FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

5-05
3 August 2005

FIRST REVIEW REPORT

APPLICATION A535

MAXIMUM RESIDUE LIMITS – NEOMYCIN (ANTIBIOTIC)

Table of Contents

EXECUTIVE SUMMARY

Application A535 seeks the establishment of maximum residue limits (MRLs) for mammalian commodities for the antibiotic, neomycin, into the *Australia New Zealand Food Standards Code* (the Code). It is an application from the Australian Pesticides and Veterinary Medicines Authority (APVMA) to update the Code in order to reflect the current registration status of agricultural and veterinary chemicals in use in Australia.

It is proposed to omit the current MRL for neomycin for edible offal, which is at the limit of quantification (LOQ)[1] designated as an asterisk (*) in the table below and establish temporary MRLs for kidney and liver of cattle, goats, sheep and pigs and in mammalian fats (except milk fats) and meat (mammalian). In addition, an increase is proposed from 0.5 to T1.5 mg/kg for neomycin residues in milk.

Therefore, the MRL amendments under consideration in this Application for neomycin are as follows:

Chemical Food	**MRL** **(mg/kg)**	
Neomycin		
Edible offal (mammalian)	Omit	*0.5
Fats mammalian [except milk fats]	Omit	*0.02
	Substitute	T0.5
Kidney of cattle, goats, pigs and sheep	Insert	T10
Liver of cattle, goats, pigs and sheep	Insert	T0.5
Meat (mammalian)	Omit	*0.5
	Substitute	T0.5
Milk	Omit	0.5
Milks	Insert	T1.5

On 15 April 2005, FSANZ was requested by the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) to conduct a Review of the decision taken at FSANZ14 (December 2004) in relation to Application A535 on the basis that public health and safety are not protected.

The Ministerial Council provided the following information concerning the grounds on which the request for the first review is based:

- the current MRL for Neomycin of 0.5 mg/kg is considered safe and should be achievable through good agricultural practices;
- a 20-fold increase is being proposed and further studies are needed to show that this higher level is safe;

[1] The LOQ is the lowest concentration of an agricultural or veterinary chemical residue that can be identified and quantitatively measured in a specified food, agricultural commodity or animal feed with an acceptable degree of certainty by a regulatory method of analysis and is indicated by an * in the above Table

- an MRL of 10 mg/kg provides levels in animal kidneys that are actively antibacterial;

- at this level concerns about antibiotic resistance including the views of the Expert Advisory group on Antimicrobial Resistance (EAGAR) need to be resolved; and

- potential increases in allergic reactions in sensitised individuals require further investigation.

FSANZ response to the issues raised by the Ministerial Council

FSANZ has thoroughly considered the issues raised by the Ministerial Council and considers that there are no public health and safety issues if the MRLs for neomycin are approved for the following reasons:

- FSANZ does not base its decisions on whether the MRLs are appropriate to reflect good agricultural practice (GAP), as this is the key role of the APVMA.

- The proposed MRL for kidney at 10 mg/kg was established and confirmed by the same rigorous risk assessment as used for liver and meat residues. Therefore there is no scientific basis on public health and safety grounds to accept the liver and meat MRLs and reject the kidney MRL.

- While the proposed MRL for kidney of cattle, goats, pigs and sheep is 10 mg/kg this does not mean that residues will be present at that level. The MRL is intended to account for the highest possible residue that could result from the use and not the level that will always be present. It should be noted that residues would only be expected in treated animals and not all animals.

- Based on dietary exposure assessments, the residues associated with the proposed MRLs in this application do not represent an unacceptable risk to public health and safety and account for < 25% of the ADI.

- FSANZ has not assessed whether residues at 10 mg/kg in kidneys would have antibacterial action, as this is not of material concern in assessing the safety of residues. However APVMA has advised FSANZ that neomycin residues in kidney are in a bound form and are not free to exert antibacterial action.

- As part of its Application, APVMA has supplied a letter from the Expert Advisory group on Antimicrobial Resistance (EAGAR)[2] in which EAGAR state that the proposed MRLs are supported, until the APVMA's review of this chemical is completed. EAGAR reconfirmed their original conclusion at a recent meeting on 20 June 2005, where FSANZ specifically asked their advice on all the issues raised by the Ministerial Council.

