

ENVIRONMENTAL ASSESSMENT 000337
FOR THE USE OF RUMENSIN® TYPE A MEDICATED
ARTICLES IN THE FEED
OF DAIRY COWS FOR THE INCREASED EFFICIENCY
OF MILK PRODUCTION AND IMPROVED BODY
CONDITION

Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

July 1997

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**ENVIRONMENTAL ASSESSMENT FOR THE USE OF RUMENSIN[®] TYPE A
MEDICATED ARTICLE IN THE FEED OF DAIRY COWS FOR THE
INCREASED EFFICIENCY OF MILK PRODUCTION AND IMPROVED BODY
CONDITION**

1. **DATE** July 1997
2. **APPLICANT** Elanco Animal Health
A Division of Eli Lilly and Company
3. **ADDRESS** Lilly Corporate Center
Indianapolis, Indiana 46285
4. **DESCRIPTION OF THE PROPOSED ACTION**

A New Animal Drug Approval is being requested for use of Rumensin[®] Type A Medicated Articles in the feed of dairy cows to increase the efficiency of milk production and improve body condition. Monensin granulated, USP is the active ingredient in Rumensin Type A Medicated Articles. Rumensin Type A Medicated Articles would be incorporated into feeds to provide monensin levels of 8 to 24 mg/kg feed or up to 473 mg/head/day. Rumensin is already approved at similar levels for the rations of feedlot cattle to increase efficiency of feed utilization (21 CFR 558.355; December 16, 1975). When incorporated into cattle rations, monensin alters the production of volatile fatty acids in the rumen. As a result of increased production of propionic acid, the usable energy derived from the ration is increased.

Rumensin[®] (monensin granulated, USP, Elanco)

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Rumensin is also approved (21 CFR 558.355; Federal Register, July 28, 1978) for use in the rations of growing cattle in pastures (up to 200 mg monensin/head/day). In 1983, approval for use of Rumensin in pastured cattle was expanded to include beef and dairy replacement heifers. In 1987, approval was granted for the use of Rumensin in reproducing beef cattle (21 CFR 558.355; Federal Register, December 15, 1988) and an Environmental Assessment was submitted for this use. In 1990, approval was granted for use of Rumensin in beef cattle for the prevention and control of coccidiosis (21 CFR 558.355; Federal Register, October, 1990).

The current Environmental Assessment addresses the use of Rumensin for increasing the efficiency of milk production and body condition in dairy cows. Approval of the proposed action would authorize the fermentation and processing plants of Eli Lilly and Company at Clinton and Lafayette, Indiana to manufacture and package Rumensin to be sold in the United States for increased efficiency of milk production in dairy cows.

Based on the proposed action, monensin could potentially be introduced into the following environments:

- a) The environment adjacent to the manufacturing plants.
- b) The environment adjacent to facilities which mix Rumensin with feed.
- c) Dairy farms where residues may be found in cattle excreta.
- d) Agricultural lands where waste products from dairy cows are used as fertilizer

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e) Aquatic systems where runoff may flow from sites receiving waste products of dairy cows.

Returned or rejected material in the United States will be disposed of at the following facility by incineration according to a Resource Conservation and Recovery Act Permit issued by the U.S. EPA under facility identification number IND072040348:

Clinton Laboratories
Eli Lilly and Company
10500 South State Road 63
Clinton, IN 47842

5. IDENTIFICATION OF CHEMICAL SUBSTANCE

A. RUMENSIN TYPE A MEDICATED ARTICLES

RUMENSIN will be incorporated into rations of dairy cows. Monensin granulated, USP and monensin sodium, USP are the active ingredients in Rumensin and are produced in granular and crystalline forms. The raw material is mixed with diluents such as rice hulls, anti-dusting oil, and densifiers to concentrations of 45, 60, 80, and 90 grams monensin/lb. of medicated article.

B. MYCELIAL MONENSIN

Monensin is produced by the fermentation of a strain of *Streptomyces cinnamomensis*, an organism isolated from soil (Haney and Hoehn, 1968). The most economical procedure to prepare a usable form of monensin is to harvest the fermentation culture in such a way as to combine monensin with the mycelial cells of the producing

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organisms and the unused components of the feed-stock used in the fermentation to achieve growth of the organism. Thus, the granulated form of monensin contains dried mycelial biomass containing nutrients commonly found in cattle feedstuff, along with pelleting aids and limestone. Occasionally, crystalline monensin sodium may be added to the granules to adjust the monensin concentration.

C. MONENSIN

Monensin consists primarily of monensin factor A, but small amounts of monensin factor B, C, and D do occur. Monensin factor A accounts for at least 90 percent of the microbiologically active material of mycelial monensin. The characteristics of monensin factor A are discussed in this section. Monensin is a monocarboxylic polyether compound which complexes with monovalent alkali cations and shows ionophorous activity with a selectivity of $\text{Na}^+ > \text{K}^+ > \text{Rb}^+ > \text{Li}^+ > \text{Cs}^+$ (Haney and Hoehn, 1968; Pressman, 1976).

Monensin Sodium:

During the manufacturing process, monensin is exposed to sodium ions during a pH adjustment giving rise to monensin sodium which is the chemical form in the product.

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UV absorption: None

pka value: 6.65 (66% DMF)

Specific Rotation: + 47.7° (acid), + 57.3° (sodium salt)

Vapor pressure: Non-volatile solid based on molecular weight, melting point, and thermogravimetric analysis.

N-octanol/Water Partition Coefficient at 25° C (Appendix B):

- 17329 at pH 5
- 567 at pH 7
- 6135 at pH 9

6. INTRODUCTION OF SUBSTANCE INTO THE ENVIRONMENT

A. INTRODUCTION OF SUBSTANCES FROM THE MANUFACTURING SITES

1. Facilities Used for Manufacturing and Packaging

The processes for manufacturing and packaging monensin, and pollution control practices at the corresponding facilities are designed and constructed to result in minimal environmental impact. Production and packaging of monensin will occur at the production facilities of Tippecanoe Laboratories of Eli Lilly and Company near Lafayette, Indiana (Lilly Road, Shadeland, Indiana) and Clinton Laboratories of Eli Lilly and Company (10500 South State Road 63, Clinton, Indiana). These facilities will effectively contain and control the liquid, solid, and gaseous wastes from the production, formulation, and packaging of monensin. These facilities are currently used to

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manufacture and package Rumensin for uses already approved by the U.S. Food and Drug Administration.

2. Environmental Regulatory Requirements

Treatment, storage, and disposal practices for solid, liquid, and gaseous wastes from Tippecanoe Laboratories and Clinton Laboratories in Indiana are defined by the regulations administered, in certain instances, by the U.S. Environmental Protection Agency (EPA) and in other instances, by the Indiana Department of Environmental Management (IDEM). Permits related to the manufacture of monensin are issued by these regulatory agencies for the discharge of wastewater (NPDES), land application of wastewater residuals (LAND APP), the treatment, storage and disposal of materials (RCRA), and air emissions (AIR). Eli Lilly and Company has made application or already has all necessary environmental permits to manufacture monensin. The environmental permits associated with monensin issued by these agencies are listed below.

<u>Location</u>	<u>Permit Number</u>	<u>Expiration</u>
Tippecanoe	NPDES IN0002861	9/30/92*
	RCRA IND006050967	4/30/93*
	AIR OP 157-4270	6/19/01
	AIR OP 79-04-90-0372	4/1/90*
	AIR CP 157-3220	none
	AIR CP 157-4466	none
	AIR A 157-7138	11/20/01
	AIR CP 157-6176	11/20/01

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AIR CP 157-2874	none
AIR CP 157-4363	9/13/01
AIR CP 157-3593	none
AIR 79-04-90-0377	4/1/90*
AIR CP 157-5244	8/21/01
AIR Registration dated 11/8/90	none
LAND APP	Agency approval pending

Clinton

NPDES IN0002852	9/30/2000
RCRA IND072040348	6/30/93*
AIR 83-09-91-0082	9/1/91*
AIR PC (83) 1458	none
AIR CP 165-3493	none
AIR CP 165-2493	none
AIR Registration for granulation	none
AIR CP 165-2436	none
LAND APP	Agency approval pending

* Applications have been filed to renew these permits

NOTE: In addition to the air permits listed above, Tippecanoe Laboratories and Clinton Laboratories have applied for Title V permits under 40 CFR 70. These permits will supercede the air permits listed above, when issued.

3. Waste stream Handling, Treatment and Control

Monensin is produced in a fermentation process. Fermentation raw materials are batch sterilized in the fermentation tank or continuously sterilized through a plate and frame heat exchanger to make product. The fermentation process starts to produce the active ingredient when the sterilized fermentation media is inoculated with a specific organism. In general, air is sparged into the fermentation tank and temperature is controlled. The fermentation produces a mixture containing the active ingredient which is harvested. Harvested active ingredient goes through a product recovery step to

manufacture the active ingredient in a form that is usable as a product (i.e. granulated or crystalline monensin).

a. Wastes from Manufacturing and Packaging Facilities

Releases into the environment of wastewater pollutants and liquid and solid wastes resulting from the production of monensin will be controlled. Emission control equipment and treatment systems are or will be in place for these manufacturing operations.

Clinton Laboratories of Eli Lilly and Company

At the Clinton facility, washes (including acid and caustic) from sterilizers are collected and mixed with other wastewater residuals for land application. Sterilizer washes may also be discharged as wastewater after proper analysis. The fermentation and product recovery processes can produce wastewater from dry-down operations (which can be discharged to the effluent), spent broth (which can be land applied) and mycelia (which is further processed). In addition, wash waters (such as recycled potassium hydroxide solutions) from fermentation tank preps and cleanups are generated. These wash waters are collected to be land applied with the sterilizer washes and spent broth. The wastes to be land applied are stored in tanks before being land applied for its nutrient value on local farm land. If any wastewater is discharged from fermentation operations for treatment and discharge into surface waters, levels of biochemical oxygen

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demand (BOD), chemical oxygen demand (COD), total suspended solids (TSS) and ammonia will be well below required NPDES limits. The pH of the discharge is within the range allowed by the NPDES permit, pH 6.0 to 9.0. The Clinton facility effluent is discharged into the Wabash River.

Harvested active ingredient goes through a product recovery step to manufacture the active ingredient in a form that is usable as a product (i.e. granulated or crystalline product). Processes which use organic solvent provide for recovery and reuse of solvent, and those operations where solvent are present are served by condensers, carbon adsorbers or scrubbers to control solvent emissions from being discharged to the atmosphere. Those manufacturing operations which use dry procedures are served by dust control facilities to prevent particulate matter emissions from being discharged to the atmosphere. Active ingredient wastes from product recovery will be incinerated on-site. Packaging materials, non-recyclable tailings and floor sweepings from these plants either are incinerated on-site or are landfilled. Essentially no hazardous wastes will be generated in these manufacturing operations.

Packaging of Rumensin will occur in facilities that are already used to package other Rumensin products and these facilities were built to contain any dust. Bags for the new product will be filled and sealed with all plies being nested and the ends of the bags being stepped for proper equalization of load-carrying capacity and sealing. Bags will be sealed

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using a standard super pinch heat seam. Bags will be packed in pallet boxes for shipment.

