IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine

Environmental Assessment

1. Date: July 15, 1991

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

   Merck & Co., Inc. is requesting approval for the use of ivermectin as a Type A Medicated Article for the treatment and control of endo- and ectoparasites in swine through medicated feed. Ivermectin will be administered in feed for seven consecutive days. A five-day withdrawal period is required for this use. The treatment regimen will usually involve administration to grower pigs upon entry into feedlot facilities. Two treatments may be used in some cases through the growout period. It is unlikely that more than two treatments will be administered before swine are marketed. The product is designed for use in growing pigs and is not recommended for use in swine weighing more than 220 pounds.

   B. Need for the action

   Ivermectin Type A Medicated Article is a treatment for the control of endo- and ectoparasites of swine. 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 swine. The swine industry suffers 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.

IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine is mixed in feed to a concentration of 2 ppm and fed for 7 consecutive days for the treatment and control of endo- and ectoparasites. The use of this product will reduce the economic loss to the swine industry caused by internal and external parasites.

C. Location where the products will be produced and types of environments adjacent to those locations

Avermectin is manufactured in the MCMD facility of Merck & Co., Inc., in Danville, Pennsylvania and converted to ivermectin in the MSD facility at Barceloneta, Puerto Rico. Formulation will be manufactured and packaged in the facility of MSD AGVET, Inc., in Barceloneta, Puerto Rico and the MSD B.V. Plant at Haarlem, Holland.

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

i) The type of environment at Danville, Pennsylvania

Location - The Danville plant is located on a 118 acre site 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. The U.S. Census Bureau listed Danville's 1980 population as 5,200 people.

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), the National Emission Standard for Hazardous Air Pollutants (NESHAPS), and the National Ambient Air Quality Standards (NAAQS). 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 (domestic sewers) and process (chemical effluents) wastewater sewers are maintained separately from storm sewers 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 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. The plant potable water quality meets all requirements of the Federal Safe Drinking Water Act and the Pennsylvania Safe Drinking Water Act. 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 of the plant there is the Mifflintown formation, a gray shale having some thin limestone beds and 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.

ii) **The Type of Environment at Barceloneta, Puerto Rico**

Location - 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′.

Weather/Air Resources - Puerto Rico generally has attained National Ambient Air Quality Standards (NAAQS) 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 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 Emission 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.

Water Resources - 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 well, or surface water bodies, are located within 1000 feet of the facility. The plant potable water quality meets all requirements of the federal Safe Drinking Water Act. Separate sewer systems exist for sanitary (domestic sewers), process (chemical effluents) 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 (230 feet) above mean sea level. The plant is located 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 consist 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 quaternary 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.

iii) The type of environment at Haarlem, Holland

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

industrial activity only. The population of Haarlem is approximately 150,000 people.

Weather/Air Resources - Dutch government laws prescribe emission standards for hazardous air pollutants. No significant air pollution generating industries are located in the vicinity. Annual rainfall is 0.754 meter (30 inches). Mean January temperature is 18° C (64° F). Prevailing wind directions are west and south-west (sea wind) at a windforce of 3 to 8 Beaufort.

Water Resources - All water used for consumption, process, and sanitary equipment is obtained from the official county supplier. Water quality constantly meets standards of potable water. Water for firefighting can be withdrawn from the River Spaarne. There are no injection wells on the plant property. The sanitary (domestic sewers) and storm sewer system are directly coupled to the municipal sewer system, while the process chemical effluents are treated before discharge into the municipal sewer. The discharge of waste water into the municipal sewer is covered by an official permit from the municipality. All wastewater from the municipal sewer is treated in the municipal wastewater treatment plant. The effluent from the treatment plant is discharged into the River Spaarne.

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 ivermectin Type A Medicated Article will be used with swine, primarily in feedlot environments. Swine feedlots are located throughout the United States in many different types of environment and predominantly in rural areas. The States with the highest swine population are found in the midwestern United states, including Iowa, Illinois, Indiana, Minnesota, Nebraska and Missouri, APPENDIX A.[1] Approximately one-third of this population would be treated

with ivermectin as injectable and medicated feed formulations. Manure from feedlots is frequently used directly as fertilizer. Alternately, the manure is diluted with water and removed as water-washed waste which is, in some circumstances, allowed to collect in a lagoon prior to use as fertilizer.

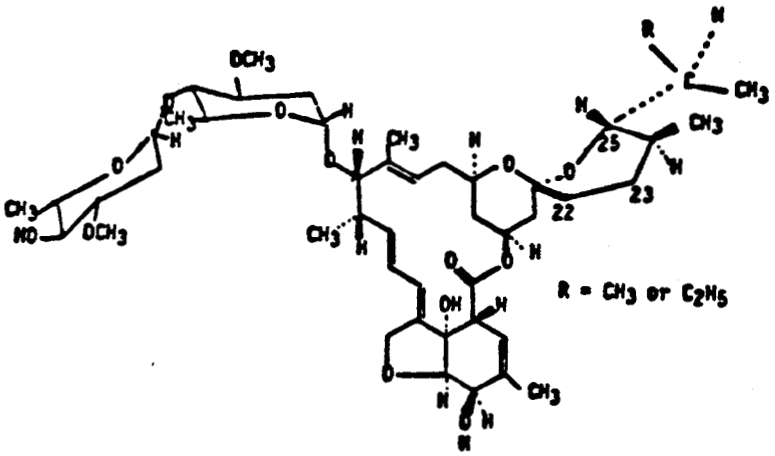
5. **Identification of chemical substances that are the subject of the proposed action**

A. **IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine:**

The active ingredient which is the subject of this document:

- Ivermectin (CAS Reg. No. 70288-86-7)
- Chemical name: 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}.

B. **The structure and properties of ivermectin**



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.

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 a 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	873
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

The introduction of substances into the environment can occur from four sources: (A) the avermectin manufacturing facility; (B) the manufacturing facilities where avermectin is converted into ivermectin; (B) and (C) the manufacturing facilities where the IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine is produced; and (D) the sites of intended use of this product in swine.

A. Danville, Pennsylvania - The following summarizes the environmental aspects of manufacturing avermectin at the Danville plant.

i) Liquid Waste

Solvent-based waste streams are generated in the isolation step and in the recovery of solvents used for the isolation. The solvent-based streams contain discarded organic by-products and some residual avermectins in a solution of organic solvents such as hexane, ethanol, and toluene. The solvent-based streams are destroyed by incineration. The incineration process is 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 262 and 265, Standards Applicable to Owners and Operators of Hazardous Waste Treatment, Storage and Disposal Facilities.

Aqueous-based waste streams consist of spent fermentation broth and wash waters that contain unconsumed fermentation nutrients, unrecovered by-products and traces of avermectins and dissolved solvents such as hexane, ethanol, and toluene. The aqueous-based stream is be treated in an onsite chemical pretreatment unit designed to destroy residual avermectins. The effluent from the pretreatment unit receives final biological treatment in the onsite two-stage secondary waste treatment plant and is discharged under the requirements of and in compliance with NPDES Permit No. PA 0008419 which is administered by the Pennsylvania Department of Natural Resources.

ii) Air Emissions

Air emissions generated during the production process consist of volatile organic compounds (such as hexane, ethanol and toluene) and dust. Air emissions are controlled as appropriate by condensers. Dust is controlled by HEPA-type filters. Air emissions are 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).

iii) Solid Waste

Dry solid waste, such as paper, trash, and HEPA-type filters, are disposed of in an incinerator which is 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).

iv) Employee Protection

Material Safety Data Sheets (MSDS) are 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 have appropriate MSDS available for their review. The MSDS for Avermectin Broth, Detoxified Avermectin Spent Broth, and Avermectin Pure are contained in APPENDIX B-1. Employee protective clothing, such as gloves, uniforms, and safety shoes, and protective equipment, such as safety glasses, are used during the manufacturing process to assure compliance with the Occupational Safety Act (OSHA) of 1971 and the Hazards Communication Act of 1985. To minimize worker exposure to avermectin, the following monitoring activities are conducted:

a. At least semi-annual monitoring of dust levels for avermectin where avermectin powder is handled; and

b. At least monthly wipe test for avermectin on equipment, floors, and production bottles in the production area.

Air, liquid, and solid waste emissions will comply with the environmental control regulations mentioned in the above sections. The plant is also in compliance with all applicable OSHA requirements.

v) **Environmental Exposure**

Quantities of substances that enter environmental media (i.e. soil, water, air, etc.) as a result of use and/or disposal of products related to the manufacturing of avermectin are inconsequential.

HEPA-type filters control the introduction of avermectin dust into the ambient air with an efficiency greater than 99.9 percent. Used HEPA-type filters are incinerated onsite at a temperature greater than 500° C.

Wastewaters containing residual avermectin from fermentation and separation operations are treated to destroy the avermectin in a high pressure reactor using caustic. Effluent from the high pressure reactor is further treated in the onsite wastewater treatment plant before being discharged into the Susquehanna River. The traces of avermectin allowed into the Susquehanna River are determined by the Pennsylvania Department of Natural Resources.

B. Barceloneta, Puerto Rico - The following summarizes the environmental aspects of converting avermectin into ivermectin and formulating IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine for the MSD Barceloneta facility.

i) **Liquid Waste**

The solvent-based waste streams are generated in the chemical processing step. They will contain discarded organic compounds in a solution of solvents such as ethanol, formamide, toluene, and water. The solvent-based stream is destroyed by incineration. The incineration process is subject to, and in compliance with, the Puerto Rico Environmental Quality Board Regulations for the Disposal of Solid Waste and Regulations for the Control of Atmospheric Pollution and the U.S. Environmental Protection Agency Regulations, 40 CFR Parts 264 and 265.

An aqueous-based waste stream consists of wash waters generated by equipment washings. Holding tanks are

provided to contain the washes prior to testing and disposal. Depending on the ivermectin concentration, the holding tank contents is managed in one of three ways:

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

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

c. Contents are incinerated.

Effluent from the Barceloneta plant is discharged to the Barceloneta Regional Wastewater Treatment Plant (BRWTP). The BRWTP operates under the requirements of NPDES Permit No. PR 0021237 which is administered by the U.S. Environmental Protection Agency.

ii) Air Emissions

Air emissions generated during the conversion of avermectin to ivermectin consist of volatile organic compounds (such as ethanol, formamide and toluene) and dust. The emissions of volatile organics are controlled as appropriate by condensers. Air in the process building is exhausted through HEPA-type filters. Air from the bulk manufacturing facility is exhausted through HEPA-type filters. Air from the formulation and sterile facilities is exhausted through HEPA-type filters. Air emissions are subject to, and in compliance with, the regulations for air emissions of the Puerto Rico Environmental Quality Board Regulations for the Control of Air Emissions.

iii) Solid Waste

Dry solid waste, such as paper, trash, and HEPA-type filters etc., is disposed of in an incinerator which is subject to, and in compliance with, the regulations for air emissions and solid waste disposal of the Puerto Rico Environmental Quality Board (EQB). Returned finished goods are either incinerated

onsite or sent offsite for incineration. In either case, the incinerator is in compliance with air & solid waste disposal regulations of the EQB.

iv) **Employee Protection**

Material Safety Data Sheets (MSDS) are 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 the manufacturing and formulation of the Type A Medicated Article for Swine have appropriate MSDS available for their review. The MSDS for ivermectin and Type A Medicated Article for Swine are contained in APPENDIX B-2. Employee protective clothing, such as gloves, uniforms, and safety shoes, and protective equipment, such as safety glasses, are used during and manufacturing and formulating process to assure compliance with the Occupational Safety Act of 1971 and the Hazardous Communication Act of 1985. To minimize worker exposure to avermectin and ivermectin, the following monitoring activities are conducted:

a. At least semi-annual monitoring of dust levels for avermectin and ivermectin where the powder for each, respectively, is handled; and

b. Wipe tests are performed to verify the cleanup of spills of ivermectin in the formulation area.

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

v) **Environmental Exposure**

Quantities of substances that enter environmental media (i.e., soil, water, air, etc.) as a result of the conversion of avermectin to ivermectin are inconsequential. In addition, quantities of substances that will enter environmental media as a result of the manufacturing and formulation of the IVOMEC® Premix (ivermectin) Type A Medicated Article for

Swine will also be inconsequential.

HEPA-type filters control the introduction of avermectin and ivermectin dust into the ambient air with an efficiency greater than 99.9%.

As per the MSDS for avermectin Pure and ivermectin, any solid waste containing either substance is incinerated at a temperature greater than 500° C.

Wastewaters from the conversion of avermectin to ivermectin are collected in a waste storage tank and either:

a) Tested for ivermectin and pumped through a filter to the chemical sewer;

b) Chemically pretreated with sodium hydroxide and pumped through a filter to the chemical sewer; or

c) Incinerated.

The discarded filters are incinerated onsite at a temperature greater than 500°C. Any residual ivermectin/avermectin remaining in the wastewaters is diluted by approximately one-half million gallons per day of total plant liquid effluent. Further dilution takes place when the total plant effluent is sent to the 6 million gallon per day Barceloneta Regional Wastewater Treatment Plant (BRWTP). Final effluent from the BRWTP is discharged into the Atlantic Ocean where additional mixing and dilution occurs.

Wastewaters from the production and formulation of the IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine will be collected in a waste storage tank and managed similar to the wastewaters described above.

