IVOMEC® (ivermectin) Pour-On for Cattle

Environmental Assessment

1. Date: March 22, 1990

2. Name of applicant/petitioner: Merck & Co., Inc.

3. Address: P.O. Box 2000
   Rahway, NJ 07065

4. Description of the proposed action:

   a. Requested action

   To approve the marketing of IVOMEC® (ivermectin) 0.5% Pour-On formulation for cattle.

   b. Need for the action

   Ivermectin topical formulation is a treatment for the control of endo- and ectoparasites of cattle. The cost of parasitism, in terms of morbidity and resultant depression of growth and feed efficiency, has long been recognized as a significant factor in the economical production of both beef and dairy products. The beef and dairy industries suffer intensive economic losses due to both internal and external parasites. These losses have been primarily attributed to the loss in feed efficiency due to internal parasites and to the interruption of feeding habits caused by external parasite infestation. Among the external parasites, the horn fly (*Haematobia irritans*) poses an especially difficult problem because it has developed resistance to many insecticides of the pyrethroid class. IVOMEC® Pour-On provides a new active ingredient for horn fly control which has a mode of action different from that of the pyrethroids and which controls horn flies resistant to the pyrethroid fenvalerate.

   Ivermectin 0.5% topical formulation is a ready-to-use method of treatment for parasite infestation which is both convenient for the applicator and non-stressful for the animal. The use of this product will reduce the economic loss to the cattle industry caused by internal and external parasites.

   c. The locations where the product will be produced and types of environments adjacent to those locations

   Avermectin will be manufactured in the facilities of Merck & Co., Inc., at Danville, Pennsylvania, and converted to ivermectin in the facilities of MSD AGVET, Inc., Barceloneta, Puerto Rico. The topical formulation will be manufactured and packaged in the facilities of MSD AGVET, Inc., Barceloneta, Puerto Rico and Merck Sharp & Dohme B.V. Plant, Haarlem, Holland.

The types of environments present at the locations mentioned above, specific to the vicinity of product formulation, are described in the following sections.

1. **The type of environment at Danville, Pennsylvania**

Location - The Danville plant is located in the Susquehanna River Valley approximately 70 miles north of Harrisburg, Pennsylvania. The plant is located adjacent to the south bank of the North Branch of the Susquehanna River. Coordinates of the plant's location are latitude N 40° 57' and longitude W 76° 38'. The plant is located in the Borough of Riverside. Danville's 1980 population was listed as 5,200 by the U.S. Census Bureau.

Weather/Air Resources - Annual rainfall at the Williamsport Airport (approximately 30 miles from the plant) is 41 inches. The mean summer temperature is 72°F, while the mean winter temperature is 28°F. The entire state of Pennsylvania is designated nonattainment for ozone. Pennsylvania has no significant nitrogen dioxide pollution. The Danville plant is located in the Central Pennsylvania Intrastate Air Quality Control Region (AQCR) which is currently in attainment with the primary standards for particulate matter, sulfur oxides, nitrogen dioxides, and carbon dioxide. The state has incorporated into its regulations the new source performance standards (NSPS), National Emission Standard for Hazardous Air Pollutants (NESHAPS), and the ambient air quality standards. There are no Class I Visibility Areas within 50 km of the plant. Prevailing winds near the plant are from the west-northwest direction.

Water Resources - Separate sanitary, process, and storm sewer systems are maintained at the plant. The sanitary sewer flows to the Borough of Danville's wastewater treatment plant, while the process sewer flows to the plant's wastewater treatment facility. Water from the storm sewer system merges with the effluent from the plant's wastewater treatment system, and the combined streams are discharged to the Susquehanna River through the plant's national pollutant discharge elimination system (NPDES) outfall. The only surface water within 1000 feet of the plant is the north branch of the Susquehanna River. There are no injection wells on the plant property, and the 100-year flood plain elevation at the plant is approximately 460 feet above mean sea level. The plant derives its potable water entirely from an on-site treatment plant, which uses the Susquehanna River as its source. Approximately 180 private wells are located within 1/4 mile from the plant boundary.

Land Resources - The terrain surrounding the plant is valley flatland with low hills on both sides. Terrain elevation near the north bank of the Susquehanna River rises abruptly to 400 feet above the base elevation of the plant. Geological data indicates

that the rocks surrounding the plant are mainly shale, with a few thin beds of siltstone, limestone and fine-grained sandstone. The Bloomsburg formation, a red silty shale, underlies the southern third of the plant property. To the northwest part of the plant, there is the Mifflintown formation, a gray shale having some thin limestone beds and a few thin beds of sandstone. Along the river, the northwest corner of the property is underlain by olive shale and thin sandstone interbeds of the Rose Hill formation.

2. **The type of environment at Barceloneta, Puerto Rico**

<u>Location</u> - The Merck Sharp & Dohme Quimica de Puerto Rico, Inc. (MSDQ) facility is located on a 166 acre site in Barceloneta, Puerto Rico. The city of Barceloneta contains a population of 20,000 people and is located 38 miles due west of San Juan and three miles south of the Atlantic Ocean. The MSDQ plant is located at km 56.4 along State Highway 2. Coordinates of the plant's location are latitude N 18° 25' and longitude W 66° 32'.

<u>Weather/Air Resources</u> - Puerto Rico generally has attained National Ambient Air Quality Standards for every criteria pollutant, although there are problems with particulates, especially in the Catano air basin. The Barceloneta plant is located in the Barceloneta air basin. The state requires both new source permits and operating permits for all point sources. Puerto Rico is part of USEPA Region II and has been delegated authority over the National Emissions Standards for Hazardous Air Pollutants Program (NESHAPS).

Meteorological data for the area is collected at the Isla Verde Airport in San Juan (about 47 miles east of Barceloneta). Annual rainfall is near 60 inches and the mean ambient temperature varies between 76 and 82°F. An easterly trade wind is the predominant wind pattern.

<u>Water Resources</u> - The entire fresh water requirements for the plant are supplied by one pumped well and two artesian wells. The artesian wells are used as the primary source of plant water. No other wells, or surface water bodies, are located within 1000 feet of the facility.

Separate sewer systems exist for sanitary, process and storm water runoff. Process wastewater flows into the plant's pretreatment system and then to the Barceloneta Regional Wastewater Treatment Plant (BRWTP). Sanitary waste from the plant joins the effluent from the pretreatment system and the combined streams flow to the BRWTP.

Storm water from the plant is collected in an independent sewer system, consisting of concrete dikes and swales and directed away

from the facility. Surface water runoff from portions of the plant discharge to the sinkhole system which is mentioned in the land resources section below. The MSDQ plant is located approximately 1.25 miles west of the Manati River and 70 meters above mean sea level. This location above sea level is well above the 100-year floodplain.

Land Resources - The plant is located in an inter-mogote depression. The depression is elongated east-west over a distance of 2 km. The mogotes are asymmetrical hills that are built of massive, thick-bedded members of the Aymamon Limestone. A series of sink holes and secondary depressions are located east and tend in a northwesterly direction from the site.

Bedrock beneath the plant site consists primarily of moderately solutioned, recrystallized limestone of the mid-miocene age Aymamon Formation. In depressions between mogotes and ridges, the limestone is overlain by the quarternary blanket sands. The blanket deposits consist mostly of silty or sandy clay which underwent rapid disposition in a subaerial fluvial plain environment. Based on soil borings from the site, 20 percent of the soil is sand. Red-brown to yellow silty clay comprises the dominant soil found in the borings.

Land use surrounding the plant includes industrial and mixed industrial. Other industries lie north and west of the facility, the community of Imbery lies north of the facility, and the rest of the surrounding area is undeveloped.

3. **The type of environment at Haarlem, Holland**

Location - The Haarlem, Holland, MSD, plant is located in the municipality of Haarlem, near the North Sea coast and approximately 20 km west (13 miles) from the city of Amsterdam. The plant is located east of the city Haarlem, on 18 hectare (approximately 45 acres) of land near the river Spaarne in the area of Waarderpolder, which is dedicated to industrial activities only. Population of the city of Haarlem is approximately 150,000.

Air Resources - Annual rainfall is 0.75 meter (30 inches). Mean July temperature is 18°C (64°F). Mean January temperature is 4°C (40°F). Prevailing wind directions are west and south-west (sea wind) at a windforce of 3 to 8 Beaufort. Dutch government laws prescribe emission standards for hazardous pollutants. No significant air pollution generating industries are located in the vicinity.

Water Resources: All water used for consumption, process, and sanitary equipment is obtained from the official county supplier. The water quality constantly meets the standards of potable water. For fire fighting, water can be withdrawn from the River Spaarne.

There are no injection wells in the plant property. No private wells are located in the vicinity of the plant. The sanitary and storm sewer system are directly coupled to the municipal sewer system, while the process effluents are treated before discharge into the municipal sewer. The discharge of waste water into the municipal sewer is covered by official permit by the municipality. All waste water from the municipal sewer is treated in the municipal waste water treatment system. The treated water is discharged into the river.

Land Resources: The land of the industrialized zone where the plant is located is reclaimed ("polder"). The soil is composed of layers of clay and sand.

d. The location where the product will be used and disposed of

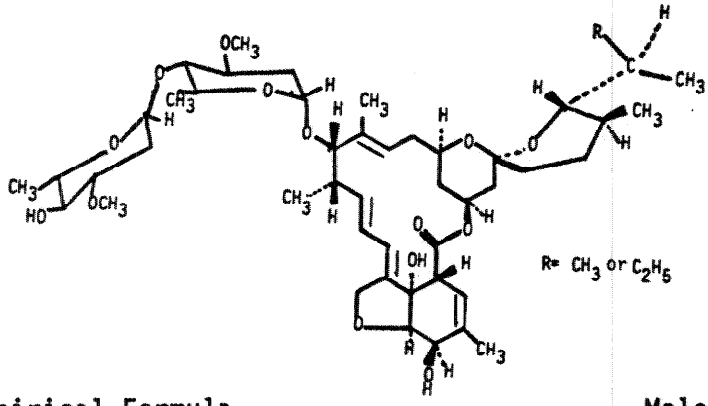
The topical formulation of ivermectin will be used on cattle in feedlot and pasture environments. Cattle feedlots and pastures are located throughout the United States in many different types of environment and predominantly in rural areas.

5. Identification of chemical substances that are the subject of the proposed action:

a. Ivermectin 0.5% topical formulation contains the following substances

(1) Ivermectin (CAS Reg. No. 70288-86-7)
(2) FD&C Blue #1
(3) Trolamine NF
(4) Crodamol CAP
(5) Isopropyl Alcohol, USP

b. The structure and properties of ivermectin are as follows



Empirical Formula	Molecular Weight
(R = C_2H_5) $C_{48}H_{74}O_{14}$	875.10
(R = CH_3) $C_{47}H_{72}O_{14}$	861.07

Ivermectin is produced by fermentation and subsequent chemical hydrogenation and is a mixture of two closely related homologues belonging to a class of compounds known as avermectins. The chemical names of the two homologues are: 22,23-dihydroavermectin B_{1a}($R=C_2H_5$) and 25-de (1-methylpropyl)-22,23-dihydro-25-(1-methylethyl) avermectin B_{1a} ($R=CH_3$). The latter is also known as 22,23-dihydroavermectin B_{1b}.

Ivermectin contains at least 80% of the compound in which R in the above structure is the ethyl group and less than 20% of the compound in which R is the methyl group. It is white to yellowish white crystalline powder and has an ill-defined melting point of about 150°C. The material is optically active and has a specific rotation $[a]_D^{25°C}$, of approximately -19° (C=0.5, CH_3OH).

The ultraviolet absorption spectrum in methanol is characterized by maxima at 237, 245 and 253 nm, with less intense absorption at ≈290 and 350 nm. Ivermectin is very insoluble in water: the concentration of a saturated aqueous solution is 4 ppm. Ivermectin is freely soluble in methanol, chloroform, p-dioxane, dimethylformamide and ethyl acetate; soluble in 95% ethanol, diethyl ether, methylene chloride and acetone and aromatic hydrocarbons; and very slightly soluble in aliphatic hydrocarbons. The infrared and nuclear magnetic resonance spectra are consistent with the proposed structures.

Ivermectin has been shown to be stable for at least six months when stored under ambient conditions. In a solution, ivermectin is photolabile.

Ivermectin contains at least 95% of the two compounds shown above as determined by UV absorption and liquid chromatography.

Based on radioactivity measurements, the octanol-water partition coefficient for ivermectin is 1651; i.e.,

$$K_D \text{ of } \frac{\text{octanol}}{\text{pH 7 buffer (or water)}} = 1651$$

The present assessment supplements ivermectin data with data generated with avermectin B_1. The structure of avermectin B_1 (AVM) only differs from that of ivermectin (IVM) by a double bond at position 22,23. Ivermectin is produced from avermectin by catalytic reduction of this double bond. Physical properties of ivermectin and avermectin are compared below.

Comparison of IVM and AVM Physical Properties

Physical Properties	IVM	AVM
Molecular Weight[a]	875	872
Octanol/Water Partition Coef.	1,651	9,900
K_{oc}[b]	12,600-15,700	≥4,000
Aqueous Solubility[c]	4 ppm	8 ppb
E (λmax), Methanol	30,100 (245)	31,850 (243)

[a] Molecular weight of the B_{1a} component
[b] Different soils used
[c] Different methods used

Both compounds possess low water solubility, high octanol/water partition coefficients and high K_{oc} values. Compounds with K_{oc} values >1000 are immobile in soil.

6. Introduction of substances into the environment:

a. As a result of the manufacture of IVOMEC® (ivermectin) Pour-On

Danville, Pennsylvania - The following summarizes the environmental effects of manufacture of ivermectin at the Danville plant:

The manufacturing process generates two liquid-waste streams; one a combination of solvent-based waste streams, the other a combination of aqueous waste streams. The solvent-based waste streams are generated in the isolation step and in the recovery of solvents used for the isolation. They will contain discarded organic by-products and some residual avermectins in a solution of organic solvents such as hexane, ethanol and toluene.