Tippecanoe Laboratories of Eli Lilly and Company

In general, aqueous fermentation waste at the Tippecanoe Laboratories is treated by a biological treatment process. The biological treatment facility includes a nitrification system which is primarily comprised of three 1.7 million gallon concrete tanks. Each tank contains a jet aeration system, spraywater/antifoam system, temperature control system, and foul air removal system. Organic and inorganic matter that enters this system come into contact with the microorganisms in these systems and can be utilized as food and oxidized to carbon dioxide, nitrogen gas and water. Effluent from these units are processed in clarification systems. Sludges from this wastewater system are stored in tanks before being land applied for its nutrient value. The Tippecanoe wastewater facility treats the materials that exhibit BOD and COD and contain TSS and ammonia to well below required NPDES limits. The pH of the discharge is within the range allowed by the NPDES permit, pH 6.0 to 9.0. The Tippecanoe facility effluent is discharged into the Wabash River.

Harvested active ingredient goes through a product recovery step to manufacture the active ingredient in a form that is usable as a product (i.e. granulated or crystalline product). Processes which use organic solvents may provide for recovery and reuse of solvent. Used solvent may also be incinerated on-site or at the Clinton Laboratories

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facility. Those manufacturing operations which use dry procedures are served by dust control facilities to prevent particulate matter emissions from being discharged to the atmosphere. Active ingredient wastes from product recovery will be incinerated on-site or at the Clinton Laboratories facility. Packaging materials, non-recyclable tailings and floor sweepings from the plant either are incinerated at Clinton Laboratories or are landfilled. Essentially no hazardous wastes will be generated in the manufacturing operations.

Packaging of Rumensin will occur in facilities that are already used to package other Romensin products and these facilities were built to contain any dust. Bags will be filled and sealed with all plies being nested and the ends of the bags being stepped for proper equalization of load-carrying capacity and sealing. Bags will be sealed using a standard super pinch heat seam. Bags will be packed in pallet boxes for shipment.

4. Packaging

Rumensin will be packed in double pinch bottom open mouth bags. These bags will be a 4-ply inside to outside design consisting of one layer of 2.5 mil linear low density polyethylene and three layers of 60# kraft with anti-skid coating on the outer ply. This packaging is necessary to protect the product and customers by reducing the damage to the product during shipping, enhancing product stability, discouraging tampering, and providing a surface for an approved labeling and marking.

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5. Compliance with Environmental Regulatory Requirements

Eli Lilly and Company will comply with all applicable Federal, State, and local regulations concerning emission control and waste treatment at all production, formulating and packaging facilities.

B. INTRODUCTION OF SUBSTANCE FROM FEED MIXING LOCATIONS

Most of the feed mixing will be done at commercial feed mills. These feed mills have to meet Good Manufacturing Practice Standards for feeds. With the required manufacturing controls for feed, inventory accountability, and quality assurance procedures, the potential for release of monensin sodium into the environment at these locations should be minimal.

C. INTRODUCTION OF SUBSTANCE AT THE USE SITE

Statistics from the United States Department of Agriculture indicate that there were about 9.5 million dairy cows in the United States in 1996 (Livestock, Dairy, and Poultry Monthly, 1997). The largest numbers of dairy cows are in the states of California, Wisconsin, Minnesota, Pennsylvania, and New York. Direct marketing of Rumensin to major commercial feed mills will help to minimize environmental exposure during the product distribution process.

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Rumensin is currently used in the supplemental rations of feedlot cattle to improve efficiency of feed utilization. Increasing the efficiency of milk production and body condition in dairy cows is another indication for the use of Rumensin. Dairy cows are expected to receive between 8 and 24 mg monensin/kg feed. At this feeding rate, the highest average daily intake for a dairy cow is expected to be 473 mg. It is estimated that on a daily basis, about 42% of the 9.5 million dairy cows will receive monensin. It is estimated that dairy cows will be fed, at most, 6.9×10^5 kg ($473 \text{ mg/head/day} \times 365 \text{ days} \times 4 \times 10^6 \text{ cattle}$) of monensin sodium in their diets each year. This represents approximately a 40% increase in the current levels of the monensin sodium already sold in the United States.

Monensin is excreted primarily in the feces of dairy cows (Appendix C) and may be introduced into the soil of dairy farms or into cropland soil by use of feces as fertilizer. Dairy cows were administered 918-1125 mg monensin/day intraruminally for 9 consecutive days. This represents approximately 2X the expected daily intake of 473 mg/day. The average fecal concentration of monensin residues over the last 5 days of the study was as high as 12 ppm. Approximately 50% of the fecal residue was unmetabolized monensin with an additional 13% represented by metabolites M-1, M-2, and M-6. Monensin was present in the feces at a concentration of about 6 ppm. Since the highest expected daily intake for monensin is 473 mg/day and is about 50% of the dose

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used in this study, the concentration of monensin in the feces of dairy cows would be expected to be up to about 3 ppm (3 ppm x 0.50).

Monensin is extensively metabolized in cattle, dairy cows, rats, chickens, dogs, sheep, pigs, and turkeys (Donoho, 1984; Donoho et al., 1978, Kennington et al. 1995). The pattern of metabolism is qualitatively similar among species, although quantitatively different. By inference, the toxicology of monensin metabolites present in cattle feces has been evaluated in toxicology studies in which rats were exposed to monensin. More than 20 metabolites of monensin have been found for rats and cattle. About 50% of the monensin in an oral dose to dairy cows is metabolized (Kennington et al. 1995). The primary monensin metabolites, M-1, M-2, and M-6, are O-demethylated. Metabolite M-1 is 20 times less biologically active than monensin, based on several test systems (Donoho, 1984). Thus, the first step in the metabolism of monensin (O-demethylation) appears to eliminate most of the biological activity of this compound (Donoho, 1984). Based on this low level of biological activity, metabolites of monensin were not considered in the estimation of the environmental concentration of monensin. Biologically inactive metabolites and the measured concentration of monensin in dairy cows support the conclusion that 3 ppm is a realistic upper limit for monensin in the feces of dairy cows.

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7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The primary manner in which measurable amounts of monensin would be introduced into the environment is through the feces of dairy cows collected from confined animals and applied to cropland. Based on its large molecular weight, relatively high melting point and thermogravimetric analysis, measurable concentrations of free monensin will not occur in the atmosphere. Monensin may be found in cropland soil which has been amended with dairy cow feces and in adjacent aquatic systems. It may also be possible to find measurable concentrations in the soil and runoff from dairy lots.

A. POTENTIAL CONCENTRATION OF MONENSIN IN SOIL

1. Potential Monensin Concentration in Cropland Soil

The highest expected initial concentration of monensin sodium in cropland soil can be estimated from the concentration of monensin sodium in wet feces and the use rate of wet feces applied to cropland. A reasonable estimate of the application rate of wet dairy cow manure as fertilizer is 2.5×10^4 kg/acre (Midwest Plan Service 1985). It is standard practice to incorporate manure into the top six inches of the soil to avoid loss of nutrients in runoff. A six inch deep soil layer in one acre weighs approximately 9.1×10^5 kg. Wet manure from dairy cows would contain, at most, 3 ppm of monensin. The highest expected concentration of monensin in cropland soil can then be calculated to be about 0.08 ppm ($3 \text{ ppm} \times 2.5 \times 10^4 \text{ kg} / 9.1 \times 10^5 \text{ kg/acre}$).

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The concentration of monensin in soil would decline from the highest expected value of 0.08 ppm, which could only occur directly after application of feces from dairy cows to soil. Studies with crystalline monensin mixed in soil show a moderately rapid decline in monensin activity (Appendices D and E). The half-life of crystalline monensin in soil under greenhouse conditions was 7.3 days. The half-life of crystalline monensin mixed with steer manure and soil in the greenhouse was 5.8 days. Monensin was considered to have degraded under the greenhouse conditions because dissipation by leaching was not possible in this study and monensin activity declined in the soil, as measured by microbiological assay (Appendix D). When crystalline monensin was mixed in soil and exposed to field conditions, the dissipation half-life was 7.5 days with manure and 7.4 days without steer manure (Appendix E). Dissipation of monensin in this study also appeared to result from degradation because the rates of loss were very similar to those found in the greenhouse study. Monensin seems to be extensively degraded in soil. In five weeks under greenhouse conditions, almost 48% of the radioactivity was lost from soil treated with crystalline ^{14}C monensin (Appendix F). Extensive degradation of monensin and its known metabolites would have had to occur to account for the apparent volatilization of ^{14}C , perhaps as $^{14}\text{CO}_2$. Because of the moderately rapid decline of monensin in agricultural soil, nontarget terrestrial organisms would presumably be exposed to monensin for a short period of time.

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2. Potential Monensin Concentration at Dairy Lots

In most dairy operations, the cows are confined and may be on either a concrete pad or packed ground. At regular intervals the manure is collected for treatment or spread onto farm fields. Within the area of confinement, the maximum concentration that monensin could reach is 3 ppm. However, the concentration is expected to be lower due to the rapid degradation of monensin.

B. POTENTIAL CONCENTRATION OF MONENSIN IN AQUATIC SYSTEMS

1. Potential Monensin Concentration in Runoff from Cropland and Dairy Lots

Runoff water from rainfall could carry some monensin from cropland into surface waters containing aquatic organisms. Because monensin concentrations decline at a moderately rapid rate in soil, a runoff event would have to occur soon after application of dairy cattle manure to soil in order for monensin to reach surface water. If it were possible for all of the monensin in the dairy cattle manure applied to one acre of cropland to be dissolved into runoff from one rainfall event, a two inch runoff event would carry 255 g of monensin, or 0.4 ppm ($(2.5 \times 10^4 \text{ kg feces/acre} \times 3 \text{ mg monensin/kg feces}) \div (2 \text{ inches} \times 102,794 \text{ L/acre-in})$).

Monensin adsorbs to moderately textured soils. It is improbable that all the monensin in a field could be lost in one large runoff event. The calculated K_d value of 9.3 (Appendix G) indicates that the concentration of monensin in runoff water would be,

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at most, 9.7% ($1 \div (1 + 9.3)$) of the concentration of monensin in cropland soil. Since the concentration of monensin in cropland soil is 0.08 ppm this would result in a monensin concentration of 0.008 ppm in runoff water. This estimated concentration of monensin in runoff water is based on the assumption that the runoff water would be in contact with an equal mass of cropland soil long enough to allow monensin concentrations in the soil and water to come to equilibrium.

Runoff water from a dairy lot could also carry monensin to surface water. The highest concentration of monensin in dairy lot soil would be no higher than 3 ppm. The calculated K_d value of 9.3 indicates that the concentration of monensin in runoff water would be, at most, 9.7% of the concentration of monensin in dairy lot soil. The highest concentration of monensin in runoff water from a feedlot would be 0.29 ppm. Well designed dairy lots have catchment systems that would collect the majority of this runoff minimizing exposure to the environment.

Dilution of the maximum possible concentration of monensin in runoff water by natural aquatic systems would result in nontarget organisms being exposed to low levels of monensin. Monensin is expected to degrade in natural bodies of water, although the process may take several weeks to occur. Moderately rapid metabolism of monensin in field soil (half-life of about 7.5 days) indicates that metabolism of monensin may occur in natural aquatic systems. Monensin does not hydrolyze but can be photolytically degraded in a buffered (pH 7) solution, with a half-life of 43.9 days (Appendix A).

Low concentrations of monensin may persist in the aquatic systems for several weeks.

