ABAMECTIN

AVERT PRESCRIPTION TREATMENT 310
(Section 3 Registration)

RISK CHARACTERIZATION DOCUMENT

MEDICAL TOXICOLOGY AND WORKER HEALTH AND SAFETY BRANCHES

DEPARTMENT OF PESTICIDE REGULATION

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

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(Revised)

ABAMECTIN
AVERT PRESCRIPTION TREATMENT 310

EXECUTIVE SUMMARY

Introduction

Abamectin is the common name for avermectin B_1, a naturally occurring miticide/insecticide, derived from the soil microorganism, Streptomyces avermitilis. The pesticidal activity of abamectin is related to the interaction with the nerve transmitter, gamma aminobutyric acid. A breakdown product (a delta 8,9-isomer) of abamectin is formed in plants by a reaction with sunlight, and this compound has similar toxicological properties as abamectin. A risk assessment of potential human health hazards from the use of abamectin as a crack and crevice bait formulation **(Avert Prescription Treatment 300)** to control cockroaches has been conducted because of adverse reproductive and developmental effects reported in animal studies using either the parent compound, abamectin, or the delta 8,9-isomer. In addition, the potential combined exposure to abamectin from **Avert** and specific food commodities was evaluated. These commodities included cottonseed, celery, head lettuce, strawberries and pears.

The Risk Assessment Process

A basic principal of toxicology is that at a sufficiently high enough dose, virtually all substances will cause some type of toxic manifestation. Although chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes, in reality, these terms describe chemicals that require low or high dosages, respectively, to cause toxic effects. Toxicological activity is determined in a battery of experimental studies which define the kinds of toxic effects which can be caused, and the exposure levels (doses) at which an effect is first seen. State and federal testing requirements, including California's Birth Defect Prevention Act of 1984 (SB 950, Petris), mandate that chemicals be tested at doses high enough to produce toxic effects, even if that testing requires levels many times higher than those to which people may actually be exposed. The critical parameters in determining the risk of any chemical, including pesticides, are the intrinsic toxicological activity of the chemical, and the level and duration of exposure to the chemical. The purpose of risk assessment is to determine potential human exposures, and to relate toxic effects in laboratory studies at high dosages to the probability of adverse health effects in people who may be exposed to the pesticide through various routes and activities.

Background Information

In 1987, a risk assessment for abamectin was conducted by the Medical Toxicology Branch, then part of the California Department of Food and Agriculture (CDFA), because of adverse developmental and reproductive effects reported in animal studies. As a result of the risk assessment, CDFA approved a Section 3 registration for the use of abamectin, (Avid 0.15 EC), in fields, shadehouses and greenhouses to control leafminers and two-spotted spider mites on flowers, foliage plants and other non-woody ornamentals.

In May 1989, the U.S. EPA (EPA) issued a conditional registration for abamectin on cotton and citrus. Temporary food tolerances were established on these commodities, as well as in animal tissues resulting from abamectin residues in animal feed (dried citrus pulp, cottonseed meal). In addition, EPA set an Acceptable Daily Intake (ADI) for abamectin at 0.0004 mg/kg/day. EPA currently uses the term, Reference Dose (RfD), rather than ADI, to indicate an acceptable level of long-term exposure to specific chemicals.

In June 1990 a CDFA risk characterization document addressed the potential human exposures from the use of abamectin, **(Zephyr 0.15 EC)**, on cotton under a Section 3 registration application. Potential occupational and dietary exposures from theoretical (tolerance) residues in cottonseed and animal tissues were evaluated. Subsequent Emergency Exemption (Section 18) dietary evaluations have addressed potential human exposure to abamectin from the consumption of strawberries, pears, celery and head lettuce.

The current Section 3 registration application is for **AVERT, PRESCRIPTION TREATMENT 310,** which contains 0.05% abamectin B_1, as a crack and crevice dust formulation. The proposed use of this product is to control cockroaches in residential, commercial (hospitals, nursing homes, hotels) or industrial (warehouses) buildings and transportation facilities (buses, ships, trains, planes). It is the first product containing abamectin as the active ingredient being proposed for indoor, residential and commercial uses.