The solvent-based stream will be destroyed by incineration. The incineration process will be subject to, and in compliance with, the Pennsylvania Rules and Regulations for the protection of Natural Resources, Title 25, Part I, Subpart C, Article I, Land Resources, Chapter 75, Solid Waste Management and Article III, Air Resources and 40 CFR Parts 264 and 265. Standards Applicable to Owners and Operators of Hazardous Waste Treatment, Storage and Disposal Facilities.

The aqueous-based waste stream will consist of the spent fermentation broth and wash waters and will contain unconsumed fermentation nutrients, unrecovered by-products and traces of avermectins and dissolved solvents such as hexane, ethanol and toluene. The aqueous-based stream will be treated in a chemical pretreatment unit designed to destroy residual avermectins; the treated stream will receive final biological treatment in the existing two-stage secondary waste treatment plant and will be discharged under the requirements of

and in compliance with NPDES Permit No. Pennsylvania 0008419 which is administered by the Pennsylvania Department of Natural Resources.

Air emissions generated during the production process will consist of volatile organic compounds such as hexane, ethanol and toluene which will be controlled as appropriate by condensers. The air emissions will be subject to, and in compliance with, the regulations for air emissions of the Pennsylvania Department of Natural Resources (Title 25, Part I, Subpart C, Article III, Air Resources).

Dry solid wastes generated during the production operations (paper, trash, etc.) will be disposed of in an incinerator which will be subject to, and in compliance with, the regulations for air emissions of the Pennsylvania Department of Natural Resources (Title 25, Part I, Subpart C, Article III, Air Resources).

Material Safety Data Sheets (MSDS) will be available onsite for all chemicals required by the Occupational Safety Act of 1971 and the Hazardous Communication Act of 1985. Employees associated with the manufacturing of avermectin will have appropriate MSDS available for their review. The MSDS for avermectin broth, detoxified avermectin spent broth and avermectin pure are contained in Section 16 of this assessment. Employee protective clothing, such as gloves, uniforms and safety shoes, and protective equipment, such as safety glasses, will be used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazards Communication Act of 1985. To minimize worker exposure to avermectin, the following monitoring activities will be conducted:

1) At least semi-annual monitoring of dust levels where avermectin powder is handled;

2) At least annual blood testing of employees in the isolation area; and

3) At least monthly wipe test on equipment, floors and production bottles in the production area.

Air, liquid and solid waste emissions will comply with the above-mentioned environmental control regulations.

<u>Barceloneta, Puerto Rico</u> - The following summarizes the environmental effects of manufacturing ivermectin and manufacturing and formulating IVOMEC® Pour-On at the Barceloneta plant:

The manufacturing process generates two liquid-waste streams: one, a combination of solvent-based waste streams, the other, a combination of aqueous waste streams.

The solvent-based streams are generated in the chemical processing steps. They will contain discarded organic compounds in a solution of

solvents such as ethanol, formamide, toluene and water. The solvent-based stream will be destroyed by incineration. The incineration process will be subject to, and in compliance with, the Puerto Rico Environmental Quality Board Regulations for the Disposal of Solid Waste and Regulation for the Control of Atmospheric Pollution and the U.S. Environmental Protection Agency Regulations, 40 CFR Parts 264 and 265.

The aqueous-based waste stream will consist of wash waters generated by equipment washings. Holding tanks are provided to contain these washes prior to testing and disposal. Depending on the ivermectin concentration, the holding tank contents will be managed in one of three ways:

1) Contents are tested for ivermectin and pumped through a filter to the chemical sewer;

2) Contents are chemically pretreated with sodium hydroxide and the treated washes are pumped through a filter to the chemical sewer. The treatment process will be periodically validated by testing; and

3) Contents are incinerated.

Discharges to the BRWTP will be under the requirements in compliance with NPDES Permit No. Pr 0021237 which is administered by the U.S. Environmental Protection Agency.

Air emissions generated during the production process will consist of volatile organic compounds such as ethanol, formamide and toluene which will be controlled as appropriate by condensers. Exhaust air in the process building and the formulation and sterile areas will be filtered. Air emissions will be subject to, and in compliance with, the regulation for air emissions of the Puerto Rico Environmental Quality Board Regulations for the Control of Air Emissions.

Dry solid waste, generated during the production operation (paper, trash, etc.) will be disposed of in an incinerator which will be subject to, and in compliance with, the regulations for air emissions and solid waste disposal of the Puerto Rico Environmental Quality Board.

Material Safety Data Sheets (MSDS) will be available onsite for all chemicals required by the Occupational Safety Act of 1971 and the Hazardous Communication Act of 1985. Employees associated with the manufacturing of ivermectin and manufacturing and formulations of IVOMEC® Pour-On will have appropriate MSDS available for their review. The MSDS for ivermectin, ivermectin pour-on, and isopropyl alcohol are contained in Section 16 of this assessment. Employee protective clothing, such as gloves, uniforms and safety shoes, and protective equipment, such as safety glasses and safety hats will be used during the manufacturing process to assure compliance with the

Occupational Safety Act of 1971 and the Hazards Communication Act of 1985. To minimize worker exposure to ivermectin, the following monitoring activities will be conducted:

1) At least semi-annual monitoring of dust levels where ivermectin powder is handled;

2) At least annual blood testing of employees in the manufacturing and formulation areas; and

3) Wipe tests are performed to verify the cleanup of spills in the formulation area.

Air, liquid and solid waste emissions will comply with the above-mentioned environmental control regulations.

Haarlem, Holland - The manufacture and packaging of IVOMEC® (ivermectin) Pour-On for Cattle at the Haarlem, Holland plant is expected to generate small quantities of isopropanol vapors and air-borne particulates; small amounts of dilute liquids, which will be generated primarily during cleanup; and small amounts of solids, which will also be generated primarily during cleanup.

Any air emissions from the process will be regulated by, and in compliance with, the State Rules and Regulations Act with regard to environmental pollution. These regulations are administered by the Haarlem Department of Environmental Control.

Any liquid wastes which result from manufacturing the final dosage form will be collected and treated with an activated carbon purification unit to remove ivermectin. The wastes will then enter the plant's general waste system which includes domestic sewage and will go via a neutralization pit (pH 6 to 8) to the municipal sewage system and ultimately to the municipal sewage treatment plant. This plant operates under the control of the Hoogheemraadschap Rijnland. MSD has a permit from the municipality for entering the sewage treatment plant with their plant-effluent. Spent activated carbon from the filter system will be collected in plastic bags, put into drums, and handled as described below for solid wastes.

Solid wastes resulting from production of the final dosage form, including spent activated carbon from the filtration system, will be combined with other plant trash and transferred via closed vehicle to the Rotterdam incinerator. A yearly permit for transport and incineration is issued by the owner of the Rotterdam incinerator under the laws regulating transport and processing of solid wastes.

Material Safety Data Sheets (MSDS) will be available onsite for all chemicals required by the Dutch Safety Law (Arbo Law) and the Dutch Safety Rules for Industry and Workshops. Employees associated with the formulation of IVOMEC® Pour-On will have appropriate MSDS available for their review (Section 16).

Workers will wear appropriate protective clothing such as gloves, goggles and aprons. In addition, workers will be given special training in how to handle the product so as to minimize their exposure. In addition, the exposure of the workers to ivermectin will be monitored in the following ways:

1) Blood test of all employees working on production of products containing ivermectin will be conducted whenever a new formulation is introduced into the factory.

2) Monthly swab test will be performed on equipment, floors and production bottles in the production area.

The manufacture will be regulated by and in compliance with the Dutch Safety Law (Arbo Law) and the Dutch Safety Rules for Industry and Workshops. The manufacture will also be regulated by and in compliance with the "Wet Algemene Bepaling Milieuhygiëne" which includes: the Public and Private Nuisance Act; Pollution of Surface Water Act; the Air Pollution Act; the Noise Abatement Act; the Drainage Sewer System Regulation; the Chemical Waste Act; the Waste Act; and, the Waste Regulation.

The maximum yearly market demand for ivermectin topical formulation for cattle is estimated to be 30 million doses. Based on the dosage rate of 500 mcg/kg, and on the assumption that the average weight of the animals treated will be 500 lb (227 kg), this corresponds to 3,405 kg ivermectin. It is reasonable to estimate that 30% of IVOMEC® Pour-On sales will replace the use of IVOMEC® Injection for Cattle. This will result in an estimate of incremental ivermectin use of 2,951 kg, worldwide. For comparison, this amount is 27 percent of the estimated amount of ivermectin produced during 1989 (11,000 kg).

Approval of this NADA will have no significant effect upon compliance with current emissions requirements at either Danville, Pennsylvania, Barceloneta, Puerto Rico, or Haarlem, Holland. All three locations are currently involved in the production of ivermectin and formulations containing ivermectin. The additional increment needed to meet the demand for the cattle topical formulation is not expected to significantly affect the environment.

b. <u>As a result of the use of IVOMEC® (ivermectin) Pour-On</u>

1. Dosing and excretion

The projected use of IVOMEC® (ivermectin) Pour-On for Cattle involves the topical administration of the drug at a dose level of 500 µg/kg body weight. Treated animals may be released to pasture or confined to feedlots. Generally, the cattle will receive only one dose of the drug; however, year-round parasite control programs could involve up to 3 or 4 treatments per year in young replacement stock.

In the case of cattle dosed with ivermectin in feedlots, the following calculations, based on the U.S. Environmental Protection Agency publication (Development Document for Effluent Limitations Guidelines and New Source Performance Standards for the FEEDLOTS - Point Source Category, U.S. Environmental Protection Agency, Washington, D.C. 20460, January, 1974) show the expected concentration of ivermectin and metabolites in the "Raw Waste" (manure) and the concentration in a field when the manure is spread as a fertilizer.

Attached is a flow diagram from the reference (loc. cit.) showing the daily raw waste produced in a typical feedlot operation in which a 270-kg calf entered the operation and in 130 to 180 days reached market weight of about 477 kg. During this period, the animal would be treated once with ivermectin at a dose level of 500 µg/kg.

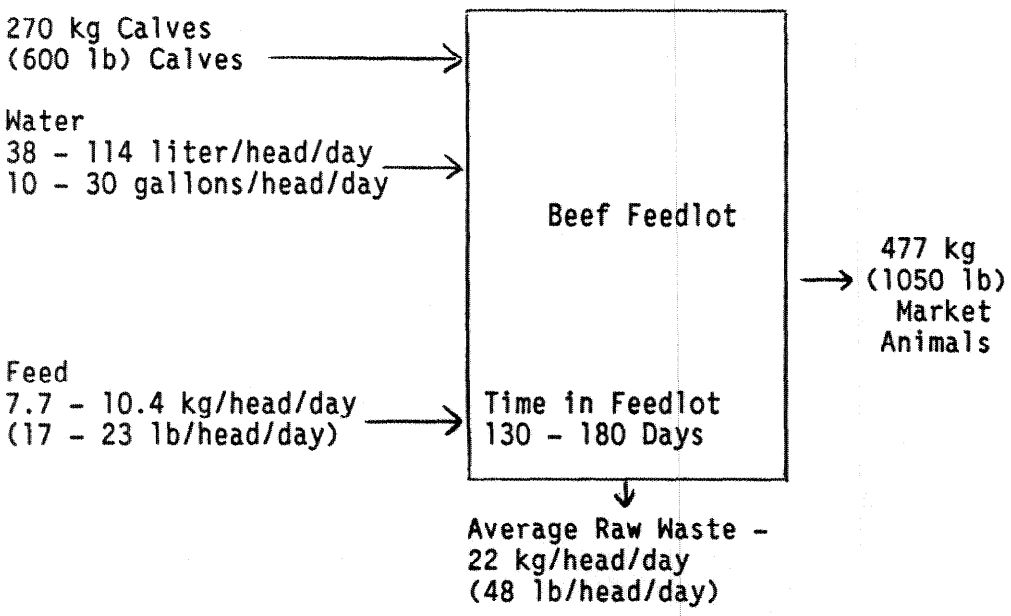


Figure 1
Typical Beef Feedlot Flow Diagram

In an indoor study (Halley, Green and Chiu, 1986, Sec. 16)* designed to examine the tissue depletion and metabolism of ivermectin dosed via the dermal route, three steers with an average weight of 228 kg were dosed topically with tritium-labeled ivermectin at 500 µg/kg in the IVOMEC® Pour-On formulation. Only about 4% of the administered radioactivity was excreted during the first 7 days post dose, and only about 11% was excreted during the first 42 days post dose. Average residue levels in feces peaked between days 3 and 7 post-percutaneous dose at ~80 ppb; they then decreased to 13 ppb by day 42, with a residue depletion half life of 12.7 days (Halley, Green and Chiu, 1986, Sec. 16).

More than half (60%) of the dose remained on the backs of these animals at 42 days, and of this, >70% was ivermectin (Halley, Taub and Wislocki, 1987, Sec. 16). Virtually all of the radioactivity in the excreta was in the feces, with only about 0.1% of the dose appearing in the urine through 7 days post dose (Halley, Green and Chiu, 1986, Sec. 16).

The milligram-equivalents of drug excreted per day from the three steers from days 4 through 42 were fit to an exponential decay equation. From the best-fit excretion half life, 12.7 days, and the extrapolated intercept, 0.84 mg/day at zero time, the amount of drug-residue excreted after any length of time can be calculated (Gibaldi and Perrier, 1975, Sec. 14)**. The cumulative percentages of dose excreted via the feces were calculated to be 4, 12 and 14%, respectively, following 7, 42 and 130 days. No further significant excretion of drug residue would be expected after 130 days. These numbers agree very well with the observed values, 4% through day 7 and 11% through day 42.

Thus, even over a 130-day period the quantity of ivermectin and its metabolites excreted into the environment will be but a small percentage of the topical dose. For a 270-kg steer, approximately 4% of the 135-mg dose excreted in the first 7 days, and only 14% excreted during the entire 130-day feedlot period, would lead to excretion of 5.4 mg and 18.9 mg, respectively, of drug-related compounds. The following calculations (based on 14% of drug and metabolites excreted) show the average concentration of ivermectin and its metabolites in the waste produced by a single animal over a 130-day period.

