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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use

## European public MRL assessment report (EPMAR)

### Neomycin (including framycetin) (All food producing species)

On 29 October 2013 the European Commission adopted a Regulation<sup>1</sup> modifying the maximum residue limits for neomycin (including framycetin) in all food producing species, valid throughout the European Union. These modified maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Neomycin (including framycetin) is intended for use in all food producing species for the treatment of bacterial gastrointestinal infections and mastitis via oral, intramammary and intramuscular administration.

Maximum residue limits had previously been established for neomycin (including framycetin) for all food producing species. Merial submitted an application for the modification of maximum residue limits to the European Medicines Agency, on 1 September 2010.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 10 November 2011 the modification of maximum residue limits for neomycin (including framycetin) in all food producing species.

On 23 November 2011, Merial informed the European Medicines Agency that it intended to request a re-examination of the CVMP opinion and the grounds for the re-examination were submitted on 9 January 2012. The Committee for Medicinal Products for Veterinary Use adopted an opinion on 8 March 2012.

On 23 April 2012 the European Commission requested a review of the opinion in order to improve the clarity of the document. The Committee for Medicinal Products for Veterinary Use adopted its final opinion on 16 May 2012.

Subsequently the Commission recommended on 8 June 2013 that the modified maximum residue limits in all food producing species are established. This recommendation was confirmed on 29 June 2013 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 29 October 2013.

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<sup>1</sup> Commission Implementing Regulation (EU) No 1056, O.J. L 288, of 30.10.2013



# European public MRL assessment report (EPMAR)

Neomycin (modification of MRLs)

## Summary of the scientific discussion for the establishment of MRLs

Substance name:	Neomycin
Therapeutic class:	Anti-infectious agents/Antibiotics
Procedure number:	EU/10/180/MER
Applicant:	MERIAL
Target species:	Bovine
Intended therapeutic indication:	Treatment of bacterial gastrointestinal infections and mastitis Treatment of sepsis of young and adult animals, pneumoniae and pleuro-pneumoniae, post-partum infections, urinary tract infections, infected wounds (such as whitlow interdigital), abscesses (such as omphalophlebitis), and postoperative infections caused by bacteria sensitive to neomycin.
Route(s) of administration:	Oral, intramammary and intramuscular injection

### 1. Introduction

Neomycin is an aminoglycoside antibiotic consisting of 3 components, A, B and C. Component B is the largest component of commercial preparations of neomycin (over 90%). Framycetin (also known as soframycin) is largely component B. Component A is present only in traces (less than 1%). Neomycin is used to treat bacterial gastrointestinal infections of cattle, sheep, pigs, goats and poultry by the oral route and to treat mastitis by intramammary administration. The therapeutic dosages are 10 to 20 mg/kg for cattle, 150 to 350 mg/infusion for intramammary use, 10 mg/kg for sheep, 10 to 15 mg/kg for pigs and 10 to 30 mg/kg for chickens, turkeys and ducks. The duration of treatment is 3 to 7 days for poultry and up to 14 days for larger animals.

Neomycin is used in cattle intramuscularly for the treatment of sepsis of young and adult animals, pneumoniae and pleuro-pneumoniae, post-partum infections, urinary tract infections, infected wounds (such as whitlow interdigital), abscesses (such as omphalophlebitis), and postoperative infections caused by bacteria sensitive to neomycin, at a dose of 1 ml/10 kg bw/day equivalent to 12 mg/kg bw/day, for 5 days, given intramuscularly at 24 hour intervals.

The CVMP has previously assessed the consumer safety of neomycin and established a toxicological ADI of 60 µg/kg bw, i.e. 3.6 mg/person.

Currently, neomycin is included in table 1 of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009 in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Neomycin (including framycetin)	Neomycin B	All food producing species	500 µg/kg 500 µg/kg 500 µg/kg 5000 µg/kg 1500 µg/kg 500 µg/kg	Muscle Fat Liver Kidney Milk Eggs	For fin fish the muscle MRL relates to 'muscle and skin in natural proportions'. MRLs for fat, liver and kidney do not apply to fin fish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'.	Anti-infectious agents/ Antibiotics

MERIAL submitted an application for the modification of the maximum residue limits for bovine species in order to take into account new residue depletion studies following parenteral administration.

