcohol ethoxysulphate was given at a concentration up to 0.5% in the diet. A NOAEL could not be established in any of the studies.

No adverse systemic effects were observed in a 91-day dermal toxicity study of rabbits administered two dishwashing detergents containing an alcohol ethoxysulphate at 23% and 27%. No NOAEL was established for dermal repeat dose toxicity.

54.5.7 *Genotoxicity*

Results of genotoxicity testing *in vitro* and *in vivo* on a variety of alcohol ethoxysulphates do not suggest these chemicals possess genotoxic potential. A structure activity analysis did not reveal any functional groups in the chemical structure of alcohol ethoxysulphates that were associated with mutagenic or genotoxic properties. It was concluded that there is no evidence that alcohol ethoxysulphates were either mutagenic or genotoxic (HERA 2003). Based on this information, the substance is not considered to be genotoxic.

54.5.8 *Carcinogenicity*

In two chronic oral studies with an alcohol ethoxysulphate, rats were administered the compound in either the drinking water at a concentration of 0.1% or in the diet at 0, 0.1 or 0.5% for two years (HERA 2003). No evidence of carcinogenicity was noted in these analogue studies and therefore the substance is also considered not to have a carcinogenic potential.

54.5.9 *Reproductive toxicity*

54.5.9.1 Fertility

In a two-generation reproduction toxicity study, rats were dosed with an alcohol ethoxysulphate via drinking water at concentrations of 0.03, 0.1 and 0.3% (corresponding to approximately 0, 30, 100 and 300 mg/kg/day) (HERA 2003). There were some indications of parental toxicity at the 0.3% dose, characterised by reduced straight line velocity of the sperm. Decreased liver weights of the F0 and F1 male dose groups were observed which was not confirmed in the F2 generation dose group. The authors concluded that there was no effect of treatment at any dose level on reproduction of the parents or offspring and they established a NOAEL >3% (>300 mg/kg/day) from this study. However, an overall NOAEL for systemic effects of 0.1% (86.6 mg/kg bw) for the F0 generation and a NOAEL of 0.1% (149.5 mg/kg bw) for the F1 generation was established based on reduced relative liver weight in F0 and F1 rats.

In the available subchronic and chronic toxicity studies with various alcohol ethoxysulphates, the primary sex organs of the males and females did not show evidence of treatment-related adverse effects at the highest tested dose of 250 mg/kg bw/day.

As part of a feeding study, rats fed diets containing 0.1% of an alcohol ethoxysulphate (50 mg/kg bw/day) were mated after 14 weeks (HERA 2003). The F1 generation was maintained on the parental diet and mated at 100 days of age. The F2 generation was fed the same diet for five weeks, and then killed. No adverse effects on fertility, lactation, litter size or survival and growth of the offspring were seen and it was concluded that the NOAEL for reproductive toxicity was greater than 50 mg/kg bw/day.

Based on these studies, the substance is not considered to be toxic to fertility.

54.5.9.2 Developmental toxicity

In several embryotoxicity studies, alcohol ethoxysulphates were administered to pregnant rats at doses as high as 1000 mg/kg bw/day (HERA 2003). No evidence of treatment-related developmental toxicity was detected in any of the studies, although some studies reported a degree of maternal toxicity indicated by a significant reduction in body weight gain observed at very high dose levels (e.g. 750 and 1000 mg/kg bw/day). Based on available data, the substance is not considered to be a developmental toxicant.

54.6 Health hazard summary

54.6.1 *Critical health effects*

Based on studies with closely related compounds, the organic sulphate is considered to have low acute oral and dermal toxicity, and is expected to be a skin irritant and severe eye irritant, but not a skin sensitiser.

No systemic treatment-related effects were observed in repeat dose oral studies with structurally related compounds up to a dose of 250 mg/kg bw/day. Based on the absence of adverse effects observed in repeat dose toxicity studies, for the purposes of quantifying the health risk the highest dose tested in the critical study (250 mg/kg bw/day) will be used in the risk assessment.

The alcohol ethoxysulphates were not genotoxic or carcinogenic. Reproductive and developmental studies with a range of alcohol ethoxysulphates indicated no adverse effects on these parameters.

Based on a lack of these effects seen with alcohol ethoxysulphates of similar carbon chain lengths, the organic sulphate is not considered to be genotoxic, carcinogenic or toxic to reproduction or development.

54.6.2 *Hazard classification*

Based on the above studies, the organic sulphate is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) and the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A54.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A54.3 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation / Corrosivity	Irritating to skin (X_i; R38) Risk of serious eye damage (X_i; R41)	Causes skin irritation – Cat. 2 (H315) Causes serious eye irritation – Cat. 1 (H318)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

Mixtures containing the substance are classified as hazardous based on the concentration (Conc) of the chemical in the mixtures. The NICNAS recommended risk phrases for this chemical are:

- 5% ≤Conc <10%: Xi R36 (Irritant: Irritating to eyes)
- Conc ≥10%: Xi; R41; (Irritant: Risk of serious eye damage)
- Conc ≥20%: Xi; R41, R38; (Irritant: Risk of serious eye damage; Irritating to skin).

54.7 References

HERA (2003) Human and Environmental Risk Assessment on ingredients of household cleaning products (Alcohol Ethoxysulphates). January 2003. Accessed in February 2014 at: http://www.heraproject.com/riskassessment.cfm

NHMRC (2011) Australian Drinking Water Guidelines 6 2011. National Health and Medical Research Council. Accessed in February 2014 at http://www.nhmrc.gov.au/guidelines/publications/eh52

NICNAS (2017a) Identification of chemicals associated with coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NICNAS (2017b) Human health hazards of chemicals used in coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. National Occupational Health and Safety Commission.