[2] This is an expert advisory group established by the Australian Government to provide specialist advice to regulatory agencies on issues in relation to antimicrobial resistance.

- Neomycin belongs to the aminoglycoside group of antibiotics and not to the β-lactam group of antibiotics. Therefore, allergic reactions to the residues of this chemical in food are not expected to occur (Joint Expert Committee on Food Additives (JECFA), WHO Food Additive Series 34 – Neomycin). There is no information available indicating that the residues have exhibited allergenic potential, including from countries where neomycin is used more widely than in Australia.

- Although allergic reactions due to antibiotic residues in food may seem to be a possibility in individuals who have previously been sensitized, an examination of the data shows that it is highly unlikely. The Office of Chemical safety (OCS) of the Therapeutic Goods Administration (TGA) of the Australian Government Department of Health and Ageing is not aware of any reports in the medical literature of hypersensitivity reactions due to neomycin residues in food.

- The proposed MRLs are temporary (T) until the APVMA completes its review of neomycin.

FSANZ Decision

FSANZ has undertaken an assessment and review of the proposed MRLs for neomycin as requested by the Ministerial Council for neomycin and reaffirms that the MRLs are appropriate for the following reasons:

- FSANZ supports the APVMA proposals to omit the current MRL for neomycin for edible offal, which is at the and establish temporary (T) MRLs for kidney of cattle, goats, sheep and pigs (T10 mg/kg), liver of cattle, goats, sheep and pigs (T0.5 mg/kg), mammalian fats (except milk fats) (T0.5 mg/kg) and meat (mammalian) (T0.5 mg/kg). In addition, an increase is proposed from 0.5 to T1.5 mg/kg for neomycin residues in milk;

- all MRLs are temporary, pending finalisation of the review being conducted by the APVMA;

- a detailed dietary risk assessment has been undertaken by FSANZ and it was concluded that there are no public health and safety concerns;

- advice from the Expert Advisory Group on Antimicrobial Resistance (EAGAR) re-confirms that the proposed MRLs are supported until the APVMA's review of neomycin is complete; and

- following an assessment of the grounds in which the Ministerial Council requested a review, FSANZ re-affirms its approval of the current drafting for Standard 1.4.2 in relation to the proposed changes to MRLs for neomycin in a range of commodities.

1. Objectives of Review

On 15 April 2005, the Ministerial Council requested a First Review of Application A535 and the draft variations to Standard 1.4.2 – Maximum Residue Limits (Australia Only) of the Code. The Ministerial Council is seeking this review on the grounds that it does not protect public health and safety.

Application A535 seeks the establishment of maximum residue limits (MRLs) for mammalian commodities for the antibiotic, neomycin, into the Code. It is an application from APVMA to update the Code in order to reflect the current registration status of agricultural and veterinary chemicals in use in Australia.

The MRL amendments under consideration in this Application for neomycin are as follows:

Chemical Food	**MRL** **(mg/kg)**	
Neomycin		
Edible offal (mammalian)	Omit	*0.5
Fats mammalian [except milk fats]	Omit	*0.02
	Substitute	T0.5
Kidney of cattle, goats, pigs and sheep	Insert	T10
Liver of cattle, goats, pigs and sheep	Insert	T0.5
Meat (mammalian)	Omit	*0.5
	Substitute	T0.5
Milk	Omit	0.5
Milks	Insert	T1.5

It is proposed to omit the current MRL for neomycin for edible offal, which is at the limit of quantification (LOQ)[3] and establish temporary (T) MRLs for kidney and liver of cattle, goats, sheep and pigs and in mammalian fats (except milk fats) and meat (mammalian). In addition, an increase is proposed from 0.5 to T1.5 mg/kg for neomycin residues in milk.

The objective of this Review is to reconsider the draft variation to Standard 1.4.2 in light of the Ministerial Council's concerns as outlined in Section 2.

