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Cross-contamination of non-target feedingstuffs by semduramicin authorised for use as a feed additive[1]

Scientific opinion of the Panel on Contaminants in the Food Chain

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PANEL MEMBERS

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SUMMARY

Semduramicin is a polyether ionophoric agent that is authorised as a coccidiostat for use in chickens for fattening with a maximum content of the active substance in feed of 25 mg/kg according to Regulation (EC) No 1041/2002. Despite the requirements set for feed business operators in Regulation No (EC) 183/2005, it is generally acknowledged that under practical conditions during the production of mixed feeds, a certain percentage of a feed batch remains in the production circuit and these residual amounts can contaminate the subsequent feed batches. This cross-contamination may result in the exposure of non-target animal species, and hence the potential health risks for non-target animal species as well as the potential residue deposition in foods derived from these non-target animal species have been evaluated.

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Semduramicin produced toxicity typical of ionophoric compounds in dogs including skeletal muscle damage, in addition, semduramicin induces retinal changes in dogs that have not been studied in other species yet. Studies conducted in food-producing animals regarding semduramicin toxicity are limited and mostly confined to short-term feed exposure. Based on the very limited tolerance studies available on short-term toxicity in non-target animal species (birds (turkeys, guinea fowls, ducks and geese), rabbits and horses), adverse effects are not expected if non-target animal species are accidentally fed a diet containing semduramicin at the maximum authorised level in feed for target animal species. In laying hens, a reduction of egg production, hatchability and shell quality was observed in some but not all feeding experiments at concentrations equal to or exceeding 12.5 mg semduramicin/kg feed.

Cross-contamination of feed for non-target animal species at 10% (2.5 mg/kg feed) of the maximum authorised level of semduramicin could result in an intake of 0.13 mg/kg b.w. per day of semduramicin. This level is the same as the overall NOAEL (0.125 mg/kg b.w. per day) based on changes in blood biochemistry parameters in a 2-year chronic toxicity and carcinogenicity feeding study in rats. The CONTAM Panel concluded that adverse health effects are unlikely to occur in non-target animals as a result of cross-contamination.

No kinetic or occurrence data were available to estimate the amount of semduramicin residues in eggs, milk, meat and offal from non-target animal species. Hence, consumer exposure was estimated using kinetic data at practical zero withdrawal time from chickens for fattening that were given the maximum authorised level of 25 mg semduramicin/kg feed. These data were extrapolated to a concentration of 2.5 mg/kg feed to correspond to feed cross-contaminated with semduramicin at a level of 10% of the maximum authorised level. Consumption of such poultry products (100 g of liver, 300 g muscle, 90 g skin/fat and 10 g kidney) could give an intake of 3.7 µg semduramicin equivalents (total radioactive residues) per person corresponding to 0.062 µg/kg b.w. for a 60 kg consumer, which represents 5% of the ADI of 1.25 µg/kg b.w. per day as established by the Scientific Committee for Animal Nutrition (SCAN). Even though kinetic and tissue deposition can differ between chickens for fattening and non-target animal species, an exceedance of the ADI is unlikely to occur. Therefore, the CONTAM Panel concluded that the very limited data provided no indication of an appreciable risk to consumers' health from the ingestion of semduramicin residues in products from animals exposed to feed cross-contaminated up to a hypothetical level of 10% of the maximum authorised level.

KEYWORDS: semduramicin, cross-contamination, carry-over, coccidiostat, anticoccidial, ionophore, feed additive, occurrence, exposure, animal health, intoxication, human health.

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BACKGROUND AS PROVIDED BY THE REQUESTOR

1. Cross-contamination

A feed manufacturing company produces a broad range of compound feedingstuffs. Therefore, in the same production line, different compound feedingstuffs have to be manufactured after each other. After the switch over from one product to the following one, traces of the first product remain in the production line and end up in the beginning of the production of the following product. The transfer from one production batch to the following batch is called "carry-over" or "cross-contamination".

Cross-contamination in purchased premixtures

Purchased premixtures can contain traces of contamination of other substances due to cross-contamination during the production.

Product related cross-contamination

The following properties of the feed additives and premixes also have an important influence on the cross-contamination behaviour:

- adhesive strength – adhesion to walls
- particle size and density (carrier, substance)
- electrostatic properties.

The cross-contamination decreases according to the product being less adhesive and electrostatic.

Establishment related cross-contamination

The design of the dosage, grinding and mixing equipment has an important influence on the level of cross-contamination. Also the transport and storage facilities and conditions are an important factor for cross-contamination

2. Legal provisions as regards minimisation of cross-contamination

Directive No (EC) 95/69[2]

Council Directive No (EC) 95/69 of 22 December 1995, laying down the conditions and arrangements for approving and registering certain establishments and operating in the animal feed sector, provides in Article 2 and 3, that establishments manufacturing coccidiostats, manufacturing premixtures prepared from coccidiostats, manufacturing compound

[2] OJ L 332, 30.12.1995, p. 15. As last amended by Council Regulation EC° No 806/2003 of 14 April 2003 (OJ L 122, 16.5.2003, p. 1)

feedingstuffs containing premixtures prepared from coccidiostats; have to receive approval to exercise these activities. Also intermediaries putting these products into circulation must be approved. The approval is subject to compliance with the minimum conditions laid down in the Annex.

One of these conditions concern the facilities and the equipment and provides that *"the lay-out, design and operation of the facilities and equipment must be as such to minimize the risk of error and permit effective cleaning and maintenance in order to avoid contamination, cross-contamination and any adverse effects generally on the quality of the products."*

Regulation No (EC) 183/2005[3]

Regulation No (EC) 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene was applicable from 1 January 2006 onwards and has replaced Council Directive No (EC) 95/69.

Article 10 of Regulation No (EC) 183/2005 provides that feed business operators shall ensure that establishments under their control, are approved by the competent area in case these establishments are manufacturing and/or placing on the market coccidiostats and histomonostats, manufacturing and/or placing on the market premixtures prepared using coccidiostats and histomonostats, manufacturing for placing on the market or producing for the exclusive requirements of their holdings, compound feedingstuffs using coccidiostats and histomonostats or premixtures containing coccidiostats and histomonostats.

Annex II to Regulation No (EC) 183/2005 contains requirements for the feed businesses mentioned in previous paragraph. As regards facilities and requirements it is provided under point 2 of Annex II that "*The lay-out, design and construction and size of the facilities and equipment shall:*

(a) permit adequate cleaning and/or disinfection;

(b) be such as to minimize the risk of error and to avoid contamination, cross-contamination and any adverse effects generally on the safety and quality of the products. Machinery coming into contact with feed shall be dried following any wet cleaning process."