Safe Work Australia (2013) Hazardous Substances Information System. Accessed 17 September 2013 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance.

TGA (2014) Poisons Standard 2014. Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Therapeutic Goods Administration.

UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe, New York and Geneva. Accessed in June 2013 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

A55 Polyamine

CAS No.	Chemical Name
CBI	Polyamine

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) Number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemical has been conducted.

A summary of the assessment findings is presented below.

55.1 Chemical Identity

Details of the chemical identity obtained from the web-based database ChemID*plus* (2012) are provided in Table A55.1.

Table A55.1 Chemical identity

	Polyamine
Molecular weight	>100
Appearance and odour	Solid

The chemical is a cationic polymer however no molecular weight data or other data such as degree of branching or levels of residual monomer were provided by industry for the chemical as used in coal seam gas extraction in Australia. According to available data sources, molecular weights of the chemical vary widely with monomer numbers ranging from 7 to 14 000 (US National Library of Medicine 2014).

55.2 Physical properties

A data search for physical properties information for the chemical in solid form revealed limited information from one manufacturer. The limited physical properties information in Table A55.2 was taken from the safety data sheet (SDS) for linear polymer of MW 10 000.

Table A55.2 Physical properties for manufacturer linear polymer MW 10 000

Property	Value
Melting point	48-53 °C*
Boiling point	No data available
Density	No data available
Vapour pressure	No data available
Water solubility	No data available

Property	Value
Partition coefficient n-octanol/water (log K_{ow})	No data available
Flash point	>100 °C

** Melting point for manufacturer's linear chemical MW 2500 is 59-64 °C.*

55.3 Current regulatory controls

55.3.1 *Hazard classification for occupational health and safety*

The chemical polymer is not classified as hazardous for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

However, the constituent monomer is classified hazardous for human health with the following risk phrases:

- Carc. Cat. 2; R45 (May cause cancer)
- Muta. Cat. 2; R46 (May cause heritable genetic damage)
- T+; R26/27/28 (Very toxic by inhalation, in contact with skin and if swallowed)
- C; R34 (Causes burns).

The SDS for the product used in the Australian coal seam gas industry containing the polymer notes that the product is non-hazardous. Also, the SDS does not list the polymer as a constituent. Listing is not required for non-hazardous ingredients (Safe Work Australia 2011).

55.3.2 *Occupational exposure standards*

55.3.2.1 Australia

There are no specific exposure standards for the chemical. However, as a solid, the permissible exposure limits (as the Time Weighted Average (TWA)) for dusts apply (10 mg/m^3 measured as inspirable dust) (Safe Work Australia 2013). The monomer has an exposure standard of 0.5 ppm (0.88 mg/m^3) TWA with a skin notation, meaning that absorption by the skin may be a significant source of exposure.

55.3.2.2 International

No specific exposure standards were identified for the chemical. However, the following exposure standards (for dusts) were identified (Galleria Chemica 2013).

TWA:

- 10 mg/m^3 [Canada, Ireland, Spain]
- 5 mg/m^3 [US].

55.3.3 *Australian food standards*

No Australian food standards were identified.

55.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for this chemical in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

55.3.5 *Additional controls*

55.3.5.1 Australia

No additional controls were identified.

55.3.5.2 International

No additional controls were identified.

55.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

55.5 Health hazard characterisation

No health effects data were available from Australian industry for the polymer. However, a large number of companies in Europe have submitted proposals for classification and labelling of the chemical in both solid and liquid forms as a pre-registration substance under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH (ECHA 2014). Variations in proposals are likely to reflect different forms of the chemical.

These proposals contain the following classification and labelling statements reflecting particular health effects:

- Acute Tox. 4 Harmful if swallowed (H302) or Acute Tox. 3 Toxic if swallowed (H301)
- Eye Dam. 1 Causes serious eye damage (H318) or Eye Irrit. 2 or Eye Irrit. 2A Causes serious eye irritation (H319)
- Skin Sens. 1 May cause an allergic skin reaction (H317).

The REACH dossiers containing health effects data supporting these proposals for classification and labelling were not available.

Quantitative Structure-Activity Relationship (QSAR) modelling was conducted on sensitisation and genotoxicity endpoints for the monomer of the chemical using the predictive modelling tool OASIS-TIMES.

55.5.1 *Toxicokinetics*

No data were available. Acute toxicity has been noted for the chemical. In the absence of purely local toxic effects, this infers some systemic absorption via the oral route. As a high molecular weight solid, absorption via the dermal route is likely to be low.

55.5.2 *Acute toxicity*

Limited acute toxicity data were available for the chemical. ChemID*plus* (2012) lists several oral LD50 values ranging from 1350 to 2300 mg/kg bw for rats, 1150 to 1600 mg/kg bw for mice and 940 to 1400 mg/kg bw for guinea pigs. No additional information, including test protocols and the chemical identity of the tested chemical, was provided.

Classification and labelling proposals under REACH indicate that the substance may have acute toxicity via the oral route.

No data were available for acute dermal or inhalation toxicity.

55.5.3 *Irritation / Corrosivity*

55.5.3.1 Skin irritation

No data were available. However, due to the cationic nature of the polymer, and as indicated by classification and labelling proposals under REACH, the polymer could be expected to be a skin irritant.