Finished return goods of the IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine will be returned to the MSD AGVET facility in Barceloneta. Returned goods that must be destroyed will be burned onsite or offsite in an incinerator with a temperature greater than 500° C.

C. Haarlem, Holland - The following section summarizes the environmental aspects of the formulation of IVOMEC® Type A Medicated Article for Swine at the Haarlem plant.

i) Liquid Waste

Small amounts of dilute liquids will be generated during the cleanout of equipment. Any liquid waste which results from manufacturing the final dosage form will be collected and treated with an activated carbon purification unit to remove the ivermectin. The effluent from the purification unit will then enter the plant's general waste sewer where it mixes with sanitary waste. The mixed waste stream (effluent from the purification unit and sanitary waste) will go via a neutralization pit (pH 6 to 8) to the municipal sewage system and ultimately to the municipal sewage treatment plant. The treatment plant operates under the control of the Hoogheemraadschap Rijnland. MSD has permit No. 1420 ('86)/V26580 from the municipality for discharging to the sewage plant. Spent activated carbon from the filtering system will be collected in plastic bags, put into drums, and handled as described below for solid waste.

ii) Air Emissions

Air-borne particulates and dust will be controlled by HEPA-type filters. Any air emissions from the plant 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.

iii) Solid Waste

Solid waste resulting from production of the final dosage form, including spent activated carbon from the filtration system and HEPA-type filters, will be combined with other plant trash and transferred via closed vehicle to the Rotterdam incinerator. The MSD facility will have to get permission and a permit for each truckload of solid waste from production of

this product as is currently obtained for other products sent to the Rotterdam incinerator.

iv) **Employee Protection**

Material Safety Data Sheets (MSDS) will be available 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 ivermectin Type A Medicated Article for Swine will have appropriate MSDS available for their review. APPENDIX B-2 contains the MSDS for Type A Medicated Article for Swine and ivermectin. As additional worker protection, monthly swab tests will be performed for ivermectin on equipment, floors, and production bottles in the production area.

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

v) **Environmental Exposure**

Quantities of substances that will enter environmental media (i.e., soil, water, air, etc.) as a result of the manufacturing and formulation of the IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine will be inconsequential.

HEPA-type Filters will control the introduction of ivermectin dust into the ambient air with an efficiency greater than 99.9%.

Wastewaters from the production of IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine will be collected in a waste storage tank and pumped through activated carbon to remove ivermectin. Used activated carbon will be burned offsite in an incinerator at a temperature

greater than 500° C. Residual ivermectin remaining in the wastewaters will mix and be diluted by 70,000 liters per day (18,500 gal/day) of total plant effluent. Further dilution will take place when the total plant wastewater effluent is sent to the 40,049,000 liter/day (10.6 million gal/day) Rioolzuivering Waarderpolder sewage treatment plant. Effluent from this treatment plant will be discharged to the Spaarne River where additional mixing and dilution will occur.

Finished return goods of the IVOMEC® Type A Medicated Article for Swine will be returned to the MSD facility. Returned goods that must be destroyed will be incinerated at the Rotterdam incinerator.

D. Introduction through use in the target animal

i) Dosing and excretion

The projected use of IVOMEC® Type A Medicated Article for Swine involves the oral administration of the drug in feed at a dose rate of 2 ppm, or approximately 100 µg/kg body weight per day for seven consecutive days. Approximately one-fourth of the swine population in the United States is treated with the injectable formulation of ivermectin. Additional use of the premix formulation in feed is estimated to extend total use of ivermectin to approximately one-third of the swine population. The large majority of treated animals (~15 kg) will be confined to feedlots.

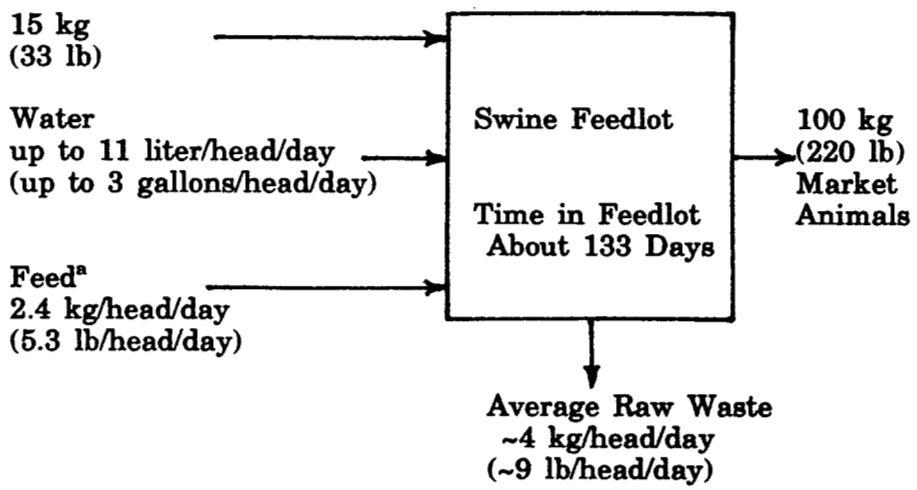
In the case of pigs dosed with ivermectin in feedlots, the following calculations, based on a U.S. Environmental Protection Agency publication, show the expected concentration of ivermectin and metabolites in the "Raw Waste" (manure) and the concentration in fields when the manure is spread as a fertilizer.[2]

The above-referenced EPA publication indicates that dirt floor feedlots contain, on average, 150 swine per acre, or about 3.5 swine per 1000 sq ft. If each pig was dosed with 15 mg of ivermectin, and the entire amount eliminated, a total of about

52.5 mg of ivermectin-related compounds would be excreted per 1000 sq ft at a swine density of 150 animals per acre, or approximately 15 mg per 286 sq. ft.

Attached is a modified flow diagram from the above reference showing the daily raw waste produced in a typical feedlot operation in which approximately 15-kg pigs enter the operation and in about 133 days reach market weight of about 100 kg.[3] Early in this period, as soon as practical after arrival at the feedlot, the animals will be treated for parasites for a single week with ivermectin at a dose level of 2 ppm in the feed.

Figure 1
Typical Swine Feedlot Flow Diagram



[a] Average for growing period in feedlot, 15-100 kg.

The following calculations (based on 100% of drug and metabolites excreted) provide an estimated concentration of the total drug residue in the waste produced by a single animal treated for one week at an initial weight of 15 kg and growing to market weight over a 133-day period.

Weight of swine	15 → 100 kg
Dose of ivermectin	2 ppm in diet for 7 days; ~1 kg feed per day during treatment.[3]
Weight of ivermectin-related compounds excreted (100% of dose)	15 mg
Total time in feedlot	133 days
Total waste produced per swine	~500 kg; ~23.8 kg waste/45.45 kg bw/wk.[4,5]

Estimated concentration of drug and metabolites in waste:

$$\frac{\text{15 mg excreted}}{\text{500 kg waste}} = \frac{\text{0.030 mg}}{\text{kg}} = \text{30 ppb}$$

For a 7-8 week old, 15 to 18-kg swine consuming about 7-8 kg of feed in a week (about 15 mg of ivermectin), the approximately 500 kg of manure produced during the 19-week feedlot residence would be expected to contain drug-related substances at an average estimated concentration of 30 ppb.

ii) Use of manure as fertilizer

Waste is frequently allowed to accumulate for long periods of time, e.g., 120-180 days, prior to use as fertilizer.[6] There are three methods of using swine manure as fertilizer, 1) direct use of the manure [commonly referred to as liquid (undiluted) manure], 2) use of water-washed waste from solid or slotted concrete-floored facilities where manure is hosed into and held in pits or tanks, and 3) a water-washed method where waste is collected in a lagoon. The last two methods result in the same concentration of residue in the water-washed waste.

a. **Direct use of manure as fertilizer**

Swine manure accumulated over the residence period of

the swine in the feedlot (residue level of 30 ppb) is used as fertilizer at the maximum recommended application rate of 25 tons per acre (Table 1). Plowed to a depth of 6 inches (see APPENDIX A-2 for calculation), the soil concentration would be 0.74 ppb (Table 1).

b. **Use of water-washed and lagoon-collected manure waste as fertilizer**

Where water-washed wastes are used, the amount of ivermectin-related residue in the fertilized soil will depend upon the amount of drug residue in the manure, the amount of dilution water and the spreading rate. With 15 mg of drug-related material present in the manure collected over 133 days, 41 kg of water-washed waste per swine per day, and a spreading rate of 8000 gal/acre, the level of ivermectin-related residue in soil fertilized (6" depth) with water-washed waste would be an estimated 0.083 ppb (Table 1; see calculation in APPENDIX A-2).[8]

The manure can be collected as water-washed waste every few weeks from the feedlot during the entire swine-raising period (133 days) and held in a lagoon until used as fertilizer.[5,6] The estimated concentration of ivermectin-related compounds in the lagoon after 133 days would be 2.76 ppb (assuming any loss of water from the lagoon by evaporation would be offset by rainfall). Use of this water-washed waste at the maximum recommended application rate of 8000 gal/acre, with a manure depth of six inches, would also result in an estimated fertilized soil concentration of 0.083 ppb (see calculation in APPENDIX A-2).[8] These residue levels are presented in Table 1.

Table 1
IVOMEC® Type A Medicated Article for Swine
Environmental Burden
2 PPM Ivermectin In-Feed for 7 Consecutive Days

	Dosing in Feed For 7 Days, Excreta (~500 kg) Collected For 133 Days[a]
TOTAL RESIDUE LEVELS	30 ppb
TOTAL RESIDUE IN MANURE-FERTILIZED PLOWED FIELD 25 TON/ACRE[b], 6"	0.74 ppb
TOTAL RESIDUE IN FERTILIZED AND PLOWED FIELD 8000 GAL WATER-WASHED WASTE/ACRE[8], 6"	0.083 ppb

[a] 7 to 26 week old swine, 15 mg ivermectin. For example, Nebraska regulations require that underfloor manure storage systems have a minimum storage capacity of 120 days, and a recommended storage capacity of 180 days.[6]

[b] The current Illinois recommendation for maximum annual application rate from liquid manure holding pits is 15 tons per acre.[7] However, to be consistent with the Environmental Assessment for IVOMEC® (ivermectin) Injection for Swine (NADA 135-008), 25 tons per acre is used in this determination.

iii) Metabolism

In a study (APPENDIX C-1) designed to examine the tissue depletion and metabolism of ivermectin administered in feed, two of the swine received tritium-labeled ivermectin equivalent to 100 µg/kg bw/day for 7 consecutive days. The medicated feed was prepared using the IVOMEC® Type A Medicated

Article for Swine formulation. More than 99% of the administered radioactivity was excreted during the on-drug period and the first 7 days post medication. Average total residue levels in excreta peaked on day 4 on-drug at 1.53 ppm, and then decreased to ~0.030 ppm by day 7 post medication. Virtually all of the radioactivity excreted was in the feces, with only about 0.2% of the dose appearing in the urine during this 14-day period.

Ivermectin accounts for approximately one-third of the swine feces residue following oral administration of the drug. The 3"-O-desmethyl (see below) and drug-like metabolites account for about 15-30% of the feces residue. Polar components, including the 24-hydroxymethyl metabolites (see below), account for another approximately 35-45%. The metabolite profile in the liver is comparable to that observed in the feces. Unchanged drug accounts for 40-45% to 30-35% of the total residue in on-drug and three-day off-drug livers, respectively. The 3"-O-desmethyl metabolites account for about 30% of the total residue, and a polar fraction with the chromatographic properties of the 24-hydroxymethyl metabolites comprise about 15% of the total residue.

For the purpose of this Environmental Assessment, the feces residue is considered to be entirely ivermectin.