2. Review on grounds requested by the Ministerial Council

The First Review was requested on the grounds that the proposed increase in the MRL for Neomycin does not protect public health and safety in that:

- the current MRL for Neomycin of 0.5 mg/kg is considered safe and should be achievable through good agricultural practices;

[3] The LOQ is the lowest concentration of an agricultural or veterinary chemical residue that can be identified and quantitatively measured in a specified food, agricultural commodity or animal feed with an acceptable degree of certainty by a regulatory method of analysis and is indicated by an * in the above

- a 20-fold increase is being proposed and further studies are needed to show that this higher level is safe;

- an MRL of 10 mg/kg provides levels in animal kidneys that are actively antibacterial;

- at this level concerns about antibiotic resistance including the views of EAGAR need to be resolved; and

- potential increases in allergic reactions in sensitised individuals require further investigation.

Following a request for a formal review, FSANZ had three months to complete the review. In this particular case, the Review was required to be completed by 15 July 2005.

2.1 FSANZ evaluation of Public health and safety issues raised by the Jurisdictions

2.1.1 The current MRL for neomycin of 0.5 mg/kg is considered safe and should be achievable through good agricultural practices.

The APVMA currently consider that the proposed MRLs are appropriate and reflect current GAP.

The proposed increases in MRLs are temporary, as an interim measure to cover the occurrence of residues resulting from approved uses, while the APVMA reviews the use of neomycin. The current MRLs for liver and meat have been evaluated as safe and are maintained at the same residue limits, although they now have a temporary status. The proposed MRL for kidney at 10 mg/kg was established and confirmed by the same rigorous risk assessment as used for liver and meat residues. Therefore there is no scientific basis on public health and safety grounds to accept the liver and meat MRLs and reject the kidney MRL.

2.1.2 A 20 fold increase is being proposed and further studies are needed to show that this higher level is safe

The Office of Chemical safety (OCS) of the TGA has considered and established an Acceptable Daily Intake (ADI) for neomycin (see http://www.tga.gov.au/docs/pdf/adi.pdf). APVMA and FSANZ carry out estimations of dietary exposure to agricultural and veterinary chemicals and compare them to the ADI. Based on dietary exposure assessments, the residues associated with the proposed MRLs in this application do not represent an unacceptable risk to public health and safety and account for < 25% of the ADI.

2.1.3 An MRL of 10 mg/kg provides levels in animal kidneys that are actively antibacterial

While the proposed MRL for kidney of cattle, goats, pigs and sheep is 10 mg/kg this does not mean that residues will be present at that level. The MRL is intended to account for the highest possible residue that could result from the use and not the level that will always be present. It should be noted that residues would only be expected in treated animals and not all animals.

FSANZ has not assessed whether residues at 10 mg/kg in kidneys would have antibacterial action, as this is not of material concern in assessing the safety of residues. However APVMA has advised FSANZ that neomycin residues in kidney are in a bound form and are not free to exert antibacterial action. After ingestion the bound neomycin residues are released in the human gut but much is adsorbed onto intestinal contents and inactivated. An *in vitro* study indicates 83 to 98% of neomycin is bound to faecal matter (the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO Food Additive Series 34 – Neomycin) http://www.inchem.org/documents/jecfa/jecmono/v34je07.htm.

Concentrations of neomycin are also diluted in the gut contents. The formula used to calculate the microbiological ADI[4] takes this into account, and with appropriate safety factors ensures that residues ingested at the MRL will not reach the Minimum Inhibitory Concentration (MIC) in the human bowel (colon). The MIC is the minimum concentration of the antibacterial agent in a given culture medium below which bacterial growth is not inhibited. When the proposed MRLs for neomycin were compared to the microbiological ADI, rather than the toxicological ADI[5], overall dietary exposure was <10% of the ADI.

Therefore concentrations resulting from consumption of residues in kidney will not exceed either the toxicological or the microbiological ADI. APVMA also advises that both JECFA and the European Agency for Evaluation of Medicinal Products (EMEA) have reported evidence that neomycin administered to humans at 30 mg/kg bw/day (equal to 1.8g/day for a 60 kg adult) produced no effect on human gut flora. As a comparison, a consumer would have to ingest in excess of 180 kg kidney/day at the MRL of 10 mg/kg to reach a level where effects on the human gut flora might be observed.