55.5.3.2 Eye irritation

No data were available. However, due to the cationic nature of the polymer, and as indicated by classification and labelling proposals under REACH, the polymer could be expected to be an eye irritant.

55.5.3.3 Respiratory irritation

No data were available. However, due to the cationic nature of the polymer, and as indicated by classification and labelling proposals under REACH regarding skin and eye irritation, the polymer could be expected to be a respiratory irritant.

55.5.3.4 Observation in humans

No data were available.

55.5.4 *Sensitisation*

55.5.4.1 Skin sensitisation

No data were available. QSAR modelling using OASIS-TIMES predicted positive results for the monomer for skin sensitisation. The polymer could be expected to be a skin sensitiser due to its cationic nature. The classification and labelling proposals under REACH also indicate the polymer to be a skin sensitiser.

55.5.4.2 Respiratory sensitisation

No data were available.

55.5.4.3 Observation in humans

No data were available.

55.5.5 *Repeat dose toxicity*

No data were available.

55.5.6 *Genotoxicity*

Cationic polymers, including both linear and branched forms of the chemical, are used as experimental gene delivery (transfection) systems and are known to elicit cytotoxicity and genotoxicity in different cell types *in vitro*. However, data were not available on the genotoxic potential of these cationic polymers *in vivo*.

QSAR modelling using OASIS-TIMES predicted positive results for the monomer for in vivo and in vitro genotoxicity, however, the concentration of any residual monomer in the polymer is not known.

55.5.7 *Carcinogenicity*

No data were available.

55.5.8 *Reproductive toxicity*

No data were available.

55.6 Health hazard summary

55.6.1 *Critical health effects*

The chemical as used for coal seam gas extraction is likely to be a high molecular weight polymer in solid form. The polymer is highly cationic. No data were available for levels of residual monomer, and so the extent to which toxicity of the polymer is related to, and can be predicted by, the presence of hazardous monomer is not known.

Limited acute toxicity data and classification and labelling proposals in the EU for structurally similar chemicals indicate that the polymer may be acutely toxic via the oral route. No data were available for dermal or inhalation toxicity. As a high molecular weight solid, dermal absorption is likely to be low and therefore dermal toxicity is not expected. However, reports of acute oral toxicity imply some oral absorption if toxicity is not due purely to local effects.

As suggested by the cationic nature of the polymer and classification and labelling proposals in the EU, the chemical is likely to be a skin, eye and respiratory irritant and a skin sensitiser.

The polymer is genotoxic *in vitro*. The extent to which the polymer is genotoxic *in vivo* is not known.

55.6.2 *Hazard classification*

Available data were insufficient to support a hazard classification for the chemical.

55.7 References

ChemID*plus* (2012) Accessed February 2014 at http://chem.sis.nlm.nih.gov/chemidplus

ECHA (2014) Submissions to the classification and labelling inventory for the pre-registered substance under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program. Accessed February 2014 at http://clp-inventory.echa.europa.euGalleria Chemica. Accessed September 2013 at http://jr.chemwatch.net/galleria/

NHMRC (2011) Australian Drinking Water Guidelines 6 2011. National Health and Medical Research Council. Accessed in February 2014 at http://www.nhmrc.gov.au/guidelines/publications/eh52

NICNAS (2017a) Identification of chemicals associated with coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NICNAS (2017b) Human health hazards of chemicals used in coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

Safe Work Australia (2011) Preparation of Safety Data Sheets for Hazardous Chemicals. Code of Practice. December 2011.

Safe Work Australia (2013) Hazardous Substances Information System (HSIS). Accessed September 2013 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance.

A56 Polymer with substituted alkylacrylamide salt

CAS No.	Chemical Name
CBI	Polymer with substituted alkylacrylamide salt

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) Number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemical has been conducted.

A summary of the assessment findings is presented below.

56.1 Chemical identity

The chemical is the residual, unreacted component in a polymer (chemical identity disclosed to NICNAS). The polymer is the main component of a product used in drilling fluid formulation for coal seam gas extraction.

Information on chemical identity was obtained from the web-based database ChemID*plus* (2012) and the Agency for Toxic Substances and Disease Registry (ATSDR). Details are provided in Table A56.1.

Table A56.1 Chemical identity

	Polymer with substituted alkylacrylamide salt
Molecular weight	<100
Appearance and odour	White or colourless, odourless, crystalline solid

56.2 Physical properties

The physical properties of the chemical are presented in Table A56.2. The information was obtained from a report by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS c).

Table A56.2 Physical properties

Property	Value
Melting point	<100 C
Boiling point	<100 °C at 0.27 kPa >100 °C at 3.3 kPa
Density	>1000 kg/m^3 at 30 °C

Property	Value
Vapour pressure	<1 x 10^{-3} kPa at 25°C
Water solubility	>2000 g/L at 30 °C
Partition coefficient n-octanol/water (log Kow)	-2 to -0.5
Conversion factor	1 ppm (in air) = 5 mg/m^3 1 mg/m^3 = 0.2 ppm

56.3 Current regulatory controls

56.3.1 *Hazard classification for occupational health and safety*

The chemical is classified as hazardous for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013) with the following risk phrases:

- Carc. (Carcinogen) Cat. (Category) 2; R45
- Muta. (Mutagenic) Cat. 2; R46
- Repr. (Toxic to Reproduction) Cat. 3; R62
- T (Toxic); R25-48/25
- X_n (Harmful); R21-48/20/21
- X_i (Irritant); R36/38, R43.