Weight of steer	270 kg
Dose of ivermectin	500 µg/kg
Weight of ivermectin-related compounds excreted (14% of dose)	18.9 mg
Waste produced per steer per day	22 kg
Total time in feedlot	130 days
Total waste produced per steer	2860 kg

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* Supporting information has been summarized and compiled in Section 16.
** Literature Cited, Section 14.

Concentration of drug and metabolites in waste:

$$\frac{18.9 \text{ mg excreted}}{2860 \text{ kg waste}} = \frac{0.007 \text{ mg}}{\text{kg}} = 7 \text{ ppb}$$

2. **Use of manure as fertilizer**

If the manure from the feedlot were spread on a field as fertilizer at a rate of 15 tons per acre, the total ivermectin plus metabolites would be **90 mg/acre** or **2.07 micrograms per square foot**:

Weight of ivermectin-related compounds excreted	18.9 mg
Waste produced per steer	2,860 kg

Concentration of ivermectin and metabolites in waste:

$$\frac{18.9 \text{ mg}}{2{,}860 \text{ kg waste}} \times \frac{1 \text{ kg}}{2.2 \text{ lb}} \times \frac{2{,}000 \text{ lb}}{1 \text{ ton}} = \frac{6.0 \text{ mg}}{\text{ton waste}}$$

at a rate of 15 tons/acre:

$$(15 \text{ tons/acre})\ (6.0 \text{ mg/ton}) = 90 \text{ mg/acre}$$

$$\frac{90 \text{ mg}}{\text{acre}} \times \frac{1 \text{ acre}}{43{,}560 \text{ sq ft}} \times \frac{1000 \ \mu\text{g}}{\text{mg}} = 2.07 \ \mu\text{g/sq ft}$$

When mixed into soil at a depth of 6 inches the **concentration of ivermectin plus metabolites would be 0.09 ppb.**

$$1 \text{ sq ft} \times 6 \text{ in depth} = (144 \text{ sq in})(6 \text{ in}) = 864 \text{ cu in}$$

$$(864 \text{ cu in}) \times \frac{16.4 \text{ cc}}{\text{cu in}} \times \frac{1.5 \text{ g}}{\text{cc soil}} = 21254 \text{ g soil}$$

$$\frac{2.07 \ \mu\text{g}}{21{,}254 \text{ g}} \times \frac{1000 \text{ ng}}{1 \ \mu\text{g}} = 0.09 \text{ ng/g soil} = 0.09 \text{ ppb}$$

Thus, raw wastes containing 7 ppb of drug-residue would lead to soil levels of only 0.09 ppb if spread at 15 tons/acre and plowed into the top 6 inches of soil. For excretion (5.4 mg) over the first 7 days, the corresponding values are **35 ppb of drug and metabolites in waste and 0.51 ppb in soil.**

It is instructive to compare (Table 1) these residue levels with those arising from steers dosed subcutaneously at 200 µg/kg as calculated in the Environmental Assessment of NADA 128-409, IVOMEC® (ivermectin) Injection for Cattle.

TABLE 1

ENVIRONMENTAL BURDEN
TOPICAL VS SUBCUTANEOUS DOSING

	Topical, 500 µg/kg		Subcutaneous, 200 µg/kg	
	7 d	130 d	7 d	130 d
Total Drug Dosed Per 270-kg Steer	135 mg	135 mg	54 mg	54 mg
Amount of Drug and Metabolites Excreted in Feces[a]	5.4 mg	18.9 mg	54 mg[b]	54 mg
Level of Drug and Metabolites in Feces	35 ppb	7 ppb	351 ppb	19 ppb
Level of Drug and Metabolites in Plowed Field (15 tons waste/acre plowed 6" deep)	0.51 ppb	0.09 ppb	5.1 ppb	0.27 ppb

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[a] 22 kg waste/steer/day
[b] "Worst-Case"

Clearly, the soil residue levels arising from topical administration of ivermectin (500 µg/kg) are less than those arising from a smaller dose (200 µg/kg) of subcutaneously administered ivermectin. Further, the soil levels are extremely low, especially in a 130-day collection of feces (much more likely than a 7-day collection). The environmental burden from the topical use of ivermectin (500 µg/kg) actually will be less than that at its subcutaneous use level of 200 µg/kg.

3. Metabolism

Ivermectin accounts for nearly 50% of the feces residue following subcutaneous injection of the drug (Halley et al., 1989. Sec. 14). The pathways for metabolism of ivermectin in the liver and fat are comparable for topically and subcutaneously dosed steers (Chiu and Lu, 1986, Sec. 16). As the metabolic profiles for the two routes of administration are similar, it can be assumed that ivermectin accounts for similar percentages of the feces residues following topical and subcutaneous administration. If the assumed metabolism were taken into account, ivermectin in feces and soil at 130-day post dose would constitute only 50% of the total residue values

presented in Table 1, i.e., 3.5 and 0.045 ppb, respectively. For the purposes of this Environmental Assessment, however, the feces residue is considered to be entirely ivermectin and the values used are 7 and 0.09 ppb.

7. Fate in the environment:

Information on the stability of ivermectin in soil and in aqueous extracts of steer feces and on its soil translocation were presented in the Environmental Assessment of NADA 135-008, IVOMEC® (ivermectin) Injection for Swine. Relevant sections of that Environmental Assessment have been summarized and are included herein as Section 17. The present assessment supplements this with additional information on the environmental fate of ivermectin plus supporting information on the environmental fate of avermectin B_1, which differs from ivermectin only in that avermectin B_1 bears a double bond at position 22,23 (Sec. 5). Ivermectin is produced from avermectin B_1 by catalytic reduction of this double bond.

a. Photodegradation

Halley (1990, Sec. 16)* used a high-pressure xenon arc lamp to simulate sunlight and calculated that ivermectin would photodegrade near the surface of open, flat bodies of water under clear skies in summer and winter sunlight with half lives of 12 and 39 hours, respectively. This rapid photodegradation in water should effect swift elimination of ivermectin from the aquatic environment. Based upon data from a preliminary study, ivermectin undergoes photodegradation as a thin, dry film on glass with an estimated T1/2 of about 3 hours in summer sunlight (Yeager and Halley, 1988, Sec. 16). Avermectin B_{1a} possesses an absorption maximum similar to that of ivermectin (Sec. 5), with less intense longer wavelength absorption at approximately 290 and 350 nm (Halley, 1990, Sec. 16), and photodegrades on soil TLC plates with a half life of 21 hours (Ku and Jacob, 1983a, Sec. 16). Rapid photodegradation is consistent with the rapid loss of avermectin B_{1a} from cotton leaves (Bull et al., 1984, Sec. 14)**.

b. Fate in feedlot runoff

A study to evaluate the environmental fate of ivermectin in cattle feedlots, requested by the FDA, was submitted to the Environmental Assessment for IVOMEC® (ivermectin) Injection for Cattle, NADA 128-409. A summary of this study can be found in Section 16 (Wallace, Wehner and Tait, 1985). This study (carried out in June) was designed

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* Supporting information has been summarized and compiled in Section 16.
** Literature Cited, Section 14.

to determine the potential for ivermectin runoff from a cattle feedlot following treatment of five steers (about 365 kg each) with ivermectin (200 µg/kg) via subcutaneous injection. Surface and subsurface water samples from the dirt feedlot pen (20x50 ft) were collected over a 28-day period following dosing and assayed for ivermectin using toxicity toward Daphnia as the readout. The water samples were also analyzed by HPLC for the H_2B_{1a} component of ivermectin. No ivermectin-related toxicity was observed, nor was any (10 ppt or greater) ivermectin found in the water samples by HPLC. A trace concentration (~1 to 2 ppb) of ivermectin was detected in one sample (top 3") of soil (28 day). Essentially all of the subcutaneously administered dose (a total of 365 mg for five steers, 73 mg per steer) would have been excreted (approximately 50% as ivermectin, 50% as metabolites) during this study into an area of only 1000 sq ft. Nevertheless, the runoff water showed no ivermectin-related toxicity toward Daphnia; further, HPLC demonstrated that H_2B_{1a} (major component of ivermectin) concentrations were below 10 ppt, the assay detection limit (and the Daphnia 48-hr NOEL). Ivermectin has been classified as "tightly bound" to soil [K_{oc} 12,578 with clay loam soil (Iowa)] and hence immobile (Halley, 1985, Sec. 16). Consequently, the possibility of translocation of ivermectin through soil from one site to another in the environment is remote. The tight binding to soil of the excreted ivermectin greatly attenuated the effective ivermectin concentration. It was also demonstrated that toxicity of ivermectin (Ostlind and Cifelli, 1980, Sec. 16) and avermectin B_1 (Forbis, 1989, Sec. 16) toward Daphnia is greatly attenuated (99%) in the presence of soil. These results agree with the known immobility of ivermectin (Halley, 1985, Sec. 16) and avermectin B_1 (Ku and Jacob, 1983a, Sec. 16) on soil. When ivermectin was partitioned between water and Iowa soil, a soil to water distribution of 333 was found, predicting that 99.7% of the drug would be bound, with only 0.3% in solution (Halley, 1985, Sec. 16).

c. Fate in rain washoff

1. Correlation of ivermectin washoff with soil K_{oc} value: It is conceivable that ivermectin could be washed from the backs of cattle treated with the pour-on formulation if they were exposed to rain shortly after dosing. The following precautionary statement, which appears on the back labels of marketed containers, mitigates against this possibility:

> **"Do not use when rain is expected to wet cattle within six hours after treatment."**

To further address this concern, a study was done to determine the extent to which ivermectin would wash from the backs of cattle if rain occurred six hours after treatment (Wehner et al., 1988, Sec. 16). This represents the extreme case with respect to timing of washoff consistent with the label. On the average, 0.6% (upper 95% one-sided confidence limit = 1.3%) of a topically-applied dose washed off each of

these 250-kg cattle exposed to 0.5 inch of rain, over 10 minutes, at 6 hours post- treatment, with a mean concentration in the washoff water of 133 ppb. Loss of such a small fraction of the dose is not unexpected, considering the nature of the pour-on formulation [~80% (v/v) isopropyl alcohol and ~20% (v/v) Crodamol CAP (cetearyl octanoate)]. The formulation is designed for rapid spreading following application; the isopropyl alcohol (boiling point = 82°C) evaporates quickly, usually within ten minutes, leaving the ivermectin distributed in the hair in the highly lipophilic or "greasy" Crodamol CAP. The octanol-water distribution coefficient for ivermectin is ~1650, hence, it is most unlikely that significant quantities of ivermectin would partition out of the Crodamol CAP and into rainwater on the back of a steer. Further, the solubility of Crodamol CAP in water (under saturation conditions) is only approximately 3 ppm, and thus very little of the Crodamol CAP would wash off (Cade, 1989, Sec. 16). Even any ivermectin not in the Crodamol CAP would be very unlikely to be removed by rainwater, as the solubility of ivermectin in water is only 4 ppm (McCauley, 1979, Sec. 16).

Correlation of the K_{oc} value obtained in the soil sorption/desorption study for ivermectin (K_{oc} of 12,578; Halley, 1985, Sec. 16) with the amount of ivermectin found in the rain washoff should further substantiate the low extent of washoff observed (average of 0.6% of dose, Wehner et al., 1988, Sec. 16). The calculation given below correlates the K_{oc} value and the washoff concentration, and the conclusion is that an average of 0.6% is a reasonable percentage of ivermectin to be washed off the back of a topically dosed steer by 0.5 inch of rain.

$$K_{oc} = \frac{K_d}{\%\ \text{organic carbon}} \times 100$$

Where: % organic carbon equals $\frac{\%\ \text{organic matter}}{1.72}$

As hair is 100% organic matter and the experimentally determined K_{oc} (Iowa clay loam) for ivermectin is 12,578 (averaging adsorption and desorption K_d values, which were similar; Halley, 1985, Sec. 16), then:

$$12{,}578 = \frac{K_d}{100/1.72} \times 100;\ K_d = 7{,}313$$

In this situation K_d = µg IVM/g hair ÷ µg IVM/g water and µg IVM/g hair = 774 ppm at 7 days post treatment in an indoor study (Halley, Taub and Wislocki, 1987, Sec. 16).

Solving for µg IVM/g water yields an ivermectin residue concentration in water of 0.106 µg/g, or 106 ppb, very close to the average value of 133 ppb observed in the runoff study.

Therefore, the amount of runoff from a steer at 6 hr after treatment does correlate with the experimentally derived K_{oc} value.

Another way to view the amount of ivermectin in the washoff is based on the water solubility of Crodamol CAP. As the latter, under saturation conditions, has a water solubility of ~3 ppm, a maximum of ~18 mg of Crodamol CAP would be expected to wash off an animal with 6 L of water. As calculated below, this is approximately 0.4% of the Crodamol CAP applied to a 250-kg steer.

One mL pour-on formulation per 10 kg bw, thus ~25 mL formulation per animal.

As Crodamol CAP is ~20% of the formulation, ~5.0 mL (~5.0 g) of Crodamol CAP per animal.

Thus, $\frac{\sim 18 \text{ mg}}{\sim 5{,}000 \text{ mg}} \times 100 \approx 0.4\%$

Because the isopropyl alcohol quickly evaporates, the ivermectin would be associated with the Crodamol CAP and ~0.4% Crodamol CAP would contain ~0.4% of the ivermectin, which correlates with the average of 0.6% washoff of ivermectin observed.

2. **Pasture/nearby stream rain washoff:** The calculated R_f for ivermectin on soil, based upon its K_{oc} value of 12,578, is 0.003 to 0.004 (Halley, 1985, Sec. 16). This is consistent with the immobility of avermectin on soil TLC plates with water as a solvent (Ku and Jacob, 1983b, Sec. 16). Because of the tight binding of ivermectin to soil and its low water solubility, only an insignificant fraction of the small amount of ivermectin washed off the backs of cattle and still in solution would be expected to move with water flowing across or percolating through land (grass-covered or barren) and then into a body of water. Even if ivermectin were to wash off onto compacted soil, some of the drug would bind to dust and any loose soil particulates, to the soil surface, to vegetation and to other organic matter such as dung. As the flow of ivermectin-containing water continued across additional soil, further binding would be expected to occur, resulting in continuous depletion of ivermectin from solution.