## 2. Scientific risk assessment

### 2.1. Safety assessment

The CVMP has previously assessed the consumer safety of neomycin. A toxicological ADI of 60 µg/kg bw (3.6 mg/person) was established based on the NOEL of 6 mg/kg bw/day for ototoxicity in the guinea-pig and applying a safety factor of 100. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this modification application.

### 2.2. Residues assessment

#### 2.2.1. Pharmacokinetics in target species

Neomycin is poorly absorbed from the gastrointestinal tract of humans and animals, and it has low absorption from the udder. In healthy humans given therapeutic oral doses of neomycin sulphate (i.e. more than 1000 mg) neomycin absorption from the gastrointestinal tract is estimated to be less than 10% based on blood and urine analysis. A study in calves dosed orally with <sup>14</sup>C-neomycin provided more direct evidence to support the view that high percentages of neomycin remain in the gastrointestinal tract. The absorption in this species was minimal (1 to 11%); about 90% was recovered in faeces and 70 to 80% was present as parent neomycin.

Neomycin undergoes negligible biotransformation after parenteral administration. It is excreted after oral doses in the faeces, but after parenteral administration it is excreted in the urine.

### 2.2.2. Residue depletion studies

Residue data following oral and intramammary administration were previously submitted in cattle, sheep, goats, pigs, chicken, turkeys, ducks and milk and eggs and were assessed resulting in the establishment of the same maximum residue limits in all food producing species. Maximum residue limits were also established in milk and eggs.

The data submitted for the establishment of the existing MRLs and their evaluation are reported below:

#### Cattle

Calves of different ages (3 to 60 days old) were given approximately 30 mg/kg bw <sup>14</sup>C-neomycin (specific activity of 3 to 9 Bq(Becquerel)/µg neomycin B) by oral administration (via bottle or capsule). Ninety six hours after treatment, in calves treated at 3 days of age, at least 96% of the radioactivity in kidney was present as neomycin. Residues were also found in liver and muscle in all calves, with highest concentrations in tissues of 3 day old calves. Ninety-six hours after oral treatment of animals of 3 days of age, the following concentrations of total radioactivity were measured: 55 000, 1930 and 91 µg equivalents/kg in kidney, liver and muscle, respectively, whereas in animals of 53 to 63 days of age, the levels of radioactivity were 7400, 330 and 64 µg equivalents neomycin/kg, respectively. Although this study showed that residues were highest in young calves, confirming that there is a significant difference in absorption of neomycin in young calves versus older animals, independent of whether the calf is ruminating or non-ruminating at the time of treatment, due to the large variation in residues measured in edible tissues of calves after oral administration with different formulations, no clear conclusion can be reached regarding the amount of residues found in edible tissues after administration of the recommended dosage.

Twenty cattle were daily administered via medicated drinking water about 20 mg neomycin sulphate/kg bw for 14 consecutive days. Animals were slaughtered at 0, 1, 3, 7 and 14 days after treatment. Liver, muscle, fat and kidney tissue samples were obtained from each sacrificed calf and analysed for neomycin residues by a microbiological method. No neomycin residues were found in muscle, liver, and fat tissues of any of the treated cattle at any sampling time. In kidney, neomycin concentrations were 2791 µg/kg immediately after treatment, 2899 µg/kg at 24 hours after treatment and 1685 µg/kg at 3 days after treatment. By 7 days after treatment, 2 of the 3 treated cattle that were sampled had detectable kidney neomycin residues below 500 µg/kg (limit of quantification of the microbiological method) and 1 animal had a level of 620 µg/kg. One of the 4 treated cattle sampled at 14 days after treatment showed residues at the limit of quantification and the other 3 animals did not have detectable residues.