Mixtures containing the chemical are classified as hazardous with the following risk phrases based on the concentration of the chemical in the mixtures. The risk phrases for different concentration (Conc) ranges are:

- Conc ≥25%: T:
  - R45 (May cause cancer)
  - R46 (May cause heritable genetic damage)
  - R62 (Possible risk of impaired fertility)
  - R25 (Toxic if swallowed)
  - R21 (Harmful in contact with skin)
  - R48/25 (Toxic: danger of serious damage to health by prolonged exposure if swallowed)
  - R48/20/21 (Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin)
  - R36/38 (Irritating to eyes and skin), R43 (May cause sensitisation by skin contact).
- 20 ≤Conc <25%: T: R45, R46, R62, R22 (Harmful if swallowed), R48/25, R48/20/21, R36/38, R43
- 10 ≤Conc <20%: T: R45, R46, R62, R22, R48/25, R48/20/21, R43
- 5 ≤Conc <10%: T: R45, R46, R62, R22, R48/22 (Harmful: danger of serious damage to health by prolonged exposure if swallowed), R43
- 3 ≤Conc <5%: T: R45, R46, R22, R48/22, R43

- 1 ≤Conc <3%: T: R45, R46, R48/22, R43
- 0.1 ≤Conc <1%: T: R45, R46.

56.3.2 *Occupational exposure standards*

56.3.2.1 Australia

The following occupational exposure standard was identified (Safe Work Australia 2013).

- Time Weighted Average (TWA) of 0.03 mg/m³

No Short-Term Exposure Limit (STEL) values were available.

56.3.2.2 International

The following exposure standards were identified (Galleria Chemica 2013).

TWA:

- 0.03 mg/m³ [Belgium, Denmark, Iceland, Korea, Mexico, New Zealand, Sweden]
- 0.3 mg/m³ [Finland, Philippines, UK]
- 0.05 mg/m³ [Russia].

STEL:

- 0.06 to 0.2 mg/m^3 [Mexico, Sweden, Russia]
- 0.9 mg/m^3 [Finland].

56.3.3 *Australian food standards*

The chemical is listed in Standard 1.3.1 of the Australia New Zealand Food Standards Code and has a permitted use as a processing aid for packaged water and in water used as an ingredient in other foods (Food Standards Australia New Zealand 2013).

56.3.4 *Australian drinking water guidelines*

The Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011) determined that the concentration of the chemical in drinking water should not exceed 0.0002 mg/L based on health considerations.

56.3.5 *Additional controls*

56.3.5.1 Australia

The chemical is included in the Australian Dangerous Goods Code Edition 7 (ADG7) (National Transport Commission 2007). The solid form of, and the solution containing the chemical are listed as Class 6.1 ‘Toxic Substances’, and are assigned to Packing Group III. The ADG7 contains detailed provisions for the packaging, transport and marking of containers in Class 6.1.

The specific chemical is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

56.3.5.2 International

The chemical is currently regulated in the European Union (EU) Cosmetic Directive 76/768/EEC in Annex II (List of substances which must not form part of the composition of

cosmetic products) (European Commission (EC) 2010). The chemical is also included in Annex VI (List of substances which are carcinogenic, mutagenic, or toxic for reproduction) of the European Classification, Labelling and Packaging (CLP) Regulation of substances and mixtures (European Chemicals Agency (ECHA) 2012).

The chemical is also currently managed under the Canadian Environmental Protection Act (CEPA) (1999), being in Schedule 1 (List of toxic substances) (Environment Canada 2013). The chemical is included in the Canadian Cosmetic Ingredient Hotlist (Health Canada 2013).

56.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

56.5 Health hazard characterisation

The information on health hazards is obtained from the following comprehensive reviews of the chemical:

- Agency for Toxic Substances and Disease Registry (ATSDR)
- NICNAS (c)
- Integrated Risk Information System (IRIS) (United States Environmental Protection Agency (US EPA)
- International Agency for Research on Cancer (IARC)
- the National Toxicology Program (NTP).

56.5.1 *Toxicokinetics*

56.5.1.1 Oral absorption

Three gavage studies in rats using administration of ^{14}C-labelled chemical found the oral absorption to be 50 to 67% (ATSDR 2013). Similar results (40 to 60% absorption) were seen in humans administered oral doses of the chemical (ATSDR).

For the purposes of risk assessment, 100% oral absorption in humans is therefore assumed.

56.5.1.2 Dermal absorption

Occlusion studies of the radiolabelled chemical in rats and human volunteers found the dermal absorption to be approximately 22% and 4.5%, respectively (US EPA 2013).

In an *in vitro* study, after application of the ^{14}C-labelled chemical to biopsied human abdominal skin, the total absorption was estimated to be 26 to 33% (US EPA 2013).

For the purposes of risk assessment, 75% dermal absorption in humans is assumed.

56.5.1.3 Inhalation absorption

Absorption of radio-labelled chemical by rodents exposed (nose-only) to the vapour was found to be 42% and 51% in rats and mice, respectively (US EPA 2013).

For the purposes of risk assessment, 100% inhalation absorption in humans is assumed.

56.5.2 *Acute toxicity*

56.5.2.1 Oral

The chemical was shown to have moderate acute oral toxicity (LD50s 150 to 413 mg/kg bw) in six studies conducted in rats (ATSDR; NICNAS c). Similar results were obtained in mice, rabbits and guinea pigs (ATSDR).