Toxicology

The current risk assessment for potential human exposure to **Avert** has been conducted because of adverse reproductive and developmental effects reported in animal studies using the active ingredient, avermectin B_1, or the delta-8,9-photoisomer. The mouse appears to be the most sensitive animal species to these compounds. Adverse effects produced in the off-spring included malformations (cleft palate) and lethality. Toxicity to the pregnant mouse (maternal toxicity) has been characterized by tremors and lethality, and the lowest dosage at which these effects did not occur, (i.e. the no-observable-effect-level or NOEL), from studies using the parent compound, avermectin B_1, or the delta 8,9-photoisomer was 0.05 mg/kg. Although the toxicological endpoints observed in the pregnant mice are designated as "maternal toxicity", these effects are not

considered to be restricted to pregnant rodents and, therefore, are of concern to other population subgroups and species.
The NOEL of 0.05 mg/kg/day was used to quantitate the short-term risk to residents (primarily infants) and commercial applicators from potential abamectin exposure under the proposed methods to control cockroaches inside homes. This NOEL was also used to determine margins of safety from potential acute dietary exposures.

Exposure Analysis

Potential acute infant exposure was estimated under two crawling scenarios, an Equilibrium Model and a Transfer Factor Model. Potential acute dietary exposure was determined for specific population subgroups using the minimum detection level or highest allowable level (action level) for residues on the specific commodities.

Risk Evaluation

The toxicological risk from potential acute exposure to abamectin was evaluated for residents (infants) and commercial applicators from the short-term home use of this product, **Avert Prescription Treatment 300**, as a crack and crevice dust to control cockroaches. The margin of safety for the crawling infant was at least 340 using the model which gave the highest potential exposure.The margin of safety for commercial applicators, who are recommended to apply this product, was 610.

In addition, the combined exposure to abamectin from the residential use of **Avert** and from potential residues on specific food commodities was evaluated for infants and for male adults. The margins of safety for the potential combined exposure ranged from 250 for infants to 227 for the applicators.

Conclusions

The risk assessment for potential short-term exposures was based on adverse effects reported in animal developmental toxicity studies. The risk assessment concluded that the margins of safety for potential infant exposure are adequate under the two crawling scenarios and for commercial applicators. Margins of safety are also adequate for infants and adults from the potential combined exposure to abamectin from the residential use of Avert and from dietary sources. Therefore, registration of this product was recommended.

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I SUMMARY

Abamectin is the common name for avermectin B_1, a naturally occurring miticide/insecticide which is derived from the soil microorganism, Streptomyces avermitilis. The pesticidal activity of abamectin is related to the interaction with the neurotransmitter, gamma aminobutyric acid (GABA). A delta-8,9-isomer of abamectin is formed in plants by a photolytic reaction and has similar toxicological properties as the parent compound.

In 1987, a risk assessment for abamectin was conducted by the Medical Toxicology Branch, then part of the California Department of Food and Agriculture (CDFA), because of adverse developmental and reproductive effects reported in animal studies **(CDFA, 1987)**. As a result of the risk assessment, CDFA approved a Section 3 registration for the use of abamectin, **(Avid 0.15 EC)**, in fields, shadehouses and greenhouses to control leafminers and two-spotted spider mites on flowers, foliage plants and other non-woody ornamentals.

In May 1989, the U.S. Environmental Protection Agency (EPA) issued a conditional registration for abamectin on cotton and citrus **(U.S. EPA, 1989a,b)**. Temporary food tolerances were established on these commodities, as well as in animal tissues resulting from abamectin residues in animal feed (dried citrus pulp, cottonseed meal). In addition, EPA set an Acceptable Daily Intake (ADI) for abamectin at 0.0004 mg/kg/day by applying a 300-fold safety factor to the No-Observable-Effect-Level (NOEL) of 0.12 mg/kg/day, based on decreased pup survival, decreased pup weight gain and retinal alterations reported from a rat reproduction study. EPA currently uses the term, Reference Dose (RfD), rather than ADI, to indicate an acceptable level of long-term exposure to specific chemicals.

In June 1990, a CDFA risk characterization document addressed the potential human exposures from the use of abamectin, **(Zephyr 0.15 EC)**, on cotton under a Section 3 registration application **(CDFA, 1990a)**. Potential occupational and dietary exposures from theoretical (tolerance) residues in cottonseed and animal tissues were evaluated.