Sixteen healthy cows received an intramammary infusion containing 330 mg lincomycin base, as lincomycin hydrochloride, and 100 mg neomycin base, as neomycin sulphate, in each of the 4 udder quarters, following each of 3 successive milkings at 12 hours intervals. Treated animals were slaughtered at 1, 7, 14 and 21 days after last treatment and the following tissues were harvested: liver, both kidneys, perineal fat, semitendinosus/semimembranosus muscle and one sample from each udder quarter. Neomycin was quantified in tissues using an HPLC method (limit of quantification: 100 µg/kg for all matrices). Measurable concentrations of neomycin residues were only present in kidney and udder. For kidney the mean concentrations were 700 µg/kg at day 1, 315 µg/kg at day 7, 205 µg/kg at day 14 and the concentrations were lower than limit of quantification or 107 µg/kg at day 21. For udder the mean concentrations were 1610 µg/kg at day 1 and 107 µg/kg at day 7 and the concentrations were lower than the limit of quantification or 425 µg/kg and 106 µg/kg at

14 and 21 days, respectively. For the other tissues residues were all below the limit of quantification at all sampling times.

Twenty four healthy cows were divided into four groups and treated with an intramammary infusion containing 330 mg lincomycin base, as lincomycin hydrochloride and 100 mg neomycin base, as neomycin sulphate in each of the four udder quarters at 12 hour intervals, following each of 3 successive milkings. Neomycin was quantified in plasma, quarter milk and pooled milk samples using an HPLC method (limit of quantification: 100 µg/l for both matrices). Mean neomycin concentrations in quarter milk samples collected at 12 hours after each of the three infusions were 22 200, 29 900 and 28 000 µg/l, and 4900 µg/l at 24 hours after last infusion. For the pooled samples, the mean neomycin concentration at 12 hours after last infusion was 24 000 µg/l. At 24 hours after last infusion, the mean concentration was 4800 µg/l. At 60, 72 and 84 hours after the last infusion, the mean neomycin concentrations in pooled milk samples were estimated to be 240, 200 and 120 µg/l, respectively.

### **Pigs**

Twenty pigs were treated for 14 consecutive days with medicated water calculated to provide approximately 20 mg of neomycin sulphate/kg bw/day. At the end of the treatment, 4 animals were sacrificed for tissue collection and drug residue analysed at each of the withdrawal intervals of 0 hours and at 1, 3, 7 and 14 days. Tissues were assayed for neomycin residues by a microbiological method (limit of quantification: 500 µg/kg). No neomycin residues were found in muscle, fat or liver tissues from any treated pig at any sampling time. For kidney mean neomycin levels were 2174 µg/kg immediately after treatment, 1920 µg/kg at 24 hours after treatment and 958 µg/kg at 3 days after treatment. At 14 days after treatment, 3 of the 4 animals had no detectable neomycin residues in kidney tissue while in one pig neomycin concentration in kidney was 906 µg/kg.

### **Sheep**

Twenty sheep were treated for 14 consecutive days with medicated water calculated to provide approximately 20 mg of neomycin sulphate/kg bw/day. At the end of the treatment, samples of tissues were collected for drug residue analyses at each of the withdrawal intervals of 1, 3, 7, 14 and 21 days. Tissues were assayed for neomycin residues by a microbiological method (limit of quantification: 500 µg/kg). No neomycin residues were found in muscle, fat or liver tissues from any treated sheep at any sampling time. In kidneys at 24 hours after treatment neomycin residue levels averaged 982 µg/kg. Of tissues collected at 3 days after treatment, only 1 of 4 animals sampled had a quantifiable kidney neomycin concentration (522 µg/kg). No detectable neomycin was measured in kidney at days 7, 14 and 21 after treatment.

### **Goats**

Twenty goats were treated for 14 consecutive days with medicated water calculated to provide approximately 20 mg of neomycin sulphate/kg bw/day. At the conclusion of the medicated period, the treated animals were sacrificed for tissue collection and drug residues analysed at each of the withdrawal intervals of 12, 24, 48 and 96 hours. Tissues were assayed for neomycin residues by a microbiological method (limit of quantification: 500 µg/kg). No neomycin residues were found in muscle, fat or liver tissues from any treated goat at any sampling time. In kidney neomycin residue levels averaged approximately 1000 µg/kg at 12 hours after treatment, 2100 µg/kg at 24 hours after treatment, 1700 µg/kg at 48 hours after treatment, 1100 µg/kg at 72 hours after treatment and 700 µg/kg at 96 hours after treatment.

