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Office of the Chief Executive Officer

Mr Stephen Hunter
Executive Director
Australian Quarantine and Inspection Service
GPO Box 858
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Dear Mr Hunter

I refer to recent correspondence between Food Standards Australia New Zealand (FSANZ) and the Imported Food Program, Australian Quarantine and Inspection Service (AQIS), in relation to a survey of antimicrobial and pesticide residues in imported seafood products (fish, crabs, eels and prawns) undertaken by AQIS from April 2006 through to March 2007. The results of the survey, provided to FSANZ in July 2007, indicated that some seafood products entering Australia contained low-level residues of antimicrobial compounds that do not comply with Standard 1.4.2 – Maximum Residue Limits in the *Australia New Zealand Food Standards Code* (the Code).

In our letter of 3 August 2007 to the Acting Manager of the Imported Food Program, FSANZ agreed to provide formal advice to AQIS concerning the risks to public health and safety posed by non-compliant antimicrobial residues detected in imported seafood. In conducting a risk assessment, FSANZ has focussed specifically on the thirteen compounds detected in the survey, which represent at least six antimicrobial chemical groups – the sulphonamides, fluoroquinolones, phenicols, tetracyclines, β-lactams, and triphenyl methane dyes (malachite green). The risk assessment involved comparing estimated dietary exposures with the established reference health standard (Acceptable Daily Intake) for each chemical. For malachite green, FSANZ has used a margin of exposure approach as used in a previous assessment completed in 2005. The completed risk assessment is Attachment 1 to this letter.

Based on the dietary modelling, the FSANZ assessment has not identified any major safety concerns associated with the low levels of antimicrobial residues detected in some imported seafood. On these grounds, the residues do not constitute a medium or high risk to public health and safety.

You would be aware that FSANZ has received advice from the Expert Advisory Group on Antimicrobial Resistance (EAGAR) of the National Health and Medical Research Council in relation to antimicrobial resistance and human health. A copy of the EAGAR advice relating to the AQIS survey of antimicrobial compounds in imported seafood is enclosed with this letter.

In considering the results of the AQIS survey in terms of antimicrobial resistance, EAGAR has expressed concerns about the presence of fluoroquinolone residues in seafood. The fluoroquinolones include flumequine, ciprofloxacin and enrofloxacin which, in this survey, were found predominantly in prawns. EAGAR notes that use of the fluoroquinolones has never been permitted in animal food production in Australia, due to the potential for generating resistance in pathogenic bacteria. The existing prohibition on the use of these antimicrobial compounds in food production is important because EAGAR considers that any development of resistance to fluoroquinolones would constitute a high risk to their efficacy in clinical medicine.

On the basis of the EAGAR advice regarding the possibility that low-level residues of antimicrobial compounds, such as the fluoroquinolones, could be present in domestically produced seafood as a result of off-label use, FSANZ encourages an active, coordinated management approach involving the States, Territories and AQIS. FSANZ notes that several key strategies are already occurring in this area. A national survey of antimicrobial resistant microorganisms, coordinated by the Department of Health and Ageing, is underway. In addition, FSANZ is aware that the Imported Food Program has initiated discussions of the survey results through the Implementation Sub-Committee and the Food Surveillance Network. Collaboration between enforcement agencies through such mechanisms should ensure that ongoing efforts to monitor compliance of seafood products with relevant standards in the *Australia New Zealand Food Standards Code* achieve the desired compliance goals.

In summary, FSANZ concludes that the levels of antimicrobial compounds detected in the AQIS survey of a range of imported seafood are all very low and do not raise safety concerns. Acknowledging the concerns expressed by EAGAR in relation to the potential for developing antimicrobial resistance through chemical residues in seafood, the preferred risk management approach would be to enhance collaboration between the relevant authorities, to optimise effective enforcement measures and ensure ongoing protection of consumer health.

Yours sincerely

D.J. Stockwell

DEAN STOCKWELL
Acting Chief Executive Officer

17th September 2007

cc. Dr Nora Galway

An Assessment of the Public Health Risk Associated with Low Residues of Antimicrobial Compounds in Imported Fish and Shellfish

Food Standards Australia New Zealand

August 2007

1. Introduction

The Australian Quarantine and Inspection Service (AQIS) recently conducted analytical surveys on chemical residues in imported fish and shellfish. The results indicate residues of a number of antimicrobial compounds present in some fish and shellfish samples from a variety of countries including New Zealand. There is no corresponding maximum residue limit (MRL) in the Code for 13 of the compounds identified in the survey results, and therefore the residues are technically non-compliant.

