Elanco US Inc.
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MONEPANTEL FOR CATTLE

Environmental Assessment

in support of an

Import Tolerance

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1. General information

Requestor: Elanco Animal Health
2500 Innovation Way
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Established name: Monepantel

2. Purpose and need for the proposed action

Elanco Animal Health is requesting an import tolerance for monepantel so that meat from cattle treated with monepantel may be more readily imported into the U.S. for human consumption. This drug is approved for use in cattle in Australia, New Zealand, Argentina and Uruguay under the product names Zolvix® and/or Zolvix® Plus, however is not currently approved for use in cattle in the U.S.

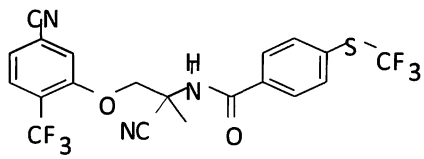
The environmental impact on the U.S. environment from monepantel residues in meat will be evaluated herein based on the expected exposure pathways and available physical-chemical properties and fate data for the drug (Section 6).

3. Identification of the substance

Monepantel is an oral drench used in sheep and cattle as an anthelmintic. One such example is Zolvix®.[1] Table 1 summarizes the most relevant physical-chemical properties of monepantel.

[1] See Appendix 2 for additional information on Zolvix® and how it is used

Table 1: Physical-chemical properties of monepantel

International Nonproprietary Name (INN)	Monepantel
Structural formula:	
Appearance:	White powder
Vapor pressure	2.8 x 10^{-9} Pa (at 25°C - extrapolated value) [Smeykal 2006]
Relative density	1.468 g/cm^3
Solubility in water:	0.08 mg/L [Meinerling 2006a]
Log Octanol / water partition coefficient (K_{ow})	4.2 – 4.7 [Meinerling 2006b]

Monepantel is not volatile and of limited water solubility. The main metabolite of monepantel in cattle is monepantel sulfone [Vance 2014].

4. Sites of introduction and exposure pathways

Following the importation of meat from monepantel-treated cattle, release of monepantel to the U.S. environment may occur via two different routes:

- through landfills, which may hold seized materials (meat) containing the drug;
- through wastewater treatment systems (via effluent and bio-solids), which may contain residues of the drug in human excreta.

A potential introduction into soils and surface waters from landfills and wastewater treatment facilities strongly depends on the inherent properties of the respective drug. Only in cases where the substance is volatile or highly mobile (i.e., will migrate out of the compartments at the site of introduction), and present at high enough concentrations to cause effects, is it possible that environmental impacts on the circumjacent ecosystems could become evident.

The environmental exposure and risk of monepantel to cause impacts on the ecosystem at the sites of introduction is evaluated in Section 5.

5. Analysis of exposure and risk

The potential exposures due to the pathways listed in Section 4 will be evaluated based on available metabolism and environmental fate data for monepantel. Metabolism of monepantel in the animal will help to determine the residues that could be present in imported meat/tissues disposed of in landfills in the U.S., as well as the amount of the drug consumed by humans in the U.S., which is then processed by wastewater treatment facilities as bio-solids and effluents. The environmental fate will help to determine if monepantel will migrate out of landfills or be persistent in terrestrial and aquatic environments.

5.1 Exposure

Metabolism in cattle

Studies investigating the absorption, distribution, metabolism and elimination of radiolabeled monepantel following oral dosing of 3.75 mg/kg BW in cattle have been conducted [Vance 2014][2].

Monepantel was rapidly metabolized, principally to the sulfone metabolite following oral administration. About 21% of the dose was eliminated via urine over 3 days, and 36% of the dose was voided in the feces, which probably included some unabsorbed parent drug. About 60% of the dose was recovered in excreta over 3 days, with the remaining material distributed in the tissues. Elimination via urine and feces continued at a decreasing rate until study termination at day 21.

In tissues, residues are principally localized in the fat and liver, and deplete steadily; kidney and muscle contribute minor amounts to total residues [Adams 2014][2]. The depletion half-lives in all tissues were <3 days except for subcutaneous fat, which depleted with a half-life of 5 days.