2. Fate of Monensin in Aquatic Organisms

Aquatic organisms could be exposed to low levels of monensin when runoff occurs from surrounding agricultural fields. Moderate bioconcentration of monensin may occur based on the range of *n*-octanol/water partition coefficients that occur in the pH range of natural waters (pH 7 to pH 9). Neely, Branson, and Blau (1974) developed a regression equation for projected steady-state residue concentrations in trout muscle versus measured *n*-octanol/water partition coefficients for a variety of synthetic compounds:

$$\text{Log BCF (bioconcentration factor)} - 0.542 (\log K_{ow}) + 0.124$$

Using this equation and the experimentally derived values for $\log K_{ow}$ (2.75 at pH 7; 3.79 at pH 9), the predicted BCF for monensin ranges from 41 to 151. This calculated BCF indicates that up to 151 times more monensin might be found in fish muscle than in the surrounding water. If fish only lived in cropland runoff water containing the highest expected concentration of monensin (0.008 ppm), the theoretical concentration of monensin in fish tissue would range from 0.33 to 1.2 ppm. Dilution of runoff in surface waters would rapidly reduce the actual concentration of monensin to which fish could be exposed. Dilution and dissipation of monensin would result in substantially lower levels of this material in fish tissue. The calculated BCF does not allow for metabolism of

monensin. Monensin is readily metabolized by food-producing animals and does not accumulate in edible tissues. There is no reason to expect accumulation in fish tissue.

C. OCCURRENCE OF MONENSIN IN GROUNDWATER

The mobility of monensin is moderate in coarse-textured soils such as sand and sandy loam, but mobility is lower in soils such as loam and silty clay loam (Appendix G). Monensin was leached somewhat through coarse soils by the equivalent of about six inches of rain and was moderately mobile when exposed to the equivalent of 25 inches of rain (Appendix G). The retardation factor for the movement of monensin through a soil column relative to the movement of water indicates that monensin adsorbs fairly strongly to loam soil (K_d estimated to be about 9.3). Given the moderately short half-life of monensin in field soil (7.5 days), it is likely that monensin would degrade before enough rainfall occurred to leach significant amounts in even coarse-textured soils.

8. EFFECTS ON THE ENVIRONMENT OF RELEASED SUBSTANCES

A. MAMMALIAN TOXICITY TESTS

An in-depth testing program has been completed with various laboratory animal species to determine the toxicological properties of monensin. Complete reports of all of these studies have been previously submitted to support the previous claims for monensin. Studies which are important for determining the safety of monensin to the

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public and to the producers and users of Rumensin Type A Medicated Articles are briefly described below.

Hazard Evaluation Studies

Acute Oral LD₅₀ with Rats: Fifty to 80 mg mycelial monensin/kg of body weight in male rats and 15 to 30 mg mycelial monensin/kg body weight in female rats.

Inhalation: No signs of toxicity found for rats exposed to an aerosol of 10 mg of monensin sodium/M³ one hour a day for 14 days. No signs of toxicity in dogs exposed for six hours a day for 90 days to 0.15 mg of monensin sodium/M³.

Ocular Irritation in Rabbits: Mycelial monensin causes severe irritation when placed in the eyes of rabbits. Rinsing eyes immediately after exposure was effective in preventing permanent damage.

Dermal Irritation in Rabbits: No irritation and no signs of dermal toxicity occurred when 500 mg of mycelial monensin/kg body weight was applied to shaved and abraded skin.

Chronic, Reproduction, and Teratology Studies

One-Year Dog Study: No effects at a daily oral dose of 1.25 mg monensin sodium activity (mycelial form)/kg body weight.

Two-Year Mouse Study: No-effect level at a dietary concentration of 10 ppm monensin sodium activity (mycelial form), or a time weighted average daily dose of 1.2 mg/kg

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for males and 1.4 mg/kg for females. Not carcinogenic at the highest dietary concentration tested, 150 ppm (22 to 25 mg/kg/day).

Two-Year Rat Study: No-effect level at a dietary concentration of 33 ppm monensin sodium activity (mycelial form), or a time weighted average daily dose of 1.40 mg/kg for males and 1.72 mg/kg for females. No carcinogenic effects at the highest dietary concentration tested, 80 ppm (3.6 to 5.0 mg/kg/day).

Rat Multigeneration Reproduction study: No evidence of reproductive impairment or effect on the offspring at a dietary level of 80 ppm monensin sodium activity (mycelial form).

Rabbit Teratology Study: No evidence of maternal toxicity with daily oral doses as high as 0.76 mg monensin sodium/kg body weight during gestation days 6 through 18 and no evidence of dose-related teratogenic effects up to this same dose, the highest tested in this study.

B. POTENTIAL ADVERSE EFFECTS OF THE PROPOSED ACTION ON HUMAN HEALTH

1. Production of Monensin and Manufacture of Rumensin Type A Medicated Articles

Monensin used to increase the efficiency of milk production and improve body condition would be produced in the same two plants that currently produce Rumensin for cattle. Engineering controls, personal hygiene precautions, and respiratory protection are effective in minimizing exposure of workers. Safety glasses or other eye protection is

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worn by workers. If accidental eye contact occurs with monensin, a worker can immediately rinse the eye thoroughly at available eye-wash stations. Precautionary labeling would advise people mixing and handling Rumensin to wear protective clothing, impervious gloves, and a dust mask. Immediate and thorough rinsing is advised if eye contact occurs. Thorough washing with soap and water is also advised after handling Rumensin. Considering these measures and the fact that in laboratory animals monensin is not a teratogen, carcinogen, or a reproductive toxin, it is concluded that workers producing Rumensin and users of Rumensin would not be adversely affected by the proposed action.

2. Human Exposure to Monensin Via the Water Supply

Extensive chemistry and toxicology data have been developed to support the safe use of monensin in dairy cows and this has been discussed in a separate part of the application. It is highly improbable that measurable concentrations of monensin would occur in ground or surface water-derived potable water supplies (Sections 7B and 7C). Exposure to humans to measurable levels of monensin via a water supply is very unlikely.

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C. EFFECTS OF MONENSIN ON NONTARGET ORGANISMS

Studies have been conducted to determine the effects of monensin on nontarget organisms. The results of these studies are summarized below and are listed in detail in the referenced appendices.

Avian Species

Bobwhite quail 14-day acute oral toxicity studies (Appendix H): Two acute oral studies with mycelial monensin and bobwhite quail (*Colinus virginianus*) have been conducted. In one study with monensin sodium doses ranging from 45 to 250 mg/kg body weight, the 14-day LD₅₀, 95% confidence interval, and slope of the dose-response curve for adult bobwhite were 85.7 mg/kg, 64.4 to 114.2 mg/kg, and 2.915, respectively. No sex-related differences in mortality were evident within treatment groups. No mortalities were found in the second study with monensin sodium doses ranging from 5 to 45 mg/kg body weight. Physical signs of toxicity noted in the first study were dose-related and included loose feces, ataxia, lethargy, emaciation, and prostration. No physical signs of toxicity were noted in the second study. Food consumption and body weight gain were reduced down to the lowest dose tested, 45 mg/kg, in the first study. Body weight gain was also reduced at the 45 mg/kg dose in the second study. A dose of 27.5 mg/kg was the highest level of monensin sodium

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tested which did not result in mortalities, signs of toxicity, or treatment-related reductions in food consumption and body weight.

Bobwhite quail five-day dietary studies (Appendix I): Two five-day dietary studies were conducted with 11 and 14-day old bobwhite quail (*Colinus virginianus*). Nominal mycelial monensin sodium concentrations from 0.0365 to 0.125% (w/w) and from 0.005 to 0.0365% (w/w) were used in the first and second studies, respectively. The birds were observed while being fed treated diets for five days, followed by three days of basal diet. Based on nominal dietary concentrations of monensin (assayed levels ranged from 94 to 105% of nominal) in the first study conducted with bobwhite, the eight-day LC_{50} , the 95% confidence interval, and the slope of the concentration-response curve were 0.109%, 0.081 to 0.147%, and 4.285, respectively. Based on estimates of total food consumed, average body weight during the 5-day exposure period, and nominal monensin concentrations, the LD_{50} , the 95% confidence interval for the LD_{50} , and the slope of the dose-response curve were 980 mg monensin sodium/kg body weight, 717 to 1340 mg/kg body weight, and 4.098, respectively. In the first study, physical signs of toxicity (ataxia, lethargy, wing droop, prostration) or reduced weight gain and food consumption were found at all dietary levels of monensin tested, down to 0.0365%. No mortalities were found in the second study and physical signs of toxicity were only found at the highest dietary level of monensin tested, 0.0365%. In the second study, body weight gain

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was also reduced in birds exposed to dietary monensin levels of 0.0365% and 0.02%. The test level of 0.01% was the highest dietary concentration of monensin sodium tested which resulted in no mortalities, no physical signs of toxicity, and no reductions in food consumption or body weight gain.

Mallard duck five-day dietary study (Appendix J): A five-day dietary study was conducted with 10-day old mallard ducks (*Anas platyrhynchos*) and monensin sodium (mycelial) at nominal dietary concentrations of 0.0, 0.0062, 0.016, 0.0365, 0.09, 0.225, and 0.5% (w/w). Assayed values ranged from 98 to 103% of nominal. The birds were observed while being fed treated diets for five days, followed by three days of basal diets. One duckling in the 0.09% treatment group died during this study. No physical signs of toxicity (lethargy, ataxia, loose feces, hyperactivity and prostration) were found for birds in this study. Mean body weight gain was reduced at dietary concentrations $\geq 0.016\%$. Food consumption was reduced for birds fed diets containing $\geq 0.09\%$ of monensin sodium. The test level of 0.0062% was the highest dietary concentration of monensin sodium tested which resulted in no mortalities, no physical signs of toxicity, and no reductions in food consumption or body weight gain.

Aquatic Species

Bluegill 96-hour toxicity study (Appendix K): A static toxicity test was conducted to determine the acute effects of monensin sodium (mycelial) on juvenile bluegill. Based on mean measured concentrations of monensin sodium, the 96-hr LC_{50} , the 95% confidence limits of the LC_{50} , and the slope of the concentration-response line were 16.6 ppm, 16.3 to 17.0 ppm, and 0.438, respectively. In this study, fish exposed to monensin concentrations ≥ 4.4 ppm displayed behavioral signs of toxicity (from hypoactivity to prostration). No mortalities or behavioral signs of toxicity were found for fish exposed to monensin sodium concentrations ≥ 3.1 ppm.

Rainbow trout 96-hour toxicity study (Appendix L): Based on mean concentrations of monensin sodium, the 96-hr LC_{50} , the 95% confidence limits for the LC_{50} , and the slope of the concentration-response curve were 9.0 ppm, 7.8 to 10.2 ppm, and 0.366, respectively. Fish exposed to monensin concentrations ≥ 1.12 ppm showed behavioral signs of toxicity in a concentration-related fashion from hypoactivity to prostration. No mortalities and no behavioral signs of toxicity were found for fish exposed to the monensin sodium concentration of 0.70 ppm.

Daphnia 48-hour toxicity study (Appendix M): Based on daphnid immobility and mean measured concentrations of monensin sodium, the 48-hr EC_{50} and the corresponding 95% confidence limits for the acute study with *Daphnia magna* were 10.7 ppm and 9.8 to 11.7 ppm. The slope of the concentration-response curve was 0.280. No

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daphnids were found to be immobile nor did any daphnids display abnormal behavior (hypo-activity, prostration) in this study at a monensin concentration of ≤ 4.2 ppm. Abnormal behavior and/or immobility were noted for monensin concentrations ≥ 5.6 ppm.