56.5.2.2 Dermal

The chemical was shown to have low acute dermal toxicity (LD50s 941 and 1148 mg/kg bw) in two studies conducted in rabbits but was moderate (LD50 252 mg/kg bw) in a rat study (ATSDR; NICNAS c).

56.5.2.3 Inhalation

No data were available on the acute inhalation median lethal concentration (LC50). After the first day of a repeated dose study, 4/7 rats died after exposure to the chemical dust at 15.6 mg/m^3 (ATSDR).

56.5.2.4 Observation in humans

Studies from worker exposure to the chemical (refer to carcinogenicity section) showed no significant correlation of exposure to incidences of death (IARC, US EPA, ATSDR).

56.5.3 *Irritation / Corrosivity*

56.5.3.1 Skin irritation

In two separate studies, an aqueous solution of the chemical (approximately 50%) was found to be irritating to the skin of rabbits but was not irritating in a third study (NICNAS c). Occlusive application of aqueous solution of the chemical for two weeks resulted in no responses at 10% and erythema at 12.5%.

The studies demonstrate that the chemical is irritating to the skin.

56.5.3.2 Eye irritation

Powdered chemical and aqueous solutions of the chemical (50 to 51%) were found to be irritating to the eyes in three separate studies in rabbits (NICNAS c).

56.5.3.3 Observation in humans

Workplace surveys and case reports indicated skin reactions on hands, palms, forearms, and soles, and possible neurotoxicity (NICNAS c). However, the reported effects did not give a clear indication of whether the irritation was primarily due to exposure to the chemical.

56.5.4 *Sensitisation*

56.5.4.1 Skin sensitisation

In two guinea pig maximisation tests the chemical was found to be a skin sensitiser (NICNAS c).

56.5.4.2 Observation in humans

Case reports of individuals wearing latex gloves while working with the chemical reported the development of exudative lesions on the hands and wrists, and eczema (NICNAS c).

56.5.5 *Repeat dose toxicity*

56.5.5.1 Oral

In short, medium, and long term repeated oral studies in rats, mice and cats, exposure to the chemical was consistently associated with clinical signs of neurotoxicity, with the most prominent being the effects on the hind limbs (ATSDR, NICNASc; NTP). For studies where histopathology results were presented, degeneration of myelin and axons was reported. The critical study for determining the effects of repeated exposures to the chemical is a reliable 90-day drinking water study in rats where the The Lowest Observed Adverse Effect Level (LOAEL) and No Observed Adverse Effect Level (NOAEL) are 1 and 0.2 mg/kg bw/day, respectively (ATSDR).

56.5.5.2 Dermal

Studies involving the application of single doses of the chemical in rats for unspecified duration, in mice for five days, and rabbits for 18 hours reported slight dermal irritation and central nervous system symptoms, which resolved during the recovery phase (ATSDR).

A 12-week application of up to 50 mg/kg bw/day of the chemical in rabbits resulted in clinical signs of neurotoxicity with complete resolution of gross signs during recovery (NICNAS c).

56.5.5.3 Inhalation

The limited data available in dogs, cats, and guinea pigs reported central nervous system effects including loss of equilibrium and coordination (ATSDR).

56.5.5.4 Observation in humans

Ingestion of 18 g of the chemical, equivalent to 375 mg/kg bw, in an individual caused hallucinations, hypotension and seizures (NICNAS c). After three days, gastrointestinal bleeding, respiratory distress, hepatic effects, and peripheral neuropathy occurred. Peripheral neuropathy was still apparent after two months.

Exposure of five people to approximately 400 ppm of the chemical (dose not quantified) in well water used for drinking resulted in signs of central and peripheral neurological deficits (ATSDR).

56.5.6 *Genotoxicity*

Numerous reliable *in vitro* and *in vivo* studies indicate that the chemical is genotoxic from observed effects of DNA damage and gene mutations (ATSDR).

56.5.7 *Carcinogenicity*

Reliable studies demonstrate that the chemical produced increased incidences of malignant tumours in various organs of rats and mice (ATSDR, NTP). In a two-year study in rats, carcinogenic activity manifested at low doses of 0.5 and 2 mg/kg bw/day in males and females, respectively (ATSDR).

Cohort mortality studies with inhalation and dermal exposure to the chemical of more than 8000 workers hired at production plants reported no significant increase in the standardised mortality ratio (SMR) for all causes of death, including cancer death (ATSDR, US EPA). Possible associations between dietary intake of the chemical and selected cancer types cannot be determined from the conflicting results of case-control and prospective cohort studies.

IARC concluded that the chemical is likely to be a human carcinogen based on insufficient human data and sufficient evidence of carcinogenicity in animals. The chemical is classified as a Group 2A carcinogen (probably carcinogenic to humans).

56.5.8 *Reproductive toxicity*

56.5.8.1 Fertility

Eight rodent studies were available (ATSDR, NICNAS c). Fertility effects caused by the chemical include post-implantation loss, reduced number of foetuses and sperm count, and degenerative effects in the testis. The LOAEL and NOAEL for fertility are 5 and 2 mg/kg bw/day, respectively, from a two-generation drinking water study in rats.

56.5.8.2 Developmental toxicity

In separate studies, no treatment-related effects on developmental parameters were observed at doses up to 15 mg/kg bw/day and 45 mg/kg bw/day in rats and mice, respectively (ATSDR, NICNAS c). Effects (including decreased numbers of live births, reduced pup bodyweight, and delayed development) were seen in four studies however it was not clear whether these were lactational or in utero effects, or secondary to maternal toxicity (ATSDR, NICNAS c). Overall, the studies show that the chemical is not a developmental toxicant.