## Chicken

A single dose of 36.7 mg neomycin base/kg bw given in the feed was administered to 150 broiler chickens for 7 consecutive days. At day 7 and for 5 consecutive days thereafter chickens were slaughtered per time point and their liver, muscle and kidneys analysed for the presence of neomycin residues, using a microbiological method (limit of detection: 500 µg/kg). Both liver and muscle were free of detectable neomycin residues at each time tested. In kidney, neomycin could be detected up to the third day after treatment cessation, with residue levels below 5 mg/kg at all time points.

A single dose of 10 mg/kg or 30 mg of neomycin/kg bw, dissolved in drinking water, was given by intubation to broiler chickens for 7 consecutive days. With 0.5 mg/kg as the detectable limit of the microbiological assay, major edible visceral organs were examined for residues. In the 10 mg/kg/day group, the neomycin residue concentrations in kidney were 870 µg/kg at day 1 and 600 µg/kg at day 3. Neomycin was below the limit of detection in the kidney at the day 13. The neomycin 30 mg/kg bw group was comparable with the 10 mg/kg bw group in residue trend. The mean neomycin concentration in kidney was 3080 µg/kg at day 1 after treatment.

One hundred and fifty laying hens were divided in three groups and were treated with different concentrations of neomycin: 40.25 mg neomycin base/kg bw for 5 days, 33.2 mg neomycin base/kg bw for 7 days and 40.25 mg neomycin base/kg bw for 7 days. Eggs were sampled from the treated groups 1, 2 and 3 days after treatment. In the third treatment group eggs were sampled also during treatment. Assay was performed according to an agar diffusion method (limit of detection: 500 µg/kg). No residues of neomycin were detected during or after drug administration in all 3 treatment groups.

## Turkeys

Fifty-four turkeys were treated for 5 consecutive days with medicated water calculated to provide approximately 20 mg of neomycin sulphate/kg bw/day. At the end of medication period, sample tissues of skin with adherent fat, abdominal fat, liver, kidney, white muscle (breast) and dark muscle (leg/thigh) were collected for residue analysis by microbiological assay (limit of quantification: 500 µg/kg) at withdrawal intervals of 12, 24, 48, 72, 120 and 240 hours. No neomycin residues were found in skin, liver, muscle or fat at any of the withdrawal intervals. Neomycin was found in measurable levels in the kidney at the 12 hour (727 µg/kg) and 24 hour (500 µg/kg) withdrawal intervals.

## Ducks

Fifty-four ducks were treated for 21 consecutive days with medicated water calculated to provide approximately 10 mg of neomycin sulphate/kg bw/day. At the end of the treatment, sample tissues of skin with adherent fat, liver, kidney and muscle were collected from 6 animals selected at random for residue analysis by microbiological assay (limit of detection: 500 µg/kg) at withdrawal intervals of 1, 2, 3, 4, 5, 7 and 14 days. No neomycin residues were found in skin plus fat, liver or muscle at any of the withdrawal intervals. Neomycin was found in measurable levels in the kidney (mean residue concentration: 890 µg/kg) until 14 days after treatment.

## New data submitted for the modification of MRLs

New residue data following intramuscular administration in cattle were submitted which are reported below:

Twenty four cattle (4 per treatment group) were treated with a commercial formulation for 5 consecutive days by intramuscular route with a dose of 1 ml/10 kg bw/day (equivalent to 12 mg/kg bw neomycin per day). Two control animals were left untreated. Tissues (muscle, liver, kidney, fat and

muscle injection site) were collected on day 7 after last injection (controls and group 1), and for the other 5 groups on days 14, 21, 30, 45 and 60 respectively, after last injection. Neomycin was assayed in tissues by an HPLC-fluorescence method of which linearity was shown from 100 to 1000 µg/kg for each tissue. Kidney was the tissue that presented the highest level of residue of neomycin followed by liver, injection site, fat and muscle. Except for fat, muscle and injection site from day 14 after last injection (from which residue levels ranged from 822 µg/kg to below 100 µg/kg) residue tissue levels were well above the highest concentrations at which the assay method was validated. The results of this study are therefore of limited value given the limitations of the analytical method.