Terrestrial Species

Earthworm (*Lumbricus terrestris*) were exposed for 14 days to nominal soil concentrations of 0.0, 10.0, 22.5, 45.0, and 100.0 ppm of monensin sodium. Six out of fifteen worms were dead by the end of the study at the highest monensin sodium concentration tested. The rest of the worms exposed to the highest concentration tested were flaccid, soft and flaccid, and moribund. Although no worms died at the exposure concentration of 45 mg/kg, one worm was moribund, one worm was soft and flaccid, and two worms were flaccid. Normal physical condition and no mortalities were noted for worms exposed to monensin sodium concentrations ≤ 22.5 mg/kg. Worms exposed to the two highest concentrations of monensin sodium lost weight during the experiment. Worms exposed to the 22.5 mg/kg treatment level gained less weight than control worms, but the reduced weight gain was not significant. All worms exposed to the monensin sodium concentration of 10 mg/kg in soil were alive, had a normal physical appearance, and gained as much weight as control worms by the end of the 14-day study.

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Phytotoxicity of monensin (Appendices O and P): A greenhouse phytotoxicity test was conducted in which fourteen mono- and dicotyledonous plants were grown from seed in untreated soils and soils treated with monensin alone, or monensin in chicken litter. The plant species tested were alfalfa (*Medicago sativa*), fescue (*Festuca elatior*), cucumber (*Cucumis sativus*), rice (*Oryza sativa*), cotton (*Gossypium hirsutum*), tomato (*Lycopersicon esculentum*), pepper (*Capsicum annum*), corn (*Zea mays*), sugar beets (*Beta vulgaris*), barley (*Hordeum vulgare*), soybean (*Glycine max*), wheat (*Triticum aestivum*), grain sorghum (*Sorghum bicolor*), and oats (*Avena sativa*). Plants were rated for phytotoxic injury (0 = no injury, to 10 = complete kill) and injury, described as chlorosis, burning, stunting, or reduced germination.

Ratings were made 18 to 21 days after planting. High levels of control chicken litter in a pilot study caused severe phytotoxicity alone. Monensin-treated soil without chicken litter in the pilot study was relatively non-phytotoxic at monensin application rates of approximately 1 to 2 ppm. Monensin concentrations of 4 to 8 ppm in the soil caused moderate to severe injury to several plants. In another study, monensin was incorporated into soil with chicken litter at litter application rates of 1, 2, 4, and 8 tons of fresh litter per acre. Litter from monensin-fed chickens was no more phytotoxic than litter from control chickens. There was some phytotoxicity due just to the litter itself at an application rate of 8 tons/acre.

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A field phytotoxicity study was conducted with 22 tons/acre (49.3×10^3 kg/ha) of manure from cattle fed monensin. The cattle feed contained 20 g monensin/ton or 40 g monensin/ton. Cattle given feed with 40 g monensin/ton had an average of 4.4 ppm of monensin in their feces. The plot containing manure from cattle fed 40 g monensin/ton of feed had, therefore, a monensin sodium concentration of approximately 0.145 ppm ($((49.3 \times 10^3 \text{ kg/ha} \times 4.4 \text{ mg/kg}) \div (4 \text{ inches} \times 375,000 \text{ kg/ha-inch soil}))$). The plant species tested were the same as those used in the greenhouse phytotoxicity study. Because of extensive rainfall, the plants in the plot treated with manure from cattle fed 20 g monensin/ton of feed could not be evaluated. The maturation, flowering, fruiting, or seed formation of oats, sorghum, soybeans, barley, sugar beets, corn, tomato, cotton, and cucumbers appeared to be the same in the control plot and the plot treated with manure from cattle fed 40 g monensin/ton feed. No differences between control and treatment plots were found for the growth or vigor of wheat, rice, pepper, alfalfa, and fescue.

D. POTENTIAL ADVERSE EFFECTS OF THE PROPOSED ACTION ON AQUATIC AND WILDLIFE ORGANISMS

1. Potential Adverse Effects on Aquatic Organisms

The influx of monensin into surface water systems is expected to be acute and episodic, depending on runoff from watersheds fertilized with cattle manure containing monensin. The half-life of monensin in soil is relatively short (7.5 days), so runoff events

would have to occur soon after application of monensin in dairy cattle manure to cropland. Because monensin does not undergo rapid photolysis or hydrolysis in water and because the microbial degradation rate of monensin in natural waters is unknown, it should be assumed that aquatic organisms could be exposed acutely and chronically to monensin. The acute safety of aquatic organisms should then be assessed by comparing the maximum expected concentration of monensin in runoff from cropland to the results of acute studies with aquatic organisms. The chronic safety of aquatic organisms could initially be assessed by comparing the maximum expected concentration of monensin in runoff to the concentrations calculated to be chemically safe to aquatic organisms.

In Section 7B, the maximum expected monensin concentration in runoff from cropland was calculated to be about 0.008 ppm. The 96-hr LC_{50} values for rainbow trout and bluegill and the 48-hr EC_{50} value for daphnids range from 9.0 to 16.6 ppm. These acute median lethal and acute median effect concentrations are about 1,125 to 2,075 times higher than the highest expected monensin concentration in runoff from cropland. In acute laboratory studies, no mortalities or behavioral abnormalities were found for fish or daphnids at 0.70 ppm. This concentration (0.70 ppm) is 87 times higher than the maximum expected concentration of monensin in runoff from cropland. The highest possible concentration of monensin in runoff water from the dairy lot (0.29 ppm) is also lower than 0.70 ppm. In most cases runoff from dairy lots would be captured by catchment systems and not be allowed into surface water.

The highest expected concentration of monensin in runoff (0.008 ppm) is substantially below concentrations which can be calculated to have no chronic effects on aquatic organisms. An application factor of 100 can be used with the results from acute studies to extrapolate the concentrations which have no observed effects on the test organisms during chronic exposure. The calculated chronic no-observed-effect concentrations for bluegill, rainbow trout, and daphnids are 0.166 ppm (16.6 ppm \div 100), 0.090 ppm (9.0 ppm \div 100), and 0.107 ppm (10.7 ppm \div 100), respectively. These calculated concentrations are between 11 and 21 times higher than the highest expected concentration (0.008 ppm) of monensin in runoff from cropland.

Based on the maximum expected monensin concentration (0.008 ppm) in runoff from cropland, the dilution of runoff in receiving waters, and the eventual dissipation of monensin from water, the proposed action would not be expected to have a significant acute or chronic effect on aquatic organisms.

2. Potential Adverse Effects on Earthworms

The concentration of monensin in dairy cattle manure is expected to be 3 ppm (Section 7C) and the highest concentration of monensin in cropland soil was estimated to be 0.08 ppm (Section 7A). These concentrations should dissipate rapidly as monensin concentrations in soil decline relatively rapidly in the greenhouse ($t_{1/2}$ = 5.8 days) and in the field ($t_{1/2}$ = 7.5 days). All earthworms tested for 14 days in soil containing 10 ppm of

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monensin were alive, had normal physical appearance, and gained as much weight as control worms. Since this test concentration is 125 times higher than its concentration in soil, earthworms should not be affected by monensin in dairy cattle manure used as fertilizer.

3. Potential Adverse Effects on Avian Species

No mortality, no significant reduction in body weight gain or food consumption, no change in appearance, and no change in behavior occurred for mallard ducks or bobwhite quail fed diets containing 62 ppm (0.0062%) and 100 ppm (0.01%) of monensin, respectively. The highest recommended dietary concentration of monensin in the feed of dairy cattle is 24 mg/kg. If wild birds foraged only on the feed of dairy cattle being treated with monensin, significant effects on body weight, food consumption, or survival would not be expected. Use of monensin for increased efficiency of milk production in dairy cattle would have no adverse effect on populations of wild avian species.

4. Potential Adverse Effects on Plants

Soil with monensin at 1 to 2 ppm was relatively non-phytotoxic to alfalfa, fescue, cucumber, rice, cotton, tomato, pepper, corn, sugar beets, barley, soybean, wheat, grain sorghum, and oats in a pilot greenhouse study. This soil concentration is at least 12.5 times higher than the highest expected monensin concentration of 0.08 ppm in cropland.

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In another study, monensin in chicken litter was found to be only as phytotoxic as the control chicken litter. In a field study where monensin containing cattle manure was applied, no phytotoxicity was found at a calculated monensin concentration of 0.145 ppm in the soil. This soil concentration is about 2 times higher than the highest expected monensin concentration of 0.08 ppm in cropland. Monensin concentrations will dissipate relatively rapidly in soil ($t_{1/2} = 7.5$ days). Based on information from these phytotoxicity studies and the relatively short half-life of monensin in field soil, adverse effects from monensin on crops are not expected.

9: UTILIZATION OF NATURAL RESOURCES AND ENERGY

Manufacturing and packaging of Rumensin for dairy cattle will occur at facilities already approved to manufacture and package Rumensin for use in beef cattle.

Endangered and threatened species will not be affected by production of monensin. Concentrations of monensin that could reach the environment are extremely low and are substantially lower than concentrations that may affect terrestrial or aquatic species.

Properties listed in the National Register of Historic Places will not be affected by the production or use of monensin.

In general, process streams from the production of monensin only utilize a portion of the waste treatment or recovery facilities already installed for these and other process

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wastes. Disposal of waste from the manufacturing processes and operations will not require unusual amounts of energy or natural resources.

Estimates of natural resources and energy (electricity, natural gas, coal and oil) used in the production of monensin include fixed costs and other miscellaneous energy usage that are not directly related to production, such as administrative office use. Activities associated with production and packaging of monensin will require less than the following percentages of the total energy-related natural resources used at each of the manufacturing, formulating and packaging sites:

Tippecanoe Laboratories: 8.5%

Clinton Laboratories: 9%

Manufacturing monensin will have relatively little impact on the existing use of energy and natural resources at these facilities.

10. MITIGATION MEASURES

The proposed action would not be expected to have any substantial adverse effect on human health or the environment. The label for Rumensin will instruct users to wear protective clothing, impervious gloves, and a dust mask when mixing and handling Rumensin. Immediate and thorough rinsing is advised if eye contact occurs. The user will also be instructed to wash thoroughly with soap and water after handling Rumensin.

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Ingestion of Rumensin by equines has been fatal. Other than these precautions listed on the label, no mitigation measures are necessary for Rumensin.

All manufacturing facility workers are trained to safely work in production areas with active materials. Appropriate exposure guidelines have been established for Rumensin manufacturing processes. Engineering controls and personal protective gear are used to minimize exposure. A material safety data sheet that lists hazard data, exposure limits, and safe handling practices is available to all workers (Appendix Q). Workers will continue to safely produce Rumensin.

11. ALTERNATIVES TO THE PROPOSED ACTION

The proposed action would not be expected to have any substantial adverse effect on human health or the environment. Therefore, alternatives to the proposed action do not need to be considered.

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12. LIST OF PREPARERS

The following personnel of Eli Lilly and Company are responsible for the preparation of this Environmental Assessment:

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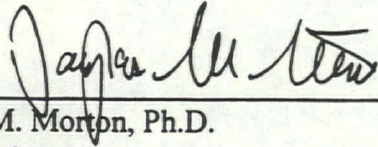
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13. CERTIFICATION

The undersigned official certifies that the information presented in the Environmental Assessment is true, accurate, and complete to the best of his knowledge.



