



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CVMP/619817/2015
Committee for Medicinal Products for Veterinary Use

European Public MRL assessment report (EPMAR) Gentamicin (all mammalian food producing species and fin fish)

On 3 March 2016 the European Commission adopted a Regulation¹ extrapolating the maximum residue limits for gentamicin to all mammalian food producing species and fin fish, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Gentamicin is an aminoglycoside antibiotic used in the treatment of a variety of bacterial infections.

Maximum residue limits had previously been established for gentamicin in bovine and porcine species².

The European Commission submitted to the European Medicines Agency a request for the extrapolation of maximum residue limits on 29 June 2015.

Based on the available data, the Committee for Medicinal Products for Veterinary Use recommended, on 8 October 2015, the extrapolation of maximum residue limits for gentamicin to all mammalian food producing species and fin fish.

Subsequently the Commission recommended, on 21 January 2016, that maximum residue limits in all mammalian food producing species and fin fish are established. This recommendation was confirmed on 11 February 2016 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 3 March 2016.

¹ Commission Implementing Regulation (EU) No 2016/305, O.J. L 58, of 04 March 2016

² Commission Regulation (EC) No 868/2002, O.J. L 137, of 25.05.2002



Summary of the scientific discussion for the establishment of MRLs

Substance name:	Gentamicin
Therapeutic class:	Anti-infectious agents / Antibiotics
Procedure number:	EMEA/V/MRL/003669/EXPL/0002
Applicant:	European Commission
Target species:	All mammalian food producing species and fin fish
Intended therapeutic indication:	Not specified
Route(s) of administration:	Not specified

1. Introduction

Gentamicin is a complex mixture, the main components being gentamicin C1, gentamicin C1a, gentamicin C2 and gentamicin C2a. Gentamicin is an aminoglycoside antibiotic used in the treatment of a variety of bacterial infections in pigs and cattle. In veterinary medicine it is normally used as the sulphate salt.

In humans, gentamicin is generally administered intramuscularly every 8 hours to provide a total daily dose of 3 mg/kg bw/day. It may also be used as an eye collyrium or ophthalmic ointment.

Gentamicin was previously assessed by the CVMP and a microbiological ADI of 4 µg/kg bw, i.e 240 µg/person was established as the overall ADI.

Currently, gentamicin is included in 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
Gentamicin	Sum of gentamicin C1, gentamicin C1a, gentamicin C2 and gentamicin C2a	Bovine, porcine	50 µg/kg 50 µg/kg 200 µg/kg 750 µg/kg	Muscle Fat Liver Kidney	For porcine species the fat MRL relates to 'skin and fat in natural proportions'	Anti-infectious agents/ Antibiotics
		Bovine	100 µg/kg	Milk		

On 29 June 2015 the European Commission submitted to the European Medicines Agency a request for an opinion on extrapolation of the maximum residue limits established for gentamicin, pursuant to Article 27(2) of Regulation (EC) 470/2009, with a view to promoting availability of authorised veterinary medicines for food producing animals and in particular, for minor species.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of gentamicin. The CVMP established a toxicological ADI of 100 µg/kg bw based on the NOEL of 10 mg/kg bw established in a 14-week toxicity study in dog and applying an uncertainty factor of 100. Based on the geometric mean MIC₅₀ for relevant bacterial strains obtained from the human gastro-intestinal flora the CVMP also established a microbiological ADI of 4 µg/kg bw (i.e 240 µg/person). As the microbiological ADI is lower than the toxicological ADI, the microbiological ADI was considered the most relevant ADI for assessing the risk to the consumer and was established as the overall ADI. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extrapolation request.

2.2. Residues assessment

Maximum residue limits for gentamicin in porcine tissues and in bovine tissues and milk are currently included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010. These maximum residue limits were adopted following a previous recommendation of the CVMP. The information reported in the published CVMP Summary Report for gentamicin is reproduced below for ease of reference. No new data were provided or reviewed in this assessment.

2.2.1. Pharmacokinetics in target species

Pigs

Several radiolabelled studies combining different analytical methods (microbiological and radioimmunoassay methods) were carried out in pigs.