Based on the data from the wash-off study (Wehner et al., 1988, Sec. 16), the total average amount of ivermectin in washoff per 250-kg animal would be 714 µg in an average of 5.4 L of wash-off water. In a pasture situation with 50 animals congregated near a stream, a total of 35,700 µg of ivermectin would wash off in a 0.5-inch rain, for which the total water falling on one acre would be 50,600 liters. The

initial concentration of ivermectin in this volume would be approximately 710 ppt. If 99% of the ivermectin were to bind to soil and other organic matter as the washoff dripped onto the ground, the concentration would be reduced to 7.1 ppt before moving toward the water at the edge of the stream. The extent of on-land adsorption could actually be greater than 99%, for some additional binding would occur as ivermectin-depleted run-off water from next to the animals flowed toward the stream and encountered fresh surfaces in the pasture and on the stream bank. Although achievement of equilibrium (99% bound) does not occur instantaneously, based on the immobility of avermectin B_1 on soil TLC plates (Ku and Jacob, 1983b, Sec. 16), the binding process must be very rapid. If it were not, the avermectin B_1 would have been carried by the water solvent up the soil TLC plate, rather than remaining at the origin. By analogy, ivermectin (for which the calculated soil TLC R_f is 0.003-0.004, based on its K_{OC}; Halley, 1985, Sec. 16) coming off the back of a steer and contacting soil next to the animal would not be expected to be readily transported by water across soil/organic matter surfaces. Even given a very conservative concentration of 7.1 ppt entering a stream, adsorption of ivermectin in the run-off water by organic matter (soil, sediment) in the stream water at the edge would occur, possibly reducing the concentration by another 99% to as little as 0.071 ppt. Even if the in-stream adsorption removed only 95% of the ivermectin, the resulting concentration would be only 0.35 ppt. Considerable dilution would result from stream volume and flow, and input of ivermectin would cease soon after the rain stopped falling.

3. Direct introduction into a pond: Examination of a scenario in which ten 250-kg animals are standing in a pond during rainfall at 6 hr post dose also demonstrates that the likelihood of introduction of even very low levels of ivermectin into this aquatic environment is remote. A farm pond, one acre in area with an average depth of 4 ft, contains 174,000 cu ft of water, or 4.9×10^6 L of water. It is possible that at any one time 10 animals could be standing in the pond during the circumstances described above. Assuming that 0.75 mg of ivermectin were to wash off the back of each animal because of rainfall, 0.75 mg would be present in 4.9×10^6 L of water, leading to a maximum ivermectin concentration of 1.53 ng/L, or 1.53 ppt.

Binding of the ivermectin to suspended soil particulates in water clearly reduces its effective concentration, and it is reasonable to assume that in a muddy farm pond, in which cattle are stirring up the sediment, most ivermectin introduced would not be bioavailable. As at least 99% of the ivermectin would probably bind to soil particulates and other organic matter, its effective concentration in the pond water would be only 0.0153 ppt. Even in a most unlikely case, wherein one hundred 250-kg cattle at 6 hr post-topical dose crowd into the one-acre pond during the same rain shower, the effective ivermectin concentration resulting from rain-induced runoff would be only 0.153 ppt. In addition, ivermectin in the water would undergo photodegradation [with calculated half lives in summer and winter of approximately 12 and 39 hours, respectively (7.A.)], thus reducing its

aqueous concentration. One can also calculate† the minimum pond area which would accommodate 100 cattle standing in the pond before an effective concentration of 10 ppt would result from a single rainfall-induced runoff. This area is only 0.0153 acre, allowing but 7 sq ft per animal.

One can calculate the percentage of the topically-applied ivermectin that could wash off each of the 100 animals during one rainstorm without the effective ivermectin concentration in the one-acre pond exceeding 10 ppt. The result is 39.2% (0.6% / 0.153 ppt = X% / 10 ppt; X=39.2). [Or, 100% of the dose could wash off 39 animals!] If 0.5 inch of rain is necessary for each 0.6% of the dose removed, 32.7 inches of rain would have to fall on the cattle. A deluge of this magnitude would drop 3.31 x 10^6 L of water on a single acre, approximately one-half the original volume of the pond; tremendous dilution of the pond water would clearly result from the runoff from such a storm.

4. **Direct introduction into a slowly moving stream:** With respect to direct introduction of ivermectin into a slowly moving stream <u>via</u> washoff, consider ten 250-kg cattle standing in a stream 2-ft wide by 2-ft deep (0.7 m x 0.7 m) flowing at 1 mile/h (1.6 km/h = 26.7 m/min) during a 10-min, 0.5-inch rainfall. If 0.75 mg of ivermectin were to wash off each of the animals, this would result in the introduction of a total of 0.75 mg. As this would enter the stream during a 10-min period, the ivermectin would be diluted by 130,830 L of water (10 min x 26.7 m/min x 0.7 m x 0.7 m x 1000 L/m^3) flowing past the cattle. Assuming that 99% of the ivermectin were bound to suspended soil, sediment and organic matter, the concentration of bioavailable ivermectin in the stream would be 0.75 mg x 0.01 (free fraction)/1.3 x 10^5 L, or only 0.58 ppt. The ivermectin level would be further reduced by rain falling directly in the stream, surface runoff from the stream's watershed (50,600 L/acre) and diffusion during flow. Faster flowing streams would have greater dilution volumes and therefore lower ivermectin levels.

As was calculated earlier, 32.7 inches of rain would be required to wash off, from one hundred 250-kg cattle standing in the pond, the amount of ivermectin sufficient to result in an effective ivermectin concentration in the pond of 10 ppt. If the 32.7 inches of rain were to fall at the high precipitation rate of 0.5 inch of rain per 10 minutes on the 10 cattle standing in a stream, with a resulting loss of 0.75 mg ivermectin per animal per 10 minutes, 490.6 mg of drug would be

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† 100 animals x 0.75 mg ivermectin washed off per animal x 1% unbound to sediment = 0.75 mg or 0.75 x 10^6 ng effective mass in the pond. A pond containing 0.75 x 10^6 ng of ivermectin requires a volume of 0.75 x 10^5 L to result in a concentration of 10 ng/L (10 ppt). This is 1.53% of the volume (and thus 1.53% of the area) of the one-acre pond.

washed off into the stream during 654 minutes. If we then assume the same stream flow as above (130,830 L/10 min), the effective ivermectin concentration would still be 0.58 ppt:

$$\frac{490.6 \text{ mg} \times 0.01 \text{ (unbound)}}{654 \text{ min} \times 1.3\times10^5 \text{ L/10 min}} = 0.00000058 \text{ mg/L} = 0.58 \text{ ppt}$$

If even in the highly unlikely situation that 100 cattle were standing in the stream (with a total washoff of 4,906 mg of ivermectin), the ivermectin concentration of the stream would rise to only 5.8 ppt. As 3.31×10^6 L of water (about 26 times the stream flow volume of 1.3×10^5 L during 10 minutes) would fall on each acre of land in the area of the stream during the rainstorm, the resulting massive dilution by the land runoff water entering the stream would reduce the ivermectin concentration very significantly.

d. <u>Fate in soil and vegetation</u>

Ivermectin degrades rapidly outdoors in soil and soil/feces mixtures during the summer (T1/2 of 7 to 14 days) to more-polar compounds (Sec. 17), and this should preclude accumulation of ivermectin in soil. The rate of degradation is reduced in winter (T1/2 of 91-217 days).

Laboratory studies (Bull et al., 1984, Sec. 14) have shown that under aerobic conditions in soil [^{3}H]avermectin B_{1a} degrades to at least thirteen radioactive products; half lives for the drug (at 1 ppm) in Lufkin fine sandy loam, Houston clay and coarse sand soils are 14-18, 28-56, and 56 days, respectively. The major degradation product is an approximately 1:2.5 equilibrium mixture of 8α-hydroxyavermectin B_{1a} (an acetal) and the corresponding ring-opened aldehyde. At all treatment levels in Lufkin fine sandy loam, 90% degradation of [^{3}H]avermectin B_{1a} occurs within 168 days of exposure. Avermectin B_{1a} is strongly adsorbed by ditch-bottom sludge (Vonk and Van den Hoven, 1985, Sec. 16) and other soil types and is immobile (Ku and Jacob, 1983b, Sec. 16).

Low levels ($\leq$0.1 ppm) of radioactivity were found in the leaves and stems of cotton seedlings grown in Lufkin fine sandy loam containing 10 ppm of [^{3}H]avermectin B_{1a}; some radioactivity ($\geq$3 ppm) was found on the seedling roots, but whether it was absorbed or adsorbed was not determined (Bull et al., 1984, Sec. 14). Little radioactivity from labeled avermectin B_{1a} or its degradates was taken into the vascular system of the cotton seedlings. This low level of uptake is consistent with the observed lack of phytotoxicity for a number of other plant species grown in soil containing avermectin B_1 (Sec. 17). The observed lack of pronounced systemic insecticidal activity for ivermectin and avermectin B_1 also indicates little or no uptake of these compounds by plants (Sec. 17).

Tritiated avermectin B_{1a} was found to undergo rapid depletion and degradation when applied to the leaves of cotton plants (Bull et al., 1984, Sec. 14). Little more than half of the applied radioactivity was still present on the leaf at 2 days post treatment, and only one-third of this was avermectin. At this time roughly 5% of the applied radioactivity was found within the leaves. By eight days post treatment only 13% of the applied radioactivity was found on the leaf surfaces, and only 15% of this residue was avermectin; 8% of the dose was within the leaves. The authors suggest that the rapid loss of applied labeled avermectin B_{1a} and its instability are related to the known photolability of this compound. A non-polar photodegradation product of avermectin B_{1a} has been identified as the $\Delta^{8,9}$-isomer (Ku and Jacob, 1983, Sec. 16).

The slight uptake by cotton seedlings of radioactivity from soil containing [^{3}H]avermectin B_{1a}, reported by Bull et al. (1984, Sec. 14), suggests that if soil were to contain the close structural analog ivermectin, uptake of the latter by plants grown in the soil would also be minor. Data from Bull et al. (1984, Sec. 14) concerning lack of uptake of radioactivity by grass from a plot treated with [^{14}C]avermectin B_{1a} ant bait formulation also support this contention. In addition, studies comparing the pesticidal activities of directly applied <u>vs</u> systemically applied (soil) avermectin demonstrated little or no uptake of the agent from soil (Sec. 17).

Moye and coworkers (1987, Sec. 14) reported radioactive residues in crops (sorghum, lettuce, carrots and turnips) grown in three types of soil to which [^{14}C]avermectin B_{1a} had been applied 3 to 12 times at 0.025 to 0.030 lb/acre/application. Radioassay of the crops indicated a maximum total residue of 14 ppb. As only 4.4% of the total radioactive residue in a lettuce leaf was extractable with acetone, it is clear that most of the residual radioactivity is either chemically different from avermectin B_{1a} or present in a strongly bound form (probably incorporated into the vegetable matter as small molecules resulting from breakdown of the avermectin B_{1a}).

Iwata et al. (1985, Sec. 14) reported that the initial rate of avermectin B_{1a} degradation on citrus fruits and leaves is very rapid. Total residue dissipation half lives were 50 days (lemon leaves), 58 days (orange rind) and 36 days (lemon rind). Comparison of total radioactive residues with percentage avermectin B_{1a} showed continuing degradation of the actual avermectin B_{1a} present in the residues. Comparison of pulp and rind radioactive residues indicated lack of translocation from the rind into the edible portion of the fruits. Residue levels (total radioactivity) were less than 0.004 µg/g (limit of detection) in new growth leaves from tips of branches whose mature leaves had been immersed in a [^{3}H]avermectin B_{1a} solution (3 µg/mL) 91 days earlier. It is reasonable to assume that the extent of translocation (both leaf to leaf, and rind to pulp) of ivermectin would also be very slight. Ivermectin would also be expected to exhibit a short persistence on fruit surfaces because of photodegradation.

e. Fate summary

Photodegradation, combined with oxidative degradation in soil under aerobic conditions, will diminish the extent of environmental contamination by ivermectin. Runoff of ivermectin to surface water is unlikely to result in contamination and, as movement of ivermectin through soil is slight, contamination of surface and subterranean water is highly improbable. Binding of ivermectin to soil sediment in water greatly reduces its effective concentration. Based on the discussion of soil binding, soil metabolism and photodegradation, it can be predicted that ivermectin present in the environment would not be expected to undergo significant movement or translocation, and should not accumulate. Given its environmental fate characteristics, ivermectin will be readily eliminated from the aquatic environment.

8. Effect on the environment:

a. Aquatic toxicity

The effects of ivermectin, avermectin and related compounds upon a number of aquatic species (including *Daphnia*), as determined in laboratory tests, are reported in Table 2. Ivermectin and avermectin B_1 show comparable aquatic toxicity. However, ivermectin is more toxic to daphnids than is avermectin B_1. *Daphnia*, the freshwater aquatic species most sensitive to ivermectin, will be used for risk assessment purposes. The concentrations at which toxicities are observed in these tests should be regarded as "worst-case" values because factors (i.e., binding to soil and other particulate matter, and photodegradation) known to reduce exposure under field conditions are absent. Ivermectin and avermectin show comparable mammalian toxicity (Lankas and gordon, 1989, Sec. 14).

1. Toxicity toward *Daphnia*

a. Toxicity: The 48-hr LC_{50}, 48-hr NOEL and calculated 21-day MATC values for ivermectin toward *Daphnia* are 25, ~10 and 4 ppt, respectively (see Table 2). As indicated in 7.B., the presence of soil in the test system reduced the toxicity of ivermectin and avermectin B_1 toward *Daphnia*.

b. Feedlot/pasture/fertilizer: The feedlot runoff study involving subcutaneously dosed steers weighing 365 kg (Wallace, Wehner and Tait, 1985, Sec. 16)*, demonstrated that, even with five steers excreting a total of 365 mg of ivermectin-related compounds (73 mg/steer) into an area of only 1000 sq ft, the runoff water showed no acute toxicity toward *Daphnia*. Tight binding to soil of the excreted ivermectin greatly attenuated its toxicity toward this aquatic species.