Douglas M. Morton, Ph.D.
Vice President
Lilly Research Laboratories

July 14, 1997
Date

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APPENDIX A: Report Summary

Title: The Solubility, Hydrolysis, and Photolysis of Monensin in Aqueous Solution

Study Number: S-AAC-81-13

Study Dates: March 27 to June 11, 1981

Name and Address of Investigators: G. M. Poole, S. D. West, and A. L. Donoho, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Test Article: Crystalline ¹⁴C Monensin Sodium

Test System: Aqueous Solutions

Summary of Experimental Design:

Solubility

The aqueous solubility of the antibiotic, monensin, was determined turbidimetrically following sterile filtration of buffer solutions containing a visible excess of monensin through a 0.2 μ filter. Triplicate assays were performed on samples taken at 24 hour intervals.

Hydrolysis

The stability of monensin in aqueous solution at pH 5.0, 7.0, and 9.0 was determined turbidimetrically in sterile buffer solutions stored in the dark at 25°C. Assays were performed in triplicate.

Photolysis

The stability of monensin in pH 7.0 aqueous solution was determined turbidimetrically in a sterile buffer solution exposed to a laboratory irradiation apparatus which simulated natural summer sunlight.

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Summary of Results
Solubility

The results of the solubility studies with monensin at pH 7 and 9 are summarized below:

<u>pH</u>	<u>Monensin Concentration ($\mu\text{g/ml}$)</u>			
	<u>24 hr</u>	<u>48 hr</u>	<u>72 hr</u>	<u>Average</u>
7.0	64	62	not tested	63
9.0	<2.5	0.8	0.9	0.85

Hydrolysis

The hydrolysis of monensin was slow at pH 5.0, 7.0, and 9.0. Little or no degradation was noted within 30 days as show below:

<u>Day</u>	<u>Monensin Concentration ($\mu\text{g/ml}$)</u>		
	<u>pH 5.0</u>	<u>pH 7.0</u>	<u>pH 9.0</u>
1	0.384	1.240	0.779
7	0.263	1.158	0.789
15	0.374	1.312	0.906
30	0.343	1.270	0.794

Photolysis

The photolytic degradation of monensin at pH 7.0 was moderate. The half-life appears to be longer than 30 days. Microbiological assay data are presented below. These data show a gradual decline of approximately 40 percent over a 30-day observation period. The positive control samples held in the dark were stable during this period.

<u>Day</u>	<u>Monensin Concentration ($\mu\text{g/ml}$)</u>	
	<u>pH 7.0</u>	<u>pH 7.0 (Dark Control)</u>
1	1.180	1.240
7	1.028	1.158
15	0.979	1.312
30	0.729	1.270
<u>Half-life (days)</u>	43.9	
<u>Rate Constant (day^{-1})</u>	0.0158	
<u>R²</u>	0.97	

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APPENDIX B: Report SummaryTitle: Octanol-Water Partition Coefficients for MonensinStudy: ABC-0438Names and Address of Investigators: A. L. Donoho and D. E. Ruggles, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140Test Article: Crystalline ¹⁴C Monensin SodiumTest System: n-Octanol and water buffered to pH levels of 5, 7, and 9

Summary of Experimental Design: The n-octanol to water partitioning coefficient of ¹⁴C monensin was determined at pH 5.0, pH 7.0, and pH 9.0 at 25 C and at a monensin concentration of 0.0002 M. It was also determined at pH 7.0 at a concentration of 0.00002 M. The samples were prepared in triplicate in 50-ml glass centrifuge tubes which were mixed by tumbling on a mixing wheel for 24 hours. Duplicate aliquots of octanol and aqueous phases were assayed by liquid scintillation counting. The method was the shake flask procedure set forth in the FDA ENVIRONMENTAL TECHNICAL ASSISTANCE DOCUMENT, Section 3.02, March 1987.

Summary of Results:

Results of the analyses are summarized in the following table:

Monensin Concentration	pH	K _{ow}	log K _{ow}
0.0002 <u>M</u>	5	17329	4.24
0.0002 <u>M</u>	7	567	2.75
0.0002 <u>M</u>	9	6135	3.79
0.00002 <u>M</u>	7	737	2.87

These results indicate a greater partitioning into octanol at both pH 5 and pH 9 than at pH 7. The good agreement between the 0.0002 M and 0.00002 M sets at pH 7 indicate that the test concentrations were sufficiently low for accurate K_{ow} determination.

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APPENDIX C: Report Summary

Title: ^{14}C Monensin Milk and Tissue Residues/Metabolism in Dairy Cows

Study Number: T1F749401

Study dates: August 2, 1994 to July 21, 1995

Name and Address of Investigator: A.S. Kennington, Animal Science Chemical Reserach, A Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Test Article: ^{14}C Monensin

Test System: Lactating Dairy Cows

Summary of Experimental Design:

Five lactating dairy cows weighing 510 to 625 kg were administered gelatin capsules containing ^{14}C monensin at a dose level of 1.8 mg/kg (918-1125 mg monensin/day) intraruminally for nine consecutive days. Animals were slaughtered 6 hours after the final dose for collection of tissues. Feces were collected daily and urine on days 2 and 6 from each animal for analysis of ^{14}C residues. Concentrations of residues were determined by LSC and residue identification was performed by LC/MS.

Summary of Results:

Results will only include those for feces and urine. Monensin residues were found in small quantities in the urine samples and averaged about 0.5 ppm on each day of sampling. Additional identification of urine metabolites was not performed. Residues were much higher in the feces. ^{14}C residues in the feces reached somewhat of a steady state by day 5 and averaged 8-12 ppm over the last 5 days of dosing. Additional analysis of the residues indicated that on average, parent monensin accounted for about 50% of the residues and the identified metabolies M-1, M-2, and M-6 accounted for about 4, 4, and 5%, respectively.

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APPENDIX D: Report Summary

Title: Monensin Greenhouse Soil Decline Study

Study Number: A22-B47-3264

Study Dates: April 15 to June 15, 1973

Name and Address of Investigator: L. L. Zornes, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Test Article: Crystalline Monensin

Test System: Soil flats maintained in the greenhouse

Summary of Experimental Design:

Crystalline monensin was incorporated into approximately 6 kg air dried potting soil at a nominal concentration of 1 ppm. The monensin was added in a small volume of methanol and the sample was blended and then air dried to remove the methanol. The soil was placed in a nominal 0.07 m² soil flat lined with plastic. The flat was maintained in the greenhouse at approximately 27°C. A similar flat was prepared in which feces from steers fed 40 g monensin/ton of feed were incorporated into the soil at 20 tons per acre equivalent along with the nominal 1 ppm monensin. Periodically, samples were taken and air dried, and then portions were assayed for monensin by the microbiological plate assay. Appropriate control and recovery samples were run with the experimental samples.

Summary of Results:

Results from the decline study are shown in Table 1. Degradation of monensin was relatively rapid. In the feces-fortified treated sample, the monensin had declined to less than 20 percent of initial in about a week and was not detectable after two weeks. The decline rate in soil without feces was somewhat slower but was still relatively rapid. This decline of monensin is due to degradation rather than to loss of compound by leaching because the flats were not watered sufficiently to cause leaching.

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Table 1
Degradation of Monensin in Soil

<u>Sampling Time</u>	<u>With Feces</u>		<u>Without Feces</u>	
	<u>ppm</u>	<u>% of Initial</u>	<u>ppm</u>	<u>% of Initial</u>
Zero	1.4 ^{1,2}	100	1.2 ^{1,2}	100
3 days	1.0	71	1.1	92
5 days	0.3	21	0.6	50
8 days	0.2	14	0.4	33
12 days	0.1	7	0.2	17
14 days	0.0	--	0.2	17
28 days	0.0	--	0.0	--
Half-life (days)		5.8		7.3
Rate Constant (day ⁻¹)		0.119 0		0.095
R ²		0.72		0.89

¹Zero-time values are the means of five determinations, and subsequent values are the means of duplicates. All values are on an air-dry basis.

²Test sensitivity was 0.1 to 0.2 ppm.

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APPENDIX E: Report Summary

Title: Monensin Field Soil Decline study

Study Number: A22-B50-3270

Study Dates: May 1 to June 30, 1973

Name and Address of Investigators: L. L. Zornes and A. L. Donoho, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Test Article: Crystalline Monensin

Test System: field soil plots

Summary of Experimental Design:

Two 9 ft² field soil plots at Greenfield, Indiana, were fortified with monensin at a concentration of approximately 1.25 ppm. One of the plots was also fortified with cattle manure equivalent to 20 tons per acre fresh weight. The top 3-inch soil layer was removed from each plot then air dried and screened. Monensin was added in a small volume of methanol while the soil was tumbling in a small concrete mixer. The methanol was evaporated and the soils were returned to the field plots. Periodically, soil cores of the 0-3 inch soil layer were taken for assay. Samples were assayed by quantitative microbiological plate assay using five replicates for zero-time samples and triplicate assays for later samples. When monensin had declined to approximately 0.2 ppm, the plate assay gave negative results and the samples were then monitored by semi-quantitative thin-layer bioautography until concentrations dropped below 0.05 ppm.

Summary of Results:

Results from this study are presented in Table 1. Monensin degradation was relatively rapid over the period of one month. Monensin did not decline rapidly during the first two weeks. This was probably due to the cool weather. The measured soil temperature was approximately 10-12°C during this time. As the soil temperature increased to 15-20°C at about 3 weeks, the degradation rate increased. The plots were negative at 20 days by the plate assay, indicating that 80% or more of the monensin had degraded. The plots were negative by bioautographic assay at 33 days indicating 95% or more degradation.

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These data alone do not demonstrate that loss of monensin activity was due to degradation rather than leaching. Therefore, at 42 days, a plate assay was performed on a 0 to 9 inch core sample and this assay was negative. These results, along with the data from greenhouse soil studies, support the conclusion that decline in monensin is due to degradation and not to leaching.

Table 1

ppm Monensin in Field Soil ^a

Sampling Time	Plot 1		Plot 2	
	Plate	TLB	Plate	TLB
Zero	1.08		1.04	
5 days	1.08		1.01	
12 days	0.86		0.80	
20 days	Neg.	Pos.	Neg.	Pos.
26 days	Neg.	Pos.	Neg.	Pos.
33 days		Neg		Neg.
Half-life (days)	7.5		7.4	
Rate Constant (day ⁻¹)	0.092		0.094	
R ²	0.91		0.91	

^a Plot 1 contained manure while Plot 2 did not. The plate assay and the thin-layer bioautographic (TLB) assay had limits of detection of approximately 0.2 ppm and 0.05 ppm, respectively.

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APPENDIX F: Report Summary

Title: Monensin Biodegradation in Soil

Study Number: B77-3306

Study Dates: March 1 to November 1, 1974

Name and Address of Investigator: J. A. Manthey, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Test Article: Crystalline ^{14}C Monensin

Test System: Soil maintained in the greenhouse

Summary of Experimental Design:

An aliquot of regular greenhouse potting soil (ca. 6 kg) was fortified with ^{14}C monensin (activity ca. 75,000 dpm/mg) to a level of 10 ppm in the soil giving about 750 dpm/g. The mixture was placed in a plastic-lined flat and placed in the greenhouse to age. The depth of soil in the flat was approximately 3 inches.

Ambient soil temperature ranged between 20-30°C. The soil was maintained in a moist condition. Periodically, soil samples were taken for determination of radioactivity. The samples were air dried, and aliquots were combusted for recovery of $^{14}\text{CO}_2$.