3. Legal provisions as regards the authorisation of coccidiostats (and histomonostats) for use as feed additive

Article 3 of Council Directive No (EEC) 70/524[4] concerning additives in feedingstuffs provides that no additive may be put into circulation unless a Community authorisation has

[3] OJ L 35, 8.2.2005, p. 1

been granted. This Community authorisation can only be granted if, taking into account the conditions of use, it does not adversely affect human or animal health or the environment, nor harm the consumer by impairing the characteristics of animal products.

Semduramicin sodium has been authorised for use as feed additive in accordance with the provisions of Council Directive No (EC) 70/524 (see Table 1).

Regulation No (EC) 1831/2003[5] of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition is applicable since 19 October 2004 and repeals Directive No (EC) 70/524 with effect from that date.

Table 1. Species or category of animals for which the use of semduramicin sodium as feed additive is authorised (target animal), and authorised maximum content in complete feed

Cocciodiostat (active substance)	**Species or category of animals for which the use of coccidiostats is authorised (target animal)**	**Authorised maximum content of active substance in complete feed**
Semduramicin sodium	Chickens for fattening	25 mg/kg (Aviax^{TM})

4. Unavoidable cross-contamination (under practical conditions)

Semduramicin is authorised for use as a feed additive for the production of feedingstuffs for target animal species according to the conditions of authorisation. However the production of feed containing semduramicin can result in cross-contamination to feedingstuffs for non-target animal species.

Of major importance is the application by the feed operator of good manufacturing practices to avoid to the largest extent possible, the cross-contamination of residues of the coccidiostat in subsequent batches of compound feedingstuffs. However, even if all prevention measures are applied, including the use of rinsing batches, the cross-contamination of residues is unavoidable under practical conditions.

5. Tolerances

Therefore, the possibility to set tolerances for these in practice unavoidable residues of coccidiostats in feedingstuffs for non-target animal species should be considered in the frame

[4] OJ L 270, 14.12.1970, p.1
[5] OJ L 268, 18.10.2003, p. 29–43

of Directive No (EC) 2002/32 of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed[6].

Such tolerances in feedingstuffs for non-target animal species could be set following the ALARA principle (As Low As Reasonably Achievable) taking into account good manufacturing practices. According to information received from professional organisations, a range of 3 - 10% with a majority at 5% or lower can be achieved after implementing thorough actions to reduce cross-contamination.

Such tolerances in feedingstuffs for non-target animal species should not have a pharmacological activity and not threaten animal health and public health, as in some cases the tolerances for feedingstuffs for non-target animal species could result in presence of residues in products of animal origin.

TERMS OF REFERENCE AS PROVIDED BY THE REQUESTOR

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002 the Commission asks EFSA to provide an opinion of the risks involved for animal health and public health as the consequence of undesirable cross-contamination of semduramicin sodium authorised as feed additive into non target feeds.

The assessment should take into account hypothetical cross-contamination rates of 2%, 5% and 10% from feed produced with the highest authorised dose of semduramicin sodium into the afterwards produced non target compound feed (for non target animal species).

The EFSA is requested to provide an opinion whereby

- the animal health risk for non target species (food producing farm animals) will be assessed
- the adverse effects as a consequence of cross-contamination of semduramicin sodium into feed for non-target animal species
- on the basis of the available information, an estimate of the level of residues present in food of animal origin from non target species as the consequence of cross-contamination is performed.
- the possible risks for human health as the consequence of the presence of such residues in food of animal origin (eggs, milk, meat, edible offal) from non target species are assessed.

[6] OJ L 140, 30.5.2002, p. 10. Directive as amended by Directive No (EC) 2005/6 (OJ L 24, 27.1.2005, p. 33)

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GLOSSARY OF TERMS USED BY THE PANEL IN ITS OPINIONS ON COCCIDIOSTATS

Considering the current EU legislation, the following terms will be applied in the Opinion:

Coccidiosis: Coccidiosis is a common protozoan infection in farm animals, affecting predominantly young animals. Under common farm conditions, herd health management cannot exclude coccidial infections in large poultry and rabbit units and the use of coccidiostatic agents (coccidiostats) remains necessary to control animal health and welfare, and to avoid substantial losses due to acute and often lethal coccidiosis.

Coccidiostats: Currently, in the EU 11 coccidiostatic substances are authorised for the prevention of coccidiosis in one or more animal species. Authorisation is given for a minimum and maximum level to be included as feed additive into the animal's diet, and may prescribe the animal species as well as the species categories (as for example chickens for fattening and chickens reared for laying) and in some cases withdrawal periods. Of the 40.65 million tonnes of feed produced annually for chickens for fattening, turkeys and rabbits, approximately 18.33 million tonnes is manufactured with the addition of a coccidiostat (IFAH, 2007, document provided to EFSA).

Various coccidiostats exert also a distinct antibacterial effect and are licensed in Third Countries (countries outside the EU) as growth promoting agents in fattening ruminants (lambs or cattle) and fattening pigs.

Target animal species: Animal species or animal category within a species for which the compound under consideration is authorised for use as a coccidiostat.

Non-target animal species: Any other animal species or category for which the compound is not authorised.

Feed additive: A substance, micro-organism or preparation, other than feed material and premixtures, which are intentionally added to feed at concentrations up to a defined maximum level (mg/kg feed). Currently, coccidiostats are authorised for use as feed additives according to the provisions of Directive No (EC) 70/524 and Regulation No (EC) 1831/2003 that repeals Directive No (EC) 70/524 (see also the background chapter). According to these provisions, authorisation and prerequisites for use of coccidiostats are defined for individual products

(brands) following review by the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) of data provided by the applicant.

Premixture: A mixture of feed additives with feed materials. Premixtures are not intended for direct consumption by animals, and are therefore not addressed in the Opinion.

Cross-contamination: Contamination of feeds that are produced after the production of a mixed feed containing additives with residual amounts of the previous feed batch.

Levels of cross-contamination: According to the mandate as described in the Terms of Reference, three levels of cross-contamination will be considered, i.e. 2%, 5% and 10% of the maximum concentration authorised for target animal species, respectively.

