

FINDING OF NO SIGNIFICANT IMPACT
for
Rumensin® (monensin sodium) 80 Type A Medicated Article
for
Cattle Fed in Confinement at 40 g/ton (480 mg/head/day)

Elanco Animal Health
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The Center for Veterinary Medicine has considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement will not be prepared.

Elanco Animal Health is requesting approval of a supplemental new animal drug application (NADA) for Rumensin® (monensin sodium) 80 Type A Medicated Article. The supplement provides for the continuous feeding of monensin sodium at 40 g/ton (480 mg/head/day) to cattle fed in confinement for slaughter. To support the approval of the supplement, Elanco has provided the attached environmental assessment (EA) dated October 2005.

At the proposed use level of 480 mg/head/day, the concentration of monensin sodium in cattle feces at the time of excretion is estimated in the EA to be 9.5 mg/kg (ppm) after accounting for metabolism. The subsequent predicted environmental concentration in soil (PEC_{soil}) is calculated at 75.5 $\mu\text{g}/\text{kg}$ (ppb), assuming no degradation of monensin in stored manure prior to application. This calculation is based on a European application rate of manure at 13.2 ton (wet weight) per acre and incorporation to a depth of 25 cm. Assuming a slightly lower manure concentration of 8.79 mg/kg, a higher manure application rate of 30 tons/acre, and a shallower incorporation depth of 15 cm (all conditions which are usually used for U.S. calculations) the PEC_{soil} has been estimated by CVM at 262.6 $\mu\text{g}/\text{kg}$.

In the EA, based on the lower calculated PEC_{soil} of 75.5 $\mu\text{g}/\text{kg}$ and assuming equilibrium partitioning conditions ($K_{oc} = 478,630$), surface water is expected to contain no more than about 0.02 $\mu\text{g}/\text{L}$ (ppb) of monensin. Because of the inconsistencies between the two calculated PEC_{soil} values, additional calculations were also performed by CVM to estimate a potential surface water concentration (PEC_{sw}) for monensin. A concentration in water as high as 4.35 $\mu\text{g}/\text{L}$ could be justified based on the higher PEC_{soil} of 262.6 $\mu\text{g}/\text{kg}$ and an estimated soil adsorption coefficient (K_{oc}) of 380 (pH 7). This estimated K_{oc} value was used in the calculations because of questions about the potential accuracy of the measured K_{oc} values in the EA. Elanco reports that a field study in southern Ontario measured monensin concentrations in surface water as high as 1.2 $\mu\text{g}/\text{L}$ (Lissemore et al., 2003). Concentrations measured in another study in Colorado were within the range of 0.008 to 0.011 $\mu\text{g}/\text{L}$ (Carlson, 2004). Because both of the estimated PEC_{sw} values are uncertain, and there is a wide range of measured concentrations in surface water, the highest measured concentration (1.2 $\mu\text{g}/\text{L}$) is used in the risk characterization.

Data from several new studies have addressed deficiencies and uncertainties in the dataset that were identified in the CVM review of the most recent (1997) EA prepared for monensin sodium by the sponsor. New soil degradation data indicate that monensin will not persist in aerobic soils for long periods of time (half-life <14 days) and that it will ultimately degrade to carbon dioxide. Based on this data, the parent compound is not expected to accumulate in soil, even with repeated applications of manure.

New toxicity data for terrestrial plants corroborate the finding of earlier studies that were considered weak. In addition, data are now available from studies with soil microorganisms that show that effects on nitrogen or carbon transformation (nutrient cycling) are not expected at predicted environmental concentrations of monensin. In addition, bioconcentration factor (BCF) estimates based on HPLC log K_{ow} values do not raise a significant level of concern for the concentration of monensin residues in aquatic species.

Risk quotients have been calculated using predicted no effect concentrations (PNECs) and PECs calculated in the EA and by CVM (Tables 1 and 2). Conservatively derived risk quotients for both aquatic and terrestrial organisms, including microorganisms, are generally less than one and indicate that Phase II Tier B studies and assessments are not needed at this time. Risk quotients for aquatic organisms are all less than one even when using the highest measured concentration of monensin in surface water, 1.2 $\mu\text{g/L}$ (Table 1). All aquatic risk quotients remain less than one, even if the highest estimated value of 4.35 $\mu\text{g/L}$ is used as the PEC_{sw} .

