



Elanco Animal Health Inc.  
DMPK & Safety  
Basel, Switzerland

# **MONEPANTEL FOR SHEEP**

## **ENVIRONMENTAL ASSESSMENT IN SUPPORT OF AN IMPORT TOLERANCE**

Original signed and on file:

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## 1. General Information

**Requestor:** Elanco Animal Health U.S., Inc.  
2500 Innovation Way  
Greenfield, Indiana 46140

**Established Name:** Monepantel

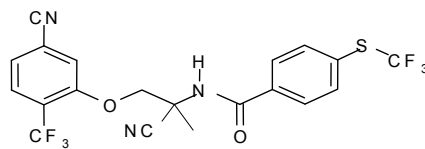
## 2. Purpose and Need for the Proposed Action

Elanco Animal Health is requesting an import tolerance for monepantel so that meat (lamb and mutton) from sheep treated with monepantel may be imported into the U.S. for human consumption. This drug is not currently approved for use in sheep in the U.S.; therefore, an import tolerance needs to be established. 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 as an anthelmintic. One such example is Zolvix®.<sup>1</sup> Table 1 summarizes the most relevant physical-chemical properties of monepantel.

**Table 1: Physical-chemical properties of monepantel**

International Non-proprietary Name (INN)	Monepantel
Company Code	AHC-2102225
Structural formula:	
Appearance:	White powder
Vapour pressure	$2.8 \times 10^{-9}$ Pa (at 25°C - extrapolated value) [Smeykal 2006]
Relative density	1.468 g/cm <sup>3</sup>
Solubility in water:	0.08 mg/L [Meinerling 2006a]
Log Octanol / water partition coefficient (K <sub>ow</sub> )	4.2 – 4.7 [Meinerling 2006b]

<sup>1</sup> See Appendix 1 for additional information on Zolvix® and how it is used

Monepantel is not volatile and of limited water solubility. The main metabolite of monepantel in sheep is monepantel sulfone [Jung 2007, Karadzovska 2007a].

#### **4. Sites of introduction and exposure pathways**

Following the importation of meat from monepantel-treated sheep, 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, 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. The environmental fate will help to determine if monepantel will migrate out of landfills or be persistent in terrestrial and aquatic environments.

##### *Metabolism in Sheep*

Studies investigating the absorption, distribution, metabolism and elimination of radiolabeled monepantel following oral dosing of 5 mg/kg BW in sheep have been conducted [Jung 2007, Karadzovska 2007d]. Monepantel was rapidly metabolized, principally to the sulfone metabolite, in sheep following oral administration. The single oral application of radiolabeled monepantel to sheep resulted in an elimination of 87-92% of the radioactivity within 12 days. Residues are principally localized in the fat and liver, and deplete steadily; kidney and muscle contribute minor amounts to total residues [Karadzovska 2007a,b,c]. The half-lives in the animal are about 6-7 days. Based on information provided to the FDA, the following tolerances are expected to be assigned: 7 ppm monepantel sulfone in sheep fat, 5 ppm monepantel sulfone in sheep liver, 2 ppm monepantel sulfone in sheep kidney, and 0.7 ppm monepantel sulfone in sheep muscle. These are the types of tissues from sheep 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 [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 mL/g (log  $K_{oc}$  of 3.86). Monepantel is, therefore, considered have a moderate to low mobility in soils.

*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  $\mu\text{g}/\text{kg}$ . 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.

Due to the rapid metabolism in the animal, the high potential of monepantel to bind to soils, the low water solubility, and a moderate ability to degrade in soils, there is expected to be minimal to no potential movement of monepantel or monepantel sulfone, out of a U.S. landfill and into the adjacent U.S. environment. Therefore, significant environmental impacts on the terrestrial and aquatic environments are not expected from residues of monepantel in meat disposed of in U.S. landfills.

The concentration of drug residues introduced into the U.S. environment from a wastewater treatment facility, due to consumption and excretion of imported lamb or mutton containing residues of monepantel by humans, is expected to be extremely low for several reasons: 1) the consumption rates of lamb and mutton in the U.S. are very low compared to other types of meats, 2) additional metabolism of monepantel and monepantel sulfone residues in lamb and mutton is likely to occur in the human body; and 3) 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 lamb and mutton in the same region on the same day and have their excreta enter the same wastewater treatment facility). Because of this, and further removal and processing of monepantel and monepantel sulfone in wastewater treatment facilities, there is expected to be little to no residues of monepantel in effluents entering the aquatic systems from wastewater treatment facilities. Therefore, significant environmental impacts on the aquatic environment are not expected from residues of monepantel in effluents from wastewater treatment facilities.