Groups of 3 six-week old pigs received ³H-gentamicin sulphate doses corresponding approximately to 12 mg/kg bw/day for 3 days via drinking water. Animals were slaughtered at 1, 3, 5 and 7 days post medication. For muscle and fat, the mean total radioactivity levels were below the limit of quantification (30 µg equivalents gentamicin/kg) at all sampling times. The levels of radioactivity in liver and kidney were 112 µg/kg and 180 µg equivalents gentamicin/kg, one day after treatment and declined to 76 and 62 µg/kg at 3 days, respectively. At later sampling, they were in the magnitude of 40 µg/kg in both tissues.

In addition, microbiological assay and radioimmunoassay also determined the concentrations of gentamicin residues in kidney. At one day after treatment, the mean concentration of microbiologically active residues was 210 µg microbiologically active residues expressed as gentamicin/kg and 160 µg/kg gentamicin when determined by radioimmunoassay. At later samplings, the concentrations of residues with antimicrobial activity were below the limit of quantification (lower than 80 µg/kg) whereas the gentamicin concentrations by radioimmunoassay were 40 and less than 30 µg/kg at 3 and 7 days after treatment. At one day after treatment, the ratio of gentamicin with regard to the total residues with antimicrobial activity was 0.76 in kidney. At later sampling the concentrations were too low to determine the ratios. No attempt was made to determine the ratios in other edible tissues.

In another study, groups of 3 or 4 three-day old piglets were treated with a single oral dose of 5 mg of ³H-gentamicin. Animals were slaughtered at 1, 3, 6, 11, 14 and 17 (2 animals only in this group) days after treatment. At 1 day after administration, the total radioactivity concentrations in fat and muscle were in the magnitude of the limit of quantification of 50 µg equivalents gentamicin/kg whereas the mean levels of total radioactivity were 4900 and 210 µg equivalents gentamicin/kg in liver and kidney, respectively. At day 3, the radioactivity levels were in the magnitude of 50 µg equivalents gentamicin/kg in liver and 450 µg/kg in kidney. At day 6, 270 µg equivalents gentamicin/kg were measured in kidney and 69 µg/kg in liver. At later sampling times, the radioactivity levels were below the limit of quantification 50 µg/kg in kidney and liver.

In another study, groups of 3-day old piglets were treated with a single intramuscular dose of 5 mg of ³H-gentamicin. Animals were slaughtered at 14 (2 animals), 28 (3 animals), 35 (3 animals), 42 (3 animals) and 49 (1 animal) days after treatment. At 14 days after administration, the total radioactivity concentrations in fat and muscle were in the magnitude of the limit of quantification of 20 µg equivalents gentamicin/kg whereas the mean levels of total radioactivity were 117, 419 and 677 µg equivalents gentamicin at the injection site, in liver and kidney, respectively. At later sampling time, the radioactivity could only be measured in liver and kidney: at day 28, 111 and 178 µg equivalents gentamicin/kg; at day 35: 60 and 73 µg/kg; at day 42: 37 and 51 µg/kg; at day 49: 24 and 22 µg/kg, respectively. Gentamicin residues in kidney were also determined by a microbiological assay and radioimmunoassay. At 14 days after treatment, the mean concentration of antimicrobiologically active residues was 610 µg equivalents of gentamicin/kg while the concentration of gentamicin measured by radioimmunoassay was 672 µg/kg. At day 28, they were 123 µg/kg and 200 µg/kg, respectively. At later sampling times, the concentrations of residues with antimicrobial activity were below the limit of quantification (lower than 80 µg/kg) whereas the gentamicin concentrations were 71, 46 and 20 µg/kg at day 35, 42 and 49, respectively.

At day 14, as the concentrations of gentamicin determined by radioimmunoassay were higher than that measured by microbiology, no conclusion could be given on the ratio of gentamicin with regard to the total antimicrobiologically active residues. No information on the ratio for the other edible tissue was provided.

Cattle

No radiolabelled studies were provided in bovine species. However, such studies were not requested as the relevant acceptable daily intake was based on a microbiological end-point.

2.2.2. Residue depletion studies

Pigs

Several non-radiolabelled residue depletion studies were performed in neonatal piglets and young pigs.

In one study, groups of 5 three-day old piglets were treated with a single oral dose of 5 mg of gentamicin. Animals were slaughtered at 1, 3, 6, 11 and 14 days post medication. Gentamicin residues in edible tissues were determined by a microbiological assay. At all sampling times, the antimicrobiologically active residues were below the limit of quantification in muscle and liver (less than 80 µg/kg) and in fat (less than 40 µg/kg). Significant amounts of antimicrobiologically active compounds were only measured in kidney: 1066, 630, 610, 175, 152, and less than 80 µg antimicrobiologically active residues/kg at 1, 3, 6, 9, 11 and 14 days after treatment.