The depletion of neomycin in bovine tissues following repeated daily administration of the commercial product for five days by intramuscular injection at a dose rate of 1 ml per 10 kg body weight in ruminating cattle was determined. Tissue samples (kidney, liver, fat, skeletal muscle, injection site) were collected on days 21, 30, 45, 60, 75 and 90 after the last treatment. Each sample was assayed for determination of neomycin using a validated HPLC-fluorescence method. The analytical method was validated in the calibration range from 100 to 1000 µg/kg in fat and muscle, from 100 to 5 000 µg/kg in injection site, from 100 to 32 000 µg/kg in liver and from 100 to 210 000 µg/kg in kidney. Muscle neomycin levels of treated animals were below the limit of quantification (LOQ) from day 21 on with all animals below the limit of detection (non-detectable) on day 90. Fat neomycin levels of treated animals were below the LOQ from day 30 on with all animals below the limit of detection (non-detectable) on days 75 and 90. Mean neomycin concentrations at the injection site were 492, 402, 342, 215, 252 and 160 µg/kg respectively 21, 30, 45, 60, 75 and 90 days after administration. Mean neomycin concentrations in liver were 8175, 5050, 3375, 2275, 1312 and 682 µg/kg respectively 21, 30, 45, 60, 75 and 90 days post-dosing. Mean neomycin concentrations in kidney were 15500, 6900, 6525, 3550, 2575 and 2350 µg/kg respectively 21, 30, 45, 60, 75 and 90 days after administration.

It is noted that the two studies show some degree of variability in the injection site residues.

### **Selection of marker residue and ratio of marker to total residues**

During the previous evaluation of neomycin residue data were available for cattle, sheep, goats, pigs, chickens, turkeys, ducks and milk after oral and intramammary administration. Neomycin B was retained as the marker residue.

The ratio of marker to total residues was not established in all relevant tissues of the target species. However, considering that the major part of neomycin administered to farm animals is excreted in an unchanged form in the urine and faeces, only a very small proportion of potential tissue residues in farm animals is likely to be in the form of a metabolite. Ninety-six hours after oral dosing of calves with 30 mg/kg bw <sup>14</sup>C-neomycin, at least 96% of the residues in kidney was present as neomycin. Therefore, the available data suggested that, like the other aminoglycosides, neomycin is not significantly metabolised and a value of 1 was retained for the ratio of marker to total residues.

The new data provided after intramuscular administration gave no reason to change the previous conclusions on the marker residue and on marker to total residues ratio.

### **2.2.3. Monitoring or exposure data**

No data provided.

### **2.2.4. Analytical method for monitoring of residues**

The proposed routine analytical method was based on HPLC with fluorescence detection. The method detects precisely the B component of neomycin i.e. framycetin. The limit of quantification of the

method for muscle, fat, liver and kidney is 100 µg/kg. The limits of detection are: muscle (24 µg/kg), muscle injection site (15 µg/kg), fat (12 µg/kg), liver (19 µg/kg) and kidney (15 µg/kg).

The method was described in an internationally recognised format and validated according to Volume 8 of the rules governing medicinal products in the European Union.

The proposed analytical method has been reviewed by the relevant European Union Reference Laboratory which confirmed the CVMP conclusions.

### **2.2.5. Findings of EU or international scientific bodies**

Codex Alimentarius, following the JECFA (Joint FAO/WHO Expert Committee on Food Additives) recommendations, adopted in 2005 the following MRLs: cattle kidney, 10 000 µg/kg; cattle liver, 500 µg/kg; and cows' milk, 1500 µg/kg. The previous MRLs of 500 µg/kg for cattle muscle and fat established in 1999 were maintained. The Codex marker residue is the parent compound, neomycin. Codex has also established MRLs for pigs, sheep, goats, turkeys, ducks and chickens. Codex Alimentarius retained neomycin as marker residue.