Assessment of animal exposure and adverse health effects in animals: Adverse health effects occurring in non-target animal species are described. A distinction is made between the likelihood of adverse health effects that are associated with an accidental consumption of feeds prepared for a target animal species by a non-target animal species, and the involuntary exposure of non-target animal species by residual amounts of coccidiostats occurring in feed as a consequence of cross-contamination.

ADI values: Acceptable daily intake (ADI) of a substance that can be consumed by a human over a lifetime without adverse health effects. As the CONTAM Panel did not have access to the complete safety (toxicological, pharmacological and microbiological) database available for the individual substances under consideration, the ADI value as derived by the FEEDAP Panel and where appropriate also the ADI(s) derived by other relevant scientific committees (e.g. the CVMP[7] or the JECFA[8]) is used for the risk characterization and assessment. The CONTAM Panel noted in some cases the divergence between ADI values derived by the FEEDAP Panel and the ADI values derived by the CVMP and/or JECFA. These differences were attributable to the application of different uncertainty factors, or the inclusion of new endpoints, such as antimicrobial activity (antimicrobial no-effect level) in the assessment. The CONTAM Panel decided to consider both values in the presentation of its risk assessment for non-target animal species.

MRL values: Maximum residue limits. The CVMP applied Regulation No (EC) 1055/2006[9] amending the Annexes I and III of Regulation No (EC) 2377/90[10] to propose maximum residue limits (MRLs) for a number of coccidiostats. However, none of the compounds under consideration are licensed at present as veterinary medicinal product. The FEEDAP has also

[7] The Committee for Medicinal Products for Veterinary Use of the European Medicines Agency
[8] The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).
[9] OJ L 192, 13.7.2006, p. 3–5
[10] OJ L 224, 18.8.1990, p. 1–8

recommended MRLs for some coccidiostats, and the CONTAM Panel considered these recommendations in the evaluation process.

Residues of coccidiostats in edible tissues, milk and eggs: According to Directive No (EC) 96/23[11] Member States are obliged to monitor certain substances and residues thereof in animals and animal products. These data are collected by the Commission and a compilation of the results from 2004 and 2005 are used in the human exposure assessment.

Equivalents: Where kinetic studies have been conducted with the coccidiostat ^{14}C-radiolabelled, the concentration of total radioactive residue levels measured in the different tissues are expressed as µg parent coccidiostat equivalents/kg tissue, to indicate that these levels could be the parent compound and/or metabolites.

Human dietary exposure: The present assessment is confined to the evaluation of residues of coccidiostats in foodstuffs derived from non-target animals. Where appropriate, total exposure originating from different products including edible tissues, milk and eggs is estimated.

Risk characterization: The risk characterization is based on the ADI and MRL values from the FEEDAP Panel, the CVMP or the JECFA as outlined above. These levels are compared with levels of residues found in tissues and/or products (for example eggs) of non-target animal species as far as these are available. Where appropriate uncertainties in the establishment of ADI values are discussed.

ASSESSMENT

1. Introduction

Semduramicin sodium belongs to the polyether monocarboxylic acid class of ionophores produced by fermentation with a selected strain of *Actinomadura*. It exerts both anticoccidial and antibacterial effects. The chemical structure of semduramicin is presented in the Figure 1.

[11] OJ L 125, 23.5.1996, p. 10–32

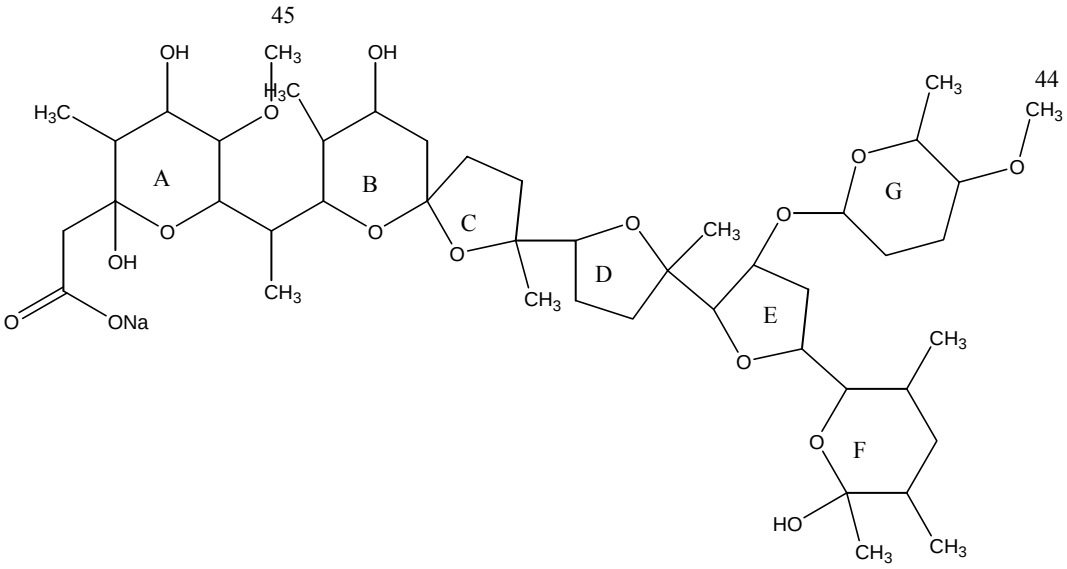

Figure 1. Chemical structure of semduramicin sodium

The IUPAC name of semduramicin sodium is 23,27-didemethoxy-2,6,22-tridemethyl-5,11-di-O-demethyl-6-methoxy-22-[(tetrahydro-5-methoxy-6-methyl-2Hpyran-2-yl)oxy]ionomycin A sodium salt and the CAS number is 113378-31-7. The molecular weight is 894.5 and the molecular formula is $C_{45}H_{75}O_{16}Na$.

The log K_{OW} is 2.21 at pH 9 and 2.58 at pH 6. The compound is non-volatile.

As summarised in the background chapter, semduramicin sodium is authorised as a feed additive in chickens for fattening at a minimum/maximum level of 20 - 25 mg/kg feed and with a withdrawal period of five days before slaughter[12].

1.1. Biological activities of semduramicin

Effect on coccidiae

Semduramicin is a polyether monocarboxylic acid ionophore. It is of comparable potency to several polyether ionophores, including monensin, salinomycin, lasalocid, narasin and maduramicin with respect to its anticoccidial activity. These compounds are branch chained, polyoxygenated carboxylic acids that act as mobile carriers of cations by rendering them lipid-soluble, thereby enabling them to pass across membranes. This process disrupts cationic

[12]Commission Regulation (EC) Nº 1041/2002 of 14 June 2002 concerning the provisional authorisation of a new additive in feedingstuffs. Official Journal, L157 15-6.2002.

cross-membrane gradients and is responsible for their anticoccidial activity (Lynch *et al.*, 1992).