56.6 Health hazard summary

56.6.1 *Critical health effects*

The chemical has moderate acute oral and dermal toxicity, is irritating to the skin and eyes, and is a skin sensitiser.

The most appropriate NOAEL for risk assessment of the chemical is 0.2 mg/kg bw/day based on neurotoxic effects from repeated oral exposure, identified in a 90-day drinking water study.

The chemical is genotoxic, carcinogenic (NOAEL = 1.32 and 0.44 mg/kg bw/day in males and females, respectively), and toxic to fertility (NOAEL = 2 mg/kg bw/day).

56.6.2 *Hazard classification*

This hazard assessment confirms the existing hazard classification under the Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004).

The chemical is recommended by NICNAS to Safe Work Australia for classification and labelling under the adopted Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A56.3. These NICNAS recommendations do not consider physical or environmental hazards.

Table A56.3 Hazard classification recommended by NICNAS to Safe Work Australia

Effect	GHS* classification
Acute toxicity	Toxic if swallowed – Cat. 3 (H301), C ≥25% Harmful if swallowed – Cat. 4 (H302), 3 ≤C <20% Harmful in contact with skin – Cat. 4 (H312), C ≥25%
Irritation / Corrosivity	Causes serious eye irritation – Cat. 2 (H319), C ≥20% Causes skin irritation – Cat. 2 (H315), C ≥20%
Sensitisation	May cause an allergic skin reaction – Cat. 1A (H317), C ≥1%
Repeat dose toxicity	Causes damage to organs through prolonged or repeated exposure [oral] – Cat. 1 (H372), C ≥10% May cause damage to organs through prolonged or repeated exposure [oral] – Cat. 2 (H373), 1 ≤C <10% May cause damage to organs through prolonged or repeated exposure [dermal and inhalation] – Cat. 2 (H373), C ≥10%
Genotoxicity	May cause genetic defects – Cat. 1B (H340), C ≥0.1%
Carcinogenicity	May cause cancer – Cat. 1B (H350), C ≥0.1%
Reproductive toxicity	Suspected of damaging fertility – Cat. 2 (H361f), C ≥5%

** Globally Harmonised System (UNECE 2009)*

56.7 References

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NICNAS (c) Chemical Assessment Report. National Industrial Chemicals Notification and Assessment Scheme, Sydney.

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NICNAS (2017b) Human health hazards of chemicals used in coal seam gas extraction in Australia, Project report, report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. National Occupational Health and Safety Commission.

NTP Technical report on the toxicology and carcinogenesis studies of the chemical in F344/N rats and B6C3F1 mice (feed and drinking water studies). National Toxicology Program, United States Department of Health and Human Services. Accessed 23 October 2013 at http://ntp.niehs.nih.gov/

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UNECE (2009) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. United Nations Economic Commission for Europe, New York and Geneva. Accessed in June 2013 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

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A57 Terpenes and terpenoids

CAS No.	Chemical Name
CBI	Terpenes and terpenoids

CBI = confidential business information

Confidentiality from public disclosure was claimed for the chemical name and Chemical Abstracts Service (CAS) Number of this chemical. Therefore in this publicly available version of the hazard assessment report, the chemical is listed by a generic name and its CAS Number has been omitted. Data on this chemical subject to commercial-in-confidence claims were provided to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and a detailed hazard assessment of the chemical has been conducted.

A summary of the assessment findings is presented below.

57.1 Chemical identity

Terpenes and terpenoids is considered as a substance of unknown or variable composition, complex reaction products or biological materials (UVCB), being a complex product of a chemical reaction.

The substance is composed of known quantities of monoterpene hydrocarbons, consisting of Constituent 1 (and two isomers), Constituent 2, Constituent 3 and other terpene hydrocarbons (United States Environmental Protection Agency (US EPA)).

The information on the identity of terpenes and terpenoids was obtained from the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2013). Details are provided in Table A57.1.

Table A57.1 Substance identity

	Terpenes and terpenoids
Appearance	Colourless to pale yellow liquid

57.2 Physical properties

The physical properties of the substance are provided in Table A57.2. The information was obtained from REACH (2013).

Table A57.2 Physical properties

Property	Value
Melting point	<0 °C
Boiling point	>100 °C at 100.589 kPa
Density	<1000 kg/m^3 at 20 °C

The physical properties of some of the chemical constituents of terpenes and terpenoids are provided in Table A57.3. The information is obtained from the US EPA.

Table A57.3 Physical properties of the chemical constituents

Property	Constituent 1	Constituent 2	Constituent 3
Melting point	<0 °C	-	<0 °C
Boiling point	100-200 °C	100-200 °C	100-200 °C
Vapour Pressure	<1 kPa at 20 °C	<0.1 kPa at 24 °C	<1 kPa at 25 °C
Water Solubility	<0.1 g/L at 25 °C	<0.01 g/L at 23 °C	0.01 g/L at 25 °C
Partition coefficient n-octanol/water (log Kow)	4-5	-	4-5

57.3 Current regulatory controls

The document from here on refers to terpenes and terpenoids as 'substance'.

57.3.1 *Hazard classification for occupational health and safety*

The substance is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia 2013).

The chemical constituents of the substance, Constituent 2 and Constituent 3, are not listed on the HSIS (Safe Work Australia 2013).