## **3. Risk management considerations**

### ***3.1. Potential effects on the microorganisms used for industrial food processing***

The effect of neomycin in milk on bacterial starter cultures used in the production of fermented milk products were previously evaluated. A number of bacterial starter culture types were used: a group of buttermilk/sour cream cultures containing *Lactococcus lactis* spp. *lactis* and spp. *cremoris* or a mixture of lactic acid producers and citric fermenters; a second group of Italian cheese cultures containing *S. thermophilus*; a third group of Italian cheese cultures containing *Lactobacillus helveticus* and a group of yoghurt cultures containing *S. thermophilus* and *Lactobacillus delbrueckii* spp. *bulgaricus*. Neomycin concentrations of 0.063, 0.125, 0.25, 0.50, 1.0, 2.0 and 4.0 µg neomycin/ml in milk were examined. The yoghurt starter cultures were the most sensitive. Results indicated that neomycin in milk at concentrations less than or equal to 2.0 µg/ml should not have an adverse effect on the growth of bacterial starter cultures used in the fermented milk products.

### ***3.2. Other relevant risk management considerations for the establishment of maximum residue limits***

The CVMP has previously established MRLs for neomycin based on data following oral and intramammary administration. The current MRLs do not reflect the depletion of residues after parenteral administration as the residue levels in some tissues can be increased due to higher relative bioavailability following parenteral administration. The CVMP considered it appropriate to take into consideration the higher residue levels observed in tissues following parenteral administration when revising the MRLs for neomycin. This increase in MRLs may allow for shorter withdrawal periods for some of the existing neomycin containing products.

### ***3.3. Elaboration of MRLs***

MRLs were previously set by the CVMP for all edible tissues, muscle, fat, liver, kidney, milk, and eggs based on data from oral and intramammary administration. Based on current MRL values, the Theoretical Maximum Daily Intake of residue is 2775 µg which represents 77% of the toxicological ADI.



New data were submitted to consider residues depletion following parenteral administration in cattle. The new residue data following intramuscular administration provide a better insight of the residue distribution and demonstrate a higher systemic exposure following parenteral administration thus supporting the increase of the MRLs for kidney and liver. Based on these data increased MRLs for liver and kidney in cattle can be recommend as follows: 5500 µg/kg for liver and 9000 µg/kg for kidney.

With regard to muscle the existing MRL does not follow the residue distribution. In the newly provided residue studies, residues in non-injection site muscle are below the limit of quantification (LOQ) (100 µg/kg) after day 21. In previous oral residue studies in cattle, no residues in muscle could be found immediately after the administration of neomycin. On the other hand residues in injection site were higher compared to non-injection site muscle. For fat the situation is similar; residues are below the LOQ (100 µg/kg) after day 30. In instances where residue levels are very low, it is current practice to establish the MRLs at twice the limit of quantification (LOQ) as indicated in Volume 8 of the Rules Governing Medicinal Products in the EU. However, reducing the MRL values already established for both muscle and fat (500 µg/kg) could have unfavourable consequences on products already available on the market and which do not represent a risk to consumers. Consequently, no changes are recommended for the MRLs in muscle and fat (500 µg/kg).

No new data relating to residues in milk were available and as a result no change to the existing milk MRL (1500 µg/kg) is recommended.

The Codex Alimentarius MRLs for cattle tissues (fat, liver and muscle 500 µg/kg, kidney 10 000 µg/kg), differ from the current EU MRL values for kidney only, where they are twice the EU MRL. The Codex MRLs are based on oral and intramammary administration of the substance.

The CVMP notes that the modification of the existing EU MRLs for liver and kidney in cattle will lead to greater disharmony with the Codex MRLs. However, the proposed increase in the kidney and liver MRLs is justified by the new residue data which reflects the residue distribution following parenteral route of administration.

#### Calculation of theoretical daily intake of residues

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product (µg)
Muscle	0.30	500	1	150
Fat (mammals)	0.05	500	1	25
Liver	0.10	5500	1	550
Kidney (mammals)	0.05	9000	1	450
Milk	1.50	1500	1	2250
Eggs	0.10	500	1	50
Honey	0.02	N/a	N/a	N/a
Theoretical Maximum Daily Intake (µg)				3475
Fraction ADI (ratio TMDI/ADI*100)				96.5%

The remaining 3.5% of the ADI would still allow for the establishment of MRLs in honey, if required.