Summary of Results:

The results are shown in Table 1. The rate of decline of radioactivity was rapid during the first few weeks and somewhat slower after nine weeks. The labeling procedure for producing the ^{14}C monensin puts the ^{14}C label in each ring except one. Therefore, the fact that such a considerable proportion of the radioactivity is lost from the soil indicates that the molecule is being extensively degraded. The loss of ^{14}C is probably through volatilization, perhaps as $^{14}\text{CO}_2$. Monensin and its known metabolites are completely non-volatile and would have to be extensively degraded to be lost through volatilization.

In a companion study, a flat of soil was prepared as above except the monensin used was not radioactive. Samples were taken at weekly intervals and processed to separate monensin from its degradation products. The fractions were examined by TLC and by

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colorimetric measurement at 520 nm of the acid-vanillin reaction product. Results of this study showed that after three weeks the monensin level was only about 10% of initial and after six weeks was less than 3% of initial. These results agree with the studies conducted by microbiological assay.

The results of this study also showed that there is no buildup of vanillin positive degradation products in soil. Together the radiochemical and colorimetric data from the soil show that monensin is biodegradable in soil and that the degradation of the molecule is extensive.

Table 1

Decline of Radioactivity in Soil Treated with ^{14}C Monensin

<u>Time Interval</u>	<u>Radioactivity dpm/g Soil</u>	<u>% of Initial</u>
Start	800	100
2 weeks	635	79
5 weeks	413	52
9 weeks	249	31
15 weeks	247	31
23 weeks	187	23
29 weeks	188	23

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APPENDIX G: Report Summary

Title: Laboratory soil Leaching Study with Monensin

Test Article: Crystalline monensin

Name and Address of Investigators: O. D. Decker and E. W. Day, Lilly Research Laboratories, Division of Eli Lilly and Company, P.O. Box 708, Greenfield, IN 46140.

Test System: Laboratory Soil Leaching

Summary of Experimental Design:

The design follows protocols as described in Guidelines for Registering Pesticides in the U.S., published in the Federal Register, Vol. 40, No. 123, June 25, 1975, pages 26884-26886. Monensin was applied at a rate equivalent to 10 pounds (10 ppm) activity per acre in 100 g on top of 30 cm high by 6.35 cm I.D. columns of four different textures of soil. One control and three treatment columns were prepared from each soil type and leached with the water equivalent of 25 inches of rainfall. The leachates were collected in four increments and analyzed for monensin. At the end of the experiment each soil column was divided into sections for monensin analysis.

Summary of Results:

Some recovery data for monensin from water and the various soils are presented in Table 1. The direct standard used to fortify the samples assayed 76.2 - 88.8% of theory by the microbiological assay. Varying standards in 400 ml of 1:1 water:methanol when extracted and assayed gave excellent recoveries with the exception of one low value. Recoveries from soils fortified at 10 ppm were from 62-85%. Because of this variability in recoveries, the observed values from the leachates and soil segments were not corrected for recovery efficiency.

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Table 1

Monensin Standard Recovery Data

<u>Sample</u>	<u>Monensin (μg)</u>		<u>% of Theory</u>
	<u>Amount Added</u>	<u>Amount Found</u>	
Standard in 1.0 ml methanol	50	38.1	76.2
Water:Methanol (1:1), 400 ml	50	49.1	98.2
	100	67.2	67.2
	250	238.8	95.5
Sand, 25 g	250	156.5	62.6
Sandy Loam, 25 g	250	195.0	78.0
Loam, 25 g	250	158.7	63.5
Silty Clay Loam, 25 g	250	212.2	84.9

The results of the laboratory leaching study are summarized in Table 2

Table 2

Percent of Monensin Applied to the Column in a Laboratory Soil Leaching Study

<u>Leachate (ml applied)</u>	<u>Sand</u>	<u>Sandy Loam</u>	<u>Loam</u>	<u>Clay Loam</u>
0 - 500	0.5	0.4	ND	ND
500 - 1000	7.5	8.0	1.6	ND
1000 - 1500	38.9	37.4	3.4	6.3
1500 - 2000	27.7	34.6	5.1	17.2
<u>Soil Section (in)</u>				
0 - 4	13.3	1.1	78.0	54.8
4 - 8	8.5	5.7	10.3	17.9
8 - 12	3.7	12.8	1.8	3.7

ND = not detectable

¹Data are averages from three columns.

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Under the conditions of this experiment, the application of the equivalent of 25 inches of rain caused substantial leaching of monensin from a sand and a sandy loam soil while there was very little leaching from a loam and a silty clay loam. Substantial losses of monensin (presumably due to degradation) were observed during the leaching process, the greater losses occurring in soils which required longer time periods for leaching. The results of this experiment indicate that monensin is moderately mobile in coarse textured soils.

The soil sorption coefficient (K_d) for monensin can be calculated from the results of the column leaching study with sandy loam soil. The velocity of water movement through the soil column relative to the velocity of monensin was 26.14. The K_d value for monensin is related to this ratio of velocities by the following equation:

$$26.14 = 1.0 + \frac{\rho K_d}{\theta_{fc}}$$

where ρ is the bulk density of sandy loam soil (1.32 g/cm³)

and θ_{fc} is the water content of soil at field capacity
(0.486 ml/cm³)

The K_d value for monensin calculated from this equation is 9.3.

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APPENDIX H: Report Summary

Titles: The Toxicity of Mycelial Monensin Sodium to Bobwhite in a Fourteen-Day Acute Oral Study

and

The Toxicity of Mycelial Monensin Sodium to Bobwhite in a Fourteen-Day Acute Oral Study: Determination of the No-Observed-Effect Dose

Name and Address of Investigator: C. C. Kehr, Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, P.O. Box 708, Greenfield, IN 46140

Study Numbers: A03680
A01882

Study Dates: A03680 - November 4 to November 18, 1980
A01882 - September 14 to September 28, 1982

Test Article: Monensin Sodium (mycelial)

Lot Number: X-30547

Species: Bobwhite quail (*Colinus virginianus*)

Age: A03680 - 18 weeks
A01882 - 20 weeks

Number of Animals: A03680 - 5/sex/group
A01882 - 6/sex/group

Dose Levels: A03680 - 0.0, 45, 62, 90, 125, 180, and 250 mg monensin sodium/kg body weight
A01882 - 0.0, 5, 9, 16, 27.5, and 45 mg monensin sodium/kg body weight

Route: Oral (gavage)

Length of Observation: 14 days

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Parameters Studied: Food consumption, body weight, physical signs of toxicity (loose feces, lethargy, ataxia, hyperactivity emaciation, prostration) and mortality.

Summary of Results:

Study A03680: The LD₅₀, 95% confidence interval for the LD₅₀, and the slope of the dose-response curve for bobwhite dosed with monensin sodium were 85.7 mg/kg, 64.4 to 114.2 mg/kg, and 2.915, respectively. No sex-related differences in mortality were evident within treatment groups. Dose-related toxic effects included loose feces, ataxia and lethargy. Some birds given the highest doses appeared emaciated or prostrate. Bobwhite given the lowest dose appeared hyperactive and had loose feces. A dose-related decline in mean body weight values occurred at all monensin treatment levels and treated birds consumed less food than control birds during the first seven days of the test.

Study A01882: No mortalities or treatment-related signs of toxicity were found for any treatment group. No treatment-related effects were found for food consumption. Mean body weights of males were slightly reduced on days three and seven in the 45 mg/kg treatment group. No treatment-related physical abnormalities (hyperactivity, loose feces, ataxia, lethargy, emaciation and prostration) no treatment-related effects on body weight or food consumption, and no mortalities were found for bobwhite dosed at ≤ 27.5 mg monensin sodium/kg body weight.

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APPENDIX I: Report Summary

Titles: The Toxicity of Mycelial Monensin Sodium to Bobwhite in a Five-Day Dietary Study

and

The Toxicity of Mycelial Monensin Sodium to Bobwhite in a Five-Day Dietary Study: Determination of the No-Observed-Effect Concentration.

Name and Address of Investigator: C. C. Kehr, Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, P.O. Box 708, Greenfield, IN 46140

Study Numbers: A03780
A01982

Study Dates: November 13 to November 21, 1980

Test Article: Monensin Sodium (mycelial)

Lot Number: X-30547

Species: Bobwhite quail (*Colinus virginianus*)

Age: A03780 - 11 days old
A01982 - 14 days old

Number of Animals: 10/treatment

Levels of Exposure: A03782 - 0.0, 0.0365, 0.056, 0.09, 0.125% w/w (nominal). Assayed values ranged from 94 to 105% of nominal values.

A01982 - 0.0, 0.005, 0.02, 0.0365% w/w (nominal). Assayed values ranged from 95 to 99% of nominal values.

Route: Dietary

Length of Exposure: Treated diets, 5 days; basal diets, 3 days.

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Parameters Studied: Food consumption, body weight, physical signs of toxicity (ataxia, lethargy wing droop, prostration) and mortality.

Summary of Results:

Study A03782: The 8-day LC_{50} , the 95% confidence limits for the LC_{50} and the slope of the concentration-response curve for bobwhite exposed to monensin sodium in feed were 0.109%, 0.081 to 0.147%, and 4.285, respectively. Based on food consumption, average body weight during the 5-day exposure period, and nominal concentrations of monensin sodium in the diet the LD_{50} , the 95% confidence limits for the LD_{50} , and the slope of the dose-response curve for monensin sodium in this dietary study were 980 mg monensin sodium/kg body weight, 717 to 1340 mg monensin sodium/kg body weight, and 4.098, respectively. No mortality or physical signs of toxicity occurred in the control group or in the group that received the lowest dietary concentration of monensin sodium. At higher dietary levels of monensin sodium, physical signs of toxicity (ataxia, lethargy, wing droop, and prostration) appeared to be concentration-related. Significant reductions in body weight gain or body weight loss occurred at all dietary levels of monensin tested in this study. Slight reductions in food consumption also occurred at all treatment levels.

Study A01982: No mortalities were found in this study. Lethargy was seen in all birds tested at the highest treatment level and one bird at this level was ataxic and had wing droop. Food consumption and body weight gain were reduced at the highest treatment level, 0.0365%, and body weight gain was reduced slightly at the 0.02% treatment level. The test level of 0.01% was the highest dietary concentration of monensin sodium tested which resulted in no mortalities, no physical signs of toxicity, and no reductions in food consumption or body weight gain.

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APPENDIX J: Report Summary

Title: The Toxicity of Mycelial Monensin Sodium to Mallards in a Five-Day Dietary Study

Name and Address of Investigator: C. C. Kehr, Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, P.O. Box 708, Greenfield, IN 46140

Study Dates: August 19 to August 27, 1982

Study Number: A01782

Test Article: Monensin sodium (mycelial)

Lot Number: X-30547

Species: Mallard Duck (*Anas platyrhynchos*)

Age: 10 days

Number of Animals: 10/treatment

Levels of Exposure: 0.0, 0.0062, 0.016, 0.0365, 0.09, 0.225, and 0.5% w/w (nominal). Assayed values ranged from 98 to 103% of nominal.

Length of Exposure: Treated diets, 5 days; basal diets, 3 days.

Route: Dietary

Parameters Studied: Food consumption, body weight gain, physical signs of toxicity (ataxia and lethargy), and mortality.