AQIS has requested advice from FSANZ on the risk to public health and safety of low residues of the 13 antimicrobial compounds detected in the seafood survey. The information will be used by AQIS to institute the appropriate monitoring regime under the Imported Food Control Act which will determine whether a 'random' or 'risk' rate of inspection will be applied. The advice from FSANZ will also be used by AQIS in discussions with the States and Territories to determine an overall strategy for management of non-compliant chemical residues in imported seafood.

The antimicrobial compounds included in this assessment are listed in Table 1. FSANZ has combined basic safety information with dietary exposure data to characterise the risk to human health posed by each of the chemicals when present in seafood at the levels detected in the AQIS survey.

2. Risk Assessment

2.1 Reference health standards

FSANZ has referred to the published literature to obtain, wherever possible, a reference health standard for each chemical. For the majority of compounds, an Acceptable Daily Intake (ADI) was available for comparison with the estimated dietary exposure. The published ADI used in the modelling was based on a scientific assessment of data by The Joint FAO/WHO Expert Committee on Food Additives (JECFA) or the Office of Chemical Safety (OCS).

Where a published reference health standard was not available, information was sought on the clinical use of the antimicrobial compounds for treating bacterial infections in humans. With the exception of malachite green, all of the compounds without an ADI had been used therapeutically at some point in time.

In calculating an ADI from this information, the lowest therapeutic dose was taken as the Lowest Observed Effect Level (LOEL), and a safety factor of 100 was applied; a factor of 10 to account for the absence of a No Observed Effect Level (NOEL), and an additional factor of 10 to account for inter-individual variability in humans.

The calculated ADI values are considered to be conservative and protective of human health because they are based on doses used in clinical practice. Furthermore, it is anticipated that intakes of seafood containing traces of antimicrobial compounds will only occur over a short time interval. An ADI is usually calculated on the basis of a lifetime of daily exposure.

Sulfonamides

The sulfonamides include a number of distinct compounds with bacteriostatic properties. They are classed as either short- or long- acting antimicrobials with therapeutic uses in humans and animals, including food producing livestock species. The long-acting sulfonamides are no longer the drugs of choice to treat various infections in humans because of unwanted side effects, however they are used widely in veterinary medicine. Five sulfonamide compounds were detected in the survey.

Sulfamethazine

Sulfamethazine has been used to treat bacterial diseases in human and veterinary medicine and to promote growth in cattle, sheep, pigs and poultry. The OCS has established an ADI of 0.02 mg/kg bw for sulfamethazine (sulfadimidine) which was used in this assessment. JECFA established an ADI of 0.05 mg/kg bw (published in 2006).

Sulfadimethoxine

A long-acting sulfonamide used predominantly in veterinary applications. There was no published ADI available however the lowest human therapeutic dose is usually 15 mg/kg bw/day (Hughes *et al.*, 1996). Applying the safety factor of 100, the calculated ADI is therefore 0.2 mg/kg bw.

Sulfamethoxypyridazine

Long-acting sulfonamide with similar usage pattern to sulfamethoxine. No published ADI was available, therefore an ADI of 0.2 mg/kg bw was calculated from the lowest therapeutic dose in humans of 15 mg/kg bw/day.

Sulfameter

The alternative name is sulfamethoxydiazine, a long-acting sulfanilamide, first used clinically in the 1960s, for example to treat urinary tract infections. The therapeutic dosage depends on the nature of the infection however was generally in the order of 500 mg/day. Based on this level of usage, an ADI of 0.1 mg/kg bw was calculated.

Sulfamethoxazole

Currently in widespread clinical use for the treatment of bacterial and protozoan infections, predominantly in combination with other drugs. An ADI of 0.2 mg/kg bw is calculated from a therapeutic dose in adults of 1600 mg/day.

Oxytetracycline

JECFA has evaluated tetracycline, chlortetracycline and oxytetracycline and has assigned a group ADI of 0.03 mg/kg bw, established at the 50^{th} meeting (1998).