For terrestrial organisms, there was one case (plants) where the risk quotient was greater than one (2.8; Table 2). This value has been discounted because the PEC_{soil} value (262.6 $\mu\text{g/kg}$) that was used to calculate this risk quotient did not account for any degradation of monensin in cattle manure prior to land application. If it assumed that the degradation rate in manure is the same as that in soil (i.e., half-life = 14 days), and there is an average manure storage period of 65 days (one-half of the minimum cattle growout period of 130 days), this reduces the estimated manure concentration and $\text{PEC}_{\text{soil-refined}}$ by a factor of 0.040 (96%) from their original levels because of degradation prior to application. This would bring the $\text{PEC}_{\text{soil-refined}}$ down to 10.5 $\mu\text{g/kg}$ from the CVM-calculated initial value of 262.6 $\mu\text{g/kg}$ and the corresponding risk quotient for terrestrial plants down to 0.11. Additionally, a peak soil concentration will persist for only a very short time due to further degradation of monensin in soil. Therefore, it is concluded that at predicted environmental concentrations, adverse effects are not expected on soil (plants, birds, earthworms, and microbes) or aquatic species (algae, bluegill, rainbow trout, and *Daphnia*).

Monensin sodium is already approved (21 CFR 558.355) for use in cattle in being fed in confinement for slaughter at up to 30 g/ton (360 mg/head/day). To date, there have been no reports of adverse environmental effects resulting from the use of monensin sodium.

The information available is adequate to conclude that use of monensin sodium in feedlot cattle at up to 40 g/ton (equivalent to 480 mg/head/day) is not expected to have a significant impact on the environment.

April 26, 2006
Date

Steven D. Vaughn, DVM
Director, Office of New Animal Drug Evaluation, HFV-100

Attachment: Environmental Assessment Dated October 20, 2005

cc: Document Control Unit for the administrative file of:
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bcc: HFV-103 (Reading Board)

Table 1. Predicted no effect concentration (PNEC) values for monensin and risk quotients for aquatic organisms from the proposed use of Rumensin.

Study	Assessment Endpoint	Assessment Factor	PNEC	Risk Quotient† (PEC:PNEC)
Algal growth inhibition	EC ₅₀ (biomass) = 0.98 mg/L	100	9.8 µg/L	0.002 / 0.12
<i>Daphnia</i> acute toxicity	EC ₅₀ (immobilization) = 10.7 mg/L	1000	10.7 µg/L	0.0018 / 0.11
Fish acute toxicity (bluegill)	LC ₅₀ (mortality) = 16.6 mg/L	1000	16.6 µg/L	0.0012 / 0.07
Fish acute toxicity (rainbow trout)	LC ₅₀ (mortality) = 9.0 mg/L	1000	9.0 µg/L	0.0022 / 0.13

† The first risk quotient shown is based on the calculated PEC_{sw-initial} (0.02 µg/L) in the EA. The second is based on the highest measured concentration of monensin in surface water (1.2 µg/L)

Table 2. Predicted no effect concentration (PNEC) values for monensin and risk quotients for soil-dwelling organisms from the proposed use of Rumensin.

Study	Assessment Endpoint	Assessment Factor	PNEC	Risk Quotient† (PEC:PNEC)
Earthworm*	14-d LC ₅₀ = 264 mg/kg	1000	264 µg/kg	0.29 / 0.99
Terrestrial plants	LC ₅₀ (emergence) = 9.8 mg/kg	100	98 µg/kg	0.77 / 2.68
Nitrogen transformation	NOEC = 18.3 mg/kg (<25% difference from control)	NA	18.3 mg/kg	0.004 / 0.014

* The endpoint and assessment factor differ from those recommended in the Phase II guidance (i.e., NOEC; 10) because data from the appropriate OECD 222 study were not available.
† The first risk quotient shown is based on the PEC_{soil} in the EA (75.5 µg/kg) which was derived using the method of Spaepen et al. (1997), a manure application rate of 29,663 kg/ha or 13.2 tons per acre (based on the EU maximum of 170 kg N/ha/yr), and a soil incorporation depth of 25 cm. The second risk quotient is based on a PEC_{soil} of 262.6 µg/kg which was derived using calculation methods historically used by CVM with an application rate of 67,211 kg manure/ha (30 tons/acre) and a soil incorporation depth of 15 cm.