The chemical constituent, Constituent 1, is classified as hazardous for human health in the HSIS (Safe Work Australia 2013) with the same risk phrases as follows:

- X_i (Irritant); R38, R43

Mixtures containing Constituent 1 are classified as hazardous with the following risk phrases based on the concentration of these chemicals in the mixtures. The risk phrases for different concentration (Conc) ranges are:

- Conc ≥20%: X_i;
  - R38 (Irritating to skin),
  - R43 (May cause sensitisation by skin contact)
- 1% ≤Conc <20%: X_i; R43

57.3.2 *Occupational exposure standards*

57.3.2.1 Australia

No specific exposure standards were available for the substance or the chemical constituents.

57.3.2.2 International

No specific exposure standards were available for the substance or the chemical constituents.

57.3.3 *Australian Food Standards*

No Australian food standards were available for the substance or the chemical constituents.

57.3.4 *Australian drinking water guidelines*

No aesthetic or health-related guidance values were identified for the substance or the chemical constituents in the Australian Drinking Water Guidelines (National Health and Medical Research Council (NHMRC) 2011).

57.3.5 *Additional controls*

57.3.5.1 Australia

The substance is not listed in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (Therapeutic Goods Administration (TGA) 2014).

57.3.5.2 International

The substance and some of its constituents, isomers of Constituent 1, and Constituent 2 are currently regulated in the European Union (EU) Cosmetic Directive 76/768/EEC in Annex III, Part 1 (European Commission (EC) 2010).

57.4 Use

The use of the substance in the coal seam gas extraction process is described in the National Coal Seam Gas Chemicals Assessment reports: Identification of chemicals report (NICNAS 2017a) and the Human health risk assessment report (NICNAS 2017b).

57.5 Health hazard characterisation

The information on health hazards is obtained from the following comprehensive reviews:

- US EPA
- Dossier submission for the substance (REACH 2013)
- A report by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS c).

Information available for the substance, one of the isomers of Constituent 1, and Constituent 2 multiconstituent (consisting of approximately 30% Constituent 2) is presented in Table A57.4. Accordingly, the data gaps for the substance are read-across from data available for the isomer of Constituent 1, and Constituent 2 multiconstituent. Read-across is a technique used here to predict endpoint information for the untested terpenes and terpenoids by using data (from the same endpoint) from the tested Constituent 1 isomer and Constituent 2 multiconstituent which are both components of the substance.

Table A57.4 Summary of available toxicity endpoint data

	Terpenes and terpenoids	Constituent 1 isomer	Constituent 2 multiconstituent
Acute oral toxicity	✓	✓	×
Acute dermal toxicity	✓	✓	×
Acute inhalation toxicity	×	×	×
Skin irritation	✓	✓	×
Eye irritation	×	✓	×

	Terpenes and terpenoids	Constituent 1 isomer	Constituent 2 multiconstituent
Respiratory irritation	×	✓	×
Skin sensitisation	×	✓	✓
Respiratory sensitisation	×	×	×
Repeat dose toxicity (oral)	×	✓	✓
Repeat dose toxicity (dermal)	×	×	×
Repeat dose toxicity (inhalation)	×	×	×
Genotoxicity *in vitro*	✓	✓	×
Genotoxicity *in vivo*	×	✓	×
Carcinogenicity	×	✓	×
Fertility toxicity	×	×	✓
Developmental toxicity	×	✓	×

✓Existing data point; × Missing data point;

57.5.1 *Toxicokinetics*

No data were available for the substance.

Toxicokinetic studies indicated that one of the isomers of Constituent 1 is readily absorbed after oral administration in rats and humans and absorbed dermally due to lipid disruption in the stratum corneum (NICNAS c). The uptake in humans exposed by inhalation to concentrations up 450 mg/m^3 of one of the isomers of Constituent 1 was reported to average 65% over a two-hour period (NICNAS c).

For the purposes of risk assessment, 100% absorption of the substance via the oral, dermal and inhalation routes in humans is therefore assumed from the available absorption data of one of the isomers of Constituent 1 in animals and humans.

57.5.2 *Acute toxicity*

The substance was shown to have low acute oral toxicity (LD50 > 2000 mg/kg bw) in a rat study (REACH 2013).

The substance was shown to have low acute dermal toxicity (LD50s > 2000 mg/kg bw) based on two semi-occlusive tests in rats (REACH 2013).

There were no data on the inhalation toxicity of the substance and its constituents.

57.5.3 *Irritation / Corrosivity*

57.5.3.1 Skin irritation

In a reliable study, the undiluted substance was found to be irritating to the skin of rabbits (REACH 2013).

57.5.3.2 Eye irritation

No data were available on eye irritation for the substance however one of the isomers of Constituent 1 was an eye irritant in rabbits (NICNAS c).

An *in vitro* eye irritation test with Constituent 2 multiconstituent (32% Constituent 2, 18% Constituent 1), used to read-across for this endpoint for the substance, showed it to be moderately irritating to human reconstructed corneal epithelium (REACH 2013).

The substance is an eye irritant based on supporting *in vivo* and *in vitro* data available for two of its constituents.

57.5.3.3 Respiratory irritation

No data were available for the substance, however animal studies indicated a potential of the isomers of Constituent 1 to cause respiratory irritation (NICNAS c).

57.5.3.4 Observation in humans

No data were available for the substance. Volunteers presented skin irritation to Constituent 1(*d*-isomer) using four different patch testing systems (NICNAS c).