In a second study, groups of 5 three-day-old piglets were treated with a single oral dose of 5 mg of gentamicin. Animals were slaughtered at 1, 3, 6, 11 and 14 days after treatment. Gentamicin residues

were determined by a microbiological assay. Significant amounts of antimicrobiologically active compounds were measured in kidney: 1078, 1028, 291, 394, 151, and 42 µg antimicrobiologically active residues/kg at 1, 3, 6, 9, 11 and 14 days after treatment.

In a third study, groups of 4 three-day old piglets were treated with a single intramuscular dose of 5 mg of gentamicin. Animals were slaughtered at 2, 3, 4, 5, 6, 7, 8 and 9 weeks post medication. Gentamicin residues in edible tissues were determined by a microbiological assay. At all sampling times, the residues with antimicrobial activity were below the limit of quantification in muscle and at the injection site (less than 100 µg/kg) and in fat (less than 40 µg/kg). Significant amounts of residues with antimicrobial activity were only measured in kidney: 470, 340, 250, and less than 150 µg antimicrobiologically active residues/kg at 2, 3, 4, and 5 weeks. At later sampling times, the concentrations were less than 90 µg antimicrobiologically active residues/kg. Significant amounts of residues with antimicrobial activity were also measured in liver: 320, 130 µg antimicrobiologically active residues/kg at 2 and 3 weeks after treatment. At later sampling times, the concentrations were less than 100 µg antimicrobiologically active residues/kg.

In a fourth study neonatal piglets were treated by the oral route with 5 mg gentamicin, daily for 3 days (equivalent to a mean dose level of about 3.7 mg/kg). Groups of 4 animals were sacrificed 13 and 29 days after the final administration. Gentamicin concentrations were determined in muscle, liver and kidney using a fluorescence polarisation immunoassay, the limit of quantification being 50 µg/kg for muscle, 250 µg/kg for liver and 500 µg/kg for kidney. The concentrations of gentamicin in kidney and liver samples were also analysed using a microbiological assay. At 13 days after the last administration, gentamicin could not be detected in muscle (lower than 50 µg/kg, the limit of detection). In liver, the concentrations of gentamicin were below the limits of quantification of the microbiological and immunoassay analytical methods (lower than 500 and 250 µg/kg respectively). In kidney, the concentrations of gentamicin were below the limits of quantification of the microbiological method (250 µg/kg) and a mean value of 265 µg/kg was measured by the immunoassay method. At 29 days, in all edible tissues, gentamicin could not be quantified or even detected.

Groups of 4 pigs were treated by the intramuscular route at a dose level of approximately 4 mg gentamicin/kg bw/day for 3 consecutive days. Samples of muscle, liver, kidney, fat and injection site were analysed by HPLC with fluorescence detection, the limit of quantification being 200 µg/kg for liver, 1000 µg/kg for kidney, 100 µg/kg for muscle and fat. Animals were sacrificed at 10, 20, 30, 40, 50, 60 and 70 days after treatment. The concentrations of gentamicin C2a (component G4) in muscle were below the limit of quantification at every sampling time. The mean residue concentrations at the injection site were 204 µg/kg at day 10 and below the 100 µg/kg for the other sampling times. The mean residue concentrations of gentamicin C2 (component G3) in fat were below the limit of quantification for each sampling time with the exception of day 30 when a mean value of 160 µg/kg was measured. The mean residue concentrations of gentamicin C2 in kidney (component G3) were 12746 µg/kg at day 10, 5094 µg/kg at day 20, 1170 µg/kg at day 30, below the limit of quantification at 40, 50 and 60 days. The mean residue concentration of gentamicin C2a (component G4) in liver at day 10, 1142 µg/kg at day 20, 685 µg/kg at day 30, 394 µg/kg at day 40, 288 µg/kg at day 50 and below 200 µg/kg at day 60 and 70.