The following tolerances (the same as for sheep) are proposed for monepantel sulfone: 7 ppm in beef fat, 2 ppm in beef liver, 1 ppm in beef kidney, and 0.3 ppm in beef muscle. These are the types of tissues from cattle that are typically imported into the U.S. and could end up in landfills or wastewater treatment facilities.

Adsorption in soil

Aqueous solutions of monepantel were equilibrated with five soil types and the adsorption coefficients and constants (K_{oc}) were determined according to OECD guideline 106

[2] See Appendix 1 for study summaries

[Meinerling 2007]. The concentrations of monepantel were determined using a liquid scintillation counting (LSC) method. The K_{oc} for monepantel in the five soils ranged from 6082 to 8880 mL/g (log K_{oc} ranged from 3.78 to 3.95), with a geometric mean of 7271.6 (log K_{oc} of 3.86). Monepantel is therefore considered to have moderate to low mobility in soils and is considered to bind moderately to strongly to soil.

Biodegradation in soil

Soil biodegradation was determined in an OECD Guideline 307 compliant study [Meinerling 2008] evaluating the aerobic transformation rates of monepantel in sand, loamy sand and silty sand at application rates of 211, 366, and 272 µg/kg. The degradation half-life (DT_{50}) values were 146, 81 and 38 days, respectively. Based on these data, monepantel is not considered to be persistent in soil.

5.2 Risk

As discussed previously, there are two theoretically possible pathways to the environment at large for monepantel residues originating in imported food

- through landfills, which may hold seized materials (meat) containing the drug;
- through wastewater treatment systems (via effluent and bio-solids), which may contain residues of the drug in human excreta.

The potential for impacts to the US environment through these two exposure pathways is evaluated further below.

Landfill

Landfills in the US are highly regulated by local, state and federal authorities to prevent environmental contamination. For example, most landfills are required to have caps and liners of clay or an impermeable membrane to prevent leaching of water or fluids therein (and any contaminants they may contain) to groundwater and/or local surface waters (e.g., rivers and lakes). As a result of these controls and monepantel's high potential to bind to soils (K_{oc} of 3.86) and low water solubility, there is expected to be minimal or no movement of monepantel out of US landfills and into the adjacent environment (groundwater or surface water).

In addition, because monepantel has a low vapor pressure (2.8×10^{-9} Pa) it is not expected to volatilize from landfills and enter air to any significant extent. Therefore, based on a lack of exposure, significant environmental impacts on the terrestrial and aquatic environments are not expected from residues of monepantel in imported food derived from treated cattle that are disposed of in US landfills.

Wastewater discharge and application of bio-solids to land

Due to the low solubility of monepantel and monepantel sulfone, the high potential to bind to organic carbon (log K_{oc} of 3.86) and further removal and processing in wastewater treatment facilities, any monepantel that enters a treatment facility is likely to be partitioned into the bio-

solid phase. There is expected to be little to no residues of monepantel in effluents entering the aquatic systems from such facilities. In the event any monepantel is found in the waste water it would be further diluted by receiving water bodies, therefore, significant environmental impacts on the aquatic environment are not expected from residues of monepantel in effluents from wastewater treatment facilities.

As a result of this high potential to bind to organic carbon (log K_{oc} of 3.86), low water solubility, and moderate ability to degrade in soils ($t_{1/2}$ = 46–139 days), any monepantel located in the bio-solid that is subsequently spread onto land as fertilizer etc. will be contained and degraded in the soil compartment. It can be expected that there would be little movement off site into groundwater or even in the case of surface water in a runoff event. Whilst highly unlikely, any unbound monepantel is found in runoff waters, it would be further diluted by receiving water bodies.

In addition, the concentration of drug residues introduced into the U.S. environment from a wastewater treatment facility; either in the form of waste water or from spreading of bio-solids to land, due to consumption and excretion of imported beef containing residues of monepantel by humans, is expected to be extremely low for several reasons:

1) additional metabolism of monepantel and monepantel sulfone residues is likely to occur in the human body; and
2) the distribution of the excreted residues in the U.S. environment will likely be spatially and temporally variable (i.e., it is very unlikely that enough humans will consume imported beef in the same region on the same day and have their excreta enter the same wastewater treatment facility).
3) the amount of imported beef consumed in the US is less than 15% of the total beef consumed in the US [USDA 2017],
4) Monepantel residues in muscle account for a very minor percentage of the total residue. The majority of what little residue is found in edible commodities is found in fat and liver. The US consumption of offal is typically quite low with less than 0.5 kg consumed per capita per year, therefore intake of monepantel will be extremely low[3]

Therefore it can be reasonably concluded that no significant environmental impacts are expected from waste water and/or bio-solids containing monepantel released from wastewater treatment facilities.