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 meat containing residues of monepantel.

## 6. Description of any alternatives to the proposed use

Elanco is proposing to establish a tolerance for monepantel in sheep (lamb and mutton) 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 sheep. 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 sheep imported into the U.S. and the no action alternative was eliminated from consideration.

## 7. Author

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## 8. Signature



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## 9. References

- Jung M, McLellan G, Karadzovska D, Strehlau G (2007) ADME and residue depletion study of [<sup>14</sup>C]AHC 2102225 in sheep. Unpublished report from Elanco, Elanco Centre de Recherché Santé Animale, Switzerland. Study Report No. CRA 05/151.
- Karadzovska D (2007a) Residues of AHC-2102225 in edible tissues of Suffolk sheep following a single oral dose of AHC-2102225 at 3.75 mg/kg. Unpublished report from Elanco Animal Health Australasia Pty. Ltd. Study Y07/21, Report Y07/21/2154.
- Karadzovska D (2007b) Residues of AHC-2102225 in edible tissues of cross-bred fattening lambs following a single oral dose of AHC-2102225 at 3.75 mg/kg. Unpublished report from Elanco Animal Health Australasia Pty. Ltd. Study Y07/17, Report Y07/17/2157.
- Karadzovska D (2007c) Residues of AHC-2102225 in edible tissues of Merino sheep following a single oral dose of AHC-2102225 at 3.75 mg/kg. Unpublished report from Elanco Animal Health Australasia Pty. Ltd. Study Y07/16, Report Y07/16/2158.
- Karadzovska D (2007d) Determination of pharmacokinetic parameters of AHC-2102225 and AHC-2144670 in sheep following IV and oral administration of AHC-2102225 and IV administration of AHC-2144670. Unpublished report from Elanco Animal Health Australasia Pty. Ltd. Study Y06/72, Report Y06/72/2159.
- 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 IIBACON, Rossdorf, Germany, Study Report No. 24878173, 09. July 2008.
- 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.
- Smeykal H (2006) AHC2102225 – Vapour pressure. Unpublished report from Siemens, Frankfurt am Main, Germany, Study Report No. 20060259-01, 28. August 2006.

## **Appendix 1**

### **Drug Information for Zolvix<sup>®</sup>**



Zolvix<sup>®</sup> is an anthelmintic drug for sheep. 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 orally as a drench at a target dose of 2.5 mg monepantel/kg body weight (0.5 mL per 5 kg body weight).

Spectrum of activity includes fourth larvae and adults of:

<i>Haemonchus contortus</i>	<i>Nematodirus spathiger</i>
<i>Teladorsagia circumcincta</i>	<i>Nematodirus filicollis</i>
<i>Teladorsagia trifurcata</i>	<i>Chabertia ovina</i>
<i>Teladorsagia davtiani</i>	<i>Oesophagostomum venulosum</i>
<i>Trichostrongylus axei</i>	<i>H. contortus</i> strains resistant to salycilanides
<i>Trichostrongylus colubriformis</i>	<i>Nematodirus abnormalis</i>
<i>Trichostrongylus vitrinus</i>	<i>Trichostrongylus</i> spp.
<i>Trichostrongylus rugatus</i>	<i>Cooperia</i> spp.
<i>Cooperia curticei</i>	<i>Nematodirus</i> spp.
<i>Cooperia oncophora</i>	
<i>Nematodirus battus</i>	

Zolvix<sup>®</sup> is currently registered in the following countries:

European Union (EU), Iceland (ISL),	Switzerland (CH)
Norway (NO), Liechtenstein (LIE)	Australia (AU)
Uruguay (URU)	New Zealand (NZ)
Argentina (ARG)	Chile
South Africa (RSA)	

A detailed list of approved indications is given in Table 2 and the disposal of any unused drug is summarized in Table 3.