IVOMEC® (ivermectin) Type A
Medicated Article for Swine

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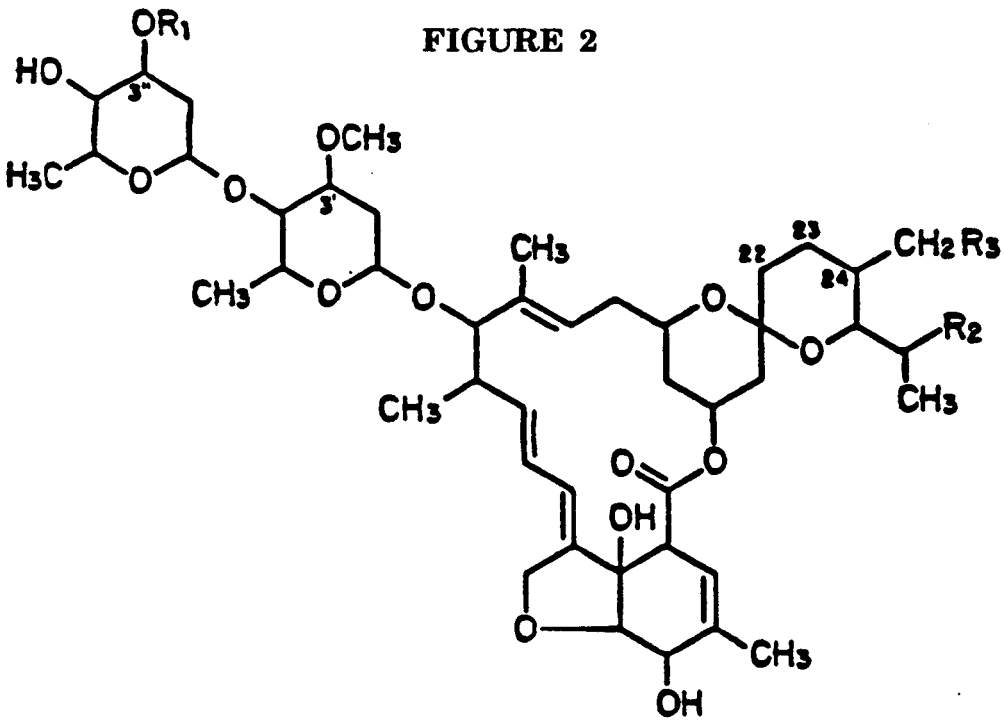
FIGURE 2



	R1	R2	R3
H_2B_{1a}	CH_3	CH_2CH_3	H
H_2B_{1b}	CH_3	CH_3	H
3"-O-Desmethyl-H_2B_{1a}	H	CH_2CH_3	H
3"-O-Desmethyl-H_2B_{1b}	H	CH_3	H
24-Hydroxymethyl-H_2B_{1a}	CH_3	CH_2CH_3	OH
24-Hydroxymethyl-H_2B_{1b}	CH_3	CH_3	OH

7. Fate in the environment

Information on the stability of ivermectin in soil and in aqueous extracts of steer, swine and sheep feces and on its soil translocation was presented in the Environmental Assessment of NADA 135-008, IVOMEC® (ivermectin) Injection for Swine.[8] The present assessment includes additional information on the environmental fate of ivermectin and 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. Key fate studies

i) Photodegradation

In a study of the photolysis of ivermectin H_2B_{1a}, Halley (1990, APPENDIX C-2) used a high-pressure xenon arc lamp to simulate sunlight. Based on the degradation of ivermectin under these conditions, it was 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 half-life of about 3 hours in summer sunlight (APPENDIX C-3). Avermectin B_{1a} possesses an absorption maximum similar to that of ivermectin (Sec. 5). Both possess low intensity long wavelength absorption at approximately 290 and 350 nm. Avermectin B_{1a} photodegrades on soil TLC plates with a half-life of 21 hours (APPENDIX C-4). Rapid photodegradation is consistent with the rapid loss of avermectin B_{1a} from the surface of cotton leaves. Radiobalance data indicated that slightly more than one-half of the applied radioactivity remained on the leaves at 2 days post-treatment, but only one-third of the recovered radioactivity was starting compound.[9] A non-polar photodegradation product of avermectin B_{1a} has been identified as the $\Delta^{8,9}$-isomer (APPENDIX C-4).

ii) Mobility in soil

Compounds possessing K_{oc} values greater than 1000 are tightly bound to the soil organic matter, and such compounds can be considered to be immobile in soil. As ivermectin has K_{oc} values of 12,600 and 15,700 with Iowa clay loam and Missouri silty clay loam soils, respectively, this drug has been classified as tightly bound to soil and hence immobile (APPENDIX C-5).[10] Avermectin B_{1a} was found to be immobile on soil TLC plates (six soil types) with water as the developing solvent (APPENDIX C-6), demonstrating the tight binding to soil of this close structural relative of ivermectin.[11] Consequently, the possibility of translocation of ivermectin through soil from one site to another in the environment is remote. 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 (APPENDIX C-5).[10]

iii) 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.[12] A summary of this study can be found in APPENDIX C-7. This study (carried out in the month of June) was designed 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 (20 x 50 ft) were collected over a 28-day period following dosing and assayed for ivermectin using toxicity toward *Daphnia* as an indication of the presence of ivermectin. 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. Essentially all of the subcutaneously administered dose, a total of 365 mg for five steers, or 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 (365 µg/sq ft). Nevertheless, the runoff water showed no ivermectin-related toxicity toward *Daphnia*; further, HPLC analysis demonstrated that H_2B_{1a} (major component of ivermectin) concentrations were below 10 ppt, the assay detection limit (and the *Daphnia* 48-hr NOEL).

iv) **Aerobic degradation in soil**

Ivermectin degrades rapidly outdoors in soil and soil/feces mixtures during the summer (half-life of 7 to 14 days) to more-polar compounds, and this would preclude accumulation of ivermectin in soil.[8] The rate of degradation is reduced in winter (half-life of 91-217 days). Such degradation will also reduce concentrations of ivermectin in manure-fertilized fields.

Laboratory studies 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.[9] 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 absorbed by ditch-bottom sludge (APPENDIX C-8) and other soil types and is immobile (APPENDIX C-6).[11] It would follow that ivermectin will be affected in a similar manner.

v) **Uptake by vegetation**

Low levels (<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 (≥3 ppm) was found on the seedling roots, but whether it was absorbed or adsorbed was not determined.[9] 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.[8] The observed lack of pronounced systemic insecticidal activity for ivermectin and avermectin B_1 in plants also indicates little or no uptake of these compounds by plants.[8]

The slight uptake by cotton seedlings of radioactivity from soil containing [^{3}H]avermectin B_{1a}, reported by Bull et al., 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.[9] Data from Bull et al. concerning lack of uptake of radioactivity by grass from a plot treated with [^{14}C]avermectin B_{1a} ant bait formulation also support this conclusion.[9] In addition, studies comparing the pesticidal activities of directly applied vs systemically applied (soil) avermectin demonstrated little or no uptake of the agent from soil[8].

Relatively low radioactive residues were found 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 by Moye and coworkers[13]. 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 endogenous small molecules resulting from degradation of the avermectin B_{1a}).

B. Fate scenarios for translocation of ivermectin in water through soil

i) Feedlot water runoff

The 365 mg of ivermectin-related compounds excreted per 1000 sq ft in the cattle feedlot runoff study can be compared with the 52.5 mg of ivermectin-related compounds excreted per 1000 sq ft (52.5 µg/sq ft) in a swine feedlot (Sec. 6. D.i.). If it is assumed that the 52.5 mg of ivermectin residue is present to a depth of six inches in the 1000 sq ft dirt feedlot,

this results in an estimated soil concentration of 2.47 ppb, only one-seventh that which would have pertained in the cattle feedlot study. In that study, less than 10 ppt of ivermectin was present in the water (HPLC assay). Therefore, in the swine feedlot, less than 1.5 ppt of ivermectin would be expected in the water. The tight binding to soil of the excreted ivermectin greatly attenuated the effective ivermectin concentration in the cattle feedlot runoff water. It was also demonstrated that toxicity of ivermectin (APPENDIX C-9) and avermectin B_1 (APPENDIX C-10) toward *Daphnia* is greatly attenuated (99%) in the presence of soil. These results agree with the known tight binding and immobility of ivermectin (APPENDIX C-5) and avermectin B_1 (APPENDIX C-6) in soil[10,11]. Consequently, the possibility of transport of ivermectin from the feedlot soil by water runoff is remote.

ii) **Fertilized field/nearby body of water**

The calculated TLC R_f for ivermectin in soil, based upon its K_{oc} value of 12,600, is 0.003 to 0.004 (APPENDIX C-5). This is consistent with the immobility of avermectin B_1 on soil TLC plates with water as a solvent (APPENDIX C-6).[11] Because of the tight binding of ivermectin to soil (soil to water distribution of 333, indicating greater than 99% binding) and its low water solubility of 4 ppm, only an insignificant fraction of the ivermectin initially present in water in contact with manure-fertilized soil would be expected to move with water flowing through soil and ultimately into a body of water. This insignificant amount would be further removed from water (in addition to the initial 99%) as the flow of ivermectin-containing water percolated through additional soil, resulting in continuous depletion of ivermectin from solution. Although achievement of equilibrium (99% bound) does not occur instantaneously, the binding process must be very rapid, based on the immobility of avermectin B_1 on soil TLC plates (APPENDIX C-6).[11] 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 (calculated soil TLC R_f of 0.003-0.004; APPENDIX C-5) in contact with soil would not be expected to be readily transported by water across soil particle surfaces.

C. Summary of fate studies and scenarios

The impact of the tight soil binding of ivermectin and of its degradation characteristics upon the estimated concentration of the drug entering the environment (see Sec. 6.D.) is addressed below.

Two initial concentrations of ivermectin in soil are considered, 0.74 ppb and 0.083 ppb (Table 1), arising from use of swine excreta (collected over 133 days) directly as fertilizer, and from use of water-washed waste collected for 133 days, respectively. These two values reflect the upper and lower estimated concentrations anticipated from use. It can be reasonably assumed that they would be reduced (99%) by soil binding to estimated concentrations of unbound ivermectin residues of 7.4 and 0.83 ppt in water that is in direct contact with the fertilized soil. The ivermectin residue concentration in water en route to a nearby body of water (e.g., pond) would be decreased by multiples of 99% because of adsorption to soil. Just one adsorption/desorption equilibration would reduce the above concentrations by a factor of 100, to 0.074 and 0.0083 ppt, respectively. A greater distance between the fertilized field and the body of water would require more extensive movement, through unfertilized soil, of water carrying dissolved unbound ivermectin, resulting in further binding and greater reduction in available ivermectin. Even if traces of ivermectin were to reach a body of water, as it entered, up to 99% of the drug would be bound by suspended soil particulates and sediment (to give estimated concentrations of 0.00074 and 0.000083 ppt). These concentration changes are summarized in Table 2, and do not include dilution effects. Further, the unbound ivermectin in the pond would undergo rapid photodegradation (calculated summertime and wintertime half-lives of approximately 12 and 39 hours, respectively, APPENDIX C-2) and the initial concentrations decrease (see Figure 3) in 4 days by factors of ~2 (winter) and ~16 (summer).

That ivermectin in contact with soil is most unlikely to undergo translocation sufficient to lead to concentrations >10

ppt in a nearby body of water is supported by the cattle feedlot runoff study. Runoff water collected directly from the feedlot (365 µg ivermectin residue per sq ft) was not toxic to *Daphnia* (used as a biological monitor for ivermectin concentrations) and was shown by HPLC analysis to contain <10 ppt of the drug. In a swine dirt feedlot the expected level of excreted ivermectin residue would be only 52.5 µg/sq ft, approximately 15% that in the cattle feedlot. It thus appears very reasonable to conclude that runoff water from a dirt swine feedlot would contain less than 1.5 ppt ivermectin.

Given the tight binding of ivermectin to soil, which greatly reduces its effective concentration, significant transport of ivermectin residues from fields fertilized with swine manure to bodies of water in the vicinity is highly unlikely. Both oxidative degradation in soil under aerobic conditions and photodegradation (especially in water) will diminish the environmental concentration of ivermectin. Based on the discussion of soil binding, soil metabolism and photodegradation, it can be reasonably predicted that ivermectin present in the environment would not be expected to undergo significant movement or translocation, and would not accumulate. Given its environmental fate characteristics, ivermectin will be readily eliminated from the aquatic and terrestrial environment.

Table 2
EFFECT OF SOIL BINDING UPON IVERMECTIN CONCENTRATIONS ARISING FROM USE OF MANURE CONTAINING DRUG RESIDUES AS FERTILIZER

	Initial Conc In soil	Conc in Water in Contact With Soil[a]	Conc Entering Pond Following Movement Through Unfertilized Soil[b]	Conc In Pond Following Binding To Soil Sediment[c]
DIRECT USE OF MANURE	0.74 ppb	7.4 ppt	0.074 ppt	0.00074 ppt
USE OF WATER-WASHED WASTE	0.083 ppb	0.83 ppt	0.0083 ppt	0.000083 ppt

[a] Assumes 99% remains bound to soil.
[b] Assumes only a single loss of 99% (i.e., fertilized soil adjacent to pond).
[c] Assumes a second loss of 99%.

8. Environmental effects of released substances

A. Environmental effects studies

i) Toxicity toward *Daphnia*

Daphnia, the freshwater aquatic species found to be most sensitive to ivermectin (48-hr LC_{50}, 48-hr NOEL and estimated 21-day MATC of 25, ~10 and 4 ppt, respectively) will be used for aquatic hazard assessment purposes. The effects of ivermectin, avermectin and related compounds upon a number of aquatic species (including *Daphnia*), as determined in laboratory tests, were reported in previously submitted environmental assessments, and are summarized in Table 3.

