

Date: May 5, 2016

UPDATED FREEDOM OF INFORMATION SUMMARY

IMPORT TOLERANCE

I. GENERAL INFORMATION

- A. Established Name:** monensin
- B. Food-Animal Species:** sheep
- C. Tolerances/tissues:** 10 parts per billion (ppb) monensin in sheep muscle and kidney
20 ppb monensin in sheep liver
100 ppb monensin in sheep fat
- D. File Number:** VMF 006-017
- E. Petitioner:** Elanco Animal Health, A Division of Eli Lilly & Co.
Lilly Corporate Center, Indianapolis, IN 46285

II. HUMAN FOOD SAFETY

A. Microbial Food Safety:

The firm submitted information from the 70th Joint FAO/WHO Expert Committee on Food Additives (JECFA) addressing monensin's impact on antimicrobial resistance. CVM reviewed the JECFA assessment and does not disagree with their conclusions at this time that monensin is not a risk to microbial food safety (antimicrobial resistance).

B. Summary of Toxicology Studies:

1. JECFA Monograph for toxicology of monensin

The toxicological evaluation of monensin was performed at the 70th JECFA meeting (2008). The report was published in the WHO Technical Report Series 954 in 2009¹.

To evaluate the toxicity of monensin in the human diet, JECFA considered data on the pharmacokinetics (including metabolism), acute toxicity, short-term and long-term toxicity, carcinogenicity, genotoxicity, reproductive toxicity, immunotoxicity, cardiovascular and respiratory toxicity, epidemiological findings, and microbiological effects of monensin. Many of the studies were conducted prior to the introduction of the Good Laboratory Practice (GLP). The series of toxicology studies included the following:

¹ http://whqlibdoc.who.int/trs/WHO_TRS_954_eng.pdf

Study Type	Description
Acute Oral Toxicity Study in Rodents:	Acute, single-dose oral toxicity studies in mice and rats
Acute Oral Toxicity Study in Non-Rodents:	Acute, single-dose oral toxicity studies in rabbits and monkeys
Chronic Oral Toxicity Study in Rodents:	3-month oral toxicity (diet) studies in mice and rats (gel capsules)
Chronic Oral Toxicity Study in Non-Rodents:	3-month oral toxicity (diet) studies in dogs (gel capsules). A NOAEL of 5 mg/kg bw per day was identified.
Chronic Oral Toxicity Study in Non-Rodents:	1-year oral toxicity (diet) studies in dogs (gel capsules). A NOAEL of 1.25 mg/kg bw per day was established.
Chronic Oral Toxicity Study in Rodents:	1- and 2-year oral toxicity (diet) studies in mice and rats (gel capsules). A NOAEL of 1.2 mg/kg bw/day was established in the rat. A NOAEL of 1.14 mg/kg bw/day was established in the rat.
Three-Generation Oral Reproductive Toxicity Study in Rats:	3-generation toxicity study in rats (diet). a NOAEL for parental and offspring toxicity could not be determined
Oral Developmental Toxicity Study in Rodents:	one-generation developmental toxicity study in rats (diet). NOEL for reproductive toxicity was 80 mg/kg in the diet (equivalent to 4 mg/kg bw/day), the highest dose tested.
Oral Developmental Toxicity Study in Non-Rodents:	teratogenicity study in pregnant rabbits (diet). a NOAEL for both maternal toxicity and teratogenicity was 0.76 mg/kg per day (highest dose tested).
Genetic Toxicology Studies:	Monensin has no genotoxic potential based on negative results obtained in adequate <i>in vivo</i> and <i>in vitro</i> genotoxicity studies.

2. Determination of No Observed Effect Level (NOEL) for chronic exposure:

Based on the no-observed-effect-level (NOAEL) of 1.14 mg/kg body weight (bw)/day in the 2-year oral rat study for a decrease in body weight gain at the next highest dose and a safety factor of 100, JECFA established an ADI of 0-10 µg/kg bw for monensin.

3. Acceptable Daily Intake (ADI):

We did not identify any additional concerns during the review of the JECFA monograph that merit more detailed review. Therefore, we can establish a toxicological ADI of 10 µg/kg bw/day in support of an import tolerance for monensin. This is the same ADI

as what was determined by JECFA. We note that JECFA concluded that there is no need to determine a microbiological ADI for monensin residues.