Beta-lactams

Ampicillin and amoxicillin are broad-spectrum antibiotics that have been used extensively to treat bacterial infections since 1961. The OCS has established an ADI for amoxicillin of 0.2 mg/kg bw. Ampicillin has no corresponding ADI, however is used in medicine both orally and for injection. Using a typical dosage of 1 g/day, the calculated ADI for ampicillin is 0.2 mg/kg bw.

Fluoroquinolones

Quinolones, including the subset fluoroquinolones, are bacteriocidal compounds, actively killing bacteria by inhibiting DNA replication and transcription. Quinolones can enter cells easily and therefore are often used to treat intracellular pathogens such as *Legionella pneumophila*.

Flumequine

Flumequine is a fluoroquinolone compound with antimicrobial activity against Gram-negative organisms and is used in the treatment of enteric infections in food animals in overseas countries. It also has limited use for the treatment of urinary tract infections in humans. Flumequine has been evaluated by JECFA on previous occasions (at the forty-second, forty-eighth, fifty-fourth and sixtieth meetings). After consideration of new data on genotoxicity, the Committee recently re-established an ADI for flumequine of 0.03 mg/kg bw.

Ciprofloxacin and Enrofloxacin

Enrofloxacin and its bioactive metabolite ciprofloxacin are fluoroquinolone antibiotics. Enrofloxacin is used in animal husbandry as a treatment for disease to control and prevent infection, and for growth promotion in some overseas countries but not in Australia. JECFA has evaluated the hazard of enrofloxacin and ciprofloxacin and established a group ADI of 0.002 mg/kg bw based on a microbiological endpoint.

Florfenicol

An ADI for florfenicol of 0.001 mg/kg bw derived from a microbiological endpoint has been published by the OCS.

2.2 Malachite Green

FSANZ completed a risk assessment of malachite green in September 2005, following positive detections in domestic and imported aquacultured fish samples tested as part of the ISC Coordinated Survey Plan. Malachite green has been previously used in other countries to treat fungal and protozoan infections on fish and fish eggs, but is not permitted in aquaculture in Australia. Leucomalachite green can also be found in fish as a metabolite of malachite green.

JECFA and the International Agency for Research on Cancer (IARC) have not evaluated the safety of malachite green or leucomalachite green, and there is no established ADI. In conducting the risk assessment, FSANZ reviewed the available toxicological data for malachite green including studies on absorption, metabolism and excretion in fish and rats; acute toxicity in rats and mice; reproductive and developmental toxicity in rabbits; and genotoxicity.

The National Toxicology Program (NTP) in the USA performed a 2-year study on toxicity and carcinogenicity in rats and mice with both malachite green and leucomalachite green (NTP, 2005). Long-term studies in rats and mice found treatment related liver toxicity. Leucomalachite green resulted in adverse effects at lower doses than malachite green. The NTP concluded that there was 'equivocal' or 'some' evidence that malachite green or leucomalachite green might produce tumours in experimental animals at levels of 5 mg/kg bw/day and above. The overall conclusion on carcinogenicity was that there is only limited evidence that malachite green and leucomalachite green could cause tumours in rodents.

In relation to the relevance for human health, the carcinogenicity and genotoxicity data together suggest that malachite green is a very low risk. Taking the non-neoplastic lesions in the rat liver as the most sensitive endpoint, the LOEL is 5 mg/kg bw/day.

3. Dietary Exposure Assessment

Dietary modelling is a tool used to estimate dietary exposure to food chemicals, including nutrient intakes, from the diet as part of the FSANZ risk assessment process. To estimate dietary exposure to food chemicals, records of what foods people have eaten are needed along with reports of how much of the food chemical of interest is in each food. The accuracy of these dietary exposure estimates depends on the quality of the data used in the dietary models. Sometimes, not all of the data needed are available or their accuracy is uncertain so assumptions have to be made, either about the foods eaten or about chemical levels, based on previous knowledge and experience. The models are generally set up according to international conventions for food chemical dietary exposure estimates. However, each modelling process requires decisions to be made about how to set the model parameters and what assumptions to make. Different decisions may result in different answers. Therefore, FSANZ documents clearly all such decisions, model assumptions and data limitations to enable the results to be understood in the context of the available data.

3.1 Chemical concentration data

The survey found residues of 13 different antimicrobial compounds above the Limit of Reporting (LOR) in imported seafood. Table 2 shows the range of seafood products containing antimicrobial compounds. For further details on sampling and levels of reporting, refer to **Attachments 1 and 2** respectively.