57.5.4 *Sensitisation*

57.5.4.1 Skin sensitisation

No data were available for the substance. A skin sensitisation test in mice with Constituent 2 multiconstituent (32% Constituent 2, 18% Constituent 1) gave a positive response (REACH 2013). The autoxidation products of one of the isomers of Constituent 1 have potential to be skin sensitisers (NICNAS c).

The substance is a skin sensitiser based on supporting data available for Constituent 2 multiconstituent.

57.5.4.2 Observation in humans

No data were available for the substance. Human studies show that Constituent 1 has a low skin sensitising capacity and the sensitisation is due to the oxidation products formed when in contact with air (NICNAS c).

57.5.5 *Repeat dose toxicity*

No data were available for the substance, however studies for one of the isomers of Constituent 1 were available in rats, mice and dogs (US EPA). The critical study for determining the effects of repeated oral exposures to one of the isomers of Constituent 1 is a 13-week gavage study in rats at doses up to 2400 mg/kg bw/day (US EPA). The No Observed Adverse Effect Level (NOAEL) in females was determined to be 1200 mg/kg bw/day based on deaths in the test animals at 2400 mg/kg bw/day. The NOAEL in males was determined to be 600 mg/kg bw/day based on reduced bodyweight gain at 1200 mg/kg bw/day. These NOAEL values will be applied to terpenes and terpenoids.

No repeated dose dermal or inhalation studies were available for the substance and its constituents.

57.5.6 *Genotoxicity*

The substance was negative in two Ames tests, both in the presence and absence of metabolic activation (REACH 2013). The substance did not induce chromosomal aberrations

in Chinese hamster ovary (CHO) cells or human lymphocytes and was negative in a gene mutation test in CHO cells in the presence and absence of metabolic activation.

No *in vivo* data were available for the substance. Constituent 3 and one of the isomers of Constituent 1 did not induce chromosomal aberrations *in vivo* and no evidence of mutagenicity was observed in an *in vivo* spot test with mice injected with Constituent 1 (isomer not specified).

Based on the available studies, the substance is not considered to be genotoxic.

57.5.7 *Carcinogenicity*

No data were available for the substance.

In a two-year study, one of the isomers of Constituent 1 was administered by gavage to rats (up to 150 mg/kg bw/day and 600 mg/kg bw/day in males and females, respectively), and mice (up to 150 mg/kg bw/day and 1000 mg/kg bw/day in males and females, respectively) (NICNAS c, US EPA). In the kidney, the increased incidences of tubular cell adenomas and adenocarcinomas reported in male rats only are associated with α2μ-globulin formation and are not considered relevant to humans.

Terpenes and terpenoids is not considered to be carcinogenic based on the data available for one of the isomers of Constituent 1.

57.5.8 *Reproductive toxicity*

57.5.8.1 Fertility

No data were available for the substance.

In a combined repeated dose/reproduction toxicity test, rats were fed Constituent 2 multiconstituent (32% Constituent 2, 18% Constituent 1) at doses up to 436 mg/kg bw/day for up to 62 days (REACH 2013). There were no treatment-related effects on mating performance, fertility, and length of gestation.

The substance is not toxic to fertility based on data available for Constituent 2 multiconstituent.

57.5.8.2 Developmental toxicity

No data were available for the substance.

Three studies available for one of the isomers of Constituent 1 demonstrate that developmental effects (including reduced foetal body weights and increased skeletal malformations) occurred only at maternally toxic doses and are considered to be secondary to maternal toxicity (NICNAS c, REACH 2013, US EPA).

Terpenes and terpenoids is not a developmental toxicant based on the data available for one of the isomers of Constituent 1.

57.6 Health hazard summary

57.6.1 *Critical health effects*

Terpenes and terpenoids, has low acute oral and dermal toxicity, and is a skin irritant. Based on read-across data available for Constituent 2 multiconstituent, the substance is an eye irritant and a skin sensitiser.

The most appropriate NOAEL for risk assessment, determined from the 13-week rat gavage study on one of the isomers of Constituent 1, is 600 mg/kg bw/day. This NOAEL will be applied to terpenes and terpenoids.

The substance is not genotoxic or carcinogenic based on data available for one of the isomers of Constituent 1, is not toxic to fertility based on data available for Constituent 2 multiconstituent, and is not a developmental toxicant based on available data for one of the isomers of Constituent 1.

57.6.2 *Hazard classification*

The substance is recommended by NICNAS to Safe Work Australia for classification and labelling under the current Approved Criteria for Classifying Hazardous Substances (National Occupational Health and Safety Commission (NOHSC) 2004) Globally Harmonised System of Classification (GHS) (United Nations Economic Commission for Europe (UNECE) 2009) as shown in Table A57.5. These NICNAS recommendations do not consider physical or environmental hazards.

Table A57.5 Hazard classification recommended by NICNAS to Safe Work Australia

	Approved Criteria (HSIS)[a]	**GHS[b] classification**
Irritation / Corrosivity	Irritating to skin (X_i; R38) Irritating to eyes (X_i; R36)	Causes mild skin irritation – Cat. 3 (H316) Causes eye irritation – Cat. 2B (H320)
Sensitisation	May cause sensitisation by skin contact (X_i; R43)	May cause an allergic skin reaction – Cat. 1B (H317)

[a] Approved Criteria for Classifying Hazardous Substances (NOHSC 2004); [b] Globally Harmonised System (UNECE 2009)

57.7 References

EC (2010) Council Directive of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products. European Council Directive 76/768/EEC

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