Because of the lack of antibacterial activity for monensin, a microbiological ADI was not needed. Therefore, the toxicological ADI was set as the final ADI. The toxicological ADI for total residues of monensin is calculated using the following formula based on the NOEL/NOAEL of 1.14 mg/kg bw/day from the 2-year oral rat study and a safety factor of 100. A safety factor of 100 was applied to the NOEL/NOAEL in calculating the ADI to account for possible animal-to-human variability and human-to-human variability in response to monensin.

$$\begin{aligned} \text{Toxicological ADI} &= \frac{\text{NOEL}}{\text{Safety Factor}} = \frac{1.14 \text{ mg/kg bw/day}}{100} \\ &= 0.010 \text{ mg/kg bw/day} = 10 \text{ } \mu\text{g/kg bw/day} \end{aligned}$$

4. Safe Concentrations for Total Residues:

The calculation of the tissue safe concentrations is based on CVM GFI #3 *General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals* (FDA/CVM, revised July 2006). The safe concentration of total monensin residues (ppm) in each edible tissue of sheep is calculated using the following formula:

$$\text{Safe Concentration} = \frac{\text{ADI} \times \text{Human Body Weight}}{\text{Food Consumption Value}}$$

The safe concentration (SC) for total residues of monensin in muscle is calculated from the ADI, assuming the average weight of a man to be 60 kg and the daily human intake of muscle to be 300 g. The safe concentration for total residues of monensin in sheep liver, kidney, and fat are determined, using food factors of 100 g, 50 g, and 50 g for these tissues respectively, as follows:

Muscle: 2 parts per million (ppm) monensin

Liver: 6 ppm monensin

Kidney: 12 ppm monensin

Fat: 12 ppm monensin

C. Summary of Residue Chemistry Studies:

1. Total Residue and Metabolism Study:

Giera, D.D., Herberg, R.J., Thomson, T.D., and Handy, P.R. (1984). ¹⁴C-Monensin tissue residue study in sheep. Unpublished GLP Study No. ABC-0270 from Agricultural Biochemistry, Lilly Research Laboratories, Eli Lilly and Company, Greenfield, IN, USA.

The JECFA review of the total residue and metabolism study was used as a basis for establishing an import tolerance (JECFA Monograph 6-2009). Liver contained the highest mean total residue concentrations compared to the other edible tissues. The data indicated that the largest extractable portion of radioactivity is parent drug.

2. Comparative Metabolism Studies:

1. Donoho, A.L. (1985). [¹⁴C] monensin metabolism study in rats. Unpublished GLP study No. ABC-0053 from Agricultural Biochemistry, Lilly Research Laboratories, Eli Lilly and Company, Greenfield, IN, USA.
2. Giera, D.D., Herberg, R.J., Thomson, T.D., and Handy, P.R. (1984). ¹⁴C-Monensin tissue residue study in sheep. Unpublished GLP Study No. ABC-0270 from Agricultural Biochemistry, Lilly Research Laboratories, Eli Lilly and Company, Greenfield, IN, USA.

The metabolic profile of the extractable residues of monensin in sheep is qualitatively similar to that in rats.

3. Target Tissue and Marker Residue Assignment:

The target tissue is liver. The marker residue in the edible tissues of sheep is the parent drug, monensin.

4. Tolerance Assignment:

Import tolerances of 10 parts per billion (ppb) monensin in sheep muscle and kidney, 20 ppb monensin in sheep liver, and 100 ppb monensin in sheep fat are assigned.

5. Withdrawal Period:

A withdrawal period is not assigned in establishing an import tolerance.

D. Analytical Method for Residues:

There are a number of validated analytical methods for measuring residues of parent drug, monensin, in edible tissues including the USDA official analytical method, thin layer, chromatography/bioautography. The thin layer chromatography/bioautography method is available from the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

E. Human Food Safety Conclusions:

The Center for Veterinary Medicine concludes that we have the appropriate information for us to assign an import tolerance for monensin in sheep. We assign import tolerances of 10 parts per billion (ppb) monensin in sheep muscle and kidney, 20 ppb monensin in sheep liver, and 100 ppb monensin in sheep fat.

III. AGENCY CONCLUSIONS

These data support the establishment of import tolerances of 10 parts per billion (ppb) monensin in sheep muscle and kidney, 20 ppb monensin in sheep liver, and 100 ppb monensin in sheep fat as provided under Sec. 512(a)(6) of the Food, Drug, and Cosmetic Act.