### 3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of using the modified maximum residue limits recommended for neomycin in cattle to other species/food commodities. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

Animal	Extrapolation	Justification

species/ food commodities	possible (YES/NO)	
All food producing species	Yes	<p>Currently the same MRL values are established in all food producing species. Pharmacokinetics of neomycin is similar in all species. Neomycin undergoes negligible biotransformation after parental administration, and the major part of neomycin administered to farm animals is excreted unchanged. The volume of distribution of neomycin is similar in all species and can be assumed that tissue distribution will also be similar in all species. Consumption figures from cattle represent a worst-case scenario. Therefore the same MRL values as established in cattle can be recommended in all food producing species without compromising the safety of the consumer.</p> <p>Additionally, an analytical method for the monitoring of neomycin residues in several animal species is available. The validation for the new values performed for cattle tissues would be applicable to other species.</p>
Honey	No	<p>Residue depletion in honey does not occur through metabolism and consequently conclusions drawn from data in other food products cannot be extrapolated to honey. Honey specific data are required in order to allow adequate evaluation of the risk to consumer safety posed by residues in honey.</p> <p>No data are available to demonstrate that the analytical method used for monitoring of residues in cattle tissues is applicable for monitoring of residues in honey.</p>

### **3.5. Conclusions and recommendation for the establishment of maximum residue limits**

Having considered that:

- The toxicological ADI of 60 µg/kg bw (i.e. 3600 µg/person) was previously established as the overall ADI for neomycin;
- The parent compound neomycin B was previously retained as the marker residue;
- The ratio of marker to total residues was previously established as 1;
- Parenteral administration of neomycin to cattle results in increased residue concentrations in liver and kidney compared to oral and intramammary administration;
- A analytical method for the monitoring of residues of neomycin B in different animal species and food commodities is available;
- The analytical method was re-validated with regard to the new MRL values in edible bovine tissues (liver, muscle, kidney and fat) and would be applicable to other species.

The Committee, recommends the modification of maximum residue limits for neomycin and the amendment of table 1 of the Annex to Regulation (EU) No 37/2010 in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Neomycin (including framycetin)	Neomycin B	All food producing species	500 µg/kg 500 µg/kg 5500 µg/kg 9000 µg/kg 1500 µg/kg 500 µg/kg	Muscle Fat Liver Kidney Milk Eggs	For fin fish the muscle MRL relates to 'muscle and skin in natural proportions'. MRLs for fat, liver and kidney do not apply to fin fish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'.	Anti-infectious agents/ Antibiotics

Based on these MRL values the theoretical maximum daily intake will be equivalent to 96.5% of the ADI.

## 4. Re-examination of the CVMP opinion of 10 November 2011

### 4.1. Grounds for re-examination

The request for re-examination concerned the fact that the CVMP recommendation did not include a modification of the MRL for muscle. The argumentation provided in support of the re-examination can be summarised as follows:

- MRLs are based on the partitioning of mean residue levels between tissues at/around the time point when mean total residues deplete below the ADI;
- An increased level for muscle would allow a practical withdrawal periods for injectable products, and complying with the observed overall distribution of residue in tissues after injections (including injection site) since current MRLs were established based on residue data after oral and intramammary administrations only;
- The MRL of 800 µg/kg for muscle would better reflect residue depletion profile at injection site;
- The MRL of 500 µg/kg for muscle would lead to an unpractical long withdrawal period of 94 days due to residues at the injection site;
- An increase of the MRL for muscle to 800 µg/kg would allow for a withdrawal period of about 56 days;
- An increase of the MRL for muscle to 800 µg/kg would leave 1% of the ADI unused which would still allow for the establishment of MRLs in honey, if required;
- The proposed modification of the muscle MRL is not substantial;

- The proposed increase of muscle MRL does not pose a risk for human safety.