Dietary risk assessments have been completed for abamectin under several Federal Emergency Exemption (Section 18) applications, including strawberries **(CDFA, 1990b)**, head lettuce **(CDFA, 1990c)**, celery **(CDFA, 1990d; DPR, 1992)**, and pears **(CDFA, 1991)**. Margins of safety were adequate (i.e. greater than 100) for all population subgroups for potential acute or chronic dietary exposures under these specific programs.

I SUMMARY (continued)

The current Section 3 registration application is for **AVERT, PRESCRIPTION TREATMENT 310**, which contains 0.05% abamectin B_1, as a crack and crevice dust formulation. The proposed use of this product is to control cockroaches in residential, commercial (hospitals, nursing homes, hotels) or industrial (warehouses) buildings and transportation facilities (buses, ships, trains, planes). It is the first product containing abamectin as the active ingredient being proposed for indoor, residential and commercial uses. The product label is included in Appendix C.

The current risk assessment for potential human exposure to **Avert** was conducted because of adverse reproductive and developmental effects reported in animal studies using the active ingredient, avermectin B_1, or the delta-8,9-photoisomer. The lowest NOEL reported from acute or chronic animal studies using the parent compound, avermectin B_1, or the photoisomer, was 0.05 mg/kg, which was the value used to evaluate the daily toxicological risk to residents (primarily infants) and commercial applicators from potential abamectin exposure from the proposed use to control cockroaches inside homes. In addition, the combined exposure to abamectin from **Avert** and from potential residues on specific food commodities was evaluated. These commodities included cottonseed, celery, head lettuce, strawberries and pears.

Potential infant exposure was estimated under two crawling scenarios. The margin of safety for the crawling infant was at least 340 using the Equilibrium Model, which gave a higher potential exposure than the Transfer Factor Model. The margin of safety for commercial applicators, who are recommended to apply this product, was 610. The margins of safety for the potential combined exposure ranged from 250 for infants to 227 for an adult applicator.

The risk assessment concluded that the margins of safety for potential infant exposure are adequate under the two crawling scenarios and for male or females commercial applicators. Margins of safety are also adequate for infants and for adult males/females from the potential combined exposure to abamectin from the residential use of Avert and from dietary sources. Therefore, registration of **Avert Prescription Treatment 310** was recommended.

II INTRODUCTION

A. CHEMICAL IDENTIFICATION

Avermectin B_1 is a miticide/insecticide developed by Merck, Sharp and Dohme **(Putter et al., 1981)**. The avermectins comprise a complex of eight unique but closely related macrocyclic lactones derived from the soil microorganism, Streptomyces avermitilis. Within this group of compounds there are four major components--avermectins A_1a, A_2a, B_1a, and B_2a and four minor homologous "b" components--A_1b, A_2b, B_1b and B_2b. Among the avermectins, avermectin B_1, and to a lesser degree avermectin B_2a, have been studied for their activity against mites, insects and nematodes. Avermectin B_1 consists of two biologically active homologous avermectin components containing a minimum of 80% avermectin B_1a and a maximum of 20% avermectin B_1b **(MSD, 1985)**. The term "abamectin" has been designated as the nonproprietary common name for avermectin B_1 **(Babu, 1988)**. A delta-8,9-isomer of avermectin B_1 is formed in plants from a photolytic reaction and has similar toxicological properties as the parent compound. Avermectin B_2a, and its soil metabolite, known as avermectin B_2a -23-ketone, have been studied for their soil nematicidal activities.

Abamectin acts by stimulating the release of gamma aminobutyric acid (GABA) from nerve endings and then enhances the binding of GABA to receptor sites on the post-synaptic membrane of an inhibitory motoneuron in the case of nematodes, and on the post-junction membrane of a muscle cell, in the case of insects and other arthropods **(Babu, 1988)**. The enhancement of GABA-binding results in an increased flow of chloride ions into the cell, with subsequent hyperpolarization and elimination of signal transmission. In non-target species (e.g. vertebrates), other mechanisms of action for avermectin (and ivermectin) have been proposed, including: release of endogenous GABA from mammalian cerebral cortex synaptosomes, specific binding to membranes from mammalian brain tissue, alterations in GABA binding to membranes from mammalian brain tissue, increased chloride ion uptake by neurosynaptosomes in mammalian brain tissue **(Turner and Schaeffer, 1989)**. The relative importance of these mechanisms, particularly between laboratory animals and humans, remains to be resolved.