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* Supporting information has been summarized and compiled in Section 16.

As the total fecal excretion of drug-related compounds is known to be lower with topical dosing than with subcutaneous administration of ivermectin (Table 1; 7 vs. 19 ppb, factor of 0.37), the likelihood of introduction of toxicologically significant amounts of drug-related compounds into the aquatic and/or terrestrial environments via runoff from manure following topical dosing of ivermectin is remote. If manure from topically dosed cattle were used as fertilizer, the already low nominal concentrations (see Table 1) would be expected to be reduced by soil binding to give maximum concentrations of unbound ivermectin residues of 5 and 0.9 ppt (7- and 135-day excreta, respectively) in water in direct contact with the fertilized soil. Any movement of unbound ivermectin into unfertilized soil would result in further binding and reduction in available ivermectin to levels below any environmental concern. Metabolites of ivermectin from cattle, sheep and swine (tested individually or as feces/soil column percolates) possess much less toxicity toward Daphnia than the drug itself (Table 2 and Sec. 17). Thus, the very low levels of total ivermectin-related residue in feces are most unlikely to pose an environmental hazard.

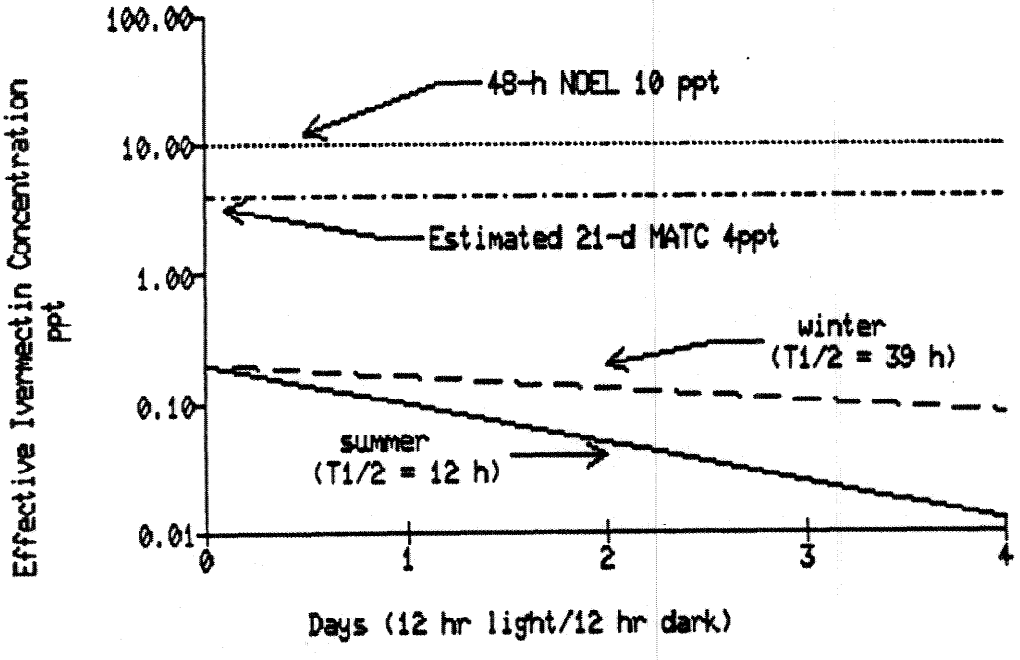
c. Pasture/nearby stream rain washoff: The rain washoff study with topically dosed steers weighing 250 kg (Wehner et al., 1988, Sec. 16) demonstrated an average loss of 0.6% of the applied ivermectin, or about 0.75 mg per steer. Because of the tight binding of ivermectin to soil, no toxic effect upon aquatic species would be expected to result from ivermectin washing off the backs of cattle, with the washoff then flowing across the land (continuously encountering fresh soil, with resulting adsorption and binding) and entering a body of water. Referring specifically to the pasture/nearby stream scenario (7.C.2.), it was calculated conservatively that the concentration of ivermectin would be only 0.35 ppt, which is well below the Daphnia 48-hr LC_{50}, 48-hr NOEL and calculated 21-day MATC values. Thus, no toxicity toward aquatic organisms will result by washoff of topically applied ivermectin from even a very large number of cattle standing near a stream during 0.5 inch of rain. Ivermectin remaining in the pasture would be degraded by sunlight and undergo aerobic oxidation in soil, attenuating any impact washed-off drug might have upon the environment.

d. Direct introduction into a pond: With respect to the pond scenario (7.C.3.) involving 100 cattle standing in a one-acre pond (a very high density) during the same 10-min rain (0.5 inch), the effective ivermectin concentration in the pond was only 0.153 ppt, well below the critical levels (i.e., the 48-hr LC_{50}, 48-hr NOEL and estimated 21-day MATC of 25, 10 and 4 ppt, respectively) for Daphnia. Based on the fate discussions, it is reasonable to conclude that, even in the most unlikely case of an extremely heavy rainfall: 1) dilution of washed-off ivermectin by pond water, 2)

the very strong binding of ivermectin to suspended soil particles, and 3) photodegradation will bring the effective concentration of ivermectin in a pond to well below its Daphnia 21-day MATC. The rate at which the ivermectin concentration would decrease, in summer and winter, based upon calculated photodegradation half lives of approximately 12 and 39 hours, respectively (Halley, 1990, Sec. 16), is illustrated in Figure 2. It is important to recognize that the initial concentration of 0.153 ppt is derived from the scenario involving washoff of 0.6% of dose from 100 cattle standing in a one-acre pond during a 0.5 inch rainfall and this value is well below critical Daphnia toxicity levels. Because of photodegradation, the already very low ivermectin concentration of 0.153 ppt should decrease rapidly, by factors of ~2 and ~16 (in winter and summer, respectively) within 4 days.

FIGURE 2

Comparison of Ivermectin 48-h NOEL and Estimated 21-d MATC for Daphnia with Effective Ivermectin Concentration in Farm Pond Water as Impacted by Photodegradation. Scenario Involves Wash-off of 0.6% of Dose from 100 Cattle Standing in Pond.



e. Direct introduction into a slowly moving stream: The stream scenarios (7.C.4.) yielded an effective ivermectin concentration of 0.58 ppt, well below critical concentrations for Daphnia. Thus, the possibility of toxicity to Daphnia, or to other less-sensitive aquatic species, from direct washoff of ivermectin from pour-on treated cattle standing in streams is remote. One-hundred cattle standing in the stream during a 32.7-inch rain storm would yield a concentration of 5.8 ppt without consideration of runoff from the watershed (3.31×10^6 L/acre). Taking into account the watershed runoff, the ivermectin concentration would undoubtedly fall below the calculated 21-day MATC for Daphnia of 4 ppt. The MATC is a measure of chronic toxicity based on a 21-day exposure, and runoff into a flowing stream would result in only transient exposure. Daphnia would be exposed to 5.8 ppt of ivermectin for only the 654 minutes required for 32.7 inches of rain to fall. As a NOEL of 10 ppt is found after 48-hr exposure, even with 100 cattle in a small stream, no toxicity to Daphnia would occur due to ivermectin.

As ivermectin is toxic toward Daphnia at very low concentrations, this Environmental Assessment has focused on this species. It is clear that the environmental fate characteristics of ivermectin, and the large dilution factors which would inevitably result from the heavy rainfall required to cause even small amounts of the drug to enter the environment, make it highly unlikely that environmental concentrations will reach levels toxic to any aquatic species, including Daphnia. Data in Table 2 also support the view that ivermectin-related compounds such as its monosaccharide and aglycone and feces/soil column percolates which contain ivermectin degradation/metabolites are much less toxic than the parent compound (based on 48-hr LC_{50} data for the former, and 48-hr NOEL data for the percolates). Avermectin B_1 is less toxic toward Daphnia than is ivermectin, and the known degradation products of avermectin B_{1a} (i.e., the $\Delta^{8,9}$ isomer and the 8α-hydroxy compound) are also much reduced in toxicity toward Daphnia compared to their parent compound (Forbis, Georgie and Burgess, 1985a and b, respectively).

2. Fish

a. Toxicity: Fish are at least 100-fold less sensitive to the toxicity of ivermectin than are Daphnia. The ivermectin 96-hr LC_{50} values (Table 2 and Sec. 17) for rainbow trout and bluegill sunfish are 3.3 and 5.3 ppb, respectively, far higher (factor of at least a thousand) than the extreme concentrations that might occur with ivermectin in ponds and streams because of the use of this drug as a pour-on for cattle. In general, the acute toxicity of avermectin toward fish [e.g., LC_{50} values of 3.6 and 9.6 ppb for rainbow trout (Sousa, 1981, Sec. 16) and bluegill sunfish (Wilson, 1981, Sec. 16), respectively] is approximately the same as that exhibited by ivermectin.

b. **Bioconcentration in sunfish:** The bioconcentration of [^{3}H]avermectin B_{1a} by the bluegill sunfish is modest and occurs gradually (Forbis and Franklin, 1983, Sec. 16). In water containing 0.099 µg of test compound per liter (0.099 ppb) the daily bioconcentration factor for whole fish was only 19 to 69, with an uptake tissue concentration for whole fish of 1.9 to 6.8 ppb; accumulation ceased by about day ten. A 95 percent clearance rate of radioactivity for whole fish was found for a 14-day depuration period; the whole-fish concentration dropped from 6.8 to 0.32 (day 14). This bioconcentration value of less than 100 and the rapid rate of depuration are favorable, as they demonstrate that concentration and retention of avermectin B_{1a} (and hence ivermectin) in fish should not be an environmental concern.

3. **Toxicity toward other aquatic species**

The toxicity of ivermectin and avermectin toward other aquatic species is also presented in Table 2. Ivermectin has a moderate effect upon the growth characteristics of Chlorella pyrenoidosa, a fresh water unicellular, non-motile chlorophyte, at the relatively high concentrations of 1 to 10 ppm (Halley et al., 1989, Sec. 14). Avermectin B_1 exhibits 14- and 9-day EC_{50} values of 3,900 and 100,000 ppb, respectively, with duckweed and a freshwater algae (Selenastrum capricornutum) (see Table 2). These concentrations are far greater than the estimated aquatic effective concentration for ivermectin of 0.153 ppt resulting from 100 cattle standing in a one-acre pond during rain (6.C.3.).

TABLE 2
EFFECT OF IVERMECTIN,
AVERMECTIN AND RELATED COMPOUNDS UPON AQUATIC SPECIES

COMPOUND	SPECIES	EFFECT	REFERENCES
Ivermectin	Daphnia	48-hour LC_{50} 25 ppt	Halley et al., 1989, Sec. 14
Ivermectin (H_2B_{1a}) monosaccharide	Daphnia	48-hour LC_{50} 400 ppt	Halley et al., 1989, Sec. 14
Ivermectin (H_2B_{1a}) aglycone	Daphnia	48-hour LC_{50} >17,000 ppt[a]	Halley et al., 1989, Sec. 14
Ivermectin	Daphnia	48-hour NOEL ~10 ppt	Halley et al., 1989, Sec. 14
Feces from ivermectin-dosed steer/soil column percolates[b]	Daphnia	48-hour NOEL ~3,200 ppt[c]	Halley et al., 1989, Sec. 14
Ivermectin	Bluegill Sunfish	96-hour LC_{50} 5.3 ppb	Sec. 17
Ivermectin	Rainbow Trout	96-hour LC_{50} 3.3 ppb	Sec. 17
Avermectin B_1	Daphnia	48-hour LC_{50} 340 ppt	Surprenant and LaBlanc, 1981, Sec. 16
Avermectin B_{1a}	Bluegill Sunfish	Estimated Lethal Threshold 6.7 ppb, NOEL 2.3 ppb (Dynamic 7-Day Toxicity Study)	Forbis, 1983, Sec. 16
Avermectin B_1	Carp	96-hour LC_{50} 42 ppb	Douglas and Pell, 1985 Sec. 16
Avermectin B_1	Channel Catfish	96-hour LC_{50} 24 ppb	McAllister et al., 1985 Sec. 16
Avermectin B_1	Mysid Shrimp	96-hour LC_{50} 22 ppt	Surprenant, D., 1988a Sec. 16
Avermectin B_1	Sheepshead Minnow	96-hour LC_{50} 15 ppb	Ward, 1985, Sec. 16
Avermectin B_1	Oyster	48-hour EC_{50} 430 ppb	Ward, 1983, Sec. 16
Avermectin B_1	Bluegill Sunfish	96-hour LC_{50} 9.6 ppb	Wilson, 1981, Sec. 16

TABLE 2 (Continued)

Avermectin B_1	Rainbow Trout	96-hour LC_{50} 3.6 ppb	Sousa, J.V., 1981, Sec. 16
$\Delta^{8,9}$-Avermectin B_{1a} (photochemical degradation product of avermectin B_{1a})	Daphnia	48-hour LC_{50} 14 ppb	Forbis et al., 1985a Sec. 16
8α-Hydroxyavermectin B_{1a} (aerobic soil degradation product of avermectin B_{1a})	Daphnia	48-hour LC_{50} 26 ppb	Forbis et al., 1985b Sec. 16
Avermectin B_1	Daphnia (Life Cycle)	21-day MATC 0.03-0.09 ppb ACR[d] 6.5	Surprenant, D.C., 1984 Sec. 16
Ivermectin	Daphnia (Life Cycle)	Estimated MATC 0.004 ppb	Calculated value[e]
Avermectin B_1	Mysid shrimp (Life Cycle)	28-day MATC 0.0035-0.0095 ppb ACR 3.8	Surprenant, D.C., 1988b Sec. 16
Avermectin B_1	Rainbow Trout (ELS)	MATC 0.52-0.96 ppb ACR 4.6	McAllister, W.A., 1986 Sec. 16
Avermectin B_1	Duckweed	14-day EC_{50} 3900 ppb	Hollister, 1981a Sec. 16
Avermectin B_1	Selenastrum capricornutum	9-day EC_{50} 100,000 ppb	Hollister, 1981b Sec. 16
Ivermectin	Chlorella pyrenoidosa	Maximum Growth Rate, No Effect at 10,000 ppb	Halley et al., 1989, Sec. 14

a LC_{50} could not be determined accurately as the highest concentration of the aglycone studied was 17,000 ppt.