3.2 Dietary exposure assessment approach

Dietary exposure assessments were undertaken to estimate dietary exposures to the antimicrobial compounds detected in the survey (see Table 1).

$$\boxed{\text{Dietary Exposure} = \text{chemical concentration x food consumption amount}}$$

Exposures were estimated by combining usual patterns of food consumption, as derived from NNS data, with the concentration of the chemical in imported seafood. Except for malachite green, dietary exposures to the chemicals were then compared to reference health standards, in this case ADIs[1].

For all chemicals except malachite green, the amount of seafood that could be consumed before the ADI is exceeded was estimated for fish and crustacea, assuming the highest detected residues of chemicals in seafood reported in these analytical data. This calculation was based on the concentration of the chemical in the seafood in question, an adult mean body weight, and the published or calculated ADI. In calculating the maximum amount of seafood, it was assumed that there was no exposure to that chemical residue from non-food sources or other foods.

$$\text{Amount of seafood before ADI exceeded} = \frac{\text{ADI x body weight}}{\text{Highest chemical concentration in seafood}}$$

Seafood included in the testing for chemical residues included:

- Fish (excluding shark)
- Crustacea (prawns and crab)
- Eels

Canned, dried, battered or mixed seafood products were not included in this survey.

Specific processing parameters for sampled seafood included:

- Wild caught and farmed
- Cooked and uncooked
- Chilled and frozen

[1] An ADI is "an estimate of the amount of a substance in food or drinking-water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable risk" (Joint FAO/WHO Expert Committee on Food Additives, 2007).

Table 1: Summary of seafood surveyed and chemical detections

Species	No. of Samples	No. of detections	Chemicals detected
Barramundi	3	1	Amoxicillin
Basa	3	0	N/A
Catfish	1	0	N/A
Crab	10	2	Oxytetracycline, Amoxicillin
Eel	2	4	Sulfadimethoxine, Sulfamethazine, Sulfameter, Sulfamethoxypyridazine
Fish not further specified	6	3	Sulfamethoxazole, Amoxicillin, Enrofloxacin
Garfish	1	1	Oxytetracycline
Gourami	1	0	N/A
Hairtail	3	1	Amoxicillin
Hake	3	0	N/A
Ling	6	2	Amoxicillin, Ampicillin
Mackerel	6	1	Flumequin
Opaka	1	0	N/A
Orange Roughy	2	1	Ampicillin
Prawn	39	6	Sulfamethoxazole, Oxytetracycline, Flumequine, Ciprofloxacin, Enrofloxacin, Florfenicol
Perch	1	2	Oxytetracycline, Malachite Green
Red Emperor	1	0	N/A
Shark	1	0	N/A
Silverfish	3	0	N/A
Spanish Mackerel	5	1	Flumequine
Swordfish	4	2	Amoxicillin, Ampicillin
Tilapia	1	0	N/A
Tuna	4	0	N/A

3.3 Scenarios for dietary modelling

Three scenarios were assessed for the purposes of this dietary exposure assessment and were as follows:

- *Fish only* – dietary exposure to chemical residues from all fish species excluding tuna, trout and salmon
- *Crustacea only* – dietary exposure to chemical residues from all crustacea species and included crabs, lobsters and prawns
- *Fish and Crustacea* – dietary exposure to chemical residues from all crustacea and fish (excluding tuna, trout and salmon)

3.4 Assumptions in the dietary modelling

The aim of this dietary exposure assessment was a worst-case scenario estimate for dietary exposure. Where significant uncertainties in the data existed, conservative assumptions were generally used to ensure that the dietary exposure assessment did not underestimate exposure.

The assumptions made in the dietary modelling were:

- each chemical was present in all fish (where chemical residues were detected in fish) at the highest residue detected for that chemical (excluding tuna, trout and salmon which were not included in this dietary exposure assessment)
- each chemical was present in all crustacea (where chemical residues were detected in crustacea) at the highest residue detected for that chemical

These assumptions are likely to lead to a very conservative estimate for chemical residue dietary exposures and assume a worst case scenario as not all species of fish included in the model will contain residues and even for species with detected residues, it is unlikely that every sample of fish would contain this level of residue or that the same species of fish would be consumed every day.