**Table 2: Approved Indications**

Genus/Species	EU, ISL, NO LIE		CH		AU		NZ		ARG		Chile		URU		RSA	
	Adult	L4	Adult	L4	Adult	L4	Adult	L4	Adult	L4	Adult	L4	Adult	L4	Adult	L4
<i>Haemonchus contortus</i> *	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Teladorsagia circumcincta</i> *	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Teladorsagia trifurcata</i> *	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Teladorsagia davtiani</i> *	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Trichostrongylus axei</i> *	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Trichostrongylus colubriformis</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Trichostrongylus vitrinus</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Trichostrongylus rugatus</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<i>Cooperia curticei</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Cooperia oncophora</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Nematodirus battus</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Nematodirus spathiger</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Nematodirus filicollis</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Chabertia ovina</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Oesophagostomum venulosum</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>*including inhibited larvae</i>	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>
<i>H. contortus</i> strains resistant to salycilanides	<input checked="" type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>	
<i>Nematodirus abnormalis</i>							<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>					<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>Trichostrongylus spp</i>															<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Cooperia spp</i>															<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Nematodirus spp</i>															<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

**Table 3: Approved use pattern of Zolvix®**

Country	Dose	Tissues Withholding Period	Export Slaughter Interval	Disposal unused drug
European Union (EU)	2.5 mg/kg bw	7 days	n/a	Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.
Uruguay Argentina Chile		7 days	n/a	No special provisions
RSA		10 days	n/a	As EU
AUS		14 days	115 days	Dispose of rinsate or any undiluted chemical according to State legislative requirements.
NZ		7 days	n/a	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.
CH		7 days	n/a	No special provisions

## **Appendix 2**

# **Executive Study Summaries**

1. **Jung M, McLellan G, Karadzovska D, Strehlau G (2007)** ADME and residue depletion study of [<sup>14</sup>C]AHC 2102225 in sheep. Unpublished report from Elanco, Elanco Centre de Recherché Santé Animale, Switzerland. Study Report No. CRA 05/151.

A pivotal GLP study investigating the ADME and residue depletion of [<sup>14</sup>C]-monepantel, using test material labeled at either of two rings of the parent molecule, was conducted. Sheep (32) were orally dosed at 5.0 mg/kg and blood, excreta, wool and tissues were collected. Collected samples were analyzed for total radioactivity, metabolite profiles and by HPLC-UV for monepantel and the sulfone metabolite.

Radioactivity is predominantly excreted through the feces with a significant contribution from urinary elimination. A tiny fraction of the drug is excreted with wool. Blood and plasma profiles indicate a very slow elimination from the systemic circulation.

Highest residues in edible tissues are found in the fat, with slightly higher residues in rendered pure fat compared with fat tissue. Liver is also an organ of accumulation. Muscle has the lowest residues.

The metabolic pathway in sheep includes two routes. The first involves oxidation of the parent to the transient sulfoxide, with rapid oxidation to the sulfone. There is a further slow oxidation; the site of the hydroxylation was not elucidated. The other route involves cleavage to yield the phenol, together with its sulfate conjugate. From the corresponding benzamide portion, an alcohol and a peptide hydrolysis product are formed and eliminated via the urine.

2. **Karadzovska D (2007a)** Residues of AHC-2102225 in edible tissues of Suffolk sheep following a single oral dose of AHC-2102225 at 3.75 mg/kg. Unpublished report from Elanco Animal Health Australasia Pty. Ltd. Study Y07/21, Report Y07/21/2154.

Suffolk lambs (36), 3-4 months old, were treated with a single oral dose of monepantel at 3.75 mg/kg. All animals were maintained on open pasture for the duration of the study. Groups of 8 sheep were sacrificed at 7, 18, 29 and 40 days after treatment. Liver, skeletal muscle, kidney and surrounding fat, and if present subcutaneous fat from the back, were taken and analyzed using a validated method.

Mean residues are shown in the table below.

Day	Mean Residues (+ SD) (µg/kg)				
	Renal fat	Subcutaneous fat	Liver	Kidney	Muscle
7	3256 ± 1106	2417 ± 1153	1757 ± 516	591 ± 201	222 ± 114
18	490 ± 326	538 ± 281	212 ± 141	71 ± 52	43 ± 17 plus 3x<10
29	115 ± 67 plus 1x<10	114 ± 38	91 ± 55 plus 1x<10	21 ± 9 plus 2x<10	15 ± 3 plus 5x<10
40	109 ± 73 plus 2x<10	114 ± 78	59 ± 43 plus 2x<10	18 ± 9 plus 4x<10	12 plus 7x<10

3. **Karadzovska D (2007b)** Residues of AHC-2102225 in edible tissues of cross-bred fattening lambs following a single oral dose of AHC-2102225 at 3.75 mg/kg. Unpublished report from Elanco Animal Health Australasia Pty. Ltd. Study Y07/17, Report Y07/17/2157.