b Feces from steers dosed with radiolabeled ivermectin were mixed with soil and applied to the tops of soil columns. Water was allowed to percolate through the columns; collected water contained no (<10 ppt) ivermectin, which binds to top of column.

c Because the low concentrations of ivermectin-related compounds in the feces/soil column percolates limited the extent of testing, sufficient data could not be collected to calculate the LC_{50} value accurately.

d ACR = Acute to Chronic Ratio; LC_{50}/MATC (Maximum Acceptable Toxicant Concentration).

e An estimated MATC for ivermectin was calculated from the 21-day MATC for avermectin (30 to 90 ppt; geometric mean of 52 ppt) and the ratio of the ivermectin and avermectin 48-hr LC_{50} values for Daphnia (25 and 340 ppt, respectively): X/52 = 25/340; X = 4 ppt.

f Early life stage, 60-day study.

b. Avian toxicity

The acute toxicity of avermectin B_1 (MK-936), when administered as a single oral dose, was determined for the bobwhite quail (Beavers, Jaber and Faulcon, 1983a, Sec. 16) and mallard duck (Beavers and Fink, 1981, Sec. 16). LD_{50} values were >2000 mg/kg and 85 mg/kg, respectively (see Table 3); at all dosage levels the mallards regurgitated immediately after dosing. With respect to sublethal effects, at the lowest dosage level employed in the mallard duck LD_{50} test (10.0 mg/kg), slight lethargy and loss of coordination occurred immediately following dosing and lasted through day one. At a dose rate of 17.8 mg/kg, prostrate posture and lower limb rigidity were evident, but all birds appeared normal by day two. These results are similar to those observed by Schepkens et al. (1985, Sec. 14), who treated pigeons with ivermectin to eliminate parasites; no adverse reactions following oral dosing at 4.3 mg/kg were reported, whereas at the higher dose rates of 17.4 to 20.3 mg/kg some impairment of equilibrium and vision occurred. The subacute LC_{50} values for avermectin B_1, when administered via the feed in an eight-day dietary study, were 3102 ppm for the bobwhite quail and 383 ppm for the mallard duck (Beavers, Jaber and Faulcon, 1983b and c, respectively, Sec. 16; Table 3). At the lowest concentration studied (162 ppm avermectin B_1) in the mallard, lethargy, reduced reaction to external stimuli, wing droop, loss of coordination and lower limb weakness were observed as sublethal effects within three hours exposure to the avermectin-containing diet. These effects lasted only during the on-drug phase of the study, and all birds appeared normal 24 hours following their return to the basal diet.

A definitive eighteen-week avian reproduction study was performed in male and female mallard ducks exposed to avermectin B_1 at levels of 3, 6 and 12 ppm in the diet for approximately 10 weeks prior to egg laying and continuing through the period (Beavers, Jaber and Hinken, 1987a, Sec. 16). The mallard duck was chosen as the test species as it is at least one order of magnitude more sensitive to the toxicity of avermectin B_1 than is the bobwhite quail. The ducks showed no treatment-related mortality, overt signs of toxicity or effects upon body weight or feed consumption. No statistically significant differences, compared to control birds, were noted in the number of eggs laid or in the number of hatchlings from live 3-week embryos. Thus, chronic exposure of mallard ducks to avermectin B_1 at concentrations of 3, 6 and 12 ppm in the feed did not affect overall reproductive success. This demonstrates a NOEL of 12 ppm. It was observed in a range-finding study (Beavers, Jaber and Hinken, 1987b, Sec. 16) that, at a concentration of 64 ppm of avermectin B_1 in the diet (6-week feeding), mallard ducks laid fewer eggs and the hatchability of the eggs laid was reduced. No other signs of sublethal toxic effects were observed, however, even at this high level. **The NOEL is 64 ppm for all except reproductive effects.**

TABLE 3

AVIAN SAFETY OF AVERMECTIN B_1
(MK-936) IN BOBWHITE QUAIL AND MALLARD DUCK

	BOBWHITE QUAIL	MALLARD DUCK
ACUTE, ORAL LD_{50}*	> 2000 mg/kg	85 mg/kg**
SUBACUTE EIGHT DAY DIETARY LC_{50}***	3102 ppm	383 ppm

* Single oral dose, birds observed for 14 days.

** Regurgitation observed at each dosing level tested.

*** Birds exposed to drug in feed for 5 days, then maintained on avermectin B_1-free diet for 3 days.

This low level of toxicity toward birds for a compound highly active against insects is not surprising, for the avermectins act within the peripheral nervous system of lower animals, by stimulating the release of the inhibitory neurotransmitter GABA from the presynaptic nerve terminals as well as by potentiating GABA binding to the post-synaptic receptors. With higher animals (e.g., birds), in which GABA serves as a neurotransmitter within the central nervous system (CNS), the blood-brain barrier is relatively impervious to avermectins, attenuating any toxic effect these compounds might have upon the CNS.

Henny et al. (1985, Sec. 14) found evidence that ingested famphur-containing hair from cattle treated topically with this organophosphate caused the deaths of magpies. Pica pica, the black-billed magpie, is found in the U.S. on the western Great Plains, in the Great Basin and Columbia Plateau regions and also in a narrow strip of eastern California (Bock and Lepthien, 1975; Kalmbach, 1927; Robbins et al., 1986, Sec. 14). The cause of death was held to be depression of brain cholinesterase activity (Henny et al., 1985, Sec. 14). It appears, based on the writings of Kalmbach (1927, Sec. 14) and Bent (1946, Sec. 14), that ingestion of cattle hair by magpies is probably not deliberate, but rather, incidental to the birds picking insects from the backs of cattle, eating flesh at wound sites or eating carrion. The possibility of secondary poisoning of raptors, occurring through the eating of disabled or dead magpies containing toxic concentrations of organophosphate insecticides, appears to be at least as much of an environmental concern as poisoning of the magpies

(Henny and coworkers, 1985, Sec. 14). Magpies are not found on any endangered species list. Concern has also been raised that eagles and other raptors are poisoned by eating carrion arising from livestock dosed topically with organophosphate insecticides (Henny et al. 1987, Sec. 14).

In a study carried out indoors with steers dosed percutaneously with [^{3}H]ivermectin at 500 µg/kg, approximately 774 µg of drug-related residue was present per gram of hair from the dosed area 7 days post administration; at 42 days post dose the residue was 522 µg/g of hair from the dosed area (Halley, Taub and Wislocki, 1987, Sec. 16). For the purpose of the calculations made below the following "extreme" assumptions are made:

* All ingested hair is from the dose site, i.e., from a zone several inches wide along the midline.

* Hair accounts for 12% of the daily dietary intake, based solely on gizzard contents.

* All of the residue is ivermectin.

It is more reasonable to assume that most of the plucked hair is from areas not dosed with ivermectin. The ivermectin formulation is applied to the backs of cattle at only 1 ml per 10 kg body weight. Ivermectin is thus applied to a narrow strip several inches wide along the back. If we assume that a magpie will pluck hair from a 1-ft wide zone along the back of a steer, about 20% of the plucked hairs will be coated with ivermectin. Based upon the known habits (Kalmbach, 1927; Bent, 1946; Linsdale, 1937; Sec. 14) of magpies, 12% of the daily diet as cattle hair is unreasonably high. Further, under outdoor conditions at least some of the ivermectin would undergo photodegradation (Yeager and Halley, 1988, Sec. 16).

Henny et al. (1985, Sec. 14) reported that cattle hair accounted for 12% of gizzard contents in magpies. If a 200-g magpie were to consume 20 g of matter in a day, and assuming hair is 12% of the diet, the bird would ingest 2.4 g of hair and thus 1858 µg (1.86 mg from 7-day residue) of ivermectin residue if all the hair were so contaminated. This amounts to a dose of 9.3 mg/kg, 10% of the acute oral LD_{50} in the mallard duck and a dose at which slight lethargy and loss of coordination might be expected. An intake of 1.86 mg of ivermectin per 20 g of diet is 93 ppm. This value is one-fourth that of the subacute 8-day dietary LC_{50} for avermectin B_1 in the mallard (383 ppm, Table 3), and about half of that (162 ppm) at which avermectin caused modest sublethal effects. As treatment-related effects of orally dosed avermectin upon reproductive performance were observed with the mallard duck at 64 ppm during a 6-week feeding period (Beavers, Jaber and Hinken, 1987b, Sec. 16), continuous dietary intake of ivermectin by magpies during the mating season might adversely affect magpie

reproduction. For this to occur, the birds would have to consume ivermectin, via ingestion of contaminated cattle hair, at a suitably high concentration and on a continuous basis during the breeding season. According to Kalmbach (1927, Sec. 14), magpies lay eggs before the middle of April in Colorado, Utah, California and southern Oregon. In Washington and Montana, the northern part of its range in the U.S., egg laying by the magpie begins about two weeks later. In these areas of the U.S., the most likely periods for use of ivermectin pour-on are late summer through the fall, the time of the year range cattle are accessible for dosing. Examination by region of sales of IVOMEC® Injection for Cattle reveals that sales in magpie-dwelling areas are 3- to 4-times higher in the fall than the spring. Sales of IVOMEC® Pour-On are expected to follow the same pattern. Thus, the magpie mating season (spring) does not coincide with the most likely period of ivermectin use in that part of the U.S. where magpies are commonly found. Problems with magpie reproduction are, therefore, not expected to arise because of use of this product.

Extensive and prolonged exposure of magpies to treated hair is unlikely. Plucking and ingestion of cattle hair by magpies, except incidental to their eating of cattle-borne insects, flesh at wound sites and carrion, is not discussed in the definitive works on this avian species by Kalmbach (1927, Sec. 14), Bent (1946, Sec. 14) and Linsdale (1937, Sec. 14). Further, Henny and coworkers (1985, Sec. 14)) reported only one sighting of a magpie perched on the back of a bovine during their study. One can speculate that the average value of 12% hair for magpie gizzard contents reported by Henny et al. (1985, Sec. 14) is unexpectedly high in view of the articles cited above. The 12% value probably represents an accumulation of hair ingested over a number of days. This seems reasonable, for Henny and coworkers (1985, Sec. 14) reported that in one magpie, gizzard content was 50% cattle hair. It appears highly unlikely that on a continuous basis half of a bird's diet would be cattle hair. If hair accumulation occurs, a daily diet consisting of 12% hair would therefore be too high. This would lead to an over-estimation of possible reproductive impairment (see below). Further, only about 20% of the hair would be ivermectin-containing. The likelihood of any toxic effects would also be lower if magpie sensitivity were closer to that of the bobwhite quail than to that of the mallard duck (Table 3).

If a magpie exposed to ivermectin were eaten by a raptor, the latter's secondary exposure to ivermectin would be minimal. Thus, if a 600-g raptor (e.g., red-tailed hawk) were to obtain its entire day's food intake (60 g) from a magpie (200 g) contaminated with 1.86 mg of ivermectin, on the average a raptor would ingest 0.56 mg of ivermectin. This is an "extreme" case, as it can be assumed that some of the ivermectin would have undergone excretion and metabolic degradation. A daily dietary intake of 0.56 mg ivermectin per 60 g feed is equivalent to only 9 ppm, below the NOEL of 12 ppm of

avermectin for the mallard as determined in an 18-week feeding study (Beavers, Jaber and Hinken, 1987a, Sec. 16). Even if we examine exposure from an acute toxicity perspective, at a raptor weight of 600 g the dose would be only 0.93 mg/kg, well below the 10 mg/kg of avermectin found to cause slight lethargy with the mallard, and far below the avermectin LD_{50} of 85 mg/kg for the mallard (Beavers and Fink, 1981, Sec. 16). Secondary poisoning of raptors would be most unlikely.

The assessment described above was generated using "extreme" assumptions: all ingested hair is from dosed area; such hair accounts for 12% of the daily dietary intake; all of the residue is ivermectin. One can reasonably speculate as follows for continuous daily dosing: only 20% of the ingested hair is from the dosed area of the animal's back, hair accounts for at most 6% of the daily dietary intake, and only half of the residue is ivermectin, the rest being inactive degradation products. Using these moderate assumptions reduces the ivermectin intake of a magpie (and hence a hawk) by a factor of twenty. This results in a dietary intake of approximately 5 ppm for the magpie, well below the avermectin B_1 NOEL of 12 ppm in the mallard (a value established in an 18-week feeding study). For a magpie-consuming hawk, this more reasonable assessment leads to a dietary intake of only 0.5 ppm.

Eagles and other raptors have died from exposure to organophosphate pour-on insecticides as a result of eating of carrion arising from dosed cattle (Henny et al., 1987, Sec. 14). However, this is highly unlikely to occur with IVOMEC® Pour-On (0.5 mg/kg). At 7- and 28-days post dose, total ivermectin residues in cattle liver, the tissue of highest residue, are 226 and 69 ppb, respectively, and the corresponding values for muscle are 8 and 2 ppb (Halley et al., 1986, Sec. 16). The following exposure assessment will use the "extreme" scenario of an eagle consuming only liver with residue of 226 ppb, of which 67% is ivermectin (Chiu and Lu, 1986, Sec. 16). Consider a 5-kg eagle consuming 500 g of a 7-day post-dose liver containing 151 ppb ivermectin as its entire day's intake. This is an oral dose of 76 µg of ivermectin, or 0.015 mg/kg body weight, which is far below the avermectin LD_{50} for the mallard, 85 mg/kg. Consumption of the 500 g of liver would result in a daily dietary intake of 0.15 ppm ivermectin, much below the avermectin dietary NOEL of 12 ppm in the mallard (Beavers, Jaber and Hinken, 1987b, Sec. 16).