B. REGULATORY HISTORY

In 1987, a risk assessment for abamectin was conducted by the Medical Toxicology Branch, then part of the California Department of Food and Agriculture (CDFA), because of adverse developmental effects reported in animal studies **(CDFA, 1987)**. As a result of the risk assessment, CDFA approved a Section 3 registration for the use of abamectin, (under the trade name, **Avid 0.15 EC**), in fields, shadehouses and greenhouses to control leafminers and two-spotted spider mites on flowers, foliage plants and other non-woody ornamentals. Using surrogate pesticide data to determine potential exposures in greenhouses/shadehouses for handgun applicators and for

workers re-entering treated areas, adequate margins of safety existed for these workers provided they comply with the protective clothing requirements that are indicated on the product label. In this initial risk assessment, potential exposures to field workers (mixers, loaders, applicators) were estimated using data obtained from the actual use of abamectin during citrus applications under an Experimental Use Permit (1987). Margins of safety were calculated to be greater than 1000 for mixers, loaders and air blast applicators.

A Special Local Need (Section 24C) use had been granted in 1987 for **Avid** on field-grown roses to control leaf miners and mites.

In May 1989, the U.S. EPA (EPA) issued a conditional registration for abamectin on food crops **(U.S. EPA, 1989a)**. The registration was made conditional because data were lacking in the areas of fish and wildlife toxicity and environmental fate. A temporary tolerance of 0.005 ppm in cottonseed for the combined residues of abamectin and the delta-8,9-isomer was established by the EPA. The tolerance expires March 31, 1993.

In August 1989, EPA set temporary tolerances for residues of abamectin and the delta-8,9-isomer of 0.005 ppm in milk; 0.02 ppm in or on whole citrus and in cattle meat and meat byproducts **(U. S. EPA, 1989b)**. In addition, a food additive tolerance was established in citrus oil of 0.10 ppm and a feed additive tolerance of 0.10 ppm in dried citrus pulp. These tolerances for abamectin also expire on March 31, 1993. A temporary tolerance was recently established for the combined residues of abamectin and the delta 8,9-isomer in or on the raw agriclutural commodity, apples, at 0.035 ppm **(U.S. EPA, 1991a)**. This temporary tolerance expires June 15, 1992.

In June 1990 a risk characterization document addressed the potential human exposures from the use of abamectin, under the trade name of **Zephyr 0.15 EC**, on cotton under a Section 3 registration application **(CDFA, 1990a)**. Potential occupational and dietary exposures from theoretical (tolerance) residues in cottonseed and animal tissues were evaluated. Margins of safety for occupational exposures were above 1000. Margins of safety from theoretical dietary residues were at least 5,000 for acute consumption and greater than 12,000 for chronic consumption. Additionally, the potential exposures to handgun applicators and reentry workers from the use of abamectin in greenhouses were reassessed using exposure data obtained by the Worker Health and Safety Branch under actual use conditions **(Rech et al., 1988)**. Margins of safety from this revision of the 1987 risk characterization document were greater than 400 for the greenhouse workers.

Dietary risk assessments have been completed for abamectin **(Avid)** under several Federal Emergency Exemption (Section 18) applications, including strawberries **(CDFA, 1990b)**, head lettuce **(CDFA, 1990c)**, celery **(CDFA, 1990d; DPR, 1992)** and pears **(CDFA, 1991)**. Margins of safety were adequate for all population subgroups for potential acute and chronic dietary exposures under these limited use programs.

B. REGULATORY HISTORY (continued)

Tolerances pending approval from EPA include: almond hulls, 0.1 ppm; almonds, 0.005 ppm; celery, 0.035 ppm; lettuce, 0.05 ppm; pears, 0.035 ppm; strawberries, 0.02 ppm; tomatoes (fresh) 0.01 ppm; tomato pomace, 0.07 ppm; and walnuts, 0.005 ppm **(U.S. EPA, 1991b)**.