Second cross lambs (Merino x Dorset), 3-4 months old were treated with a single oral dose of monepantel. The mean dose received was 3.9 mg/kg. Groups of 8 animals were sacrificed at

7, 19, 29, 40, 70 and 77 days after treatment, in order to determine depletion down to 10 µg/kg. Mean residues are shown in table below.

Day	Mean Residues (± SD) (µg/kg)				
	Renal fat	Subcutaneous fat	Liver	Kidney	Muscle
7	3068 ± 1050	3667 ± 1316	2056 ± 733	460 ± 170	155 ± 76
19	681 ± 298	751 ± 364	354 ± 169	99 ± 47	32 ± 11 plus 1x<10
29	83 ± 45	114 ± 91	51 ± 40	18 ± 5 plus 5x<10	All <10
40	22 ± 13 plus 2x<10	21 ± 14 plus 2x<10	18 ± 7 plus 1x<10	All <10	All <10
70	All <10	All <10	11 plus 7x<10	All <10	Not analyzed
77	15 plus 7x<10	All <10	12 ± 2 plus 2x<10	Not analyzed	Not analyzed

4. **Karadzovska D (2007c)** Residues of AHC-2102225 in edible tissues of Merino sheep following a single oral dose of AHC-2102225 at 3.75 mg/kg. Unpublished report from Elanco Animal Health Australasia Pty. Ltd. Study Y07/16, Report Y07/16/2158.

Merino sheep, 2-3 years old were treated with a single oral dose of monepantel. The mean dose received was 3.8 mg/kg. Groups of 8 animals were sacrificed at 7, 18, 29, 35 and 70 days after treatment; thereafter, due to a shortage of treated animals, 4 sheep were sacrificed at 120 and 127 days, in order to determine depletion to 10 µg/kg. Mean residues are shown in the table below.

Day	Mean Residues (± SD) (µg/kg)				
	Renal fat	Subcutaneous fat	Liver	Kidney	Muscle
7	3109 ± 834	3010 ± 1028	1376 ± 258	366 ± 90	199 ± 110
18	474 ± 380	638 ± 497	325 ± 259	82 ± 62	40 ± 39
29	202 ± 132	265 ± 197	138 ± 84	35 ± 12 plus 2x<10	23 ± 6 plus 2x<10
35	67 ± 52	89 ± 46	54 ± 47 plus 1x<10	22 ± 6 plus 6x<10	15 ± 4 plus 6x<10
70	22 ± 10 plus 1x<10	27 ± 15 plus 2x<10	15 ± 6 plus 3x<10	All <10	All <10
120	All <10	All <10	All <10	All <10	All <10
127	All <10	All <10	All <10	Not analysed	Not analysed

5. **Karadzovska D (2007d)** Determination of pharmacokinetic parameters of AHC-2102225 and AHC-2144670 in sheep following IV and oral administration of AHC-2102225 and IV administration of AHC-2144670. Unpublished report from Elanco Animal Health Australasia Pty. Ltd. Study Y06/72, Report Y06/72/2159.

A GLP-compliant PK study was conducted in cross-bred lambs with the final oral formulation (A-20072B; 1, 3 and 10 mg/kg), and with iv administration of monepantel and monepantel sulfone AHC- 2144670 (each at 1 mg/kg). Collected blood and fecal samples were analyzed for monepantel and AHC-2144670.

The calculated PK parameters are shown in table below.

Product	Route	Dose mg/kg	AHC-2102225			AHC-2144670			
			AUC(0-7d)	Tmax	Cmax	AUC(0-∞)	Tmax	Cmax	T1/2
			[(ng/mL)*h]	h	(ng/mL)	[(ng/mL)*h]	h	(ng/mL)	days
AHC-2102225	iv	1	676	0	740	3651	2-4	62	6.2
AHC-2144670	iv	1				3701	0	643	5.3
	oral	1	226	2-8	7	3564	24	30	4.2

A-20072B	oral	3	703	4-24	19	11571	24	96	5.2
	oral	10	1967	4-8	130	19200	4-24	294	3.7

6. **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.