TABLE 3
EFFECT OF IVERMECTIN, AVERMECTIN AND RELATED COMPOUNDS
UPON AQUATIC SPECIES

COMPOUND	SPECIES	EFFECT	REFERENCES
Ivermectin	Daphnia	48-hour LC_{50} 25 ppt	Reference 10
Ivermectin (H_2B_{1a}) Monosaccharide	Daphnia	48-hour LC_{50} 400 ppt	Reference 10
Ivermectin (H_2B_{1a}) Aglycone	Daphnia	48-hour LC_{50} >17,000 ppt[a]	Reference 10
Ivermectin	Daphnia	48-hour NOEL ~10 ppt	Reference 10
Feces from ivermectin-dosed swine/soil column percolates[b]	Daphnia	48-hour LC_{50} >730 ppt[c]	Reference 10
Feces from ivermectin-dosed steer/soil column percolates[b]	Daphnia	48-hour LC_{50} ~3,200 ppt[c]	Reference 10
Ivermectin	Bluegill Sunfish	96-hour LC_{50} 5.3 ppb	Reference 8
Ivermectin	Rainbow Trout	96-hour LC_{50} 3.3 ppb	Reference 8
Avermectin B_1	Daphnia	48-hour LC_{50} 340 ppt	Appendix D-10
Avermectin B_{1a}	Bluegill Sunfish	Estimated Lethal Threshold 6.7 ppb, NOEL 2.3 ppb (Dynamic 7-Day Toxicity Study)	Appendix D-19
Avermectin B_1	Carp	96-hour LC_{50} 42 ppb	Appendix D-11
Avermectin B_1	Channel Catfish	96-hour LC_{50} 24 ppb	Appendix D-12
Avermectin B_1	Mysid Shrimp	96-hour LC_{50} 22 ppt	Appendix D-13

TABLE 3 (Continued)
EFFECT OF IVERMECTIN, AVERMECTIN AND RELATED COMPOUNDS
UPON AQUATIC SPECIES

COMPOUND	SPECIES	EFFECT	REFERENCES
Avermectin B_1	Sheepshead minnow	96-hour LC_{50} 15 ppb	Appendix D-14
Avermectin B_1	Oyster	48-hour EC_{50} 430 ppb	Appendix D-15
Avermectin B_1	Rainbow Trout	96-hour LC_{50} 3.6 ppb	Appendix D-1
Avermectin B_1	Bluegill Sunfish	96-hour LC_{50} 9.6 ppb	Appendix D-2
$\Delta^{8,9}$-Avermectin B_{1a} (photochemical degradation product of avermectin B_{1a}	Daphnia	48-hour LC_{50} 14 ppb	Appendix D-8
8α-Hydroxyavermectin B_{1a} (aerobic soil degradation product of avermectin B_{1a}	Daphnia	48-hour LC_{50} 26 ppb	Appendix D-9
Avermectin B_1	Daphnia (Life Cycle)	21-day MATC 0.03-0.09 ppb ACR[d] 6.5	Appendix D-16
Ivermectin	Daphnia (Life Cycle)	Estimated MATC 4 ppt	Calculated Value[e]
Avermectin B_1	Mysid Shrimp (Life Cycle)	28-day MATC 0.0035-0.0095 ppb ACR 3.8	Appendix D-17
Avermectin B_1	Rainbow Trout (ELS)[f]	MATC 0.52-0.96 ppb ACR 4.6	Appendix D-18
Avermectin B_1	Duckweed	14-day EC_{50} 3900 ppb	Appendix D-4
Avermectin B_1	Selenastrum capricornutum	9-day EC_{50} 100,000 ppb	Appendix D-5
Ivermectin	Chlorella pyrenoidosa	Maximum Growth Rate, No Effect at 10,000 ppb	Reference 10

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

[b] Feces from swine or steers (see footnote[c]) dosed with radiolabeled ivermectin was mixed with soil and applied to the tops of soil columns. Water was allowed to percolate through the columns and tested.

[c] Because the low concentrations and low toxicities of ivermectin-related compounds in feces/soil column percolates limited the extent of testing, sufficient data could not be collected to calculate toxicities 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.

Ivermectin and avermectin B_1 show comparable aquatic toxicity; however, ivermectin is more toxic to daphnids than is avermectin B_1. The concentrations at which toxicities are observed in these tests should be regarded as "worst-case" and not be directly compared to estimated exposure concentrations in Sec. 6.D. without consideration of environmental fate discussed in Sec. 7. Ivermectin and avermectin B_1 show comparable mammalian toxicity.[14]

ii) **Fish**

Fish are at least 100-fold less sensitive to the toxicity of ivermectin than are *Daphnia*. The ivermectin 96-hr LC_{50} values (Table 3) for rainbow trout and bluegill sunfish are 3.3 and 5.3 ppb, respectively.[8] In general, the acute toxicity of avermectin toward fish [e.g., LC_{50} values of 3.6 and 9.6 ppb for rainbow trout (APPENDIX D-1) and bluegill sunfish (APPENDIX D-2), respectively] is approximately the same as that exhibited by ivermectin.

iii) **Bioconcentration in sunfish**

The bioconcentration of [^{3}H]avermectin B_{1a} by the bluegill sunfish is modest and occurs gradually (APPENDIX D-3). 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 a tissue uptake concentration for whole fish of 1.9 to 6.8 ppb; accumulation ceased by about day ten. A 95 percent clearance of radioactivity for whole fish was found for a 14-day depuration period; the whole-fish concentration dropped from 6.8 to 0.32 ppb (day 14). This bioconcentration value of less than 100 and the rapid depuration are favorable, as they demonstrate that avermectin B_{1a} (and hence ivermectin) in fish does not concentrate and is not retained.

iv) **Toxicity toward other aquatic species**

The toxicity of ivermectin and avermectin B_1 toward other aquatic species is also presented in Table 3. 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.[10] Avermectin B_1 exhibits 14- and 9-day EC_{50} values of 3,900 and 100,000 ppb, respectively, with duckweed (APPENDIX D-4) and a freshwater algae (*Selenastrum capricornutum*)(APPENDIX D-5).

v) Phytotoxicity

The lack of phytotoxicity or other adverse effects on plant growth by avermectins have 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.[8] 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.

vi) Toxicity toward insects

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.[15] A review article by Strong and Brown discusses the avermectins in insect control.[16]

vii) Nitrification

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 (APPENDIX D-6). There was no effect upon nitrification or respiration for soil containing 30 ppb (the highest concentration tested) of ivermectin and metabolites in feces from subcutaneously dosed (300 µg/kg) steers.[10]

viii) Antibacterial and antifungal activities

Avermectins do not have significant antibacterial activity except at extremely high concentrations.[17] Onishi and Miller reported that avermectin B_{1a} lacks detectable antifungal activity at 400 ppm.[18] Using standard antibacterial and antifungal screens, ivermectin has been shown to have no antibacterial or antifungal effects at concentrations as high as 2000 ppm).[10]

ix) Methanogenesis

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 or 1000 ppm, the NOEC (APPENDIX D-7). 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.

x) Earthworm toxicity

The LC_{50} earthworm toxicity for ivermectin is 315 mg/kg soil (315 ppm) and the corresponding 96-hr NOEL is 12 ppm.[10]

xi) Additional pharmacology and toxicity information

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.[8] The present Environmental Assessment supplements this with recent information on ivermectin and supporting information on avermectin B_1 as discussed above. Summaries of these reports can be found in the Appendices.

B. Environmental hazard assessment

i) Hazard assessment in aquatic ecosystems

As mentioned earlier, *Daphnia* is the freshwater aquatic species found to be most sensitive to ivermectin. 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 3). As indicated in Sec. 7.B.i. the presence of soil in the test systems reduced the toxicity of ivermectin and avermectin B_1 toward *Daphnia*.

The feedlot runoff study involving subcutaneously dosed steers weighing 365 kg (APPENDIX C-7) 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* and no (<10 ppt by HPLC analysis) ivermectin. Tight binding to soil of the excreted ivermectin greatly attenuated its toxicity toward this aquatic species. Lack of toxicity should also pertain with a swine feedlot runoff, as the expected amount of ivermectin residues introduced in swine excreta will be only about 15% that for the above-described cattle feedlot (52.5 µg/sq ft vs 365 µg/sq ft). It can be reasonably concluded that runoff water from a swine feedlot would contain no more than 1.5 ppt of ivermectin residue, which is below the calculated 21-day MATC value of 4 ppt.

The likelihood of introduction of toxicologically significant amounts of drug-related compounds into the aquatic environment through runoff from swine manure used as fertilizer is remote. As calculated in Sec. 6.D.ii.a., spreading swine manure on a field at the rate of 25 tons/acre results in 15.7 µg of ivermectin residue per sq ft, vs 365 µg/sq ft for the cattle feedlot study (factor of 1/23). As no toxicity toward *Daphnia* was observed with runoff water from the cattle feedlot, it is highly unlikely any would occur with water from a swine-manure fertilized field. As was estimated in Sec. 7.C., because of tight binding to soil and sediment, ivermectin concentrations (ranging from a high exposure to a low

exposure; Table 2) in a body of water (as a result of use of drug-containing manure as fertilizer) would be 0.00074 to 0.000083 ppt, far below the 48-h LC_{50}, 48-NOEL and calculated 21-day MATC for *Daphnia*. 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 3).[8] Further, photodegradation of the unbound ivermectin in water would rapidly remove the traces of drug from the aquatic environment. This is graphically illustrated in Figure 3. The initial concentration of only 0.00074 ppt would drop [by factors of ~2 and ~16 (in winter and summer, respectively) within 4 days] to even farther below any levels of toxicological concern, even toward *Daphnia*. If the swine received medicated feed during the midpoint of their stay in the feedlot, i.e., the week during which they receive 2.4 kg of feed per day, direct use of the manure collected over the entire feedlot period as fertilizer would lead to an initial concentration of ivermectin in the aquatic environment of only 0.002 ppt (0.00074 ppt x 2.4/1), rather than 0.00074 ppt (see Table 2). This higher concentration is still far below any level of concern with respect to toxicity toward *Daphnia* (see Figure 3). Even if the swine were given medicated feed twice, once when they are ~15 kg b.w. and receive ~1 kg of feed per day, and also later when they receive 2.4 kg of medicated feed per day, the initial aqueous concentration would only be 0.003 ppt (0.00074 ppt + 0.00074 x 2.4/1).

According to the Environmental Assessment report for IVOMEC (ivermectin) 1% Injection for Swine (NADA 135-008), in certain instances 57 to 60 tons of manure per acre appears to be the highest application rate used for swine wastes. At 60 tons per acre, the concentration of ivermectin in the aquatic environment would be 0.007 ppt (0.003 ppt x 60/25) when swine are given medicated feed twice, see above paragraph. The photodegradation pathway (plus degradation resulting from aerobic metabolism in soil) increases an already more than adequate margin of safety for the use of ivermectin in feed for swine.

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 make it highly unlikely that environmental concentrations will reach levels toxic to any aquatic species, including *Daphnia*. Data in Table 3 also support the view that ivermectin-related compounds such as its monosaccharide and aglycone, and cattle and swine feces/soil column percolates, which contain ivermectin degradates/metabolites, are much less toxic than the parent compound. Avermectin B_1 is less toxic toward *Daphnia* than is ivermectin, and the known degradation products of avermectin B_{1a} (e.g., the $\Delta^{8,9}$-isomer and the 8α-hydroxy compound) are also much reduced in toxicity toward *Daphnia* compared to their parent compound (APPENDIX D-8 and D-9, respectively).

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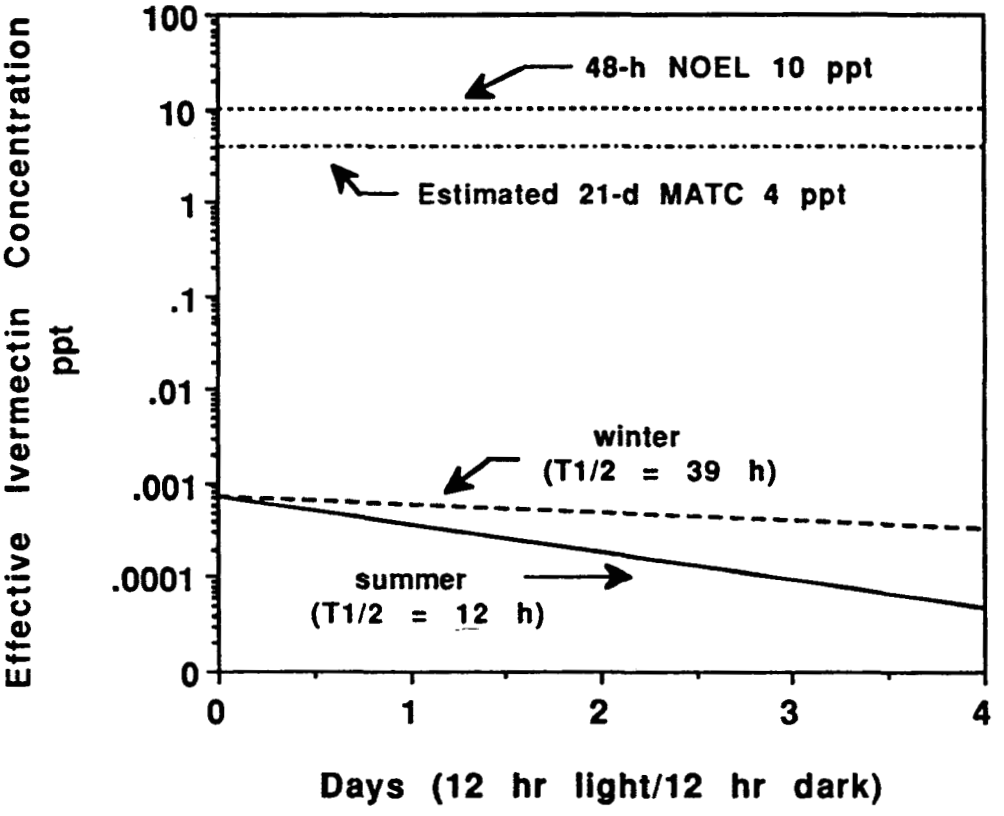
FIGURE 3

Comparison of Ivermectin 48-h NOEL and Estimated 21-d MATC for Daphnia with Effective Ivermectin Concentration in Pond as Impacted by Photodegradation. Scenario Involves Introduction of Ivermectin from Nearby Fields in which Swine Manure is Used as Fertilizer.