It can be reasonably assumed that a carrion-eating eagle would preferentially take tissue from the underbelly of a carcass, rather than from the narrow-band dorsal dose site. The dorsal approach is made difficult by the presence of the spine and ribs. The ventral approach allows access to the internal organs and other easily obtained meat. With regard to the consumption of carrion hair by an eagle, the calculations given below using the following assumptions [500 g dietary intake includes 6% hair; dose site is ~1% of the surface area of a

steer† (thus ~1% of the ingested hair is from the dose site); 50% of the total residue (774 ppm) is ivermectin] demonstrate that the intake of ivermectin via this route would be much below any level of toxic concern.

500 g diet	x	6% of diet is hair	x	1% hair from dose site	x	50% % IVM in residue	x	774 µg/g = total residue

intake = 116 µg ivermectin

116 µg yields 0.023 mg/kg body weight
and 0.23 ppm in diet

Combined with the exposure resulting from the intake of liver tissue (0.15 ppm), total dietary exposure would be 0.38 ppm, only 3% of the NOEL observed for avermectin in an 18-week mallard reproduction study.

c. Dung pats

A publication by Wall and Strong (1987, Sec. 14) discusses the possible environmental impact of excreted ivermectin upon dung-dependent insects and fecal pat degradation. Using data based upon continuous ruminal dosing (experimental, non-commercial bolus) of ivermectin to cattle at 40 µg/kg/day, they concluded that degradation of manure pats was prolonged and populations of dung-degrading insects in the pats were decreased. They speculated that ivermectin treatment could lead to an increase in the amount of pasture land fouled by dung. Assuming excretion of ~40 µg/kg/day of ivermectin and metabolites by the bolus-fitted animals, Strong and Wall (1988, Sec. 14) estimate a steady state fecal residue concentration of ~400 ppb. This level is much greater than the observed peak of ~80 ppb total residue during days 3 to 7 in the percutaneous administration (500 µg/kg) study (Halley et al., 1989, Sec. 14) described earlier (6.B.1.). In that study, fecal residues decreased to 13 ppb by day 42 with a depletion half life of 12.7 days. Wall and Strong (1987, Sec. 14) indicate that continuous ruminal dosing of ivermectin "is likely to have a more pronounced insecticidal effect in dung than injection, because the bolus may remain active for many months releasing much of its ivermectin directly into the gut and into the feces." Thus, any effect topically

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†Surface area (m^2) = $(0.13 \times \text{wt in kg})^{0.56}$ (S. Brody, 1964, Sec. 14)

$(0.13\ m^2/kg \times 365\ kg)^{0.56} = 8.7\ m^2$

0.060 m width of dose site	x	1.5 m length of dose site	=	$0.09\ m^2$; $0.09\ m^2/8.7\ m^2$ ≈1%

dosed ivermectin might have upon dung-dependent fauna and manure persistence would be expected to be far less that that suggested by Wall and Strong (1987, Sec. 14).

Strong and Wall (1988, Sec. 14) recently reported toxicity of ivermectin upon dung-breeding insects. Ivermectin was added to manure from untreated cows to achieve concentrations of 500, 250 and 125 ppb ivermectin. Dung insects colonized the control pats and those containing up to 500 ppb ivermectin. Larval Scarabaeidae were found in pats containing 0 and 125 ppb; no larvae were found in pats containing 250 or 500 ppb. Some Diptera, however, were unaffected by concentrations of ivermectin up to 500 ppb. It is evident that the total residue levels in feces from topically dosed steers (~80 ppb; Halley et al., 1986, Sec. 16) are below the ivermectin concentrations found by Strong and Wall (1988, Sec. 14) to be toxic to dung beetles and dung flies, and much below the residue level these authors predicted for the experimental bolus (~400 ppb). Further, only approximately one-half of the residue is expected to be ivermectin (the other half being less bioactive metabolites and degradates), based upon data from subcutaneous and oral dosing of cattle, sheep and swine (Halley et al., 1989, Sec. 14).

With respect to the effect of ivermectin on the degradation of dung pats, McKeand et al. (1988, Sec. 14) found, in a preliminary trial, that the breakdown rates for dung pats from untreated calves and calves treated with IVOMEC® Pour-On (500 µg/kg) were similar. The treated calves were dosed three times, "after three, eight and thirteen weeks on grass". Pats were randomly selected one week following the final treatment, and decreases in pat diameter, depth and weight measured for nine weeks. Although not a definitive study, it is supportive of the opinion that IVOMEC® Pour-On fecal residues are not expected to alter the degradation rate of dung pats. Schmidt (1983, Sec. 14) reported that manure from cattle given a single injection of ivermectin at 200 µg/kg appeared to disintegrate at a rate similar to that of manure from uninjected controls. He concluded that ivermectin treatment should not cause pasture fouling. Schmidt (1983, Sec. 14) also found that emergence of several insect species (Diptera), endemic to Texas, was reduced in manure of ivermectin-treated cattle. Coleoptera (beetles) were not examined. Commenting on this experiment, Strong and Brown (1987, Sec. 14) suggest that dung-degrading beetles would not be killed under the conditions of the Schmidt (1983, Sec. 14) study. This is because manure from animals dosed <u>via</u> injection should contain less drug-related residue than that produced by the higher dose used by Wall and Strong (1987, Sec. 14). Dung from IVOMEC® Pour-On dosed animals contains much less ivermectin residues than dung from animals receiving IVOMEC® Injectable (see Table 1). The available body of evidence offers convincing support for the contention that ivermectin residues in feces from topically dosed cattle will have no detrimental impact upon dung pat degradation or dung-dependent insects.

d. Other

An overview of the pharmacology of ivermectin and information on the toxicity of ivermectin to soil microbes, plants, various aquatic organisms, nematodes, arachnids, insects, and annelids, as well as a literature review, can be found in the summary of the Environmental Assessment for IVOMEC® (ivermectin) Injection for Swine (Sec. 17). The present Environmental Assessment supplements this with recent information on ivermectin and supporting information on avermectin B_1. Summaries of these reports can be found in the Section 16.

The lack of phytotoxicity or other adverse effects on plant growth by avermectin B_{1a} has been demonstrated with avermectin B_1 and three analogs in approximately eighty greenhouse and field studies with numerous plant species (alfalfa, apples, cabbage, collards, corn, cotton, cucumbers, grapefruit, lima beans, oranges, peaches, pears, peanuts, potatoes, and sweet corn) at a wide variety of foliar and soil application rates (Sec. 17). The soil application rates ranged from 1650 to 33,000 times greater than would arise from application of manure from cattle dosed topically at 500 µg/kg body weight, i.e., manure application rate of 15 tons/acre, or 90 mg ivermectin residue/acre. Slight stunting of tomato plants was noted in one field trial when avermectin B_1 was applied at 136 g/acre; however, in two other trials conducted by the same researcher under similar conditions and at up to 10-fold higher avermectin soil-incorporation rates no phytotoxicity was observed. Given the low concentration of ivermectin residues in soil fertilized with manure from drug-treated steers (0.09 ppb), no phytotoxic effects would be expected. Any potential effect the low concentrations of ivermectin or its metabolites in soil might have upon plants would be greatly diminished by degradation of ivermectin in the soil and its tight binding to soil.

Both ivermectin and avermectin are toxic toward a wide variety of agricultural pests including the Mexican bean beetle, Southern army worm, aphids, and mites. The effect of ivermectin upon animal ectoparasites including flies, fleas, lice, ticks, and mites has also been determined (Fisher and Mrozik, 1984, Sec. 14). A review article by Strong and Brown (1987, Sec. 14) discusses the avermectins in insect control.

Avermectin B_1 has no effect upon nitrification in humic sandy or loam soils at up to 0.4 mg/kg soil, or 0.4 ppm (Barug and Van Agteren, 1985, Sec. 14). There was no effect upon nitrification or respiration (Halley et al., 1989, Sec. 14) for soil containing 30 ppb of fecal ivermectin and metabolites from subcutaneously dosed (300 µg/kg) steers. These are much greater concentrations than would be found (0.09 ppb) in soil fertilized with manure from steers dosed topically with ivermectin.

Avermectin B_1 was found to impair the total gas production and the methane production of anaerobic methane-forming bacteria above a concentration of 1000 mg/L (Hanstveit, et al., 1985, Sec. 16) (1000 ppm, the NOEC). The EC_{50} for total gas production was determined (by extrapolation) to be >>3200 mg/L; a significant inhibition of methane production rate could not be detected. These are concentrations far above any anticipated to arise in the environment from topical application of ivermectin to cattle.

The LC_{50} earthworm toxicity for ivermectin is 315 mg/kg soil (315 ppm) and the corresponding 96-hr NOEL is 12 ppm (Halley et al., 1989, Sec. 14). These concentrations are much greater than those expected to occur in soil fertilized with ivermectin-containing feedlot cattle waste at 15 tons/acre.

e. Effects summary

Because of 1) the limited amount of ivermectin introduced into the environment through its use as a pour-on anthelmintic for cattle, and 2) its rapid elimination from the environment, there will be no undesirable, adverse effect of this drug with respect to aquatic species, avians, dung fauna or other life forms of environmental concern.

f. Handler safety considerations

IVOMEC® Pour-On contains isopropanol (q.s. to volume), crodamol CAP (20% v/v), triethanolamine (.05% w/v) and ivermectin (0.5% w/v) (See Material Safety Data Sheet, Sec. 16).

The containers and delivery devices for IVOMEC® Pour-On have been chosen in large part because they minimize exposure of the operator to the formulation. The product is available in either bottles or packs. Each bottle is accompanied by a contained metering device which is threaded onto the bottle after the tamper-evident screw cap used for shipping has been removed. The metering device is equipped with a ratchet at its base which assures that it does not unscrew during use. The device is totally enclosed except for a drip-proof spout on its top and for a small vent hole, which is located on its top opposite from the drip-proof spout. The following label instructions minimize the risk of exposure to the operator:

ADMINISTRATION:

Attach the metering cup to the bottle.

Set the dose by turning the top section of the cup to align the correct body weight with the pointer on the knurled cap. When body weight is between markings, use the higher setting.

Hold the bottle upright and squeeze it to deliver a slight excess of the required dose as indicated by the calibration lines.

By releasing the pressure, the dose automatically adjusts to the correct level. Tilt the bottle to deliver the dose. The off (stop) position will close the system between dosing.

When the formulation is provided in packs, the label instructions are as follows:

ADMINISTRATION:

Connect the dosing drencher to the collapsible pack as follows:

Attach the open end of the draw-off tubing to the dosing equipment. (Because of the solvents used in the formulation, only the Protector Drench Gun from Instrument Supplies Limited, or equivalent, is recommended. Other drenchers may exhibit compatibility problems, resulting in locking, incorrect dosage or leakage.)

Attach draw-off tubing to the cap that has the stem. Replace the shipping cap with the cap having the draw-off tubing. Tighten this draw-off cap using the enclosed cap wrench.

Gently prime the drencher, checking for leaks.

Follow the manufacturer's directions for adjusting the dose of the drencher.

As was the case for the bottles and their metering device, the dosing system is enclosed and the only time the formulation is exposed to the environment is when the formulation is squeezed from the drencher gun onto the back of the animal.

It should also be added that two springs encircle the draw-off tube for the pack. One is intended to be pushed over the male fitting of the drencher gun and the second is intended to be pushed over the male fitting on the cap which is screwed onto the pack. In these positions, the springs serve two functions: (1) they prevent the tube from crimping at the fitting; and (2) they lock the tube to the fitting. This second function is relevant to operator safety since it assures that there is virtually no chance of the draw-off tube being inadvertently pulled from a fitting and thereby producing a spill of the formulation.

Finally, it should be noted that the dosage volume is very small relative to the size of the animal (1 ml per 10 kg). When applied to the back of a cow as per instructions the formulation spreads to form a band which is about 6 cm wide. Thus, there is virtually no chance that the formulation will run-off the animal and onto the operator.

The following precautionary statements on the label of IVOMEC® Pour-On provide additional protection for the operator:

> **"This product should not be applied to user or others because it may be irritating to human skin and eyes and may be absorbed through the skin. To minimize accidental skin contact, the user should wear a long-sleeved shirt and rubber gloves. If accidental skin contact occurs, wash immediately with soap and water. If accidental eye exposure occurs, flush eyes immediately with water and seek medical attention."**

For products of this type, the hands are at the greatest risk for exposure and the efficacy of rubber gloves in reducing exposure to the hands is well documented by studies with insecticides. For example, an exposure study using the insecticide abamectin shows that a "mixer-loader" (i.e., the individual who dilutes concentrate and loads the tank of the sprayer) was exposed on his hands to an arithmetic average of 10,597 ng active ingredient per each gram active ingredient handled (Grosso and Dybas, 1986, Sec. 16)*. When rubber gloves were worn, exposure to the hands was reduced by more than 99% to 52 ng active ingredient per gram handled.

The mixer-loader provides a useful surrogate for an individual dispensing IVOMEC® Pour-On from bottles since in both cases the key motion is a pouring motion. In the Grosso and Dybas (1986, Sec. 16) study, the mixer-loader had an unprotected whole body exposure rate of 14.11 µg active ingredient per gram active ingredient handled when the rate was calculated as a geometric mean. Wearing long pants, long sleeve shirt, and rubber gloves and washing hands at the end of a four-hour shift reduced the geometric mean exposure rate by more than 95% to 554 ng per gram handled. The label for the pour-on recommends wearing a long-sleeve shirt and rubber gloves, and in the U.S. long pants are customary when working with cattle. Washing of the hands before the mid-day meal or at the end of the work day is also customary, especially when working with cattle. Thus, 554 ng per g of active ingredient handled is an appropriate estimate of the rate of exposure to the pour-on.

For the sake of assessing exposure, it is assumed that an individual in one day doses 500 cattle each weighing 250 kg. This individual uses 12.5 L of IVOMEC® Pour-On which contains 62.5 g of ivermectin. If one calculates exposure from the exposure rate of 554 ng of active ingredient per gram handled (i.e., with protective clothing and washing

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* Supporting information has been summarized and compiled in Section 16.

of hands), the estimated exposure is 34.6 µg, which for a 60-kg individual corresponds to a dose rate of 0.58 µg per kg.