Cattle

In one non-radiolabelled study, groups of 5 to 3 calves weighing approximately 60 kg were treated with repeated intramuscular doses of 4 mg of gentamicin per day for 3 days. Animals were slaughtered at 7, 30, 60, 70 and 80 days after the last injection. Gentamicin residues in edible tissues were determined by a microbiological assay using *Staphylococcus epidermidis* as test organism, the limit of quantification being 50 µg/kg. At all sampling times, the antimicrobiologically active residues were below the limit of quantification in muscle. Significant amounts of antimicrobiologically active compounds were measured in liver and kidney: 3600 and more than 10 000 µg antimicrobiologically active residues/kg at day 7, 800 and 2000 µg/kg at day 30, 500 and 1100 µg/kg at day 60, 300 and 900 µg/kg at day 70 and 30 and 600 µg/kg at day 80, respectively.

Groups of 4 calves received gentamicin by intramuscular route at a dose level of approximately 4 mg gentamicin/kg bw for 3 consecutive days. Animals were sacrificed 10, 20, 30, 40, 50, 60, 70 and 80 days after the last administration. Residues of gentamicin in muscle, liver, kidney, fat and the injection site were analysed by HPLC with fluorescence detection, the limit of quantification being 200 µg/kg for liver, 1000 µg/kg for kidney, 100 µg/kg for muscle and fat. The mean residue concentrations of gentamicin C2a (component G4) in liver were 2784 µg/kg at day 10, 1462 µg/kg at day 20, 726 µg/kg at day 30, 809 µg/kg at day 40, 404 µg/kg at day 50, 612 µg/kg at day 60, lower than 200 µg/kg at day 70 and 208 µg/kg at day 80. The mean residue concentrations of gentamicin C1a (component G2) in kidney were 20758 µg/kg at day 10, 2121 µg/kg at day 20, 2689 µg/kg at day 30, 1315 µg/kg at day 40 and 1261 µg/kg at day 50, below 1000 µg/kg at day 60, 70 and 80. Gentamicin C2 (component G3) residues in muscle and fat were always below 100 µg/kg, the limit of quantification of the analytical method. The mean residue concentrations at the injection site samples were in the magnitude of 200 µg/kg up to 70 days after treatment. At 80 days, they were below the limit of quantification (100 µg/kg).

Several depletion studies were carried out using intramammary or intrauterine administration of gentamicin sulphate at different dosages. Significant amounts of antimicrobiologically active residues could be measured only in kidney samples taken up to 20 days after the end of treatment.

Milk

Several cold studies were provided to follow the depletion of gentamicin in bovine milk.

In one study, five lactating cows were treated with repeated intramuscular doses of 4 mg gentamicin/kg bw/day for 3 days. Milk samples were collected up to 90 hours after treatment. Gentamicin residues in edible tissues were determined by a microbiological assay using *Staphylococcus epidermidis* as test organism, the limit of quantification being 50 µg/kg. No antimicrobiologically active residues could be detected in any milk sample collected.

In a second study, 5 lactating Holstein cows were treated with three successive infusions of 10 ml containing 100 mg gentamicin sulphate and 100 000 units of procaine penicillin per quarter. Samples of milk were taken from the total production of each quarter at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132 and 144 hours following the third injection. The concentrations of gentamicin were analysed by a microbiological assay using *Staphylococcus epidermidis* with a sensitivity of 10 µg/kg. The mean concentrations of gentamicin were 19250 µg/l at 12 hours after treatment, then they declined to 1910, 330, 80, 40, to 20 and to 10 µg antimicrobiologically active residues expressed as gentamicin equivalents/kg at 24, 36, 48, 60, 72 and 132 hours after treatment.

In a third study, five lactating Holstein cows were treated with three successive infusions of 10 ml containing 50 mg gentamicin sulphate and 100 000 units of procaine penicillin per quarter. Samples of

milk were taken from the total production of each quarter at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132 and 144 hours following the third injection. The concentrations of gentamicin were analysed by a microbiological assay using *Staphylococcus epidermidis* with a sensitivity of 40 µg/kg. The highest concentration of gentamicin was 2500 µg/l at 12 hours after treatment, then declined to 148 µg/kg, and to 40 to 100 µg/kg at 24, 36 hours after treatment, respectively.

Selection of marker residue and ratio of marker to total residues

No information was provided on the ratio of gentamicin with regard to the total antimicrobiologically active residues in most of the edible tissues including milk. However, having considered that this substance belongs to the aminoglycosides, which are not metabolised to any extent and are excreted unchanged *via* the kidney, such information was not considered as necessary. The parent compound was assumed to represent all the relevant antimicrobiologically active residues. The marker residue was retained as the sum of gentamicin C1, C1a, C2 and C2a, which corresponds to more than 90% of the antimicrobial activity of gentamicin. Based on this and on the absence of metabolism the marker to total residues ratio is taken as 1.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than that described elsewhere in this report were available for review.