Fish are at least 100-fold less sensitive to the toxicity of ivermectin than are *Daphnia*. The ivermectin 96-hr LC_{50} values (Table 3) for rainbow trout and bluegill sunfish are 3.3 and 5.3 ppb, respectively.[8] These concentrations are far higher (factor of at least one-hundred thousand) than the estimated concentrations that might occur in ponds as the result of swine receiving ivermectin in feed. Other aquatic species (e.g., chlorophytes, duckweed and algae) would also be exposed to ivermectin concentrations (resulting from the use of ivermectin-containing manure as fertilizer) far below those (ppm) that would exhibit an effect on such species.

ii) **Hazard assessment in terrestrial ecosystems**

Given the low concentration of ivermectin residues in soil fertilized at 25 tons/acre with manure from ivermectin-treated swine (0.74 ppb), no deleterious effects would be expected toward plants, earthworms, fungi or bacteria. For example, the ivermectin LC_{50} toward the earthworm is 315 ppm (96-hr NOEL of 12 ppm). Application of manure to a field at the maximum use rate of 25 tons/acre would lead to a concentration of 0.74 ppb. Use of water-washed waste (also 133-day collection) would result in a lower soil concentration of 0.083 ppb. Any potential effect the low concentrations of ivermectin or its metabolites in soil might have upon life forms in soil would be greatly diminished by degradation of ivermectin in the soil.

C. <u>Handler safety considerations</u>

IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine contains ivermectin at 0.6% weight/weight in a finely ground corncob premix formulation. This premix is intended to be blended with swine feed at the rate of 303 g per ton of swine feed resulting in 1.82 grams of active ivermectin in a ton of feed. The product is intended to be used in a 7-day treatment program in growing swine.

Ivermectin has been tested for acute oral toxicity in a variety of laboratory animal species.[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 hours occluded exposure in rabbits and rats are 406 mg/kg and >660 mg/kg, respectively. The potential for percutaneous absorption of ivermectin contained in the IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine is discussed in more detail below.

In assessing the toxicity of ivermectin, it is important to note that rodents, and mice in particular, are poor models for predicting the effects of ivermectin in humans. For example, doses of ivermectin of 0.2 mg/kg produced clinical signs of drug effects (tremors and ataxia) in mice.[14] This dose (0.2 mg/kg) of ivermectin (MECTIZAN®) is used to treat onchocerciasis infections in humans. To date, more than 300,000 people have been treated for onchocerciasis with no serious drug-related adverse effects; MECTIZAN® is approved for use in more than 20 countries.[19]

A comparison of acute exposure data in Rhesus monkeys with humans suggest that primates are a better model for predicting the effects of ivermectin exposure in man. In monkeys, the minimum acutely toxic oral dose is 2 mg/kg based on a 25% incidence of emesis in treated animals.[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 available information indicates that the primate is a better model for predicting the effects of human exposure of ivermectin than rodents. In addition, a two-week repeat dose monkey study with ivermectin administered at dosage levels up to 1.2 mg/kg/day produced no evidence of toxicity.

Developmental toxicity studies conducted with ivermectin in rats, rabbits and mice have shown that the drug is not

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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 pregnant animals, therefore, a risk assessment for developmental effects based on maternal exposure will provide even greater safety margins for developmental toxicity.[14] This is supported by target animal safety studies conducted in a variety of domestic animal species at 2- or 3-fold the recommended use level of ivermectin with no evidence of developmental toxicity. In addition, an 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 primary route of potential exposure during handling of the IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine is dermal. The risk of systemic toxicity to the users of the IVOMEC® Premix (ivermectin) Type A Medicated Article formulation is low, based on the limited use of the product (one 7-day feeding period), and on results of acute dermal penetration studies and dermal toxicity studies in rabbits and monkeys. As mentioned earlier, the dermal LD_{50} value for ivermectin following a 24-hour occluded exposure in rabbits and rats is 406 mg/kg and >660 mg/kg, respectively. Additional information on the potential for percutaneous absorption of ivermectin can be found in the dermal penetration study conducted in Rhesus monkeys with avermectin B_{1a}.[20] Avermectin B_{1a} is the precursor for the synthesis of ivermectin B_{1a}, differing from the latter only in being unsaturated at the 22, 23 position. Based on this similarity, the percutaneous absorption of avermectin B_{1a} is believed to be a good model for assessing ivermectin dermal penetration.
To determine the percutaneous absorption of avermectin B_{1a}, the amount of radioactivity excreted in the feces was determined in a group of four monkeys after an i.v. dose or dermally applied doses of 6 or 300 micrograms/monkey spread over a 6 cm^2 area.[20] A comparison of these amounts in the dermal exposure group to those achieved following i.v. treatment (representing 100% absorption) gives the percentage of the dose absorbed percutaneously. Tritiated avermectin B_{1a} was applied to the skin in an isopropanol:water (6.7%

isopropanol) suspension, or in a hexanol based formulation or this formulation diluted with water. Topical exposures of one and 10 hours were done with collection of plasma, feces and urine to determine areas under the plasma concentration-time curve (AUC) and total amount excreted. 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 >99% of the dose recovered was recovered at the topical site of application. A comparison of the excretion data confirmed these results by indicating that only about 0.5% of the dermally applied dose was absorbed even after a 10-hour exposure to all three vehicles. The poor penetration of avermectin B_{1a} through skin is consistent with it relatively high molecular weight (873) and high lipophilicity, preventing it from penetrating into the plasma compartment.

The dermal absorption of avermectin (ivermectin) through monkey skin, which is similar to human skin in regard to its percutaneous absorption characteristics, was found to be about 0.5% after 10 hours.[20,21] The fact that ivermectin is present in the swine premix adsorbed on fine ground corncob carrier makes the potential for dermal absorption after incidental contact extremely small.

Discussion of the toxicology studies relevant to human safety can be found in the Freedom of Information Summaries associated with notification of approval of ivermectin for previous antiparasitic indications.[8,12]

9. <u>Use of resources and energy</u>

The raw materials utilized to manufacture avermectin, ivermectin, and the IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine are in ample commercial supply. Energy usage for the manufacturing and formulation of IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine will result in a small increase

in energy utilization since production will occur at existing Merck facilities.

No effects upon endangered or threatened species and upon property listed or eligible for listing in the National Register of Historic Places are anticipated.

10. Mitigation measures:

The measures taken to avoid potential adverse environmental impacts associated with the manufacture of IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine include proper disposal of Liquid and Solid Waste as described in Section 6 of this Environmental Assessment.

The following paragraph on the label minimizes the potential adverse impacts associated with the use and disposal of IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine:

"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 swine. Compared to the majority of the agents now used, IVOMEC® Premix (ivermectin) Type A Medicated Article for Swine 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® Premix (ivermectin) Type A Medicated Article for Swine poses an environmental risk which is minimal compared to the alternatives.

12. List of preparers:

Bruce A. Halley

B.A. - Chemistry, 1970
The College of Wooster
Wooster, Ohio

Ph.D. - Organic Chemistry, 1977
The University of California,
Santa Barbara
Santa Barbara, California

Research Fellow,
Animal and Exploratory Drug Metabolism
Merck Sharp & Dohme Research Laboratories

Richard Robertson

B.S. - Chemistry, 1967
The Citadel
Charleston, South Carolina

M.S. - Bio-Chemistry, 1969
University of Georgia
Athens, Georgia

Ph.D. - Bio-Chemistry, 1971
University of Georgia
Athens, Georgia

Executive Director,
Toxicology and Developmental Biology
Safety Assessment

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W.J.A. VandenHeuvel	A.B. - Chemistry, 1956 Princeton University Princeton, New Jersey Ph.D. - Organic Chemistry, 1960 Princeton University Princeton, New Jersey Senior Investigator, Animal and Exploratory Drug Metabolism Merck Sharp & Dohme Research Laboratories
Bruce Wallington	B.S. - Chemical Engineering, 1982 New Jersey Institute of Technology, Newark, New Jersey Engineering Associate Corporate Environmental Resources
Theodore Wishousky	B.S. - Chemistry, 1971 The Pennsylvania State University University Park, Pennsylvania B.S. - Bio-Chemistry, 1971 The Pennsylvania State University University Park, Pennsylvania M.S. - Chemistry, 1976 Villanova University Villanova, Pennsylvania Ph.D. - Analytical Chemistry, 1980 Villanova University Villanova, Pennsylvania Director, Regulatory Affairs - ASR Merck Sharp & Dohme Research Laboratories

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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.

Signature: Edward M Convey (Edward M. Convey, Ph.D.) Date: 7/31/91

Title: Executive Director, Regulatory Affairs

Signature: Dorothy P Bowers (Dorothy P. Bowers, P.E.) Date: 7/31/91

Title: Executive Director, Corporate Environmental Resources

14. References

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APPENDIX B-1

Material Safety Data Sheets for Avermectin in Broth; Avermectin Spent Broth, Detoxified; and Avermectin Pure

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MERCK & CO.,INC., P.O. BOX 2000, RAHWAY, NJ 07065
Merck Chemical Manufacturing Division

***** MATERIAL SAFETY DATA SHEET *****

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LABEL NAME: AVERMECTIN BROTH

PLANT MSDS CODE
CH-068

Emergency Telephone (201) 594-5555

SECTION 1 - MATERIAL IDENTIFICATION . . . . . .

Chemical Name----------A fermentation broth of Avermectins (primarily Avermectin B1a and B1b)

Synonyms (Common)----------Avermectin Broth, Avermectin Whole Broth
(Chemical)----------Unknown

Material Statistical Number-------2-99427

Material Product Number----------Unknown

Chemical Classification----------Glycosides

Intended Use----------Avermectin Process

SECTION 2 - PRINCIPAL HAZARDOUS COMPONENT(S) . . . . . .

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
A mixture of avermectins in fermentation broth-primarily Avermectin B1a and Avermectin B1b	Unknown	Unknown	B1a=65195-55-3	Variable

SECTION 3 - PHYSICAL PROPERTY DATA . . . . . .

Appearance----------Amber colored liquid

Odor/Threshold Level (ppm)--------Characteristic fermentation odor

Boiling Point (°C/°F)----------Unknown

Freezing Point (°C/°F)----------Unknown

Melting Range (°C/°F)----------Unknown

pH ----------Unknown

Solubility in water----------Soluble

Specific Gravity (Water = 1)-------ca. 1

Vapor Density (Air=1)----------Unknown

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LABEL NAME: AVERMECTIN BROTH

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Vapor Pressure (mm Hg @ °C/°F)——Unknown

Volatile Components (% w/w)————Not applicable

SECTION 4 - FIRE AND EXPLOSION HAZARD DATA . . . . . .

Flash Point (°C/°F)——————Not applicable

Flash Point Test Method————Not applicable

Autoignition Temperature (°C/°F)—Unknown

Flammable Limits -LEL (%)————Not applicable
-UEL (%)————Not applicable

Combustibility Information————Unknown

Dust Explosivity Information——Unknown

Shock Sensitivity Information——Unknown

Extinguishing Media——————Use water to fight fires involving avermectin whole broth.

Special Fire Fighting Procedures—Firefighters must wear full protective equipment including self-contained breathing apparatus. A decontamination station must be used by firefighters at the completion of their job.

Fire/Explosion Hazards————None known

Hazardous Decomposition Products Resulting From A Fire—None known

SECTION 5 - REACTIVITY DATA . . . . . .

Stability (Normal Storage Conditions)—Stable solution under normal conditionsof storage, use or misuse.

Storage Conditions to Avoid————None known

Thermal Stability/Instability Information—Unknown

Incompatabilities (Chemical Entities)—None known

Incompatabilities (Materials of Construction)—Unknown

Hazardous Polymerizations————None known

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

Eye Contact----------Flush eyes with plenty of water for 5 minutes and get medical attention.

Skin Contact----------Flush affected area with soap and water and get medical attention if irritation develops.

Inhalation----------Remove victim to fresh air supply and seek quick medical attention.

Ingestion----------Drink large volumes of water and get inmediate medical attention.

Notes to Physician----------none

SECTION 7 - HEALTH HAZARD DATA . . . . . .

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH-1988-89 Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
A mixture of avermectins in fermentation broth - primarily Avermectin B1a and Avermectin B1b	Not established	Not established	Not established

Carcinogen Designation----------Unknown

Effects of Acute Exposure

Eye Contact----------May cause slight eye irritation.

Skin Contact----------Non-irritating to the skin when topically applied, but skin absorption may cause toxic reactions.

Inhalation----------Animal studies show a low order of toxicity via inhalation of pure active ingredient.

Ingestion----------Pure active ingredient has caused central nervous system effects via ingestion in animal studies.

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: AVERMECTIN BROTH

PLANT MSDS CODE
CH-068

Emergency Telephone Number 201-594-5555

Effects of Chronic Exposure--------No information on chronic health effects in humans. Avermectin has been shown to be non-mutagenic in the Ames Test and the Micronucleus Test.

Quantitative Toxicity Data

LC_{50} - Daphnia Magna, 48 hours	0.34 ppb
LC_{50} - Rainbow Trout, 96 hours	3.2 ppb
LC_{50} - Bluegill Sunfish, 96 hours	9.6 ppb

SECTION 8 - SPILL/LEAK/DISPOSAL PROCEDURE . . . . . .

Steps to be taken in case materials released:
Immediately contact emergency response personnel. Keep unnecessary persons away. If emergency response personnel are unavailable, absorb small spills on spill pillows or other suitable absorbing material and place in a sealed container for disposal. Dike large spills and transfer to an appropriate container for disposal. Use suitable protective equipment (Section 9). Follow all fire prevention procedures (Section 4).

For additional assistance, CHEMTREK provides a toll-free Hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 800-424-9300.