5.3 Conclusion

Based on the available information on the metabolism, environmental fate, and exposure of monepantel, there is expected to be little to no exposure of monepantel in the U.S. environment. Therefore, environmental impacts are not expected from the importation of beef containing residues of monepantel.

[3] http://www.fao.org/faostat/en/#data/CL

6. Description of any alternatives to the proposed use

Elanco is proposing to establish a tolerance for monepantel in cattle imported into the U.S. for human consumption. The only alternative to the proposed action is the 'no action' alternative, which would be the failure to establish a tolerance for monepantel in beef. However, based on our analysis in this EA, we do not believe that significant environmental impacts will occur from this action; therefore, the preferred alternative is the establishment of a tolerance for monepantel in beef imported into the U.S. and the no action alternative was eliminated from consideration.

7. Document Author

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8. List of Agencies and persons consulted

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Dr. John McHenery	Research Advisor Ruminant Parasiticides and Aqua Development Team
Dr. Allen Bridges	Research Scientist, Global Regulatory, New Product Development

9. References

Adams S. (2014) Depletion of residues of monepantel sulfone in edible tissues of beef cattle following three oral administrations 21 days apart of Zolvix at 3.75 mg monepantel/kg BW. Unpublished report from Novartis Animal Health Australasia Pty Ltd. Study Report No. NAH-13-069.

Meinerling M. and Hermann S. (2006a) Determination of water solubility of AHC 2102225. Unpublished report from IIBACON, Rossdorf, Germany, Study Report No. 28845186, 20 June 2006.

Meinerling M. and Hermann S. (2006b) Determination of the partition coefficient (n-Octanol/Water) of AHC 2102225 by shake flask method. Unpublished report from IIBACON, Rossdorf, Germany, Study Report No. 28844185, 05. April 2006.

Meinerling M. (2007) Determination of the adsorption / desorption behavior of AHC2102225. Unpublished report from IIBACON, Rossdorf, Germany, Study Report No. 24877195, 11. Oct. Sept. 2007.

Meinerling M. (2008) Aerobic transformation of AHC-2102225 in soil. Unpublished report from IBACON, Rossdorf, Germany, Study Report No. 24878173, 09. July 2008.

Vance C. (2014), Total radioactive residue depletion and metabolism of [14C]-monepantel following oral administration to beef cattle. Unpublished report from Charles River, Edinburgh Scotland, Study No.: 286778, Report No. 35014, 22 October 2014

Smeykal H. (2006), AHC2102225 – Vapour pressure. Unpublished report from Siemens, Frankfurt am Main, Germany, Study Report No. 20060259-01, 28. August 2006.

USDA (2017), Statistics and Information (internet). Available from: <https://www.ers.usda.gov/topics/animal-products/cattle-beef/statistics-information> (accessed 27 June 2017)

10. Appendices

9.1 Appendix 1 – Study Summaries

Study No.: 286778 (Vance C. 2014)

Four groups of beef cattle, three per group, were treated with a single oral dose of [14C]-monepantel at a mean dose level of 3.80 mg monepantel per kg of body.

Urine and feces samples were collected from one group of animals until 3 days post dose. Blood samples were collected from a second group of animals at selected time points until 21 days post dose. One group of animals was euthanized at intervals between 3–21 days post dose. Following euthanasia, liver, kidney, loin muscle, renal fat, bile and whole blood were collected and retained.

All samples listed above were subject to total radioactive residue (TRR) analysis. Selected samples were then subject to metabolite profiling. Overall within the first three days ca. 60% of the total radioactivity administered was eliminated in urine and feces.

In blood, the sulfone metabolite was dominant, peaking at 24 h and dissipating with a terminal half-life of about 3 days. Monepantel levels peaked at 12–24 h and depleted faster reaching the LOQ about 7 days after dosing. Accumulation after repeat dosing was not apparent

Bile TRR was high at day 3 but declined progressively by day 21.