Because of the developmental effects reported in several animal developmental toxicity studies, the EPA established a Reference Dose (RfD) by using a more restrictive uncertainty factor of 300 applied to the No-Observable-Effect-Level (NOEL) from the rat reproduction study. The RfD, based on the NOEL of 0.12 mg/kg/day (decreased pup survival, decreased weight gain, retinal changes), was established at 0.0004 mg/kg/day **(U.S. EPA, 1989a)**

C. TECHNICAL AND PRODUCT FORMULATIONS

Abamectin is the active ingredient (a.i.) in **AVID 0.15 EC**, an emulsifiable concentrate containing 0.15 pounds of active ingredient per gallon (18 g/liter). **AVID** is currently registered by the U.S. EPA for application to field and greenhouse grown ornamental plants at a maximum rate of 0.02 pounds (0.32 oz) per acre. Other trade names used by Merck, Sharp and Dohme for this formulation include **AGRIMEC, AGRI-MEK, DYNAMEC, VERTIMEC** (West Germany) and **ZEPHYR.** Abamectin is also registered by the U.S. EPA as a 0.011% corn cob grit bait **(AFFIRM)** applied at a rate of 50 mg a.i. per acre on non-crop land for use against red fire ants. It is also used in Australia as a cattle anthelmintic and ectoparasiticide as a 1% injectable solution under the trade name **AVOMEC.**

A synthetic derivative of abamectin, 22,23-dihydroavermectin B_1, known as ivermectin has a similar toxicological profile to abamectin. Ivermectin has been used worldwide since 1981 and in the United States since 1983 in veterinary medicine to control endo- and ecto-parasites. Ivermectin is formulated as **Ivomec** for cattle, sheep and swine, and as **Equalan** for use in horses **(Campbell et al., 1983; Campbell and Benz, 1984)**. Ivermectin, as **Mectizan**, is currently being evaluated as a treatment for Onchocera volvulus (river blindness) in humans **(Awadzi et al., 1985; Cupp et al., 1986; MSD, 1988)**. In addition, ivermectin, as **Heartgard-30**, has been recently introduced as a preventative agent to control canine heartworm disease **(Anon., 1989)**.

The current Section 3 registration application is for **AVERT, PRESCRIPTION TREATMENT 310,** which contains 0.05% abamectin B_1, as a crack and crevice dust formulation. The product is for controlling cockroaches in residential, commercial (hospitals, nursing homes, hotels) or industrial (warehouses) buildings and transportation facilities (buses, ships, trains, planes). It is the first product containing abamectin as the active ingredient being proposed for indoor, residential and commercial uses. The product label is included in Appendix C.

D. PHYSICAL/CHEMICAL PROPERTIES (MSD, 1985)

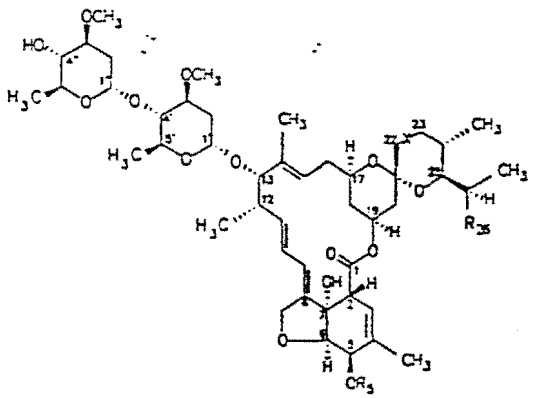
1. Chemical Name: Avermectin B_1
   - Avermectin B_{1a} (80%)
   - Avermectin B_{1b} (20%)

2. Common Name: Abamectin

3. Empirical Formula: Avermectin B_{1a} $C_{48}H_{72}O_{14}$

   Avermectin B_{1b} $C_{47}H_{70}O_{14}$

4. Chemical Structure:



components A : $R_5 = CH_3$ components 1: X = -CH=CH-

components B : $R_5 = H$ components 2: X = $-CH_2\overset{OH}{\overset{|}{C}}H-$

components a : $R_{26} = C_2H_5$
components b : $R_{26} = CH_3$

5. Molecular Weight: Avermectin B_{1a} 873.11

   Avermectin B_{1b} 859.08

6. Melting Point: 155-157°C

7. Vapor Pressure: 1.5 x 10-9 mm Hg

8. Solubility (21°C): 6-9 ug/L (water)
   100 mg/ml (acetone)
   350 mg/ml (toluene)

E. ENVIRONMENTAL FATE

Note: Although the principle use of this product would be indoors, the product label allows for outdoor use. Therefore, the Environmental Fate Section, which addresses the distribution and persistence of abamectin and the delta 8,9-photoisomer primarily from agricultural uses, has been included in this document.