2.1.4 At this level[6] concerns about antibiotic resistance including the views of the Expert Advisory group on Antimicrobial Resistance (EAGAR) need to be resolved.

As part of its application, APVMA has supplied a letter from EAGAR in which EAGAR state that the proposed MRLs are supported, until the APVMA's review of this chemical is completed (refer to Section 2.2).

2.1.5 Potential increases in allergic reactions in sensitised individuals require further investigation

Neomycin belongs to the aminoglycoside group of antibiotics and not to the β-lactam group of antibiotics. Therefore, allergic reactions to the residues of this chemical in food are not expected to occur (Joint Expert Committee on Food Additives (JECFA), WHO Food Additive Series 34 – Neomycin). There is no information available indicating that the residues have exhibited allergenic potential, including from countries where neomycin is used more widely than in Australia.

---

[4] The microbiological ADI is a new health reference level which incorporates the microbiological effects of antibiotic residues, which also takes into consideration the possibility of selection of antibiotic resistant micro organisms.

[5] Established by the Office of Chemical Safety of the TGA

[6] This relates to a change from an MRL of 0.5 mg/kg in edible offal (mammalian) to a temporary MRL of 10 mg/kg in kidney of cattle, goats, pigs and sheep.

APVMA bases its evaluation of the issue of allergenicity on information evaluated by OCS who provides APVMA with a toxicology report, which includes any available information on immunotoxicity derived from appropriate tests and sources. APVMA also sources information from other evaluations, such as JECFA. Any significant issues that arise concerning specific immunotoxicological effects of antibiotics are dealt with in APVMA reports. Through this process FSANZ can be assured that all potential immunotoxic effects of antibiotics are evaluated.

Information from OCS indicates no evidence of primary sensitisation through oral exposure to the low level of antibiotic residues in food. This indicates that, in most instances, primary sensitisation will have resulted from human therapeutic use, which is at substantially higher levels than those incurred through consumption of neomycin residues in food. In these cases any information regarding potential allergenicity would be known from studies related to use in humans.

Although allergic reactions due to antibiotic residues in food may seem to be a possibility in individuals who have previously been sensitized, an examination of the data shows that it is highly unlikely. The OCS is not aware of any reports in the medical literature of hypersensitivity reactions due to neomycin residues in food.

2.2 Advice from EAGAR meeting on 20 June 2005

The National Health and Medical Research Council established EAGAR to provide advice to government and regulatory agencies on antibiotic resistance and especially measures to reduce the risks of antibiotic resistance. As part of its Application, APVMA has supplied a letter from EAGAR in which EAGAR stated that it supported the proposed MRLs as a temporary measure only, until the APVMA's review of this chemical was completed.

In light of the issues raised by the Ministerial Council, FSANZ raised these specific issues with EAGAR at its meeting on 20 June 2005. EAGAR reconfirmed its original conclusion that it supported the proposed MRLs as a temporary measure only, until the APVMA's review of this chemical is completed. EAGAR did not agree that further studies were needed to show that the increase in the MRL for kidneys was safe, as the safety has already been adequately established and discussed extensively by EAGAR at a previous meeting (**Attachment 2**).

3. Background

Neomycin is an aminoglycoside antibiotic; it is used is to treat bacterial enteritis (scours) in cattle and pigs. Aminoglycosides are mostly bactericidal antibiotics with activity limited to aerobic bacteria and mycoplasma. This chemical has limited use in human medicine, as there are a number of alternative antibiotics available. The data before APVMA indicates that the present MRLs, based on the usage of neomycin, should be reviewed due to concerns about residues in kidney exceeding the current MRL. Both the New South Wales and Victorian Departments of Agriculture have indicated an on-going problem with neomycin residues in kidney exceeding the MRL following therapeutic use on culled cows and also on calves. Some of the above cases were the result of parenteral use. However, none of the residues found by the States in kidney exceeded the Codex MRL of 10 mg/kg.