Results: One duckling in the 0.09% treatment group died during this study. No physical signs of toxicity (lethargy, ataxia, loose feces, hyperactivity and prostration) were found for birds in this study. Mean body weight gain was reduced at dietary concentrations $\geq 0.016\%$. Food consumption was reduced for birds fed diets containing $\geq 0.09\%$ of monensin sodium. The test level of 0.0062% was the highest dietary concentration of monensin sodium tested which resulted in no mortalities, no physical signs of toxicity, and no reductions in food consumption or body weight gain.

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APPENDIX K: Report Summary

Title: The Acute Toxicity of Mycelial Monensin Sodium to Bluegill in a Static Test System.

Name and Address of Investigators: D. W. Grothe and P. C. Francis, Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Study Dates: August 23 to August 27, 1982

Study Number: F10082

Test Article: Monensin sodium (mycelial)

Lot Number: X-30547

Species: Bluegill (*Lepomis macrochirus*)

Experimental Design: Groups of ten juvenile bluegill (mean weight, 0.93 g) were exposed to average assayed monensin sodium concentrations of 0.0, 1.15, 1.65, 3.1, 4.4, 7.6, 12.1, 14.2, 14.6, 17.0, and 17.6 mg/L for 96 hours. Jars with 15 L of test or control solution were used to contain each group of ten fish. Dissolved oxygen concentrations, pH, and temperature of the solutions were recorded daily. Behavioral signs of toxicity (hypoactive, minimal swimming behavior, disorientation, labored respiration, and prostration) and mortality were monitored for fish in each jar on a daily basis.

Results: The temperature of the test solutions averaged 20°C, pH values ranged from 8.2 to 8.7 and dissolved oxygen concentrations were above 89% of saturation. Fish exposed to monensin sodium concentrations ≥ 4.4 mg/L showed behavioral signs of toxicity in a concentration-related fashion, from hypoactivity to prostration. The 96-hr LC50, the 95% confidence limits for the LC50, and the slope of the concentration-response curve were 16.6 mg/L, 16.3 to 17.0 mg/L, and 0.438, respectively. No mortalities and no behavioral signs of toxicity were found for fish exposed to monensin sodium concentrations ≤ 3.1 mg/L.

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APPENDIX L: Report Summary

Title: The Acute Toxicity of Mycelial Monensin Sodium to Rainbow Trout in a Static Test System.

Name and Address of Investigators: D. W. Grothe and P. C. Francis, Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Study Dates: August 23 to August 27, 1982

Study Number: F10182

Test Article: Monensin sodium (mycelial)

Lot Number: X-30547

Species: Rainbow trout (*Oncorhynchus mykiss*)

Experimental Design: Groups of ten juvenile rainbow trout (mean weight, 1.14 g) were exposed to average assayed monensin sodium concentrations of 0.0, 0.70, 1.12, 1.48, 4.3, 5.2, 6.6, 8.2, 10.6, 12.5, and 15.7 mg/L. Jars with 15 L of test or control solution were used to contain each group of ten fish. Dissolved oxygen concentrations, pH, and temperature of the solutions were recorded daily. Behavioral signs of toxicity (hypoactivity, minimal swimming behavior, disorientation, labored respiration, and prostration) and mortality were monitored for fish in each jar on a daily basis.

Results: The temperature of the test solutions averaged 12.0°C, pH values ranged from 8.0 to 8.4 and dissolved oxygen concentrations were above 95% saturation. Fish exposed to monensin sodium concentrations ≥ 1.12 mg/L showed behavioral signs of toxicity in a concentration-related fashion, from hypoactivity to prostration. The 96-hr LC_{50} , the 95% confidence limits for the LC_{50} , and the slope of the concentration-response curve were 9.0 mg/L, 7.8 to 10.2 mg/L and 0.366, respectively. No mortalities and no behavioral signs of toxicity were found for fish exposed to the monensin sodium concentration of 0.70 mg/L.

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APPENDIX M: Report Summary

Title: The Acute Toxicity of Mycelial Monensin Sodium to *Daphnia magna* in a Static Test System

Name and Address of Investigators: P. C. Francis and D. W. Grothe, Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Study Dates: May 25 to May 27, 1982

Study Number: C02382

Test Article: Monensin sodium (mycelial)

Lot Number: X-30547

Species: *Daphnia magna*

Summary of Experimental Design: Groups of 30 *Daphnia*, ≤ 24 hours old, were exposed to average assayed monensin sodium concentrations of 0.0, 2.6, 4.2, 5.6, 7.1, 10.8, 14.4, and 18.1 mg/L for 48 hours. Each of three beakers with 200 ml of solution were used to contain 10 *Daphnia* for each treatment or control solution. Test solutions were maintained at 20°C and pH values ranged from 8.2 to 8.6 in all of the test and control solutions. Dissolved oxygen concentration remained above 66% saturation in all test solutions.

Results: Based on immobility, the 48-hour EC₅₀, the 95% confidence interval, and the slope of the concentration-response curve for monensin sodium were 10.7 mg/L, 9.8 to 11.7 mg/L, and 0.280, respectively. The highest monensin sodium concentration tested which did not result in physical signs of toxicity (hypoactivity or prostration) and did not result in immobilization was 4.2 mg/L. Hypoactivity and immobilization were concentration-related at monensin sodium concentrations ≥ 5.6 mg/L.

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APPENDIX N: Report Summary

Title: The Toxicity of Soil-Incorporated Mycelial Monensin Sodium to Earthworms in a 14-Day Test.

Name and Address of Investigators: P. C. Francis and D. W. Grothe, Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Study Dates: May 12 to May 26, 1982

Study Numbers: W01082

Test Article: Monensin sodium (mycelial)

Lot Number: X-30547

Species: *Lumbricus terrestris*

Average Initial Wet Weight: 3.67 g

Number of Animals: 15/treatment

Route: Incorporated into test media (rabbit feces, water, and loamy sand soil)

Levels of Exposure: 0.0, 10.0, 22.5, 45.0, and 100 ppm (nominal)

Length of Exposure: 14 days

Parameters Studied: Body weight gain, mortality, and physical appearance (flaccid, soft and flaccid, moribund).

Experimental Design: Test media was placed in 2-L cylindrical glass jars. Three jars were used for controls and three jars were used for each exposure level. Five worms were placed into each jar at the beginning of each study. The study was conducted at 12°C.

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Results: Six out of fifteen worms were dead by the end of the study at the highest monensin sodium concentration tested. The rest of the worms exposed to the highest concentration tested were flaccid, soft and flaccid, and moribund. Although no worms died at the exposure concentration of 45 mg/kg, one worm was moribund, one worm was soft and flaccid, and two worms were flaccid. Normal physical condition and no mortalities were noted for worms exposed to monensin sodium concentrations ≤ 22.5 mg/kg. Worms exposed to the two highest concentrations of monensin sodium lost weight during the experiment. Worms exposed to the 22.5 mg/kg treatment level gained less weight than control worms, but the reduced weight gain was not significant. All worms exposed to the monensin sodium concentration of 10 mg/kg in soil were alive, had a normal physical appearance, and gained as much weight as control worms by the end of the 14-day study.

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APPENDIX O: Report Summary

Title: Greenhouse Test for Monensin Phytotoxicity

Study Numbers: WB71-1 and WB1-31

Study Dates: January 2 to July 1, 1971

Name and Address of Investigators: R. B. Bevington and M. E. Callendar, Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Test Article: Crystalline Monensin and Litter from Monensin-Fed Chickens

Test System: Plants grown from seed in greenhouse soil flats.

Summary of Experimental Design: Monensin or litter from monensin-fed chickens was incorporated into soil at concentrations shown in Table 1. A standard greenhouse phytotoxicity test was conducted in which fourteen mono- and dicotyledonous plants were grown from seed in the treated and untreated soils. The plant species were alfalfa (*Medicago sativa*), fescue (*Festuca elatior*), cucumber (*Cucumis sativus*), rice (*Oryza sativa*), cotton (*Gossypium hirsutum*), tomato (*Lycopersicon esculentum*), pepper (*Capsicum annuum*), corn (*Zea mays*), sugar beet (*Beta vulgaris*), barley (*Hordem vulgare*), soybean (*Glycine max*), wheat (*Triticum aestivum*), grain sorghum (*Sorghum bicolor*), and oats (*Avena sativa*). Plants were rated for phytotoxic injury (0 = no injury, to 10 = complete kill) and injury, described as chlorosis, burning, stunting, or reduced germination, was noted 18 to 21 days after planting.

Summary of Results: A pilot experiment (WB71-1) was conducted in which chicken litter was applied at rates equivalent to 2-1/2 to 10 tons per acre on a dry matter basis. This exposure level proved to be too high because of severe phytotoxicity even with the control litter treatment. Monensin itself without any litter present was relatively nonphytotoxic at application rates of approximately 1-2 ppm (lb/acre equivalent). However, rates of 4-8 ppm caused moderate to severe injury on several plant species.

A second experiment (WB1-31) was conducted in which litter from control chickens and monensin-treated chickens was applied at rates equivalent to 1, 2, 4, and 8 tons of fresh

litter per acre. Litter samples were weighed, dried, and milled, and the litter was incorporated into the test soils at the appropriate rates.

Results are shown in Table 1. Litter from monensin-fed chickens was no more phytotoxic than litter from control chickens. There was some phytotoxicity due just to the litter itself at an application rate of 8 tons/acre.

Table 1

Phytotoxicity Ratings^a on Chicken Litter Treatments

Treatment ^b Rate (tons/acre)	Litter from Monensin Treated Chickens				Litter from Control Chickens				No Litter	
	1	2	4	8	1	2	4	8	0	0
Cotton	0	0	0	1.5	0	2	3	1.5	0	0
Sugar Beets	0	0	3	4	0	0	0	10	0	0
Tomatoes	0	0	0	1.5	0	0	0	1.5	0	0
Alfalfa	0	0	0	0	0	0	0	2	0	0
Peppers	0	0	0	0	0	0	0	0	0	0
Cucumbers	0	0	0	0	0	0	1	0	0	0
Soybeans	0	0	0	1	0	0	0	1.5	0	0
Wheat	0	0	0	0	0	0	0	0	0	0
Barley	0	0	0	0	0	0	0	1	0	0
Rice		0	0	0	0	0	0	0	0	0
Corn	0	0	0	0	0	0	0	0	0	0
Fescue	0	0	0	0	0	0	0	0	0	0
Oats	0	0	0	0	0	0	1	2	0	0
Sorghum	0	0	0	0	0	0	0	2	0	0

^aRating scale was 0 to 10. A rating of 0 represents no injury and 10 represents complete kill.

^bMonensin treated chickens received 110 g monensin per ton of feed.

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APPENDIX P: Report Summary

Title: Field Phytotoxicity Study of Manure from Monensin-Treated Cattle

Study Number: B48-3273

Study Dates: February 1 to September 30, 1973

Name and Address of Investigators: J. A. Manthey, Lilly Research Laboratories,
Division of Eli Lilly and Company, Box 708, Greenfield, IN 46140

Test Article: Manure from Cattle fed Monensin

Test System: Crops grown in field plots

Summary of Experimental Design: During the winter of 1973, manure was collected from the pens of cattle which were fed with feed that contained monensin. The dosing levels of monensin were 20 and 40 g/ton of feed. On June 1, the manure from the piles was weighed and spread on the test plots at the rate of 22 tons/acre. Each plot was 23 ft x 54 ft. Such plots were large enough to accommodate the rows of 14 selected crop plants. The manure was disked into the upper 4 inches of the soil. During the next three weeks, the plots were made fallow by disking.