Antibacterial activity

Minimum Inhibitory Concentration (MIC) data demonstrated high MICs of semduramicin, generally >100 mg/L, against aerobic and anaerobic Gram-negative bacteria, including *Escherichia coli, Pseudomonas aeruginosa, Salmonella* spp, *Campylobacter jejuni* and *Yersinia enterocolitica*. These results confirm that a broad range of Gram-negative bacterial species are resistant to this ionophore (EC, 2002). For some Gram-positive bacterial species, *Lactobacillus* spp. and *Staphylococcus aureus*, high MICs (>76 to 100 mg/L) were observed. However, *Clostridium perfringens* (10 mg/L), *Clostridium difficile* (28 mg/l), *Eubacterium limosum* (22 mg/L), Group C and group E *Streptococci* (16 mg/L), *Bifidobacterium* spp. (4 to 16 mg/L), *Enterococcus faecium* (4 to 32 mg/L) and *Lactobacillus* spp. (2 to 8 mg/L) were more susceptible (EC, 2002). No cross-resistance to antibiotics used in human and animal medicine has been observed in faecal coliforms or in strains of *Salmonella typhimurium*, *Enterococcus faecium* and *Campylobacter jejuni* from chickens for fattening fed for around six weeks with a feed containing 20 or 25 mg/kg of semduramicin (EC, 2002).

Semduramicin does not significantly increase *Salmonella* shedding or the risk of internal organs to become colonised by the bacterium (EC, 2002).

The effect of semduramicin on the bacterial populations that make up the human gut flora has not been evaluated and a antimicrobial ADI has not been established.

1.2. Previous evaluations of the toxicological properties and the safety of semduramicin

Semduramicin has been assessed by the SCAN in 2002 (EC, 2002) resulting in an ADI of 0.00125 mg/kg b.w. by applying an uncertainty factor of 100 to the toxicological NOAEL of 0.125 mg/kg b.w. per day from a 2-year dietary study in rats. Slight non-specific toxicity indicated by changes of blood biochemistry parameters (decreased serum protein and sodium levels) were seen at 0.25 mg/kg b.w. per day in this study. The original data were not available to the CONTAM Panel. In dogs (1, 6 and 12-month studies), the NOAEL was 0.3 mg/kg b.w. day and retinal changes (degeneration of rods and cones) were seen at 1 mg/kg b.w. per day. At higher doses there were adverse effects on skeletal muscle histopathology. The effects on the retina and skeletal muscle were thought to be due to the ionophoric properties of semduramicin. No evidence of effects on cardiac function were revealed by electrocardiogram readings at doses of up to 4 mg/kg b.w. per day, although some dogs from the top-dose group (given 1 mg/kg b.w. per day) had increased systolic blood pressure at the end of the 12-month study. The SCAN did not have access to any special studies of

pharmacological effects on the cardiovascular function of the dog. A three-generation reproduction study in rats gave a NOAEL of 0.5 mg/kg b.w. per day based on decreased maternal bodyweight gain. The NOAEL for developmental toxicity in rats and rabbits was 0.5 mg/kg b.w. per day, based on maternal toxicity and foetotoxicity at higher doses. There was no evidence of teratogenicity. A suitable range of mutagenicity tests gave negative results and there were no results to suggest carcinogenicity (studies in mice and rats). Microbiological data were submitted and were discussed by the SCAN, which decided not to use these data, and hence a microbiological ADI for semduramicin has not been established yet (EC, 2002).

1.3. Cross-contamination of feed batches

Feed additives, such as coccidiostats, are marketed as premixes, intended, to be incorporated into mixed feeds during the mixing and production process. Cross-contamination refers to the fact that under the practical conditions in a commercial feed mill, residual amounts of feed materials remain in the production line (see also the background chapter) and may contaminate the subsequent feed batches. The degree of cross-contamination depends on the technical facilities and procedures, as well as on product characteristics.

1.3.1. Factors influencing the rate of cross-contamination

Several studies have shown that a completely contamination-free production of premixes and compound feeds in existing multi-product plants is impossible in practice (Strauch, 2003). Various process parameters and physicochemical characteristics of the product act together to determine the residual amount remaining in the circuit and hence the rate of cross-contamination from one feed batch to the subsequent batches produced in the same production line (Kennedy *et al.,* 1996, 1998; Mc Evoy *et al.,* 2003; Harner *et al.,* 1996). In a similar way, the purchased premix that is incorporated into the feed can itself contain traces of contamination of other substances, due to cross-contamination during the production of the premixes.

The **technological equipment** in the feed mill can influence the amount of cross-contamination that may occur. The following sites in the circuit have been identified as being places where fractions of feeds can be retained, with the possible consequence of contamination of later batches:

- Areas of reduced flow in piping, material ledges, and non-plane surfaces (screw couplings, weld seams, moulded tanks) can lead to a sedimentation of feed materials.
- Oversized and long conveying systems, and non-continuous earthing of parts of the production plant.

- In silos or containers, differences in flow rate may cause segregation of the bulk material, which accumulates in dead zones with solidification of the bulk material.
- Conveyors which do not empty completely, such as screw conveyors and elevator boots.
- Wear of mixing equipment and conveying systems can cause a reduced flow in certain areas at which material can accumulate.
- Filter systems may accumulate residues, in particular when material featuring high dusting potential and strong aspiration flow.

The **physicochemical characteristics** of additives can contribute to cross-contamination in the following ways:

- High dusting potential, low product moisture, adherence due to electrostatic charge, as well as environmental conditions (e.g. adhesions caused by surrounding moisture) contribute to cross-contamination. The more dispersed in air and the lower the density of the components, the more sensitively they react to current fields. Basically, particle sizes < 500 µm are dispersible in the air, which facilitates the discharge of suitable, airborne components by aspiration air. An accumulation of feed material in filters and incomplete or inappropriate cleaning (see above) can lead to cross-contamination of these components into the next production batch. Also a high electrostatic loading potential, as well as higher product moistures can cause adhesions inside production plants and can result in cross-contamination.