There is no change to the dose rates, methods of use for neomycin or the withholding period. The current method of uses include:

- cattle – injection, orally and topically;
- pigs – injection or orally; and
- sheep – injection only.

4. Conclusions from the Final Assessment Report

The dietary exposure assessments indicate that the residues associated with the proposed MRLs for neomycin do not represent an unacceptable risk to public health and safety. APVMA has already registered this chemical product and rejection of the MRLs would result in legally treated food not being able to be legally sold. Therefore, accepting the requested changes will benefit all stakeholders by maintaining public health and safety while permitting the legal sale of food treated with agricultural and veterinary chemicals to control pests and diseases, and improve agricultural productivity and animal welfare.

The use of neomycin and its MRLs are to be reviewed as part of APVMA's Existing Chemical Review Program. Further information on the APVMA's review process can be found at the APVMA website at http://www.apvma.gov.au/chemrev/chemrev2.shtml.

In addition, regulatory agencies involved in the regulation of chemical products continue to monitor health, agricultural and environmental issues associated with the use of chemical products.

The residues in food are also monitored through:

- State and Territory residue monitoring programs;
- Australian Government programs such as the National Residue Survey; and
- dietary exposure surveys such as the Australian Total Diet Survey.

These monitoring programs and the continual review of the use of agricultural and veterinary chemicals mean that considerable scope exists to review MRLs on a continual basis.
At this time it is proposed that the proposed MRL amendments should come into effect upon gazettal and continue to be monitored by the same means as other residues in food.

4.1 Impact of Regulatory options

The following options were identified for Application A535:

4.1.1 Option 1 – status quo – no change to the existing MRLs in the Code

Under this option, the status quo would be maintained and there would be no changes in the existing MRLs to the Code.

4.1.2 Option 2(a) – adopt the change to MRLs to delete or decrease some existing MRLs

Under this option, only those variations that were reductions and deletions would be approved for inclusion into the Code. The proposed increases and inclusions of new MRLs would not be approved.

4.1.3 Option 2(b) – adopt the changes to MRLs to include new or increase some existing MRLs

Under this option, only those variations that were increases and additions of MRLs would be approved for inclusion into the Code. The proposed decreases and deletions of MRLs would not be approved.

FSANZ's preferred approach was to adopt Options 2(a) and 2(b) – to adopt the change to MRLs in the Code to include new or increase some existing MRLs and to delete or decrease some existing MRLs. FSANZ preferred this approach because:

- the residues associated with the MRL amendments would not result in an unacceptable risk to public health and safety (this benefit also applies to Option 1);
- the changes would minimise the potential costs to primary producers and rural and regional communities in terms of legally being able to sell legally treated food;
- the changes would minimise residues consistent with the effective use of agricultural and veterinary chemicals to control pests and diseases; and
- the changes would remove discrepancies between agricultural and food legislation and assist enforcement.

4.2 Consultation

FSANZ undertook one round of public consultation in relation to this Application. A total of 5 submissions were received. Issues raised in the public submissions consisted of the following:

- the potential for development of antimicrobial resistance;
- antibiotics as allergens;
- time limits placed on MRLs for permits;
- Limit of Quantification;
- stakeholders reviewing the submissions;
- harmonisation of the FSANZ and APVMA processes for establishing MRLs;
- establishing MRLs and control of agricultural and veterinary chemicals under the proposed primary production standards;
- end point for MRLs i.e. where is the MRL to be established, the point of sale or the farm gate;
- violations of the existing milk MRL for neomycin;
- use of antibiotics;
- minimising the dietary exposure to residues of neomycin; and
- internationally recognised acceptable daily intakes.

FSANZ made a comprehensive assessment of all the above issues, which is contained in the Final Assessment Report.

4.3 Statement of Reasons

FSANZ agreed at FSANZ14 to progressing this Application for the following reasons:

- The dietary exposure assessment indicates that the residues associated with the proposed MRLs for neomycin do not represent an unacceptable risk to public health and safety.