2.2.4. Analytical method for monitoring of residues

Analytical methods, using liquid chromatography with mass spectrometric detection (LC/MS) were available for the determination of gentamicin in bovine and porcine tissues and in bovine milk. Molecular ions for the components of the marker residue were individually detected in positive ion mode with unit mass resolution to a common 322.1 m/z transition. The methods were well described according to ISO 78/2 and were fully validated according to Volume VI in force at the time of the initial assessment (currently replaced by Volume 8) of the Rules Governing Medicinal Products in the European Union. The limits of quantification in bovine and porcine species were 100 µg/kg for liver, 25 µg/kg for muscle and for fat, 375 µg/kg for kidney and 50 µg/kg for bovine milk.

2.2.5. Findings of EU or international scientific bodies

JECFA evaluated gentamicin at its 43rd and 50th meetings. Based on its microbiological ADI of 22 µg/kg bw i.e. 1320 µg/person the JECFA established the following MRLs for gentamicin in bovine and porcine species: 100 µg/kg for muscle and fat, 2000 µg/kg for liver, 5000 µg/kg for kidney and 200 µg/l for bovine milk. The parent substance, gentamicin, was established as the marker residue.

3. Risk management considerations

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

Three GLP studies were provided on the effects of gentamicin on micro-organisms used in the food industry.

The MIC of gentamicin against 15 pure starter cultures isolated from mixed commercial starter cultures was determined in the presence and absence of milk using a broth microdilution method. There was no

inhibiting effect on growth of any starter culture at a gentamicin concentration of 62 µg/l. The presence of milk did not significantly affect the gentamicin sensitivity of 8 strains.

The MIC of gentamicin against 6 mixed starter cultures used in the food industry was determined using a broth microdilution method in the presence and absence of milk. There was no inhibitory effect on the growth of any mixed culture at a gentamicin concentration of 500 µg/l. The presence of milk did not significantly affect the gentamicin sensitivity of 3 mixed cultures.

The effect of gentamicin was determined on the acidification performance of 3 commercial dairy starter cultures containing mixed bacterial strains. Gentamicin concentrations of 10, 100 and 500 µg/l were tested. Gentamicin concentrations of 10 and 100 µg/l did not inhibit acid production significantly and would not have any detrimental impact on an industrial process.

The concentration of 100 µg/l was retained as the concentration without effects on dairy starter cultures.

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

Gentamicin is used for first or second choice treatments in a variety of clinical situations, particularly in horses, for which there are only limited choices available for the treatment of Gram-negative infections.

No other relevant factors were identified for consideration of the risk management recommendations.

3.3. Elaboration of MRLs

The following maximum residue limits in porcine and bovine tissues and bovine milk were recommended by the CVMP, and subsequently adopted by the European Commission, based on the residue profile seen in these species:

Muscle:	50 µg/kg
Fat:	50 µg/kg
Liver:	200 µg/kg
Kidney:	750 µg/kg
Milk:	100 µg/kg

The established EU MRLs differ from the Codex MRLs because the CVMP and JECFA have established different ADIs for gentamicin.

Calculation of theoretical daily intake of residues

Detailed 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	50	1	15
Fat	0.05#	50	1	2.5
Liver	0.10	200	1	20
Kidney	0.05	750	1	37.5
Milk	1.50	100	1	150

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product (µg)
Total				225 (94% of ADI)

fat and skin in natural proportion for pigs

Based on these MRLs the total maximum theoretical daily intake from tissues and milk equates to 225 µg, which represents 94% of the ADI.

3.4. Considerations on possible extrapolation of MRLs

Following the request from the European Commission submitted to the European Medicines Agency on 29 June 2015, pursuant to Article 27(2) of Regulation (EC) No 470/2009 and with a view to promoting availability of authorised veterinary medicines for food producing animals and in particular, for minor species, the CVMP considered the possibility of extrapolating the established maximum residue limits for gentamicin in porcine and bovine species to other food producing species and commodities.

Taking into account the current scientific knowledge the recommendations on extrapolation are justified as described below.