Finally, it should also be mentioned that activities inside or outside the feed mill may contribute to undesired contamination of non-target animal feed, for instance, insufficient rinsing or no rinsing during product changes will result in a greater amount of cross-contamination. The beneficial effect of using rinsing batches can be reduced considerably if the residual material adhering to the equipment cannot be fully removed by the material flow of the rinsing batch (Mc Evoy *et al.,* 2003; Noser *et al.,* 2006; Dorn *et al.,* 1988). Further cross-contamination can occur at the feed plant during conveying (contaminated conveying equipment) and on-farm (e.g. during storage and transport to the feeding location).

1.3.2. Assessing cross-contamination in feed mills

In investigations involving the majority of German compound-feed plants (approximately 450), more than half of the examined production plants had a level of cross-contamination of less than 4% (Strauch, 2002). A survey of Belgian compound-feed production companies showed similar values for pelleted products (OVOCOM, 2004, document provided to EFSA). Similar results were achieved with mashed (not pelleted) feeds (approx. 69% containing less than 5% cross-contamination).

The investigations, described above, refer to a general technical control of the mixing facilities used by commercial feed mills. Comparable investigations on the behaviour of coccidiostats during compound-feed production have not been carried out. As yet, analytical controls of the produced feeds for the presence of coccidiostats were only conducted in cases for which residual amounts of the coccidiostatic agents were found in food obtained from accidentally exposed animals. Systematic investigations of the behaviour of coccidiostats at compound-feed production companies have been carried out for lasalocid, narasin, nicarbazin and monensin (Kennedy *et al.,* 1996, 1998; Mc Evoy *et al.,* 2003; Noser *et al.*, 2006). These authors concluded that:

- Cross-contamination can be reduced significantly by suitable measures.
- Contamination by coccidiostats was detected in several rinsing batches.

1.4. Specific data for semduramicin-based feed additive products

The stability of semduramicin sodium has been evaluated under a range of environmental conditions including elevated temperature and relative humidity and in the presence of light. In addition, the compound was evaluated under severe conditions to determine potential pathways of degradation. The stability studies showed that there was no loss of potency under any of the conditions tested up to 75% relative humidity for 12 weeks, 50ºC for 12 weeks and in the light cabinet for 12 weeks. The degradation studies showed that semduramicin is susceptible to acid, but not to alkaline, degradation. Feed pelleting at 90°C resulted in a loss of 5% of the semduramicin sodium (EC, 2002).

Semduramicin is a white/off white powder with a particle size of 5 - 34 µm. Semduramicin is not hygroscopic (EC, 2002). There is no additional information available for semduramicin concerning cross-contamination and physical parameters.

2. Methods of analysis

2.1. Analysis of semduramicin in premixes and animal feeds

In the process of approval of a feed additive containing semduramicin the applicant presented an analytical method for quantification of semduramicin in feed (EC, 2002). However, this method does not meet the sensitivity requirements needed to monitor cross-contamination of feed.

A cross-contamination of 1% of the maximum authorised dose of 25 mg semduramicin/kg feed would result in a contamination of feed for non-target animal species of 0.25 mg/kg feed. Analytical methods for analysis of semduramicin in premixes and animal feeds should be

validated to a limit of quantification (LOQ)[13] of 0.25 mg/kg feed or lower. No methods were identified which would be sensitive enough to detect such low levels of semduramicin.

2.2. Analysis of semduramicin residues in animal products

According to the list of methods used by the National Reference Laboratories (NRL) for residue control, edited by the Community Reference Laboratory (CRL) (Bohm *et al.,* 2005), semduramicin residues methods are reported for meat and for eggs by 2 of the 20 NRLs within the EU. The Member States used liquid chromatography – tandem mass spectrometry (LC-MS/MS) for screening and confirmatory purposes. The decision limits were 1 µg semduramicin/kg for both liver tissues and eggs.

No maximum residue limit (MRL) or minimum required performance level (MRPL) has been established for semduramicin in eggs or animal tissues.

2.2.1. Screening methods

Enzyme-linked immunosorbent assay (ELISA) has been applied as a screening method. Watanabe *et al.,* 2004 presented a quantitative ELISA method for semduramicin. In chicken liver and muscle the limit of detection (LOD) for semduramicin was 5 µg/kg. In addition, a rapid test kit having a LOD of 100 µg/kg for semduramicin in chicken muscle was developed (Watanabe *et al.,* 2004).

2.2.2. Quantitative and confirmatory methods

High performance liquid chromatography (HPLC) and HPLC-MS techniques are used for quantification and confirmation of semduramicin in tissue samples. Schneider *et al.* (1991) were the first to apply electrospray LC-MS for the detection of carboxylic acid ionophores. By this method semduramicin concentrations of approximately 30 µg/kg in chicken liver were detectable. Samples were extracted with methanol and cleaned up on C8 and silica solid phase cartridges. The limit of quantification (LOQ) and the recovery of the method were not stated.

[13]Definitions of limit of detection (LOD), limit of quantification (LOQ), decision limit (CCα) and detection capability (CCβ): Commission decision 2002/657of 12 August 2002 implementing Directive No (EC) 96/23 concerning the performance of analytical methods and the interpretation of results (OJ L 221, 17.08.2002, p. 8-36) define the performance of analytical methods used for residue control and the interpretation of results. CCα means the limit at and above which it can be concluded with an error probability of α that a sample is non-compliant. CCβ means the smallest content of the substance that may be detected, identified and/or quantified in a sample with an error probability of β. CCα is equivalent to the LOD defined by IUPAC guidance (IUPAC, 1995). The LOQ (ISO, 1997) is defined by the relative standard deviation of the estimated quantity. Generally, it corresponds to the lowest concentration tested with a relative standard deviation below the performance value needed, such as the performance for repeatability defined by Decision No (EC) 2002/657 (OJ L 221, 17.8.2002, p. 8–36).

Derivatisation of semduramicin with vanillin has also been applied to determine semduramicin in broiler liver (Ericson *et al.*, 1994). First semduramicin sodium was extracted from liver with methanolic ammonium hydroxide, then separated and concentrated by sequential C8 and silica gel solid phase clean-up steps, and finally determined by LC with postcolumn derivatisation using vanillin as derivatisation reagent. The mean recovery for semduramicin in chicken liver was 95% over the 40 - 320 µg/kg concentration range, the LOQ was 40 µg/kg and the LOD was 25 µg/kg (Ericson *et al.*, 1994).

France uses a LC-MS/MS method in the official control for analyses of eggs and poultry, sheep and goat liver with below LOD of 1 µg/kg (data provided by the European Commission), more details on the method is not publicly available.