Hydrolysis

Hydrolysis is not a primary factor in the environmental breakdown of abamectin. Buffered aqueous solutions of avermectin B_1a at pH 5, 7, and 9 were incubated at 25°C for 28 days. Solutions were fortified with a 2% avermectin formulation containing proprietary emulsifiers to a concentration of 10 ug/ml **(Maynard and Ku, 1982)**. At the end of the incubation period 95% of the avermectin was recovered; the 5% loss was not attributed to hydrolysis.

Photolysis:

Photodegradation is a prominent and toxicologically significant process in the transformation of abamectin. The delta 8,9-isomer of avermectin B_1a, which is one of the photodegradation products, has similar qualitative and quantitative toxicological properties to the parent compound.

In one study, the half-life of avermectin B_1a in aqueous solution and on soil surfaces was 18 hours **(Ku and Jacob, 1983a)**. The degradation was enhanced by sunlight.

Avermectin B_1a applied to soil surfaces under simulated field conditions (outdoor tanks) was found to degrade rapidly when exposed to sunlight **(Wislocki, 1986)**. The half-life of avermectin B_1a on soil under these conditions was 5 to 10 hours.

The half-lives of avermectin B_1a in aqueous suspensions and thin soil plates exposed to sunlight were 3.5 to 12 hours, and 21 hours, respectively **(Ku and Jacob, 1983b)**. The non-polar photodegradation products consisted of the delta 8,9-isomer of B_1a and an unidentified, moderately polar isomer of avermectin B_1a.

Microbial Degradation

Aerobic and anaerobic soil metabolism of avermectin B_1a was examined under laboratory conditions over a three month period **(Ku and Jacob, 1983c)**. Under aerobic conditions the half-lives in sandy loam soil were 20 days at concentrations of 0.1 and 1.0 ppm, and 40 days at 50 ppm. The half-lives in clay soil were 28 and 36 days at 0.1 and 1.0 ppm, respectively. The half-life in sandy soil at 1.0 ppm was 47 days. Avermectin degraded to approximately the same 13 radioactive products in all of the soil types tested. The major soil degradation products were the 8 alpha-hydroxy derivative and the corresponding open ring aldehyde derivative of avermectin B_1a.

E. ENVIRONMENTAL FATE (continued)

Under anaerobic conditions no apparent degradation occurred during the three month storage period. The amount of bound, unextractable radioactivity increased with time indicating that avermectin does bind to all of the soil types examined.

Aerobic and anaerobic degradation of tritium-labeled avermectin B_1a was examined in fine sandy loam (Lufkin) and clay (Houston) soil under dark conditions for 100 days **(Bull, 1985)**. The reported half-life under aerobic conditions in sandy loam soil was 14 days. In clay soil the half-lives increased to 28 days at 0.1 ppm and 50 days at 1.0 ppm. The half-life of ^3H avermectin at the concentration of 1.0 ppm in a course sand soil was cited as eight weeks. There was no degradation of ^{14}C avermectin in sandy loam soil held under anaerobic conditions.

Avermectin B_2a was incubated in a sandy loam soil under greenhouse conditions **(Gullo, et al., 1983)**. It was rapidly degraded to a 23-keto metabolite with an apparent half-life of 2.5 to 3 days for the parent material .

Soil Mobility

The leaching potential of avermectin B_1a was examined in six soil types. Soil thin-layer plates were prepared with loam, silt loam, clay loam, sandy loam, and sand (two types) soils and treated with ^{14}C avermectin. Avermectin B_1a was classified as immobile based on comparisons of the soil thin-layer plate autographs **(Ku and Jacob, 1983c)**.