An OECD 106 guideline compliant GLP-study investigated the decrease in concentration when aqueous solutions of monepantel were in contact with different soil types at room temperature. Aqueous solutions of the test item were equilibrated with five soil types, which varied in clay content, organic carbon content and pH. The adsorption coefficients and constants were determined.

In a preliminary study the soil/solution ratio was estimated. The equilibrium time for adsorption and the amount of test item adsorbed at equilibrium as well as potential adsorption of the test item on surfaces of the test vessels and the stability of the test item were estimated. In a screening test the adsorption with five different soil types was studied by means of the adsorption kinetic at a single concentration and the determination of the distribution coefficient  $K_d$  and  $K_{OC}$ . The concentration of the test item was determined using a LSC (liquid scintillation counter) method.

With the adsorption coefficient in the range from 6082 to 8880 mL/g monepantel is considered to bind moderately to strongly to soil. The geometric mean of the 5 different soil  $K_{OC}$  values is 7271.6 mL/g. Testing for desorption showed less than 1% loss, so this adsorption can be considered as irreversible.

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

The purpose of this OECD 307 guideline compliant GLP-study was to evaluate the aerobic transformation of monepantel in soil. For the determination of transformation pathway and rates  $^{14}C$ -radiolabelled test item and various analytical methods were used.

The transformation pathway of the test item was followed in one soil by chemical analysis for parent substance and for transformation products. Volatile transformation products were collected with appropriate devices and analyzed. Transformation products which account for more than 10% of the amount of the parent compound were identified.

The transformation rate was determined in three different soils, which varied in clay content, organic carbon content, microbial biomass and pH.

The application rate was the maximum expected PEC in soil.

In all soils the content of the test item decreased steadily over the incubation period. The half-lives varied from 38 days in silty sand soil to 146 days in sand soil. The most rapid degradation was observed in the silty sand soil and correlated with the highest organic carbon content and the highest microbial activity at test start. The higher pH of this soil may have contributed to faster breakdown.

The major degradation product was identified by LC-MS/MS as the sulfoxide metabolite.

8. **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.

The purpose of the study (OECD 105, GLP) was to determine the solubility of monepantel in water which is specified by the saturation mass concentration of the test item in water at a specified temperature.

The water solubility of the test item was estimated to be smaller than 0.01 g/L in a preliminary test (non-GLP) and therefore the column elution method was used in the main test. The method is based on the elution of the test item with water from a micro-column which is charged with an inert support material, previously coated with an excess of the test item. The water solubility is given by the saturation mass concentration of the eluate when this has reached a plateau as a function of time.

The water solubility of monepantel was determined to be 0.08 mg/L at 20°C ± 0.7°C using the column elution method for the performance of the main test.

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

The purpose of the study was to determine the partition coefficient of monepantel between n-octanol and water using the shake flask method.

The concentrations in both phases were determined using HPLC method. The concentration in the aqueous phase was below the limit of quantification. Therefore, the water solubility value was used for calculation of the logP<sub>ow</sub>.

The difference between the three different test variants was less than ± 0.3 log units. Therefore, the study was considered to be valid.

According to this study the logarithmic partition coefficient (n-octanol / water) of the test item was estimated to be 3.0 at approx. pH 7 using the shake flask method at 20 ± 1°C.

A log K<sub>ow</sub> of 4.2 has been recalculated based on the data of the above study report and using the analytical method limit of detection (LOD) of 0.005 mg/L as the assumed water concentration. According to the laboratory which conducted this partition coefficient study, using either the water solubility or the LOD of the analytical method to calculate the log K<sub>ow</sub> is acceptable. OECD guideline 107 does not provide detailed guidance on this point. The expert considers that the log K<sub>ow</sub> = 3 is not justified in view of the higher values obtained upon calculation and upon molecular structure modeling. It is concluded that a correct value is likely to be in the range of 4.2-4.7.

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

The purpose of this study was the determination of the vapor pressure of monepantel according to OECD test guidelines 104 and 113. A vapor pressure of 2.8 x 10<sup>-9</sup> Pa was extrapolated at 25°C.