Ivermectin has been tested for acute oral toxicity in a variety of laboratory animal species (Lankas and Gordon, 1989, Sec. 14)**. Acute toxic effects are characterized by signs of CNS toxicity including tremors, mydriasis, and lethargy. The acute oral LD_{50} values range from about 80 mg/kg in dogs to about 30 mg/kg in mice. The dermal LD_{50} values for ivermectin following 24-hour occluded exposure in rabbits and rats are 406 mg/kg and > 660 mg/kg, respectively. The percutaneous absorption of ivermectin in the IVOMEC® Pour-On for Cattle formulation is discussed in more detail below.

The potential for systemic oral toxicity of the pour-on product due to ivermectin, the active ingredient of the pour-on, is considered to be low. The oral LD_{50} of ivermectin in mice is approximately 30 mg/kg. When IVOMEC® (ivermectin) Pour-On was given orally to mice, its oral LD_{50} was found to be approximately 5 ml/kg which is equivalent to 25 mg/kg of ivermectin (Lankas, Bokelman and Scolnick, 1986, Sec. 16). Thus, the excipients in the pour-on do not potentiate the toxicity of ivermectin.

In assessing the toxicity of ivermectin, it is important to note that rodents, and mice in particular, are poor models for predicting effects of ivermectin in humans. For example, doses of ivermectin of 0.2 mg/kg produce clinical signs of drug effects (tremors and ataxia) in mice (Lankas and Gordon, 1989, Sec. 14). This dose (0.2 mg/kg) of ivermectin (MECTIZAN®) is used to treat onchocerciasis infections in humans. To date, over 100,000 people have been treated for onchocerciasis (0.15 - 0.2 mg/kg) with no serious drug-related adverse effects (Greene et al., 1989, Sec. 14). MECTIZAN® is approved for use in more than 20 countries internationally.

A comparison of acute exposure data in rhesus monkeys with humans suggests that primates are a better model for predicting the effects of ivermectin exposure in humans. In monkeys the minimum acutely toxic oral dose is 2 mg/kg based on a 25% incidence of emesis in treated animals (Lankas and Gordon, 1989, Sec. 14). Peak plasma levels at this dose were 110 ng/ml or about 5-fold the human therapeutic plasma concentration. Doses of 8-24 mg/kg in monkeys produced mydriasis and sedation in addition to emesis with no deaths, despite plasma levels up to 680 ng/ml. These signs are similar to those reported in a carefully documented case of a child after accidental ingestion of about 8 mg/kg ivermectin. Emesis, mydriasis, and sedation were reported in this individual followed by complete recovery. Therefore, the primate is a better model for predicting the effects of human exposure to ivermectin than rodents. In addition, a 2-week repeat dose study in monkeys with ivermectin administered at dosage levels up to 1.2 mg/kg/day produced

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** Literature Cited, Section 14.

no evidence of toxicity. For comparison, this dosage level is equivalent to a daily intake of over 14 ml of the topical formulation for a 60-kg individual. Therefore, the potential for toxicity after accidental oral exposure to this formulation is low.

Developmental toxicity studies conducted with ivermectin in rats, rabbits, and mice have shown that the drug is not selectively toxic to the fetus. No-effect levels for embryo/fetal toxicity were at or near those that produced severe maternotoxicity and even death in some dams (Lankas and Gordon, 1989, Sec. 14). Therefore, a risk assessment for developmental effects based on maternal exposure will provide even greater safety margins for developmental toxicity. This is supported by target animal safety studies conducted in a variety of domestic animal species treated at 2-fold or 3-fold the recommended use level of ivermectin with no evidence of developmental toxicity. In addition, extensive clinical use of ivermectin in these same species with over a billion doses administered to cattle, sheep, horses, swine, and dogs has confirmed the safety of this drug in pregnant animals.

The risk of systemic toxicity to users of the topical formulation, following accidental dermal exposure, is low based on safety studies conducted in rabbits and miniature swine. In rabbits the formulation was applied at a dose of 2.5 ml/kg over about 10% of the body surface area and occluded for 24 hours to maximize percutaneous absorption (Lankas, Bokelman and Scolnick, 1986, Sec. 16). No signs of systemic toxicity were observed in any of the treated animals. Therefore, in a species with consistently greater skin permeability to a variety of agents compared to humans, no adverse effects were noted at a human equivalent dose of 150 ml spread over 1,800 cm^2 surface area.

The potential of the IVOMEC® (ivermectin) Pour-On for dermal irritation was evaluated in Hanford mini-pigs, whose skin has been shown to be similar to human skin with regard to percutaneous absorption (Bartek, et al., 1972, Sec. 14). To determine the effects of repeated daily exposure, a 29-day dermal irritation study in Hanford mini-pigs was conducted in which the animals were exposed dermally with 5 ml of either the ivermectin formulation (0.5% ivermectin), the vehicle only or normal saline for a 6-hour semi-occluded exposure each day for 28 consecutive doses (Lankas, Bokelman and Scolnick, 1986, Sec. 16). This treatment regimen was designed to simulate repeated dermal exposure which could potentially occur in persons treating large numbers of cattle over a prolonged interval in a species with skin permeability similar to humans. No treatment-related physical signs of toxicity were noted in any of the animals on study at a human equivalent dose level of about 15 ml (72 mg of ivermectin) spread over a 300 cm^2 surface area. A slight, treatment-related erythema without edema at the application site occurred in both the ivermectin formulation and its vehicle control group. This irritation only became evident after 3 weeks of daily exposure and was confirmed histologically in the affected animals as very slight or slight focal

dermatitis. Based on this relatively weak response after repeated and prolonged daily exposure, it appears that the ivermectin cattle topical formulation poses a minimal risk of causing dermal irritation in people. Based on the above dermal studies and the relatively large ratios of acute dermal LD_{50}/acute oral LD_{50} values of >13 and about 20 in rats and rabbits, respectively, the dermal absorption of ivermectin appears to be low.

Additional information on the potential for percutaneous absorption of ivermectin can be found in a dermal penetration study conducted in rhesus monkeys with avermectin B_{1a} (Wislocki et al., 1988, Sec. 14). Avermectin B_{1a} is the precursor for the synthesis of ivermectin B_{1a}, differing from the latter in being unsaturated at the 22,23 position. Based on high molecular weight, similarities in structure, and biological activity, the percutaneous absorption of avermectin is likely the same as ivermectin.

To determine the percutaneous absorption of avermectin, plasma levels of radioactivity were determined in a group of four monkeys after both an i.v. dose and a dermally applied dose of 300 ug/monkey spread over a 6 cm^2 area for up to 10 hours. A comparison of plasma levels in the dermal exposure group to those achieved following i.v. treatment (representing 100% absorption) gives the percentage of the dose absorbed percutaneously. The tritiated-avermectin B_{1a} was applied to the skin in an isopropanol:water (6.7% isopropanol) suspension or in acetone. Topical exposures of 10 hours were done with collection of plasma, feces and urine to determine areas under the plasma concentration-time curve (AUC) and total dose recovered. Each monkey received the drug intravenously to establish its individual pharmacokinetic parameters, and after a 6-week wash-out period, the animals were retreated dermally with each animal serving as its own control.

When the monkeys were treated i.v., more than 96% of the administered dose was recovered from feces, whereas with dermal application greater than 99% of the dose was recovered at the topical site of application. A comparison of the AUC values confirmed these results by indicating that only about 0.5% of the dermally applied dose was absorbed during a 10-hour exposure for both vehicles. The poor penetration of avermectin B_{1a} through skin is consistent with its relatively high molecular weight (873) and high lipophilicity, preventing it from penetrating into the plasma compartment.

The dermal absorption of abamectin (ivermectin) through monkey skin, which is similar to human skin regarding percutaneous absorption (Wester and Maibach, 1975, Sec. 14), was found to be about 0.5% after 10 hours. The use of adjuvants such as crodamol in the topical formulation may potentially increase absorption of ivermectin through skin. This conclusion is based upon studies designed to optimize percutaneous absorbtion, using a variety of penetration enhancers,

which demonstrate that increases of up to 5- to 10-fold are rarely achievable in practice. However, based on data with other agents, increases in absorption of greater than 10-fold appear unlikely (Barry, 1985, Sec. 14). However, assuming a 10-fold increase from 0.5 to a maximum of 5% dermal absorption, exposure of handlers to about 50 ml spread over 1,000 cm^2 for 10 hours would result in a dose equivalent to the therapeutic oral dose in humans (Greene, et al., 1989, Sec. 14).

A crude estimate of the low bioavailability of ivermectin after dermal exposure to the topical formulation can be derived from comparison of peak plasma levels of drug following oral or dermal dosing in male rats. In rats treated with 0.3 mg/kg orally, peak plasma levels were 16 ng/ml compared to 0.8 ng/ml after treatment with the topical formulation at 0.5 mg/kg (Eline and Chiu, 1987, Sec. 16).

Under recommended conditions of use, exposure to handlers of the ivermectin topical formulation will be negligible, i.e., about 0.6 ug/kg based on the previously discussed worker exposure study (Grosso and Dybas, 1986, Sec. 16). Even with repeated daily exposure to this amount of formulation, a steady-state plasma level would be reached after about 3 days based on the 13-hour plasma half-life of ivermectin in humans. Using the 0.6 ug/kg/day exposure, a dermal penetration factor of 5% and the therapeutic oral dose in humans of 0.15 mg/kg/day, a safety margin of greater than 2,400-fold can be calculated assuming 50% bioavailability of the oral dose. Therefore, the risk of toxicity due to accumulation of ivermectin after low level dermal exposure to handlers would be minimal, and as shown above, acute dermal exposure to relatively large volumes up to 50 ml would not be toxic based on the low dermal absorption and safety of ivermectin in humans.

The ocular irritation potential of the ivermectin cattle topical formulation or vehicle alone was determined in rabbits (Lankas, Bokelman and Scolnick, 1986, Sec. 16). Both treated groups were subdivided into either rinsed (tap water rinse after 20-second exposure) or unrinsed (60-second exposure). Similar signs of ocular irritation consisting of scleral injection, chemosis, and a clear discharge were produced by either the ivermectin-containing formulation or the vehicle in both the rinsed and unrinsed groups. For both the pour-on formulation and its vehicle, the rabbit's eyes returned to normal within 4 days when washed 20 seconds after exposure and within 4 to 7 days when not washed. Therefore, following accidental eye exposure with this formulation, irrigation of the affected area with water as soon as possible is recommended to minimize ocular irritation.

The potential for systemic toxicity due to the excipients of IVOMEC® (ivermectin) Pour-On is considered to be very low. In the case of crodamol CAP, no toxic signs were noted when rats were given an oral dose of 2 g/kg. In the case of isopropanol, the oral LD_{50} in rats is given in the Merck Index, Tenth Edition, as 5.8 g/kg. In the case of triethanolamine, the oral LD_{50} in rats is given as 8680 mg/kg.

Among the components of the pour-on, only isopropanol is volatile to an appreciable degree. Although isopropanol vapors are toxic, they pose relatively little potential for inadvertent toxicity because they are readily detectable and because people are experienced in dealing with isopropanol as a result of their day-to-day exposure to the large number of household items which contain it (e.g., rubbing alcohol, hand rubs, after shaves and various cosmetics). As opposed to these indoor use household items, IVOMEC® (ivermectin) Pour-On will be used almost exclusively in the open environment.

The major danger of isopropanol and its vapors arise from its flammability and for this reason the labeling bears in several places the following warning and precautionary statements:

"WARNING! FLAMMABLE!
KEEP AWAY FROM HEAT, SPARKS, OPEN FLAME, AND OTHER SOURCES OF IGNITION.

PRECAUTIONS:
Store away from excessive heat (104°F/40°C) and protect from light.
Use only in well-ventilated areas or outdoors.
Close container when not in use."

In conclusion, the acute oral and dermal toxicity, estimates of exposure and percutaneous absorption, and the ocular and dermal irritation studies conducted with ivermectin 0.5% w/v cattle topical formulation suggest that routine handler safety precautions including the use of rubber gloves and a long-sleeved shirt are sufficient to insure safe use of this formulation under anticipated use conditions.

9. Use of resources and energy:

The raw materials used to manufacture IVOMEC® (ivermectin) Pour-On are common organic compounds. The amounts of these which will be consumed by production of the pour-on will be insignificant compared to the amounts consumed for other applications. Energy will also be used to produce and transport the pour-on and to dispose of wastes associated with the production and use of the pour-on, but in amounts which will be negligible. The land to be used for production of the pour-on is already committed to production of pharmaceuticals.

We know of no effect of approval of IVOMEC® (ivermectin) Pour-On upon an endangered or threatened species or upon property listed or eligible to be listed in the National Registry of Historic Places.

10. Mitigation measures:

The measures taken to avoid potential adverse environmental impacts associated with the manufacture of IVOMEC® (ivermectin) Pour-On include proper disposal of Liquid and Solid Waste as described in Section 6 of this Environmental Assessment.

The following paragraph in the package insert minimizes the potential adverse impacts associated with the use and disposal of IVOMEC® (ivermectin) Pour-On:

"Environmental Safety. Studies indicate that when ivermectin comes in contact with the soil, it readily and tightly binds to the soil and becomes inactive over time. Free ivermectin may adversely affect fish and certain water-borne organisms on which they feed. Do not permit water runoff from feedlots to enter lakes, streams or ponds. Do not contaminate water by direct application or by the improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration."

11. Alternatives to the proposed action:

At this time there are no alternatives to chemotherapeutic agents for the control of the important endo- and ectoparasites of cattle. In addition, control of horn fly has become more difficult as resistance to older products has developed. Compared to the majority of the agents now used, IVOMEC® (ivermectin) Pour-On has two important attributes. It has a very broad spectrum and therefore obviates the need for multiple treatments with different agents; and it results in the release into the environment of negligible amounts of active ingredient and metabolites. From an environmental standpoint, IVOMEC® (ivermectin) Pour-On poses an environmental risk which is small compared to the alternatives.

12. List of preparers:

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13. Certification:

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the prospective contractor or applicant submitting the environmental assessment.

Date: 3/22/90

Signature: (Edward M. Convey, Ph. D.)

Title: Executive Director, Regulatory Affairs