Environmental Data----------Unknown

Waste Disposal Information--------This material is very toxic to certain aquatic species. Avoid contact of spilled materials and runoff with soil and surface waterways. Residual surface material should be removed with towels moistened with methanol. Incinerate all spill material and residues at temperatures greater than 500°C.

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: AVERMECTIN BROTH

PLANT MSDS CODE
CH-068

Emergency Telephone Number 201-594-5555

SECTION 9 - SPECIAL PROTECTION INFORMATION . . . . . .

Respiratory	No specific respiratory protection is required when handling avermectin whole broth.
Hands/Arms	Wear rubber gloves when handling exposed solution.
Eye/Face	Wear chemical splash goggles when handling exposed solution.
Additional Protective Equipment	Wear sleevelets, a rubber apron, and rubber boots.
Ventilation	Local exhaust ventilation should be provided.

SECTION 10 - SPECIAL PRECAUTIONS . . . . . .

Special Precautions to be taken when:

Handling	Handle with great care, ensuring proper personal and environmental protection.
Storing	Store in a cool, well-ventilated location.
Other	Avoid allowing material from entering streams and other waterways.

SECTION 11 - BASIC TRANSPORTATION DESCRIPTION . . . . . .

U.S. DOT
ICAO/IATA
IMO

This material is not normally shipped commercially.

Hazardous Substance-Reportable Quantity (RQ)---Not available

SECTION 12 - INTER-PLANT COMMUNICATION . . . . . .

List all other MCMD plants requiring a copy of this MSDS:

*** Continued on next page ***

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****** MATERIAL SAFETY DATA SHEETS ******

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LABEL NAME: AVERMECTIN BROTH

PLANT MSDS CODE
CH-068

Emergency Telephone Number 201-594-5555

SECTION 13 - MSDS PREPARATION - Revision 2 . . . . . .

J.W. Maize
Safety----------Date: June 13, 1989
L. Overholt
Technical Operations----------Date: June 13, 1989
T.J. LaBuz
Site Environmental----------Date: June 13, 1989

R. Ronquillo
Corporate Environmental Resources----------Date: June 13, 1989
R. Cutro
Rahway Technical Operations----------Date: June 13, 1989
E.V. Sargent, Ph.D.
Corporate Safety & Industrial Hygiene----------Date: June 13, 1989

SECTION 14 - MERCK DISCLAIMER . . . . . .

While this information and recommendations set forth are believed to be accurate as of the date hereof, MERCK & CO., INC. makes no warranty with respect hereto and disclaims all liability from reliance thereon.

MERCK & CO.,INC., P.O. BOX 2000, RAHWAY, NJ 07065
Merck Chemical Manufacturing Division

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***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: AVERMECTIN SPENT BROTH, DETOXIFIED

PLANT MSDS CODE
CH-069

Emergency Telephone (201) 594-5555

SECTION 1 - MATERIAL IDENTIFICATION . . . . . .

Chemical Name----------Detoxified avermectin broth

Synonyms (Common)----------Avermectin Spent Broth, Detoxified
(Chemical)----------Unknown

Material Statistical Number-------Not applicable

Material Product Number----------Unknown

Chemical Classification----------Not applicable

Intended Use----------None, Spent Broth

SECTION 2 - PRINCIPAL HAZARDOUS COMPONENT(S) . . . . . .

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
Not applicable				

SECTION 3 - PHYSICAL PROPERTY DATA . . . . . .

Appearance----------Amber colored basic solution

Odor/Threshold Level (ppm)--------Characteristic fermentation odor

Boiling Point (°C/°F)----------Unknown

Freezing Point (°C/°F)----------Unknown

Melting Range (°C/°F)----------Unknown

pH ----------+12.5

Solubility in water----------Soluble

Specific Gravity (Water = 1)------ca. 1

Vapor Density (Air=1)----------Unknown

Vapor Pressure (mm Hg @ °C/°F)----Unknown

Volatile Components (% w/w)-------Not applicable

*** Continued on next page ***

MERCK & CO., INC., P.O. BOX 2000, RAHWAY, N.J. 07065
Merck Chemical Manufacturing Division

****** MATERIAL SAFETY DATA SHEET ******

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LABEL NAME: AVERMECTIN SPENT BROTH, DETOXIFIED

PLANT MSDS CODE
CH-068

Emergency Telephone Number (201) 594-5555

SECTION 4 - FIRE AND EXPLOSION HAZARD DATA . . . . . .

Flash Point (°C/°F)----------Not applicable

Flash Point Test Method----------Not applicable

Autoignition Temperature (°C/°F)--Unknown

Flammable Limits -LEL (%)---------Not applicable
-UEL (%)---------Not applicable

Combustibility Information--------Unknown

Dust Explosivity Information------Unknown

Shock Sensitivity Information-----Unknown

Extinguishing Media----------Use water to fight fires involving avermectin treated broth.

Special Fire Fighting Procedures--Firefighters must wear full protective equipment including self-contained breathing apparatus.

Fire/Explosion Hazards----------None known

Hazardous Decomposition Products Resulting From A Fire--None known

SECTION 5 - REACTIVITY DATA . . . . . .

Stability (Normal Storage Conditions)--Stable solution under normal conditions of storage or use.

Storage Conditions to Avoid--------Reacts with water to generate heat. Heat may be sufficient to ignite flammable materials under certain conditons.

Thermal Stability/Instability Information--None known

Incompatabilities (Chemical Entities)--Reacts rapidly with strong acids and many organic compounds.

Incompatabilities (Materials of Construction)--Unknown

Hazardous Polymerizations---------None known

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MERCK & CO., INC., BOX 2000, RAHWAY, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEET ******

LABEL NAME: AVERMECTIN SPENT BROTH,DETOXIFIED

PLANT MSDS CODE
CH-069

Emergency Telephone Number (201) 594-5555

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

Eye Contact----------Flush eyes with plenty of water for 15 minutes and get medical attention.

Skin Contact----------Flush affected area with plenty of soap and water for 15 minutes. Get medical attention.

Inhalation----------Move victim to fresh air supply and get quick medical attention.

Ingestion----------Drink large volumes of water and get immediate medical attention.

Notes to Physician----------none

SECTION 7 - HEALTH HAZARD DATA . . . . . .

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH-1988-89 Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
Not applicable	Not established	Not established	Not established

Carcinogen Designation----------Unknown

Effects of Acute Exposure

Eye Contact----------May cause severe eye burns.

Skin Contact----------May cause severe skin burns.

Inhalation----------Inhalation of caustic mist/aerosol vapors may cause burning sensation in mucous membranes and upper respiratory tract.

Ingestion----------May cause severe burns to the mouth, throat and gastrointestinal tract.

Effects of Chronic Exposure----------No known chronic effects of overexposure.

*** Continued on next page ***

MERCK & CO., INC., BOX 2000, RAHWAY, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: AVERMECTIN SPENT BROTH, DETOXIFIED

PLANT MSDS CODE
CH-069

Emergency Telephone Number 201-594-5555

Quantitative Toxicity Data

No toxicity data established for avermectin treated broth.

SECTION 8 - SPILL/LEAK/DISPOSAL PROCEDURE . . . . . .

Steps to be taken in case materials released:
Immediately contact emergency response personnel. Keep unnecessary persons away. If emergency response personnel are unavailable, absorb small spills on spill pillows or other suitable absorbing material and place in a sealed container for disposal. Dike large spills and transfer to an appropriate container for disposal. Use suitable protective equipment (Section 9). Follow all fire prevention procedures (Section 4).

For additional assistance, CHEMTREK provides a toll-free Hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 800-424-9300.

Environmental Data----------Unknown

Waste Disposal Information--------This material is very toxic to certain aquatic species. Avoid contact of spilled materials and runoff with soil and surface waterways. Residual surface material should be removed with towels moistened with methanol. Incinerate all spill material and residues at temperatures greater than 500°C.

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MERCK & CO., INC., P.O. BOX 2000, Rahway, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: AVERMECTIN SPENT BROTH, DETOXIFIED

PLANT MSDS CODE
CH-069

Emergency Telephone Number 201-594-5555

SECTION 9 - SPECIAL PROTECTION INFORMATION . . . . . .

Respiratory——No specific respiratory protection is required when handling avermectin whole broth.

Hands/Arms——Wear neoprene rubber gloves when handling exposed solution.

Eye/Face——Wear chemical splash goggles when handling exposed solution.

Additional Protective Equipment——Wear sleevelets, a rubber apron, and rubber boots.

Ventilation——Local exhaust ventilation should be provided.

SECTION 10 - SPECIAL PRECAUTIONS . . . . . .

Special Precautions to be taken when:

Handling——Handle with great care, ensuring proper personal and environmental protection.

Storing——Store in a cool, well-ventilated location.

Other——Avoid allowing material from entering streams and other waterways.

SECTION 11 - BASIC TRANSPORTATION DESCRIPTION . . . . . .

U.S. DOT——

ICAO/IATA——

IMO——

This material is not normally shipped commercially.

Hazardous Substance-Reportable Quantity (RQ)——Unknown

SECTION 12 - INTER-PLANT COMMUNICATION . . . . . .

List all other MCMD plants requiring a copy of this MSDS:

*** Continued on next page ***

MERCK & CO., INC., P.O. BOX 2000, Rahway, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: AVERMECTIN SPENT BROTH, DETOXIFIED

PLANT MSDS CODE
CH-069

Emergency Telephone Number 201-594-5555

SECTION 13 - MSDS PREPARATION - Revision 2 . . . . . .

J.W. Maize
Safety----------Date: June 13, 1989
L. Overholt
Technical Operations----------Date: June 13, 1989
T.J. LaBuz
Site Environmental----------Date: June 13, 1989

R. Ronquillo
Corporate Environmental Resources----------Date: June 13, 1989
R. Cutro
Rahway Technical Operations----------Date: June 13, 1989
E.V. Sargent, Ph.D.
Corporate Safety & Industrial Hygiene----------Date: June 13, 1989

SECTION 14 - MERCK DISCLAIMER . . . . . .

While this information and recommendations set forth are believed to be accurate as of the date hereof, MERCK & CO., INC. makes no warranty with respect hereto and disclaims all liability from reliance thereon.

MERCK & CO.,INC., P.O. BOX 2000, RAHWAY, NJ 07065
Merck Chemical Manufacturing Division

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***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: AVERMECTIN PURE

PLANT MSDS CODE
CH-005

Emergency Telephone (201) 594-5555

SECTION 1 - MATERIAL IDENTIFICATION . . . . . .

Chemical Name----------Avermectin mixture containing primarily Avermectin B1a and B1b

Synonyms (Common)----------Avermectin Pure, CO 76
(Chemical)----------Unknown

Material Statistical Number-------2-56189

Material Product Number----------Unknown

Chemical Classification----------Glycoside

Intended Use----------Veterinary anti parasitic agent

SECTION 2 - PRINCIPAL HAZARDOUS COMPONENT(S) . . . . . .

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
B1a=5-O-demethyl-avermectin A1a	C48H72O14	873.08	86753-29-9	))**97
B1b=5-O-demethyl-25-de(1-methyl-propyl)-25-(1-methylethyl) avermectin A1b	C47H70O14	859.05	Not avail.	))
Ethyl Alcohol	C2H5OH	46.06	64-17-5	Max. 5.0
n-Hexane	C6H14	86.17	110-54-3	Max. 0.5
Toluene	C7H8	92.13	108-88-3	Max. 0.5
Methanol	CH3OH	32.04	67-56-1	Max. 0.5

**Calc. on water and solvent free basis.

SECTION 3 - PHYSICAL PROPERTY DATA . . . . . .

Appearance----------Clean, moist, off-white to slightly yellow lumpy solid

Odor/Threshold Level (ppm)--------Odorless

Boiling Point (°C/°F)----------Not applicable

Freezing Point (°C/°F)----------Not applicable

Melting Range (°C/°F)----------Unknown

pH ----------Not applicable

Solubility in water----------Insoluble

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MERCK & CO., INC., P.O. BOX 2000, RAHWAY, N.J. 07065
Merck Chemical Manufacturing Division

****** MATERIAL SAFETY DATA SHEET ******

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LABEL NAME: AVERMECTIN PURE

PLANT MSDS CODE
CH-005

Emergency Telephone Number (201) 594-5555

Specific Gravity (Water = 1)------Not applicable

Vapor Density (Air=1)----------Not applicable

Vapor Pressure (mm Hg @ °C/°F)----Not applicable

Volatile Components (% w/w)-------Not applicable

SECTION 4 - FIRE AND EXPLOSION HAZARD DATA . . . . . .

Flash Point (°C/°F)----------Not applicable

Flash Point Test Method----------Not applicable

Autoignition Temperature (°C/°F)--Unknown

Flammable Limits -LEL (%)---------Not applicable
-UEL (%)---------Not applicable

Combustibility Information--------Unknown

Dust Explosivity Information------Unknown

Shock Sensitivity Information-----Unknown

Extinguishing Media----------Use carbon dioxide or dry chemical fire extinguishers.

Special Fire Fighting Procedures--Avoid creating significant airborne dust. Use full protective clothing and self-contained respiratory apparatus. Contain all runoff water. See spill procedures section. All exposed personnel and equipment should be dectntaminated at the site.

Fire/Explosion Hazards----------Material will burn if ignited. Can form an explosive mixture with air in dusty conditions. All contaminated material and protective gear should be decontaminated to prevent spread of contaminated residual material. Prevent/collect runnoff of contaminated water from fire/spill for proper disposal. (See Section 8.)