3. Occurrence of semduramicin

3.1. Occurrence of semduramicin residues in feed materials for non-target animal species

Data on cross-contamination of feed are scarce. The Czech Republic reported the results of 254 analyses that were performed during 2006 of different feed commodities. None of the samples contained semduramicin with a LOD of 0.5 mg/kg (data provided to EFSA).

Information from the Rapid Alert System for Food and Feed (RASFF)[14] that was collected between April 2002 and April 2006 showed no incidents of semduramicin in feed for non-target animal species (data provided by the European Commission).

3.2. Occurrence of semduramicin residues in animal products derived from non-target animal species

Residues of semduramicin in non-target animal tissues and eggs can arise from cross-contamination but also if a non-target animal is given feed formulated for target animal species, intentionally or accidentally.

Eggs, muscle and liver from different animal species are analysed for residues of coccidiostats by the Member States according to requirements in Directive No (EC) 96/23[15]. In 2004 no Member States analysed for presence of semduramicin in animal products, but in 2005, a total of 300 food samples were analysed (100 egg, 100 poultry liver and 100 sheep/goat liver) and no samples were found to be "non-compliant". The LOD was below 1 µg/kg. (data provided by the European Commission). Results from 2006 from France show one non-compliant egg

[14]For more information on the RASFF system: http://ec.europa.eu/food/food/rapidalert/index_en.htm
[15]Directive No (EC) 96/23 of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products. OL L 125, 23.5.1996, p 10-32.

sample out of 100 samples analysed. The sample contained 0.8 µg semduramicin/kg egg (data provided to EFSA).

There were no analyses for semduramicin in the UK surveys for residues in foods over the period 1995-2005.

4. Toxicity of semduramicin

4.1. Mechanism of toxicity

Ionophores modify the permeability of biological membranes by forming lipid soluble, dynamically reversible cation complexes which transport cations across biological membranes. Different carboxylic ionophore compound may have different characteristic inorganic ion selectivity patterns. Furthermore, ionophores also differ in molecular polarity, which affects their differential distribution in biological membranes. Accordingly, different carboxylic polyether ionophores exert their toxicity in a characteristically distinct manner on biological membrane systems.

The specific mechanism of toxicity for semduramicin has not been established. Semduramicin, as a monovalent polyether ionophore, is considered to promote perturbations in the intracellular cation balance: Na^+ increases and K^+ decreases. The increase in intracellular concentration of Na^+ is believed to result in Na^+:Ca^{2+} exchange, leading to a dramatic increase in the intracellular free Ca^{2+} concentration (Elliot *et al.*, 1998).

4.2. Toxicity of semduramicin in target animal species

The target animal species for semduramicin is the chicken for fattening. Two types of safety studies for the use of semduramicin in chickens for fattening have been assessed (EC, 2002): exploratory safety margin and safety margin floor-pen studies. During the exploratory safety margin study, doses of 20, 25, 30 and 35 mg/kg feed of semduramicin were fed for 21 days to germ free birds under battery conditions with control and salinomycin-treated birds (60 mg/kg) used as negative and positive controls. Overall, no increase in mortality or feed consumption was observed in any of the treated groups. However, mean body weight gain was reduced by 11 and 13% at 30 and 35 mg/kg, respectively. Chickens for fattening were exposed to levels of semduramicin of 25, 50 and 75 mg/kg feed for 49 days. A few birds at the two highest doses showed juvenile or thin feathering together with lower haemoglobin values. Moreover, mean body weight gain was also reduced by 19 and 46% at these doses, respectively. From the results of both studies, the maximum recommended dose of

semduramicin in the complete feedingstuffs for chickens for fattening has been established at 25 mg/kg feed. It was concluded that, at such a concentration, the margin of safety for the birds is narrow, as reduced body weight gain is observed with a dose of 30 mg/kg feed (EC, 2002).

4.3. Toxicity of semduramicin in non-target animal species

4.3.1. Hens

A study has been carried out in 30 week-old chicken breeder hens to assess the effect of semduramicin on body weight, feed consumption, egg production, egg fertility, embryo mortality and hatchability at dose levels of 3, 6 and 25 mg/kg feed for 7 days. None of these parameters were affected at the dose levels tested during the period of medication (days 0 - 7) or during the 7-day period following when all hens were fed a non-medicated diet. Adverse clinical signs were not observed in any of the treatments and there were no mortalities (data provided by industry).

Three experiments were conducted by Brake *et al.* (2001) to assess the effects on chicken breeder hens from exposure to semduramicin. In experiment 1, individually caged females received 0, 12.5, or 25 mg/kg semduramicin in the diet for 3 weeks from 48 to 50 weeks of age. In experiment 2, males and females in floor pens received 0, 12.5, or 25 mg/kg semduramicin in the diet for 3 weeks from 63 to 65 weeks of age. In experiment 3, individually caged males and females received 0, 3, 6, or 25 mg/kg semduramicin in the diet for 1 week at 31 weeks of age and were mated by artificial insemination. There was a dose-related decrease in cumulative egg production and percentage shell (an indirect measurement of shell thickness) in experiment 1 after more than 1 week exposure, but these effects were not observed in the other experiments. There was a decrease in cumulative fertile hatchability, and a dose-related decrease after 3 weeks exposure due to an increase in early embryonic mortality in experiment 2, but these changes were not observed during the 1-week exposure in experiment 3. The data showed that adverse effects in laying hens cannot be excluded at concentrations equal to or exceeding 12.5 mg/kg feed. These effects of semduramicin require more than one week of exposure to become evident.

4.3.2. Turkeys

Groups of 480 turkeys, housed in floor-pens, were randomly allocated to two groups, and received semduramicin at a dose of 0 or 25 mg/kg in the feed for 12 weeks (data provided by industry). The turkeys were observed daily for abnormal clinical signs. At 0, 28, 56 and 84 days of age, the turkeys were weighed and feed intake was recorded. Doses of semduramicin

of 25 mg/kg for 84 days caused no clinical abnormalities. Weight gain and feed conversion were improved.

4.3.3. Guinea Fowls

A study carried out in guinea fowls by adding 25 mg/kg of semduramicin to the feed of 52 to 140-day old chicks for 28-days indicated that semduramicin was well tolerated at this dose (with the exception of a reported death in one guinea fowl (1.9%) from the semduramicin group). No effects were seen at body weight, feed consumption and mortality (data provided by industry).

4.2.4. Ducks

A study was carried out in ducks by adding 25 mg/kg of semduramicin to the feed of 52 males and 52 females for 28-days. Overall, semduramicin was well tolerated at this dose and did not affect body weight gain, feed consumption, feed conversion and mortality (data provided by industry).