3.5 Estimated mean consumption levels

The estimated mean consumption for consumers of the seafood types analysed for this exposure assessment (derived from the 1995 Australian NNS data) was 100 grams/day. The mean daily consumption is 75 grams for prawns, and 35 grams for crab. For fish only (species assessed for the purposes of this analysis), estimated mean consumption was 95 grams.

3.6 Estimation of seafood consumed to exceed reference health standard

Table 3 shows calculated estimates of the amount of seafood species that would need to be consumed before the reference health standard (ADI) is exceeded. These calculations are based on the assumption that there is no exposure to chemical residues from non-food sources or any background exposure from other foods.

Table 2: Chemical detections above the Limit of Reporting (LOR) for fish and crustacea

	Sulfadimethoxine	Sulfamethazine (Sulfadimidine)	Sulfameter	Sulfamethoxazole	Sulfamethoxypyridazine	Oxytetracycline	Malachite green	Amoxicillin	Ampicillin	Flumequin	Ciprofloxacin	Enrofloxacin	Florfenicol
Barramundi								✓					
Crab						✓		✓					
Eel, dried	✓	✓	✓		✓								
Fish not further specified				✓				✓				✓	
Garfish						✓							
Hair tail								✓					
Ling								✓	✓				
Mackerel										✓			
Orange Roughy									✓				
Prawn				✓		✓				✓	✓	✓	✓
Perch, climbing						✓	✓						
Spanish Mackerel										✓			
Swordfish								✓	✓				

Table 3: Estimated maximum dietary exposures to chemical residues with concentrations above the LOR for consumers of seafood only*

Chemical	Estimated Mean Dietary Exposure for Consumers					
	(µg/day)			(%ADI*)		
	Fish Only	*Crustacea Only*	*Fish and Crustacea*	*Fish Only*	*Crustacea Only*	*Fish and Crustacea*
Sulfamethazine (Sulfadimidine)	0.9	n/a	0.9	<1	n/a	<1
Sulfadimethoxine	0.3	n/a	0.3	<1	n/a	<1
Sulfamethoxypyridazine	1.2	n/a	1.2	<1	n/a	<1
Sulfameter	1.2	n/a	1.2	<1	n/a	<1
Sulfamethoxazole	0.5	0.4	0.5	<1	<1	<1
Oxytetracycline	0.6	0.7	0.7	<1	<1	<1
Amoxicillin	12.9	29.5	19.9	<1	<1	<1
Ampicillin	12.9	n/a	12.9	<1	n/a	<1
Flumequine	0.8	1.3	1.1	<1	<1	<1
Ciprofloxacin	n/a	0.2	0.2	n/a	<1	<1
Enrofloxacin	3.3	10.1	5.9	3	8	5
Florfenicol	n/a	0.9	0.9	n/a	1	1

* Assumes maximum concentration level reported

3.7 Malachite green margin of exposure

In the case of malachite green, no ADI is available on which to base estimates of safe levels of consumption. To estimate the health risk from potential exposure of malachite green relative to the observed effect level (taken previously as 5 mg/kg bw/day), a margin of exposure approach has been used.

The survey found malachite green at 7.8 µg/kg in climbing perch. Based on mean daily consumption of fish, this residue equates to a level of exposure of approximately 0.011 µg/kg bw/day. The level of exposure reported in the survey is therefore 450,000 times below the Lowest Observed Effect Level (LOEL). At this level of dietary exposure, the health risk from malachite green residues in fish is extremely small.

Table 4: Estimate of seafood consumption required to exceed the ADI

Chemical	Commodity	Maximum detected concentration (µg/kg)	ADI (mg/kg bw)	Approximate consumption amounts required to exceed ADI (kg/day)
Sulfamethazine (Sulfadimidine)	Eel	8.6	0.02	155
Sulfadimethoxine	Eel	3.4	0.20	3,941
Sulfamethoxy-pyridazine	Eel	12	0.2	1,116
Sulfameter	Eel	12	0.1	558
Sulfamethoxazole	Fish (NFS)	5	0.2	2.680
	Prawns	5.4	0.2	2.481
Oxytetracycline	Crab	6.7	0.03	300
	Garfish	2	0.03	1.005
	Prawn	8.6	0.03	233
	Climbing perch	5.9	0.03	340
Amoxicillin	Barramundi	35	0.2	382
	Crab	380	0.2	35
	Fish NFS	58	0.2	231
	Hairtail	130	0.2	103
	Ling	71	0.2	188
	Swordfish	51	0.2	262
Ampicillin	Orange Roughy	10	0.2	1.340
	Ling	16	0.2	837
	Swordfish	130	0.2	103
Flumequine	Mackerel	2	0.03	1,005
	Prawns	17	0.03	118
	Spanish Mackerel	8.2	0.03	245
Ciprofloxacin	Prawn	3.1	0.002	43
Enrofloxacin	Fish NFS	33	0.002	4
	Prawns	130	0.002	1
Florfenicol	Prawns	11	0.001	6