Metabolite profiles in tissues were very simple with monepantel sulfone dominating in all tissues. The order of residues in tissues is fat > liver > kidney > muscle, indicative of lipophilic substances. Total residues were more persistent in liver than in the other tissues and in sheep liver.

Study No. NAH-13-069 (Adams S. 2014)

A GLP tissue residue depletion study was conducted in beef cattle dosed three times 21 days apart at 3.75 mg/kg bw monepantel in the Zolvix formulation, a dose marginally in excess of the proposed maximum dosage of 3.7 mg/kg bw.

Male and female Angus cross cattle of about 250 kg were enrolled in the study and maintained on pasture. Groups of five animals were slaughtered at four time points after the last dose; 4, 7, 10 and 13 days.

Renal fat, subcutaneous back fat, liver, kidney and muscle were collected and analyzed for monepantel sulfone only using a validated LC-MS/MS method. Residues in tissue were below the proposed MRLs for fat (7,000 µg/kg), liver (2,000 µg/kg), kidney (1,000 µg/kg and muscle (300 µg/kg) by the first sample collection. The depletion half-lives were <3 days except for subcutaneous fat, which depleted with a half-life of 5 days.

Blood was collected from one group at regular intervals after each dose, starting at 4 h. Blood samples were analyzed for monepantel and the sulfone using a validated LC-MS/MS method. In blood, the sulfone metabolite was dominant, peaking at 24 h and dissipating with a terminal half-life of about 3 days. Monepantel levels peaked at 12–24 h and depleted faster reaching

the LOQ of 0.25 ng/mL about 7 days after dosing. Accumulation after repeat dosing was not apparent.

9.2 Appendix 2 – Use pattern of Zolvix in cattle

Zolvix® is an anthelmintic drug for sheep and cattle. The active ingredient in this drug product is monepantel. The product is formulated as a solution containing 25 mg monepantel/mL. It is administered to sheep and cattle orally as a drench at a target maximum dose of 3.71 and 3.75 mg monepantel/kg body weight (1 mL per 10 kg body weight), respectively. The minimum label dose for both species is 2.5 mg/kg.

Zolvix® is currently registered for cattle in New Zealand (see label below), Australia, Argentina and Uraguay

New Zealand (similar in all other countries)

Dose	Tissue withholding period	Label instructions
1mL/10 kg bw (equivalent to 2.5 mg monepantel/kg bw)	5 days	Environmental protection: Product is designed for biocidal action against gastro-intestinal roundworms (nematodes). Avoid contamination of any water supply with product or used containers. Disposal: Preferably dispose of the product by use. Dispose of product and packaging at an approved landfill or other approved facility. Triple rinse container with water and dispose of rinsate away from waterways. Crush or puncture and bury in a suitable landfill. Do not use container for any other purpose.

DIRECTIONS

1. Maintain applicator gun carefully to ensure accurate dosage.
2. Give full dose orally according to dosing schedule.
3. A representative sample of animals should be weighed before treatment either with scales or weigh band.
4. Dose the mob to the heaviest animal by liveweight in each group (bulls, heifers, steers, calves). Do not under dose.
5. If there is a large variation in size within the group, draft into two or more lines based on bodyweight to avoid excessive overdosing.
6. After use, clean gun and tubing by flushing with warm, soapy water. Rinse with cold water.

Spectrum of activity includes fourth stage larvae and/or adults of:

- Haemonchus placei
- Haemonchus contortus
- Ostertagia ostertagi
- Trichostrongylus axei
- Cooperia punctata
- Cooperia oncophora
- Cooperia mcmasteri
- Nematodirus helvetianus
- Bunostomum phlebotomum

WITHHOLDING PERIODS (NZ)

MEAT: Cattle producing meat or offal for human consumption must not be sold for slaughter either during treatment or within 5 days of the last treatment.

MILK: Milk (colostrum) from the first 8 milkings after calving must be prevented from directly entering the human food chain. If calving occurs within 7 weeks of the last treatment, milk to be sold for human consumption may be taken only after the full 7 weeks from treatment and a further 8 milkings have elapsed. Milk from animals treated during lactation and intended for human consumption must be discarded during treatment and for not less than 35 days from the last treatment.