4.3.5. Geese

A study was carried out in geese by adding 25 mg/kg of semduramicin to the feed of 72 chicks (75-day old) for 28-days. This dose was well tolerated, and did not affect body weight gain, feed consumption, feed conversion and mortality (data provided by industry).

4.3.6. Rabbits

A study was carried out in rabbits by adding 25 mg/kg of semduramicin to the feed of 27 males and 27 females for 42-days. This dose was well tolerated, and no clinical signs, abnormal or adverse reactions were found in the medicated group compared to the control group with the exception of a reported death in one rabbit (1.9%) from the semduramicin group (however no gross lesions were observed). Weight gain, feed consumption, feed conversion and mortality were unaffected (data provided by industry).

4.3.7. Horses

Groups of 6 horses received semduramicin at a dose of 0 or 25 mg/kg for 21 days (0.25 mg/kg b.w. per day) (data provided by industry). The measured end-points included clinical signs, and heart rate, rectal temperature, faecal consistency and respiratory rate. Each horse was

weighed weekly. Haematology and clinical chemistry were performed before and after the 21-day feeding period. No significant effects on body weights, haematology, clinical chemistry and clinical signs were observed.

4.3.8. Dogs

No semduramicin intoxications in dogs have been reported and experimental studies are described in section 1.2.

4.3.9. Fish

No data are available on oral toxicity of fish.

In summary, studies conducted in food-producing animals regarding semduramicin toxicity are limited and mostly confined to short-term feed exposure. Studies in turkeys, guinea fowls, ducks and geese as well as in rabbits and horses given doses of 25 mg/kg feed for almost 3 weeks showed no adverse effects in these animals. In laying hens, a decrease in egg production and reduced hatchability rates were observed in some experiments conducted with feed concentrations of 12.5 mg and 25 mg semduramicin per kg feed , but not in others. Therefore it is concluded that cross-contamination at a level of 2, 5 and 10% of the maximum authorised level for target animal species is unlikely to comprise a short-term risk for non-target animal species.

4.4. Common drug interaction

The interaction between semduramicin and tiamulin has been recently investigated. In a 35-day study, semduramicin was administered in the feed (25 mg/kg) to 10 replicates of female broilers and tiamulin was given on day 15 through 19 in drinking water (250 mg of TIA/kg of water). Results indicated that simultaneous administration of the two drugs during the third week of the trial reduced water and feed intake resulting in a temporary growth depression. However, these negative effects in body weight were not observed during the fourth week of the test and by the end of the experiment, no adverse effects were observed in the final performance of the broilers and no histopathological or heamatological parameters were affected. The authors concluded that the effects of the simultaneous administration of semduramicin and tiamulin produce temporary impairments of water and feed intake but do not result in an increase in mortality nor long-term effects on performance variables in broilers (Schuhmacher *et al.,* 2006).

5. Kinetics and tissue distribution

5.1. Kinetics of semduramicin in target animal species

Semduramicin residue levels were determined in the liver of chickens for fattening slaughtered after 6, 12, 18, 24, 36 and 48 hours withdrawal from feed containing 25 mg unlabelled semduramicin sodium/kg which had been fed for 44 days. Semduramicin depleted from a level of 166 μg/kg at 6 hours to less than 17 μg/kg after 24 hours withdrawal (Lynch *et al.,* 1992; EC, 2002).

Chickens for fattening received feed with 25 mg/kg ^{14}C-labelled semduramicin sodium for 7 days. Samples of plasma, bile, liver, kidney, muscle, fat and skin/fat were collected 6 (practical zero withdrawal), 12, 24 and 48 hours after the seventh day. Low levels of radiolabel were observed in plasma, muscle, kidney, fat and skin, but higher levels in bile and liver. Mean plasma and bile radioactivity at 6 hours withdrawal were 25 and 22600 μg semduramicin equivalents (total radioactive residues)/L, respectively and declined below the LOQ of 9 μg semduramicin equivalents/L after 24 hours in plasma, whereas levels of 80 μg semduramicin equivalents/L could be measured in bile by 120 hours. Total radioactive residue levels in liver, kidney, muscle, fat, and skin/fat at 6 hours withdrawal were 273, 51, 15, 74 and 57 μg semduramicin equivalents/kg, respectively (Lynch *et al.,* 1992; EC, 2002). By linear extrapolation, a concentration of approximately 5.5, 14 and 27 μg semduramicin equivalents/kg liver could be anticipated if the chickens had been given feed cross-contaminated at a level of 2, 5 and 10% of the maximum authorised level, respectively. The same calculation for skin/fat gives 1.1, 2.9 and 5.7 μg semduramicin equivalents/kg, for kidney 1, 2.5 and 5.1 μg semduramicin equivalents/kg and for muscle 0.30, 0.75 and 1.5 μg semduramicin equivalents/kg for 2, 5 and 10% of the maximum authorised level, respectively.

Following a five day oral administration of ^{14}C-labelled semduramicin at the maximum authorised level for chickens for fattening, (i.e. 25 mg/kg in feedstuffs), excreta, bile and liver were examined for total radioactivity and identification of the metabolites. Semduramicin was extensively metabolised with the production of 19 metabolites that were more polar than semduramicin. The three main metabolites have been identified and were: metabolite E (O-desmethyl (G-ring) semduramicin), metabolite F (O-desmethyl (A-ring) semduramicin) and metabolite C, a compound corresponding to the ring opening of metabolite F. In chicken excreta, the distribution of the extractable radioactivity (about 50%) was as follows: 23.8% metabolite F, 16.2% semduramicin and a great number of metabolites for a total of less than 10%. Metabolite F was the major compound excreted through the bile. Parent semduramicin was the main residue in the liver (45%) after 6-hour withdrawal, each of the other 19 metabolites representing less than 10% of the total radioactivity (Lynch *et al.*, 1992; EC, 2002).

5.2. Kinetics of semduramicin in non-target animal species

No studies were available in food producing animals other than chickens for fattening.

6. Risk characterization

6.1. Animal health risks in non-target animal species associated with the accidental consumption of feed materials designated for target animal species

Based on very limited tolerance studies performed by industry on non-target animals (see chapter 4.2), there is some evidence for the toxicity of semduramicin in non-target animals exposed to the maximum authorised feed level for target animal species. However, there are no reports available from intoxications under field conditions.