- The proposed MRLs in this Application are not the result of changes to the usage pattern for neomycin. The data before APVMA indicates that the present MRLs, based on the usage of neomycin, should be reviewed due to residues in kidney exceeding its current MRL. The requested changes will benefit all stakeholders by maintaining public confidence in the health and safety of this chemical while permitting the legal sale of products treated with neomycin.

- APVMA has assessed appropriate toxicology, residue, animal transfer, processing and metabolism studies, in accordance with the *Guidelines for Registering Agricultural and Veterinary Chemicals, the Ag and Vet Requirements Series, 1997*, to support the use of neomycin.

- The Office of Chemical Safety (OCS) of the Therapeutic Goods Administration (TGA) of the Australian Government Department of Health and Ageing has undertaken an appropriate toxicological assessment of the neomycin and has established relevant ADI.

- The Expert Advisory Group on Antimicrobial Resistance (EAGAR) has evaluated the impact of the potential residues of neomycin in the food supply and has supported the proposed MRLs in this Application.

- FSANZ has undertaken a regulation impact assessment process. That process concluded that the amendment to the Code is necessary, cost effective and of benefit to both producers and consumers.

- None of FSANZ's section 10 objectives of food regulatory measures are compromised by the proposed changes.

The proposed drafting to amend the Code is shown in **Attachment 1**.

5. Review Options

There are three options proposed for consideration under this Review:

1. reaffirm approval of the draft variation to Standard 1.4.2; or

2. reaffirm approval of the draft variation to Standard 1.4.2 subject to any amendments FSANZ considers necessary; or

3. withdraw approval of the draft variation to Standards 1.4.2 as notified to the Council.

No additional data has been presented to the Board to justify a consideration under option 2 and 3.

The recommended option is Option 1.

6. Conclusion

Following an assessment of the grounds in which the Ministerial Council requested a review, FSANZ reaffirms that the MRLs for neomycin are appropriate for the following reasons:

- FSANZ supports the APVMA proposals to omit the current MRL for neomycin for edible offal, which is at the LOQ and establish temporary (T) MRLs for kidney of cattle, goats, sheep and pigs (T10 mg/kg), liver of cattle, goats, sheep and pigs (T0.5 mg/kg), mammalian fats (except milk fats) (T0.5 mg/kg) and meat (mammalian) (T0.5 mg/kg). In addition, an increase is proposed from 0.5 to T1.5 mg/kg for neomycin residues in milk.

- All MRLs are temporary, pending finalisation of the review being conducted by the APVMA.

- A detailed dietary risk assessment has been undertaken by FSANZ and it was concluded that there are no public health and safety concerns.

- Advice from EAGAR re-confirms that the proposed MRLs are supported until the APVMA's review of neomycin is complete.

ATTACHMENT

1. Draft variation or standard to the *Australia New Zealand Food Standards Code*

ATTACHMENT 1

Draft Variations to the *Australia New Zealand Food Standards Code*

To commence: On gazettal

[1] ***Standard 1.4.2*** *of the Australia New Zealand Food Standards Code is varied by –*

[1.1] *omitting from* Schedule 1 *the food and associated MRLs for the following chemical –*

NEOMYCIN	
INHIBITORY SUBSTANCE, IDENTIFIED AS NEOMYCIN	
EDIBLE OFFAL (MAMMALIAN)	*0.5
MILK	0.5

[1.2] *inserting in* Schedule 1 *the foods and associated MRLs for the following chemical –*

NEOMYCIN	
INHIBITORY SUBSTANCE, IDENTIFIED AS NEOMYCIN	
KIDNEY OF CATTLE, GOATS, PIGS AND SHEEP	T10
LIVER OF CATTLE, GOATS, PIGS AND SHEEP	T0.5
MILKS	T1.5

[1.3] *omitting from* Schedule 1 *under the entries for the following chemical, the maximum residue limit for the food, substituting –*

NEOMYCIN	
INHIBITORY SUBSTANCE, IDENTIFIED AS NEOMYCIN	
FATS (MAMMALIAN) [EXCEPT MILK FATS]	T0.5
MEAT (MAMMALIAN)	T0.5