The leaching potential of avermectin B_1a was examined in unaged and aged sand, sandy loam, clay loam, and silt loam soils **(Ku and Jacob, 1983c)**. Soil columns were fortified with either ^{14}C or ^3H avermectin B_1a and exposed to the equivalent of 22-23 inches of rain over a 28 day period. Results were similar for the aged and unaged soils, irrespective of the type of soil. In all cases, greater than 79% of the radioactivity remained in the upper 6 cm of the soil column. Avermectin B_1a degraded into several unidentified polar metabolites in all of the soils studied. Avermectin is considered to have a low leaching potential in all of the soils examined.

Avermectin B_1a was applied to fallow ground at the rates of 0.02 and 0.04 lbs a.i./200 gal water/acre every seven days for 12 weeks **(Jenkins, 1986)**. The leaching potential of avermectin was examined up to 90 days after the last application. The field site was located in Florida and the soil type was a fine sand ammended with peat. Avermectin residue levels indicated that there was substanial residue carry over from repeated weekly applications. No residues were found at the 4-6 inch soil depth post-application, indicating that avermectin is relatively immobile even in sandy soils.

E. ENVIRONMENTAL FATE (continued)

The potential for avermectin B_1a to drift or drain from application sites and contaminate aquatic environments was examined under simulated field conditions **(Wislocki, 1986)**. In a mobility study, the highest level of avermectin found in the water was on day one (0.052 ppb) and in the sediment on day two (0.091 ppb). The half-life of avermectin in water was four days, and in sediment the half-life was two to four weeks. Avermectin binds strongly to sediment or soils (K_{oc} = 4940). Under simulated runoff conditions, fortified, aged soils with concentrations of avermectin B_1a up to 16 ppb introduced into an aquatic environment did not result in detectable levels of avermectin in water or sediment (Minimum Detection Limit, MDL, = 0.1 ppb). Data indicate that avermectin use under field conditions would result in minimal contamination of aquatic ecosystems through drift or runoff.

The dissipation of residues from fruit and soil was examined following four applications of avermectin B_1a to a Florida tangelo grove **(Guyton, 1986)**. Formulated avermectin B_1a was applied at the rates of 0, 0.025, and 0.05 lbs a.i./acre to three field plots (blanton fine sand) at intervals of approximately three months. At the maximum recommended use rate, avermectin B_1a residues ranged from 0.001 to 0.003 ppm in the 0-2 inch depth on day 0 and were not detected (MDL = 0.003 ppm) on day 1. Avermectin was not detected in subsequent soil samples at all sampling depths. The data indicate that initial avermectin residues are low following an application, they dissipate rapidly from the soil surface, and do not leach or translocate through the soil under the conditions encountered during this study.

Plant Residues

The degradation and translocation of ^{14}C or ^{3}H avermectin B_1a were examined on and in foliage following application to cotton plants **(Bull, et al., 1984)**. Additionally, the potential uptake of avermectin B_1a residues by cotton plants grown in previously treated soil was examined **(Bull, 1985)**. The parent compound was found to be unstable on the leaf surface with a half-life of approximately 24 hours. The degradation of surface residues was presumed to be due to photolysis. In conjunction with photodegradation, avermectin residues on the leaf surfaces of cotton plants can also be removed by heavy dew and rainfall. The plant uptake studies indicated that after two months following two averemctin applications radioactive residues were found throughout the plant with the highest concentrations in the foliage (0.4 ppm) and the lowest concentrations in the lint (0.04 ppm) and seeds (0.09 ppm). Small amounts of radioactivity was found in cotton seedlings grown in soil previously treated with avermectin at the rate of 10 ppm. Approximately 0.1 ppm radioactivity was detected in the stem and leaf samples and 3 ppm in root samples.

One of the primary photodegradation products of avermectin B_1a is the delta 8,9 isomer. The delta-8,9-photoisomer of avermectin B_1a can comprise between 5 and 10% of the residue on cotton **(U.S. EPA, 1989c)**. In addition to the parent compound and the delta-8,9-

photoisomer, polar metabolites ("degradates") can constitute up to 70% of the total residue on cotton . The polar metabolites do not have the same toxicological properties as the parent avermectin B_1a or the 8,9-isomer (See Toxicology Profile Section).