Notes: No other background exposure from other foods considered.
(NFS) = Not further specified
Mean body weight of 67 kg used for Australians aged 2 years and above.

4. Risk Characterisation

Based on the calculations performed using appropriate reference health standards for each chemical (ADIs) and a worst-case scenario, the quantities of a particular seafood that would need to be consumed before reaching levels of exposure that would exceed the acceptable daily intake are very large. In the majority of cases, the upper limit is not reached unless hundreds of kilograms of a particular seafood were to be consumed each day over a lifetime (see Table 4).

The most significant level of exposure is to the fluoroquinolone antimicrobial enrofloxacin, where, based on the maximum concentration found in the survey, exposure would represent only 8% of the ADI. Consumption of at least 1 kg of prawns per day would be required to exceed the acceptable daily intake level for this compound. While it would be possible for an individual to reach this level of consumption, it is very unlikely that this quantity of prawns would be consumed on a daily basis over a lifetime. In addition, enrofloxacin residues are very unlikely to be present at the detected level in every serve of seafood consumed, in every sitting over a lifetime. Given the low level of detection and these qualifying conditions, the levels of enrofloxacin residues detected in the survey do not represent a safety risk.

A previous risk assessment for malachite green (and leucomalachite green) in 2005 indicated a wide margin of exposure between the intake of malachite green residues from fish and the observed effect dose. The level of malachite green residues detected in climbing perch in this survey leads to a similarly wide margin of exposure, and is therefore not considered to pose a safety concern.

5. Conclusion

The chemical residues detected in various species of fish and other types of seafood included in the AQIS survey are not permitted in the Code. In some cases, the residues may arise from the illegal use of antimicrobial compounds to treat protozoa and fungal infections on fish, fish eggs and crustacea particularly under aquaculture conditions.

On the basis of information available to FSANZ and at the levels of dietary exposure to chemical residues estimated in this assessment, the risk to public health and safety from the consumption of various types of fish and crustacea is considered to be very low.

6. References

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ATTACHMENT 1

Sampling and testing

In April 2006, AQIS conducted imported seafood sampling from regions around Australia to test for chemical residues, namely antimicrobial and pesticide residues. In July 2007, FSANZ was provided with the results for 100 imported seafood samples from various regions, which were based on import data from 2005. See Table below for details of sampling.

Summary of seafood data provided to FSANZ by AQIS based on species and region caught

State	Commodity	Sample numbers	Total
New South Wales	Fish	20	44
	Prawn	15	
	Crab	4	
	Eel	5	
Victoria	Fish	20	30
	Prawn	10	
	Crab	0	
	Eel	0	
Queensland	Fish	10	16
	Prawn	2	
	Crab	4	
	Eel	0	
Western Australia	Fish	5	10
	Prawn	3	
	Crab	2	
	Eel	0	
Total	Fish	55	**100**
	Prawn	30	
	Crab	10	
	Eel	5	

ATTACHMENT 2

Following is a list of antimicrobial compounds assessed and the respective Limit of Reporting (LOR).