*** Continued on next page ***

MERCK & CO., INC., BOX 2000, RAHWAY, N.J. 07065
Merck Chemical Manufacturing Division

****** MATERIAL SAFETY DATA SHEET ******

LABEL NAME: AVERMECTIN PURE

PLANT MSDS CODE
CH-005

Emergency Telephone Number (201) 594-5555

Hazardous Decomposition Products Resulting From A Fire--If involved in a fire, toxic gases (including CO, CO_2), toxic dust and smoke may be generated.

SECTION 5 - REACTIVITY DATA . . . . . .

Stability (Normal Storage Conditions)--Stable compound under reasonably foreseeable conditions of storage and use.

Storage Conditions to Avoid-------None known

Thermal Stability/Instability Information--Unknown

Incompatabilities (Chemical Entities)--Can be hydrolyzed by strong caustic solution.

Incompatabilities (Materials of Construction)--Unknown

Hazardous Polymerizations---------None known

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

Eye Contact----------Flush with plenty of water for at least 5 minutes. Seek medical aid if irritation develops.

Skin Contact----------Wash affected area with soap and large volumes of water.

Inhalation----------Immediately remove victim from contaminated area and get medical attention.

Ingestion----------Get immediate medical attention. Induction of vomiting may be performed by physician depending on the quantity ingested.

Notes to Physician----------None

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MERCK & CO., INC., BOX 2000, RAHWAY, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: AVERMECTIN PURE

PLANT MSDS CODE
CH-005

Emergency Telephone Number 201-594-5555

SECTION 7 - HEALTH HAZARD DATA . . . . . .

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH-1988-89 Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
B1a=5-O-demethyl-avermectin A1a	Not establ.	Not establ.	)*40mcg/m^3
B1b=5-O-demethyl-25-de(1-methyl-propyl) -25-(1-methylethyl) avermectin A1b	Not establ.	Not establ.	)
Ethyl Alcohol	1900 mg/m^3	1900 mg/m^3	Not establ.
n-Hexane	180 mg/m^3	180 mg/m^3	Not establ.
Toluene	375 mg/m^3	375 mg/m^3	Not establ.
Methanol	260 mg/m^3	260 mg/m^3	Not establ.

Carcinogen Designation----------Dietary carcinogenesis studies in mice and rats are negative.

Effects of Acute Exposure

Eye Contact----------Slightly irritating to the eyes in rabbits.

Skin Contact----------Non-irritating to the skin in topical skin testing. Slightly toxic in animal tests when absorbed through skin.

Inhalation----------Animal studies demonstrated a low order of toxicity via inhalation of avermectin.

Ingestion----------Acute health effects in humans are not known. Avermectin is highly toxic via ingestion in animal studies, cuasing central nervous system effects.

Effects of Chronic Exposure---------No information on chronic health effects in humans. Avermectin has been shown to be a reproductive toxin in laboratory animal studies but only at doses which are acutely toxic to the maternal animcal. Avermectin has been shown to be non-mutagenic in the Ames test and the Micronucleus Test. Dietary carcinogenesis studies in mice and rats are negative. In 14 week oral toxicity studies in monkeys, no effects were seen at 0.2, 0.5 or 1.0 mg/kg/day; , emesis was seen at 2.0 mg/kg/day; delayed pupillary construction at 6 and 8 mg/kg/day and mydriasis at 12 mg/kg/day.

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MERCK & CO., INC., P.O. BOX 2000, Rahway, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: AVERMECTIN PURE

PLANT MSDS CODE
CH-005

Emergency Telephone Number 201-594-5555

Quantitative Toxicity Data

The following toxicity data is based on the pure active compound.

LD50 - Mouse (F), oral, 14 days	10-29.7 mg/kg
LD50 - Rat (M,. F), oral, 2 days (DOT)	18.4 mg/kg
LD50 - Rat, dermal, 14 days	330 mg/kg
Skin (AC) - Rabbit, topical, 14 days	Non-irritating
Eye (AC) - Rabbit, direct contact, 14 days	Slight ocular irritant
Acute Inhalation Toxicity - Rat, inhalation, 14 days	At 5.73 mg/L-no deaths, normal behavior and body weights
LC_{50} - Daphnia Magna, 48 hours	0.34 ppb
LC_{50} - Rainbow Trout, 96 hours	3.2 ppb
LC_{50} - Bluegill Sunfish, 96 hours	9.6 ppb

SECTION 8 - SPILL/LEAK/DISPOSAL PROCEDURE . . . . . .

Steps to be taken in case materials released:
Immediately contact emergency response personnel. Eliminate all ignition sources. Keep unnecessary persons away. If emergency response personnel are unavailable, sweep up spilled material in a manner that produces the least amount of airborne dust and place in an appropriate container for disposal. Use suitable protective equipment (Section 9). Follow all fire prevention procedures (Section 4).

For additional assistance, CHEMTREK provides a toll-free Hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 800-424-9300.

Environmental Data——————Unknown

Waste Disposal Information————This material is very toxic to certain aquatic species. Avoid contact of spilled materials and runoff with soil and surface waterways. Residual surface material should be removed with towels moistened with methanol. Incinerate all spill material and residues at temperatures greater than 500°C.

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MERCK & CO., INC., P.O. BOX 2000, Rahway, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: AVERMECTIN PURE

PLANT MSDS CODE
CH-005

Emergency Telephone Number 201-594-5555

SECTION 9 - SPECIAL PROTECTION INFORMATION . . . . . .

Respiratory	An airline mask or air supplied hood is necessary for direct dust exposure.
Hands/Arms	Nitrile rubber gloves are required when handling this compound.
Eye/Face	Chemical goggles are recommended for direct exposure.
Additional Protective Equipment	Full body garments should be worn when handling this compound. Disposable protective clothing including Tyvek syits, head cover, and shoe protectors should be worn.
Ventilation	Local exhaust ventilation must be provided where dust may enter the work room environment. Containment areas should have dedicated exhaust and dust collection systems (HEPA filters or collectors).

SECTION 10 - SPECIAL PRECAUTIONS . . . . . .

Special Precautions to be taken when:

Handling	None
Storing	Store in a tightly closed container in a cool, dry, well-ventilated location. Compound should be handled in a contained area with access limited to authorized personnel and arranged so that material is prevented from entering unregulated areas.
Other	Protective clothing must be removed prior to leaving the controlled area. Showers are required after handling the material at the end of the work day. Always wash hands with sopa and water prior to eating, drinking or smoking.

*** continued on next page ***

MERCK & CO., INC., P.O. BOX 2000, Rahway, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: AVERMECTIN PURE

PLANT MSDS CODE
CH-005

Emergency Telephone Number 201-594-5555

SECTION 11 - BASIC TRANSPORTATION DESCRIPTION . . . . . .

U.S. DOT----------Poison B solid N.O.S., (Avermectin), UN 2811, Chemicals NOI

ICAO/IATA----------IATA-Poisonous solids NOS (Avermectin); 6.1, UN 2811, Cargo Aircraft only; 615, II

IMO----------Not applicable

Hazardous Substance-Reportable Quantity (RQ)---No RQ

SECTION 12 - INTER-PLANT COMMUNICATION . . . . . .

List all other MCMD plants requiring a copy of this MSDS: Puerto Rico

SECTION 13 - MSDS PREPARATION - Revision 2 . . . . . .

J. W. Maize
Safety----------Date 3/20/89

L. Overholt
Technical Operations----------Date 3/23/89

J. LaBuz
Site Environmental----------Date 4/5/89

R. Ronquillo
Corporate Environmental Resources----------Date 6/9/89

R. Cutro
Rahway Technical Operations----------Date 6/9/89

E. Sargent, Ph.D.
Corporate Safety & Industrial Hygiene---------- Date 6/9/89

SECTION 14 - MERCK DISCLAIMER . . . . . .

While this information and recommendations set forth are believed to be accurate as of the date hereof, MERCK & CO., INC. makes no warranty with respect hereto and disclaims all liability from reliance thereon.

APPENDIX B-2

Material Safety Data Sheets for Ivermectin and IVOMEC® Type A Medicated Article (Premix)

MERCK & CO.,INC., P.O. BOX 2000, RAHWAY, NJ 07065
Merck Chemical Manufacturing Division

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***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: IVERMECTIN

PLANT MSDS CODE
PR-20

Emergency Telephone (809) 846-3620

SECTION 1 - MATERIAL IDENTIFICATION . . . . . .

Chemical Name----------Ivermectin

Synonyms (Common)----------Eqvalan, Ivomec, Heartgard, Chewable
(Chemical)----------Not available

Material Statistical Number--------Not available

Material Product Number----------SP-2097

Chemical Classification----------Theoretical mixture of 80% (minimum 22.23 dihydro C-076 B1a and 20% (maximum) 22.23 dihydro C-076 B1b

Intended Use----------Not available

SECTION 2 - PRINCIPAL HAZARDOUS COMPONENT(S) . . . . . .

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
Dihydro C-076 B1a	$C_{48}H_{74}O_{14}$	875	70161-11-4	80
Dihydro C-076 B1b	$C_{47}H_{72}O_{14}$	861	70209-81-3	20

SECTION 3 - PHYSICAL PROPERTY DATA . . . . . .

Appearance----------Clear, moist, off-white to slightly yellow powder

Odor/Threshold Level (ppm)--------Odorless

Boiling Point (°C/°F)----------Not applicable

Freezing Point (°C/°F)----------Not applicable

Melting Range (°C/°F)----------Approx. 150°C

pH ----------Not available

Solubility in water----------Negligible

Specific Gravity (Water = 1)------Not applicable

Vapor Density (Air=1)----------Not applicable

Vapor Pressure (mm Hg @ °C/°F)----Not applicable

Volatile Components (% w/w)--------Not applicable

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MERCK & CO., INC., P.O. BOX 2000, RAHWAY, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEET ******

LABEL NAME: IVERMECTIN

PLANT MSDS CODE
PR-20

Emergency Telephone Number (809) 846-3620

SECTION 4 - FIRE AND EXPLOSION HAZARD DATA . . . . . .

Flash Point ($^{o}C/^{o}F$)----------Not applicable

Flash Point Test Method----------Not applicable

Autoignition Temperature ($^{o}C/^{o}F$)--Not available

Flammable Limits -LEL (%)---------Not available
-UEL (%)---------Not available

Combustibility Information--------Not available

Dust Explosivity Information------Not available

Shock Sensitivity Information-----Not available

Extinguishing Media----------Use carbon dioxide or dry chemical fire extinguishers.

Special Fire Fighting Procedures--Avoid creating significant airborne dust. Use full protective clothing and self-contained respiratory apparatus. Contain all runoff water. See spill procedures section. All exposed personnel and equipment should be decontaminated at the site.

Fire/Explosion Hazards----------Material will burn if ignited. Can form explosive mixture with air in dusty conditions.

Hazardous Decomposition Products Resulting From A Fire--If involved in a fire, toxic gases includding CO, CO_2, and smoke may be generated.

SECTION 5 - REACTIVITY DATA . . . . . .

Stability (Normal Storage Conditions)--Stable compound under reasonably foreseeable conditions of storage and use.

Storage Conditions to Avoid-------Not applicable

Thermal Stability/Instability Information--Not availble

Incompatabilities (Chemical Entities)--Can be hydrolyzed by strong caustic solution.

Incompatabilities (Materials of Construction)--Not available

Hazardous Polymerizations---------Will not occur.

*** Continued on next page ***

MERCK & CO., INC., BOX 2000, RAHWAY, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEET ******

LABEL NAME: IVERMECTIN

PLANT MSDS CODE
PR-20

Emergency Telephone Number (809) 846-3620

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

Eye Contact----------Flush with plenty of water.

Skin Contact----------Wash affected area with soap and large volumes of water.

Inhalation----------Remove from contaminated area immediately. Get medical attention.

Ingestion----------Get immediate medical attention. Induction of vomiting may be performed by a physician depending on the quantity ingested.

Notes to Physician----------None

SECTION 7 - HEALTH HAZARD DATA . . . . . .

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH-1988-89 Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
Dihydro C-076 B1a	Not available	Not available	0.08 mg/m^3
Dihydro C-076 B1b	Not available	Not available	0.08 mg/m^3

Carcinogen Designation----------Not available

Effects of Acute Exposure

Eye Contact----------Slightly irritating to the eyes in rabbit tests.

Skin Contact----------Absorption: The skin is considered a primary route of exposure to the compound in liquid formulations and a secondary route of exposure to the dry solid compound.

Inhalation----------Animal inhalation demonstrated a low order of toxicity by this route. It is considered the primary route of exposure to the dry solid compound.

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MERCK & CO., INC., BOX 2000, RAHWAY, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: IVERMECTIN

PLANT MSDS CODE
PR-20

Emergency Telephone Number (809) 846-3620

Ingestion---------- No toxic effects seen in humans at doses up 200 micrograms. Absorption following oral administration is slow. Compound is considered highly toxic in acute animal toxicity studies.

Effects of Chronic Exposure---------- No information on maternotoxic dosage levels or chronic health effects in humans. In 14 week oral toxicity studies in monkeys, no effects were seen at 0.2, 0.5, or 1.0 mg/kg/day; emesis was seen at 2.0 mg/kg/day; delayed pupillary constriction at 6 and 8 mg/kg/day; mydriasis at 12 mg/kg/day; and sedation at 24 mg/kg/day. Ivermectin has been shown to be a reproductive toxic in laboratory animal studies, but only at doses which are acutely toxic to the maternal animal. Compound is negative in the Ames test for mutagenicity.