The plots were arranged in the following fashion:

I	II	III	IV
Control	40 g/ton	No	20 g/ton
Manure	Manure	Manure	Manure

Direction of rows → → → → → → → → → →

On June 25, 1973, the field plots were seeded with the crops shown in Table 1. Subsequently, weeds were controlled by cultivation, and insecticide sprays were used as needed to maintain the seedlings in good condition.

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Extreme rainfall washed out part of a test plot. It became necessary to reseed the tomatoes and peppers. This was done on July 11, 1973.

Summary of Results: The evaluation of crop injury from this test is shown in Table 1. There were no adverse effects from the manure of animals fed the highest level of monensin (40 g/ton). No evaluation of the lower (20 g/ton) monensin level plot could be made. This plot was in a poorly drained area of the field. The very wet season of 1973 caused extensive water damage to all crops in that plot.

There were no indications of monensin-related phytotoxicity to any of the crops.

Table 1

Crop Injury Rating

Oats (<i>Avena sativa</i>)	There were no observable differences in maturation, flowering, fruiting, or seed formation between Sugar untreated, blank manure Corn plot and the plot with monensin in the manure.
Sorghum (<i>Sorghum bicolor</i>)	
Soybean (<i>Glycine max</i>)	
Barley (<i>Hordeum vulgare</i>)	
Beet (<i>Beta vulgaris</i>)	
Corn (<i>Zea mays</i>)	
Tomato (<i>Lycopersicon esculentum</i>)	
Cotton (<i>Gossypium hirsutum</i>)	
Cucumber (<i>Cucumis sativus</i>)	
Wheat (<i>Triticum aestivum</i>)	No observable differences in growth or vigor of these plants between treatments. Due to short duration of this trial, no fruit or seeds were formed to date.
Rice (<i>Oryza sativa</i>)	
Pepper (<i>Capsicum annum</i>)	
Alfalfa (<i>Medicago sativa</i>)	
Fescue (<i>Festuca elatior</i>)	

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Appendix Q. Material Safety Data Sheet

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MSDS

MATERIAL SAFETY DATA SHEET



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Page 1

COMMON NAME: Monensin Sodium
(Lilly Nos.: ID0802, ID0831, QA166H, QA322B, QA331Z,
QA342A, QA375V, QI0188, LSN047039, LSN063080)

REVISED DATE: September 11, 1995

SECTIONS REVISED: Sections 2, 5, 9

U.S. TELEPHONE NUMBERS: EMERGENCY 317-276-2000 CHEMTREC 800-424-9300

As of the date of issuance, we are providing available information relevant to the handling of this material in the workplace. All information contained herein is offered with the good faith belief that it is accurate. THIS MATERIAL SAFETY DATA SHEET SHALL NOT BE DEEMED TO CREATE ANY WARRANTY OF ANY KIND (INCLUDING WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE). In the event of an adverse incident associated with this material, this safety data sheet is not intended to be a substitute for consultation with appropriately trained personnel. Nor is this safety data sheet intended to be a substitute for product literature which may accompany the finished product.

See attached glossary for abbreviations.

----- SECTION 1 - MATERIAL IDENTIFICATION -----

Common Name: Monensin Sodium

Chemical Name: Monensin, monosodium salt; 1,6-Dioxaspiro[4.5]decane-7-butyric acid, 2-[5-ethyltetrahydro-5-[tetrahydro-3-methyl-5-[tetrahydro-6-hydroxy-6-(hydroxymethyl)-3,5-dimethyl-2H-pyran-2-yl]-2-furyl]-2-furyl]-9-hydroxy-beta-methoxy-alpha,gamma,2,8-tetramethyl-, monosodium salt

Synonyms/Trade Names: Monensin; EL-980; EL980; Monensin Monosodium Salt; Antibiotic A-3823A, Sodium Salt; Monensin Sodium Salt; Rumensin*; Coban*; LSN067314 Sodium

CAS Number: 22373-78-0

Molecular Formula: C₃₆ H₆₁ O₁₁ . Na

Chemical Family: Ionophore

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SECTION 2 - PHYSICAL DATA

Appearance: Off white to tan crystalline powder
Odor: Slight musty
Boiling Point: NA
Melting Point: 267-269 C (513-515 F)
Specific Gravity: NAIF
pH: (50% solution) 6 - 9
Evaporation Rate: NAIF
Solubility in Water: Slightly soluble
Vapor Density: NAIF
Vapor Pressure: NAIF
Density: 27-32 lbs/cu. ft.

SECTION 3 - FIRE AND EXPLOSION INFORMATION

Extinguishing Media: Use water, carbon dioxide, dry chemical, foam, or Halon. Do not allow water run-off from fire site to enter nearby streams, ponds, or lakes.

Unusual Fire and Explosion Hazards: As a finely divided material, may form dust mixtures in air which could explode if subjected to an ignition source.

Flash Point: NAIF

Method: NA

UEL: NAIF

LEL: 0.25 oz/cu ft.

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SECTION 4 - REACTIVITY INFORMATION

Stability: Stable at normal temperatures and pressures. Data have not been generated for this material at elevated temperatures.

Incompatibility: May react with strong oxidizing agents (e.g., peroxides, permanganates, nitric acid, etc.).

Hazardous Decomposition: May emit toxic fumes when heated to decomposition.

Hazardous Polymerization: None known.

SECTION 5 - HEALTH HAZARD INFORMATION

Human - Occupational

Effects, Including Signs and Symptoms, of Exposure: Skin rash and skin and respiratory tract irritation have been reported. Based on animal studies, may cause burns or permanent tissue damage to eyes.

Medical Conditions Aggravated By Exposure: Hypersensitivity to Monensin Sodium.

Primary Route(s) of Entry: Inhalation and skin contact.

Exposure Guidelines: PEL and TLV not established.
LEG 15 micrograms/m³ TWA for 12 hours

Animal Toxicity Data Single Exposure

Data for Monensin Sodium and a 24% monensin sodium mixture are presented as indicated.

Oral: Monensin sodium - Rat, median lethal dose 34 mg/kg, incoordination, reduced activity, skeletal muscle weakness, diarrhea, decreased weight gain.

Skin: 24% Monensin sodium mixture - Rabbit, 500 mg/kg, no deaths or toxicity.

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----- SECTION 5 - HEALTH HAZARD INFORMATION (continued) -----

Animal Toxicity Data Single Exposure

Inhalation: 24% Monensin sodium mixture - Rat, 370 mg/m³ for one hour,
no deaths.

Skin Contact: 24% Monensin sodium mixture - Rabbit, nonirritant

Eye Contact: 24% Monensin sodium mixture - Rabbit, corrosive, but
permanent damage prevented by immediate rinsing

Animal Toxicity Data Repeat Exposure

Target Organ Effects: Heart effects (degenerative and reparative tissue
changes, electrocardiogram changes, congestive
heart failure), muscle effects (skeletal muscle
changes, elevated blood enzymes of muscle
origin).

Other Effects: Decreased body weight gains, increased kidney, heart,
thyroid, adrenal, prostate, testes, liver, and spleen
weights.

Reproduction: No effects identified in animal studies.

Sensitization: Guinea pig, not a contact sensitizer.

Mutagenicity: Not mutagenic in bacterial cells.

Carcinogenicity: Not listed as a carcinogen or potential carcinogen by
IARC, NCI/NTP, ACGIH, or OSHA. Not considered to be
carcinogenic in lifetime feeding studies conducted by
Lilly.

----- SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES -----

Eyes: Hold eyelids open and flush with a steady, gentle stream of water
for 15 minutes. See an ophthalmologist (eye doctor) or other
physician immediately. Immediate rinsing may prevent permanent
damage.

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----- SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES (continued) -----

Skin: Remove contaminated clothing and clean before reuse. Wash all exposed areas of skin with plenty of soap and water. Get medical attention if irritation develops.

Inhalation: Move individual to fresh air. Get medical attention if breathing difficulty occurs. If not breathing, provide artificial respiration assistance (mouth-to-mouth) and call a physician immediately.

Ingestion: Call a physician or poison control center. Drink one or two glasses of water and give 1-2 tablespoons syrup of ipecac to induce vomiting. Do not induce vomiting or give anything by mouth to an unconscious person. Immediately transport to a medical care facility and see a physician.

----- SECTION 7 - HANDLING PRECAUTIONS -----

Respiratory Protection: Use an approved respirator.

Eye Protection: Chemical goggles and/or face shield.

Ventilation: Extensive local exhaust or enclosed process equipment.

Other Protective Equipment: Chemical-resistant gloves and body covering to minimize skin contact. If handled in a ventilated enclosure, as in a laboratory setting, respirator and goggles or face shield may not be required. Safety glasses are always required.

Other Handling Precautions: In production settings, airline-supplied, hood-type respirators are preferred. Shower and change clothing if skin contact occurs.

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----- SECTION 8 - SPILL, LEAK AND DISPOSAL PROCEDURES -----

Spills: Contain dry material by sweeping up or vacuuming. Vacuuming may disperse dust if appropriate dust collection filter is not part of the vacuum. Be aware of potential for dust explosion when using electrical equipment. Wear protective equipment, including eye protection, to avoid exposure (see Section 7 for specific handling precautions). Prevent spilled material from flowing onto adjacent land or into streams, ponds, or lakes.

Waste Disposal: Dispose of any cleanup materials and waste residue according to applicable federal, state, and local regulations.

----- SECTION 9 - SHIPPING INFORMATION -----

(Proper Shipping Name / Hazard Class / UN Number)

DOT: Toxic solids, organic, N.O.S. (monensin sodium) / 6.1 / UN2811

ICAO: Toxic solid, organic, N.O.S. (monensin sodium) / 6.1 / UN2811

IMO: Toxic solid, organic, N.O.S. (monensin sodium) / 6.1 / UN2811

Packing Group: II

For additional information call: Occupational Health and Safety
Eli Lilly and Company 317-276-3494

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GLOSSARY

Abbreviations Used in Material Safety Data Sheets

ACGIH = American Conference of Governmental Industrial Hygienists
BEI = Biological Exposure Index
CAS Number = Chemical Abstract Service Registry Number
CERCLA = Comprehensive Environmental Response Compensation and Liability Act (of 1980)
CHEMTREC = Chemical Transportation Emergency Center
CWA = Clean Water Act
DOT = Department of Transportation
EP = Extraction Procedure as defined under RCRA Regulations
EPA = Environmental Protection Agency
HEPA = High Efficiency Particulate Air (Filter)
HSDB = Hazardous Substance Data Base
IARC = International Agency for Research on Cancer
ICAO = International Civil Aviation Organization
IMO = International Maritime Organization
LEG = Lilly Exposure Guideline
LEL = Lower Explosive Limit
MSDS = Material Safety Data Sheet
NA = Not Applicable, except in Section 9 where NA = North America
NAIF = No Applicable Information Found
NCI/NTP = National Cancer Institute/National Toxicology Program
NIOSH = National Institute for Occupational Safety and Health
NOS = Not Otherwise Specified
OHS = Occupational Health Services
OSHA = Occupational Safety and Health Administration
PEL = Permissible Exposure Limit
PSN = Proper Shipping Name
RCRA = Resource Conservation and Recovery Act
RTECS = Registry of Toxic Effects of Chemical Substances
SARA = Superfund Amendments and Reauthorization Act
STEL = Short Term Exposure Limit
TLV = Threshold Limit Value
TSCA = Toxic Substances Control Act
TWA = Time Weighted Average/8 Hours Unless Otherwise Noted
UEL = Upper Explosive Limit
UN = United Nations

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