Antimicrobial Compounds			
Group	**Chemicals**		**Limit of reporting (mg/kg)**
Malachite green	Malachite green	Leucomalachite green	0.002
Quinolones	Oxolinic Acid		0.002
Phenicols	Florfenicol	Thiamphenicol	0.02
Macrolides	Tylosin	Erythromycin	0.002
Fluoroquinolones	Ciprofloxacin	Ofloxacin	0.002
	Enrofloxacin	Gatifloxacin	
	Levofloxacin	Moxifloxacin	
	Flumequine	Norfloxacin	
	Sarafloxacin		
Tetracyclines	Chlortetracycline	Tetracyclines	0.002
	Doxycycline	Oxytetracycline	
Sulphonamides	Sulphamerazine	Sulphamethoxazole	0.002
	Sulphadimethoxine	Sulphamethoxypyridazine	
	Sulphachlorpyridazine	Sulphapyridine	
	Sulphadiazine	Sulphaquinoxaline	
	Sulphadoxine	Sulphathiazole	
	Sulphamethaziine	Sulphatroxazole	
	Sulphameter	Sulphisoxazole	
Penicillin	Ampicillin	Benzyl penicillin	0.01
	Amoxycillin	Cloxacillin	
Other antibiotics	Trimethoprim		0.01

Australian Government
National Health and Medical Research Council

COPY

Ms Melanie Fisher
Acting CEO
Food Standards Australia New Zealand
PO Box 7186
Canberra BC ACT 2610

Dear Ms Fisher

The Australian Quarantine and Inspection Service (AQIS) wrote to the National Health and Medical Research Council (NHMRC) on 31 July 2007 seeking advice on the safety associated with the residues of antimicrobial chemicals detected in a survey of imported seafood. The survey was conducted from April 2006 to March 2007.

I am providing the NHMRC's advice directly to you so it can be included in the full toxicological risk assessment of the survey results being undertaken by Food Standards Australia New Zealand (FSANZ). It is my understanding that the risk assessment will inform AQIS's approach given that its legislation (including the *Quarantine Act 1908* and the *Imported Food Control Act 1992*) depend on advice from FSANZ.

The NHMRC has consulted with members of its Expert Advisory Group on Antimicrobial Resistance (EAGAR) in formulating its advice on the implications of the survey results for antimicrobial resistance and human health.

The survey found a number of antibiotic residues in both raw and cooked seafood samples, albeit at low levels. Of these, the two classes of antibiotics of greatest concern are the quinolones and the fluoroquinolones. The EAGAR *Importance ratings and Summary of Antibiotic Uses in Humans in Australia* (NHMRC website, 2006) classifies quinolones and fluoroquinilones as being of medium and high risk to human health respectively. A high risk rating indicates that if resistance were to develop, there are limited or no alternatives available to treat serious bacterial infections in humans. Neither quinolones nor fluoroquinolones are licensed for use in animal food production of any kind in Australia. The presence of these two classes of antibiotics at any level in the seafood samples tested is of concern.

Transfer of quinolone and fluoroquinolone resistance genes between bacteria is being described with increasing frequency. Robicsek et al (2006) say "Their insidious promotion of substantial resistance, their horizontal spread and their coselection with other resistance elements indicate that a more cautious approach to quinolone use… [is] needed". There is obviously a risk of either potentially pathogenic human bacteria that are quinolone or fluoroquinolone resistant contaminating the seafood, or of resistance being transferred from non-pathogenic bacteria to pathogenic bacteria in the environment and in those handling the raw seafood.

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The AQIS survey contained samples of both cooked and raw seafood. Although it might be assumed that cooked, ready to eat frozen products such as prawns would not contain live pathogens, this is not always the case. For example, Duran and Marshall (2005) were able to isolate numerous resistant human pathogens, including *Escherichia coli*, *Enterococcus* spp, *Salmonella*, *Shigella flexeri*, *Staphloccocus* spp; and *Vibrio* spp., from frozen ready to eat shrimp imported into the US, while Zhao et al (2006) isolated *Salmonella* with resistance to eight antimicrobials from a sample of frozen squid imported into the US from Taiwan.

There is a lack of testing in locally farmed seafood for unlicensed antimicrobials. Although no antibiotics are registered for use in aquaculture in Australia, there is evidence for significant off label use and support for the view that there is a risk of transfer of resistant bacteria to humans from consumption of aquaculture products (Akinbowale et al. 2006).

In light of the above mentioned studies, the NHMRC would encourage FSANZ in future surveys to include both domestic and imported samples and to monitor not only the presence of antibiotic residues but to assess the patterns of resistance in the microbes present. Given that some of the wild caught samples in the survey were detected with antimicrobial residues, it is possible that there has been misidentification of those samples, or that the antimicrobials may have been used post catch.

Please do not hesitate to contact Dr David Abbott at the NHMRC (02 6217 9330 or david.abbott@nhmrc.gov.au) if you require further information.

Yours sincerely

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