#### **4.2. Overall conclusion on grounds for re-examination**

Muscle injection site residues are not the basis for establishing a muscle MRL. In principle, the muscle MRL reflects residue distribution in muscle (non-injection site). Residue distribution is considered on the basis of the 4 standard target tissues which are muscle, fat, liver and kidney and does not include injection site. The individual MRLs in each edible tissue should reflect the kinetics of the depletion of the residues leading to set MRL figures proportionally to the marker residue concentrations around the time point when mean total residues deplete below the ADI. As far as an MRL for muscle is established that value will also apply to muscle at the injection site.

It should be noted that residue distribution has to consider all types of products including different routes of administration. An increase of the muscle MRL to 800 µg/kg is not justified, as such an increase would further deviate from the tissue residue distribution.

When establishing MRLs consideration is also given to the practicability of the withdrawal periods. However, the shortening of the withdrawal period for injectable products cannot be justified as the sole basis for the modification of the muscle MRL, especially when other non-injectable forms are available. An increase from 500 to 800 µg/kg represents an increase of 60%. Although an MRL of 500 µg/kg for muscle will lead to longer withdrawal periods for injectable products, considering the need to follow tissue residue distribution as much as possible for monitoring purposes, the proposed increase of the muscle MRL cannot be accepted. In addition, it is noted that the two new studies showed some degree of variability in the injection site residues and the calculation of the withdrawal period was based on one residue depletion study following intramuscular injection using the statistical approach.

The CVMP acknowledges that the portion of the ADI left, were the muscle MRL be set at 800 µg/kg, would be sufficient for setting MRLs for honey and that the ADI would not be exceeded.

The Committee considered that from the residue depletion studies performed in cattle, the target tissues are kidney and liver. The residue depletion studies provided with the application justify the increase of the MRL values for kidney (9000 *versus* 5000 µg/kg) and for liver (5500 *versus* 500 µg/kg) as these new MRL values better reflect tissue residue distribution in bovine species, but do not justify the increase of the muscle MRL. Residue levels of neomycin in fat and muscle are lower than those for kidney and liver.

### **5. Conclusions and recommendation for the establishment of maximum residue limits following re-examination**

Having considered that:

- The toxicological ADI of 60 µg/kg bw (i.e. 3600 µg/person) was previously established as the overall ADI for neomycin;
- The parent compound neomycin B was previously retained as the marker residue;
- The ratio of marker to total residues was previously established as 1;
- The studies submitted justified the increase of the liver and kidney MRLs;
- Muscle MRLs are not based on injection site residues;
- The MRL values are also recommended for oral and intramammary formulations for all food producing species;

- The analytical method was re-validated with regard to the new MRL values in edible bovine tissues (liver, muscle, kidney and fat) and would be applicable to other species.

Having considered the arguments raised in the detailed grounds for re-examination and taking into account all the supporting data on safety of residues, the Committee confirms its previous recommendation of maintaining the MRL value of 500 µg/kg for muscle and therefore recommends the modification of MRLs for neomycin and the amendment of table 1 of the Annex to Regulation (EU) No 37/2010 in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Neomycin (including framycetin)	Neomycin B	All food producing species	500 µg/kg 500 µg/kg 5500 µg/kg 9000 µg/kg 1500 µg/kg 500 µg/kg	Muscle Fat Liver Kidney Milk Eggs	For fin fish the muscle MRL relates to 'muscle and skin in natural proportions'.  MRLs for fat, liver and kidney do not apply to fin fish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'.	Anti-infectious agents/ Antibiotics

Based on these MRL values the theoretical maximum daily intake will be equivalent to 96.5% of the ADI.

## 6. Background information on the procedure

Submission of the dossier	1 September 2010
Steps taken for assessment of the substance	
Application validated:	14 September 2010
Clock started:	15 September 2010
List of questions adopted:	12 January 2011
Consolidated response to list of questions submitted:	12 August 2011
Clock re-started:	13 August 2011
CVMP opinion adopted:	10 November 2011
Submission of grounds for examination	9 January 2012
Oral explanation	7 February 2012
Adoption of final opinion	8 March 2012
Request for review by the Commission	23 April 2012
Revised CVMP opinion adopted	16 May 2012