6.2. Adverse health effects in non-target animal species as a consequence of cross-contamination of feed batches

In accordance with the Terms of Reference, levels of cross-contamination of 2, 5 and 10% of the maximum level authorised for target animal species (corresponding to 0.5, 1.25, or 2.5 mg semduramicin per kg feed, respectively) have been evaluated. At an average feed consumption of 50 g/kg b.w. in monogastric species, these concentrations would result in doses of approximately 0.03, 0.06 and 0.13 mg/kg b.w., respectively. At a level of cross-contamination of 10% of the maximum authorised level the intake of semduramicin would be at the same level as the overall NOAEL (0.125 mg/kg b.w. derived from a two-year rat study) (see chapter 1.2). The Panel concluded that adverse health effects in non-target animals are unlikely to result from cross-contamination of feed up to a level of 10% of the maximum authorised level.

6.3. Residues of semduramicin in foods derived from non-target animal species

In the very limited surveillance data of residues of semduramicin in animal products one non-compliant sample was found in eggs containing 0.8 µg/kg.

No kinetic studies in non-target animal species were available. Therefore, the exposure of consumers to semduramicin as a result of consumption of foods derived from non-target animal species cannot be estimated from kinetic studies. To have a rough indication of the exposure, the CONTAM Panel decided to apply the data available from chickens for fattening to all non-target animal species.

The kinetic data from chickens for fattening show that residues occur predominantly in liver tissues, whereas the residue levels in fat/skin, kidney and muscle tissues are considerably lower. No kinetic data were available on residues of semduramicin in eggs. By linear extrapolation, a concentration of approximately 5.5, 14 and 27 µg semduramicin equivalents/kg liver would be anticipated if the chickens had been given feed cross-contaminated with 2, 5 and 10% (0.5, 1.25 and 2.5 mg/kg) of the maximum authorised level, respectively. About half of these levels would be present as semduramicin. For the other edible tissues the estimated levels would be 1.1, 2.9 and 5.7 µg semduramicin equivalents/kg skin/fat, 1, 2.5 and 5.1 µg semduramicin equivalents/kg kidney and 0.30, 0.75 and 1.5 µg semduramicin equivalents/kg muscle for 2, 5 and 10% cross-contamination, respectively.

No data were available on the possible carry-over of semduramicin into dairy milk.

6.4. Human health risk associated with residues in foods derived from non-target animal species following exposure of these animals to contaminated feed batches

A person eating 100 g of egg containing 0.8 µg/kg (as found by a Member State) would be exposed to 0.08 µg semduramicin (0.001 µg/kg b.w. for a 60 kg person), which is approximately 0.1% of the ADI of 1.25 µg/kg b.w.

No data were available to estimate the amount of semduramicin residues that might appear in milk or in meat and offal from non-target animal species. Hence, consumer exposure was estimated by extrapolating kinetic data from chickens for fattening. The predicted concentrations of semduramicin equivalents from a diet cross-contaminated with semduramicin at 10% of the maximum authorised level were 27, 5.7, 5.1 and 1.5 µg semduramicin equivalents/kg liver, skin/fat, kidney and muscle, respectively. The values for daily human food consumption relevant for calculation of human exposure to semduramicin from cross-contaminated feed are 100 g of liver, 90 g skin/fat and 300 g muscle[16]. Such consumption would lead to exposure to 3.7 µg semduramicin equivalents/person per day (corresponding to 0.062 µg/kg b.w. per day for a 60 kg adult), which represents 5% of the ADI of 1.25 µg/kg b.w. per day. Even though the behaviour of the kinetic and tissue deposition can differ between chickens for fattening and non-target animal species, an exceedance of the ADI is unlikely to occur. In addition, it was recognised that consumer exposure to residues of semduramicin resulting from cross-contamination of feed is likely to be infrequent.

[16] Values for daily human food consumption, as defined in Directive No (EC) 2001/79 are for birds: 300 g muscle, 100 g liver, 10 g kidney (50 g for mammals), 90 g skin/fat in natural proportions (50 g for mammals) and 100 g eggs (and 1500 g milk). Values for mammals are given in parenthesis when they differ from bird values

Therefore the Panel concluded that the very limited data provided no indication of an appreciable risk to the health of consumers from the ingestion of semduramicin residues in products from animals exposed to feed cross-contaminated up to a hypothetical level of 10% of the maximum authorised level.

CONCLUSIONS

- Semduramicin exerts signs of toxicity typical of ionophoric compounds in the dog (including skeletal muscle damage). However, semduramicin induces also retinal changes in dogs that have not been studied in other species yet.
- Based on the very limited tolerance studies available adverse effects are not expected in turkeys, guinea fowls, ducks, geese, rabbits and horses if these non-target animal species are accidentally fed a diet containing semduramicin designated for target animal species. For laying hens data are equivocal, and an impairment of egg production and hatchability can not be excluded. There are no reports available from intoxications under field conditions.
- At a rate of cross-contamination of 10% of the maximum authorised level, the intake of semduramicin (0.13 mg/kg b.w. per day) would be at the same level as the overall NOAEL (0.125 mg/kg b.w. per day in rats), thus adverse health effects in non-target animals are unlikely to occur.
- No occurrence data or kinetic studies were available to estimate the human exposure to semduramicin residues in milk or in meat and offal from non-target animal species. Therefore, the exposure of consumers to semduramicin as a result of consumption of foods, derived from animals that had been exposed to cross-contaminated feed, was estimated from residues of semduramicin in the liver, muscle, skin/fat and kidney of chickens for fattening that were given semduramicin in their feed at 25 mg/kg, extrapolated to a concentration of 2.5 mg/kg feed.
- Human exposure estimated to result from consumption of food products from non-target animal species exposed to cross-contaminated diet was shown to remain well below the ADI of 1.25 μg/kg b.w. established by the SCAN. Even though kinetic and tissue deposition can differ between chickens for fattening and non-target animal species, an exceedance of the ADI is unlikely to occur.
- The Panel concluded that the very limited data provided no indication of an appreciable risk to consumers' health from the ingestion of semduramicin residues in products from animals exposed to feed cross-contaminated up to a hypothetical level of 10% of the maximum authorised level for semduramicin.

RECOMMENDATIONS

- Sensitive analytical methods that have become available for the detection of semduramicin in animal products should be validated also for feed concentrations below the maximum authorised level, to assess their applicability in the control of cross-contamination of feed batches during the production process.
- In countries where semduramicin is used, regular surveys for residues in animal products are recommended in order to evaluate human exposure to semduramicin.

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