Quantitative Toxicity Data

LD50 - mouse (F), oral, 14 days	37 mg/kg
LD50 - rat, (M,F,), oral, 2 days	51.8 mg/kg
LD50 - rat, dermal, 14 days	660 mg/kg
LD50 - rabbit, dermal, 14 days	406 mg/kg
Skin (AC) - rabbit, topical, 14 days	Non-irritating
Eye (AC) - rabbit, direct contact, 14 days	Very slighty irritating
LC50 - rat, inhalation, 14 days	Respirable fraction 0.37%. Animal dose calculated at 0.4 mg/kg. Slight eye irritation. No deaths or systemic toxicity observed.

SECTION 8 - SPILL/LEAK/DISPOSAL PROCEDURE . . . . . .

Steps to be taken in case materials released:
Immediately contact emergency response personnel. Keep unnecessary persons away. If emergency response personnel are unavailable, vacuum, shovel or sweep up spilled material in a manner that produces the least amount of

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MERCK & CO., INC., P.O. BOX 2000, Rahway, N.J. 07065
Merck Chemical Manufacturing Division

****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: IVERMECTIN

PLANT MSDS CODE
PR-20

Emergency Telephone Number (809) 846-3620

airborne dust and place in an appropriate container for disposal. Use suitable protective equipment (Section 9). Follow all fire prevention procedures (Section 4).

For additional assistance, CHEMTREK provides a toll-free Hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 800-424-9300.

Environmental Data----------Not available

Waste Disposal Information------- This material is very toxic to certain aquatic species. Avoid contact of spilled materials and runoff with soil and surface waterways. Residual surface material should be removed with towels moistened with methanol. Incinerate all spill materials and residues at temperatures greater than 500°C.

SECTION 9 - SPECIAL PROTECTION INFORMATION . . . . . .

Respiratory----------An airline mask or air-supplied hood is necessary for direct dust exposure.

Hands/Arms----------Impervious gloves are required when handling the compound.

Eye/Face----------Chemical goggles are recommended for direct exposure.

Additional Protective Equipment---Full body garmets should be worn when handling this compound. Disposable clothing including tyvek suits, head cover, and shoe protectors should be worn.

Ventilation----------Local exhaust ventilation must be provided where dust may enter the workroom environment. Containment areas should have dedicated exhaust and dust collection systems (HEPA filters or collectors).

*** Continued on next page ***

MERCK & CO., INC., P.O. BOX 2000, Rahway, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: IVERMECTIN PLANT MSDS CODE PR-20

Emergency Telephone Number (809) 846-3620

SECTION 10 - SPECIAL PRECAUTIONS . . . . . .

Special Precautions to be taken when:

Handling----------Compound should be handled in a contained area with access limited to authorized personnel and arranged so that material is prevented form entering unregulated areas.

Storing----------Store in a tightly closed container in a cool, dry well ventilated location.

Other----------Protective clothing must be removed prior to leaving the controlled area. Showers are required after handling the material at the end of the workday. Always wash hands with soap and water prior to eating, drinking, or smoking.

SECTION 11 - BASIC TRANSPORTATION DESCRIPTION . . . . . .

U.S. DOT----------Not available

ICAO/IATA----------Not available

IMO----------Not available

Hazardous Substance-Reportable Quantity (RQ)---Not available

SECTION 12 - INTER-PLANT COMMUNICATION . . . . . .

List all other MCMD plants requiring a copy of this MSDS:

SECTION 13 - MSDS PREPARATION - Revision 2 . . . . . .

C. Rodriguez
Safety----------Date: June 22, 1989
E. Cardona
Technical Operations----------Date: June 22, 1989
C. Bassat
Site Environmental----------Date: June 22, 1989

R. Ronquillo
Corporate Environmental Resources----------Date: July 20, 1989
R. Cutro
Rahway Technical Operations----------Date: June 22, 1989
E.V. Sargent, Ph.D.
Corporate Safety & Industrial Hygiene----------Date: June 22, 1989

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MERCK & CO., INC., P.O. BOX 2000, Rahway, N.J. 07065
Merck Chemical Manufacturing Division

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****** MATERIAL SAFETY DATA SHEETS ******

LABEL NAME: IVERMECTIN

PLANT MSDS CODE
PR-20

Emergency Telephone Number (809) 846-3620

SECTION 14 - MERCK DISCLAIMER . . . . . .

While this information and recommendations set forth are believed to be accurate as of the date hereof, MERCK & CO., INC. makes no warranty with respect hereto and disclaims all liability from reliance thereon.

MSD AGVET DIVISION, P.O. Box 2000, RAHWAY, NJ 07065

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***** MATERIAL SAFETY DATA SHEET *****

PRODUCT NAME: IVOMEC PREMIX FOR SWINE

MSDS CODE AG-043

Emergency Telephone Numbers

Product usage & Animal Health adverse experiences:	8:30 am-4:30 pm (CST)	(800) 325-2577
(emergency calls only after 4:30 pm)	after 4:30 pm (CST)	(908) 594-5555
Human health adverse experiences:	8:30 am-4:30 pm (EST)	(215) 661-7300
	after 4:30 pm (EST)	(215) 661-5000

SECTION 1 - MATERIAL IDENTIFICATION . . . . . .

Chemical Name----------Ivermectin (active ingredient) is a theoretical mixture of 80% (minimum) 22.23 dihydro C-076 Bla and 20% (maximum) 22.23- dihydro C-076 B1b.

Synonyms----------None

Merck ID Code----------41284/41285/41240

Chemical Classification----------Multicomponent Solid

Intended Use----------A 0.6% Type A Medicated Article to be used as a veterinary anthelmintic for swine by administration in a complete feed.

SECTION 2 - PRINCIPAL COMPONENT(S) . . . . . .

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
Ivermectin Comp. Bla	$C_{48}H_{74}O_{14}$	875	70288-86-7	0.6
Comp. B1b	$C_{47}H_{72}O_{14}$	861	(mixture)	
Fine Ground Corn Cob	Not established	Not established	Not established	70.1
Inert Ingredients	Not established	Not established	Not established	29.3

SECTION 3 - PHYSICAL PROPERTY DATA . . . . . .

Appearance----------Clean, free-flowing, non-dusty, slightly yellow to light brown fine fibrous meal mixture.

Odor/Threshold Level (ppm)--------Practically odorless. Do not test for odor to avoid breathing powder.

Boiling Point (°C/°F)----------Not applicable

Freezing Point (°C/°F)----------Not applicable

Melting Range (°C/°F)----------Not established

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pH ----------Not applicable

Solubility in water----------Not soluble

Specific Gravity (Water=1)--------Not applicable

Vapor Density (Air=1)----------Not applicable

Vapor Pressure (mm Hg @ °C/°F)----Not applicable

Volatile Components (% w/w)-------Not established

SECTION 4 - FIRE AND EXPLOSION HAZARD DATA . . . . . .

Flash Point (°C/°F)----------Not established

Flash Point Test Method----------Not applicable

Autoignition Temperature (°C/°F)--Not established

Flammable Limits-LEL-(%)----------Not established
-UEL (%)----------Not established

Extinquishing Media----------Use water spray or all purpose dry chemical.

Special Fire Fighting Procedures--Fire fighters should wear self-contained breathing apparatus and full protective equipment. Avoid creating dusty conditions.

Fire and Explosion Hazards--------As with all organic dust, finely divided particles dispersed with air in sufficient concentrations may generate an explosive mixture if an ignition source is present.

Hazardous Decomposition Products Resulting From A Fire--If involved in a fire, toxic gases including carbon monoxide and carbon dioxide may be generated.

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SECTION 5 - REACTIVITY DATA . . . . . .

Stability----------Stable, protected from light.

Storage Conditions to Avoid-------None known.

Incompatibilities----------None known

Hazardous Polymerizations---------None known

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

Eye Contact----------Flush thoroughly with plenty of water for at least 5 minutes. Get medical attention if irritation occurs or persists.

Skin Contact----------Emergency treatment is not necessary. However, wash contact area with soap and water after handling. Remove contaminated clothing and wash before reuse. If irritation occurs or persists, get medical attention.

Inhalation----------In case of accidental overexposure, get to fresh air. If irritation occurs or persists, get medical attention.

Ingestion----------If ingested, get medical attention immediately.

Medical Conditions Aggravated By Exposure--None known

SECTION 7 - HEALTH HAZARD DATA . . . . . .

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH-1990-91 Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
Ivermectin	Not established	Not established	0.08 mg/m^3

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Carcinogen Designation----------Not listed as a carcinogen with NTP, IARC, or OSHA.

Quantitative Toxicity Data---------For pure Ivermectin

TEST	SPECIES	ROUTE	RESULT
LD50	Mouse	Oral	25 mg/kg
LD50	Mouse	Intraperitoneal	30 mg/kg
LD50	Rat	Oral	50 mg/kg
LD50	Rat	Intraperitoneal	55 mg/kg
LD50	Rat (infant)	Oral	2 to 3 mg/kg
LD50	Rat	Inhalation	*
LD50	Rat	Dermal	More than 660 mg/kg
LD50	Rabbit	Dermal	406 mg/kg
LD50	Dog	Oral	About 80 mg/kg
LD50	Rhesus monkey	Oral	More than 24 mg/kg

*Maximum attainable concentration of 5.11 mg/liter produced transient irritation of mucous membranes but no deaths or other signs of toxicity after 1 hour exposure.

Effects of Acute Exposure

Eye Contact----------Slight ocular irritant in animal studies.

Skin Contact----------Ivermectin is nonirritating in animal studies. Although skin absorption of this formulation of Ivermectin is not established, it has been shown that less than 1% of the closely related compound abamectin is absorbed through the skin of rhesus monkeys when it is applied as emulsifiable concentrate or suspended in alcohol.

Inhalation----------Animal inhalation demonstrated a low order of toxicity by this route but this is accounted for by the large particle size of the sample used in this test. Inhalation is considered the primary route of exposure to the dry solid compound.

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Ingestion----------Pure Ivermectin is considered highly toxic in acute animal studies. The acute oral toxicity studies of Ivermectin have shown clear differences among species in sensitivity to Ivermectin toxicity. Rodents are uniquely sensitive compared to the other species in which the compound has been tested. It is therefore inappropriate to base human risk assessment on the response in mice. Ivermectin is used at a therapeutic dose of 200 mcg/kg in a variety of species, including human. Ivermectin can be excreted in milk.

If overexposed to Ivermectin, symptoms may include decreased activity, slow rate of breathing, dilation of the pupils, muscle tremors, and incoordination.

Effects of Chronic Exposure---------Unknown for product mixture. Ivermectin has tested negative in several mutagenicity studies. Ivermectin was administered to dogs daily for 3 months and to monkeys daily for 2 weeks. In dogs there was no effect up to 500 mcg/kg/day and in adult rhesus monkeys there was no effect at the maximum dosage used 1.2 mg/kg/day. At higher doses in dogs there was dilation of the pupils, and at still higher doses tremor and anorexia were noted.

Ivermectin can be given during gestation in horses, cattle, pigs and sheep.

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SECTION 8 - SPILL/LEAK/DISPOSAL PROCEDURE . . . . . .

Steps to be taken in case materials are released:

Vacuum or shovel up spilled material and place in an appropriate container for disposal. Use suitable protective equipment (Section 9). Follow all fire prevention procedures (Section 4). Inform emergency response personnel for large spills. Keep unnecessary persons away.

Ivermectin is very toxic to certain aquatic species. Avoid contact of spilled materials and runoff with soil and surface waterways. Residual surface material should be removed with towels moistened with methanol. Incinerate all spill material and residues at temperatures greater than 500°C.

Do not flush into drains or natural waterways or areas draining into potable water supplies.

Environmental Data----------Pure Ivermectin: LC50 (Daphnia Magna) = 25 ppt (parts per trillion)

SECTION 9 - SPECIAL PROTECTION INFORMATION . . . . . .

Respiratory----------An MSHA-NIOSH approved respirator for dusts is recommended for any direct exposure to the dust.

Hands/Arms----------Rubber gloves or other impervious gloves.

Eye/Face----------Safety goggles to prevent direct eye contact.

Additional Protective Equipment---Protective clothing such as coveralls and/or apron.

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Ventilation----------Proper ventilation should be maintained at all times to prevent high dust concentrations.

SECTION 10 - SPECIAL PRECAUTIONS . . . . . .

Special Precautions To Be Taken When:

Handling and Storing, Etc.--------Store in a cool, dry place away from direct sunlight. Avoid generating dust. Avoid contact with eyes and skin. Do not ingest. Refrain from smoking or eating when handling. Wash thoroughly after use.

Other ----------Keep container closed when not in use. Keep out of the reach of children.

SECTION 11 - BASIC TRANSPORTATION DESCRIPTION . . . . . .

Shipping Requirements----------Not regulated

SECTION 12 - MSDS PREPARATION - Revision 1, September 1991 . . . . . .

Corporate Safety & Industrial Hygiene-------- Date: June 5, 1990
Merck & Co., Inc., Rahway, New Jersey, U.S.A.

MSD AGVET ---------- Date: June 6, 1990
Merck & Co., Inc., Rahway, New Jersey, U.S.A.

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