Animal species/ food commodities	Extrapolation possible (Yes /No)	Justification
Ruminants	Yes	Gentamicin belongs to the aminoglycosides, which are not metabolised to any extent and are excreted unchanged via the kidney in all mammalian species for which data are available. Therefore the marker residue established for cattle is assumed to also be present in other ruminant tissues and milk. Although it was not specifically demonstrated, the analytical method for monitoring of residues in cattle tissues is expected to be basically applicable for monitoring of residues in other ruminants tissues and milk.
Poultry (including eggs)	No	Metabolism can be significantly different in poultry compared to cattle and pigs. Consequently, species specific metabolism and residue data are considered necessary to allow adequate evaluation of the risk to consumer safety posed by residues in poultry-derived food commodities. No data on metabolism in eggs is available for evaluation.
Horses	Yes	Gentamicin belongs to the aminoglycosides, which are not metabolised to any extent and are excreted unchanged via the kidney in all mammalian species for which data are available. Therefore, the marker residue established for cattle and pigs is assumed to also be present in horse tissues.

		<p>Although it was not specifically demonstrated, the analytical methods for monitoring of residues in cattle and pig tissues are expected to be basically applicable for monitoring of residues in horse tissues.</p>
Rabbits	Yes	<p>Gentamicin belongs to the aminoglycosides, which are not metabolised to any extent and are excreted unchanged via the kidney in all mammalian species for which data are available. Therefore, the marker residue established for cattle and pigs is assumed to also be present in rabbit tissues.</p> <p>Although it was not specifically demonstrated, the analytical methods for monitoring of residues in cattle and pig tissues are expected to be basically applicable for monitoring of residues in rabbit tissues.</p>
Salmonidae and other fin fish	Yes	<p>Metabolism is generally less complicated in fish than in warm blooded species. As the marker residue in cattle and pigs is a large component of the parent compound and is excreted unchanged, the assumption can be made that the same marker residue would be the predominant residue in Salmonidae and other fin fish. Therefore, extrapolation from the muscle MRL established in cattle and pigs is recommended (50 µg/kg).</p> <p>Although it was not specifically demonstrated, the analytical method for monitoring of residues in pig and cattle muscle is expected to be basically applicable for monitoring of residues in Salmonidae and other fin fish muscle.</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 degradation products in honey.</p>

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

Having considered that:

- a microbiological ADI of 4 µg/kg bw i.e. 240 µg/person was established as the overall ADI for gentamicin,
- gentamicin is an aminoglycoside, which, in all mammalian species for which data are available, are not metabolised to any extent and are excreted unchanged via the kidney; consequently, the marker residue (sum of gentamicin C1, C1a, C2 and C2a) and the marker to total residues ratio (1.0) established for bovine and porcine species are considered to be appropriate for all mammalian food producing species,
- metabolism is generally less complicated in fish than in warm blooded species and consequently the marker residue (sum of gentamicin C1, C1a, C2 and C2a) and the marker to total residues ratio (1.0) established for bovine and porcine species are considered to be appropriate for fin fish,
- although it was not specifically demonstrated, the analytical method for monitoring of residues in bovine and porcine food commodities is expected to be basically applicable for monitoring of residues in all mammalian food producing species as well as in fin fish,

the CVMP, having considered the request and the data available for the previous evaluation, recommends the extrapolation of the maximum residue limits for gentamicin to all mammalian food producing species and to fin fish, and the amendment of the entry for gentamicin in Table 1 of the Annex to Commission 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
Gentamicin	Sum of gentamicin C1, gentamicin C1a, gentamicin C2 and gentamicin C2a	All mammalian food producing species and fin fish	50 µg/kg 50 µg/kg 200 µg/kg 750 µg/kg 100 µg/kg	Muscle Fat Liver Kidney Milk	For fin fish the muscle MRL relates to 'muscle and skin in natural proportions' For porcine species the fat MRL relates to 'skin and fat in natural proportions'	Anti-infectious agents / Antibiotics

Based on these MRLs, the total theoretical maximum daily intake (TMDI) from tissues and milk equates to 225 µg, which represents 94% of the ADI.

4. Background information on the procedure

Submission of the request from the Commission:	29 June 2015
Steps taken for assessment of the substance	
Application validated:	Not applicable
Clock started:	29 June 2015
CVMP opinion adopted:	8 October 2015