In spite of the observed rapid degradation of the surface deposits, abamectin can show high post-application residual insecticidal activity on leaves. This anomaly can be explained by the translaminar activity of abamectin, which is the movement of the chemical from the surface into the leaf. This activity has been demonstrated in bean, cotton and chrysanthemum leaves, where the variability in penetration capability is thought to be from differences in the amount or types of cuticular waxes **(Babu, 1988)**. The rapid disappearance of the surface deposits of abamectin is an advantage in terms of nontarget, beneficial organisms, such as honeybees, and with regard to agricultural workers who come in contact with plant foliage.

Lemon, grapefruit, and orange trees were treated with ^{14}C labeled avermectin B_1a applied as formulated material at 1x and 10x the proposed field rate of 0.025 lbs a.i./acre **(Maynard, et al., 1989a)**. A second degradation study was performed in the laboratory with oranges collected from untreated trees. The individual fruits were treated with ^{14}C or ^{3}H avermectin at approximately 1x, 10x, or 25x the application rate of 0.025 lbs a.i./500 gal water per acre **(Maynard et al., 1989b)**. Results from the field and laboratory studies were similar. The degradation of avermectin from the fruits appears to be biphasic. Within the first week, 78-94% of the avermectin B_1a degraded into volatile and non-volatile components. The rate of degradation was considerably slower after the first week. Most of the degradation occurred on the fruit surface. However, avermectin was found to "rapidly" partition from the fruit surface into the rind where avermectin was apparently protected from further degradation. Within two to four weeks after treatment, most of the radioactivity was found in the rind when compared with the fruit surface. Although the investigators did not identify the degradation products, they believe that non-volatile ^{14}C avermectin residues may have been incorporated into linoleic fatty acid esters. Under field conditions, the half-life of avermectin B_1a on citrus fruits during a twelve week study period ranged from 20-38 days depending on the type of citrus fruit (lemon < grapefruit < orange).

A rotational crop study was performed to determine if avermectin residues resulting from treatments to cotton would affect subsequent plantings of grain, and root and leaf vegetables **(Moye, 1986)**. ^{14}C avermectin B_1a was applied to sandy, sandy loam, and muck soils at 1.25 to 1.5x the maximum rate of 0.02 lbs a.i./acre for cotton.

E. ENVIRONMENTAL FATE (continued)

Three applications at 50 day intervals or 12 applications at 7 day intervals were performed. Vegetables were planted in treated soils 30, 120, and 365 days after the last avermectin application. The total amounts of residue found in the rotated crops were uniformly low regardless of time of planting or harvesting. Radiolabeled residues in these crops ranged from below the level of quantification (8.33 to 9.66 ppb) to 11.6 ppb. Although residues were not identified, they may be comprised of a firmly bound form of the parent compound and/or breakdown products, or a breakdown product that is chemically disimilar to the parent compound because most residues were not extractable.

III TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Avermectin

Animal metabolism studies with avermectin B_1a or the delta-8,9 isomer were conducted to determine the distribution, excretion and metabolite formation **(Maynard et al., 1986a, 1986b)**. Radiolabeled (^{14}C and/or ^{3}H) parent compound or 8,9-isomer were administered orally to rats and goats. The results indicated that the majority of avermectin B_1a was excreted unchanged in the feces. Two metabolites were identified in the rat and one in the goat.

Oral-Rat

Rats were given single oral doses of vehicle, 0.14 mg/kg, or 1.4 mg/kg of ^{14}C and/or ^{3}H avermectin B_1a **(Maynard et al., 1986a)**. Urine and feces samples were collected daily. Three rats were sacrificed at 1, 2, 4, or 7 days after dosing. There was 85 to 95% recovery in the feces, urine and tissues. The majority of the dose, 69-82%, was eliminated in the feces, with approximately 1% or less of the radioactivity in the urine. Most of the radioactivity was eliminated in the first 4 days after dosing. Residues were 7-11% in the gastro-intestinal tract and 2-3% in the muscle tissue. The average half-life of the parent compound in the tissue of male and female rats was approximately 1 day.

Two major metabolites were identified in the muscle tissue and were designated as 24-hydroxymethyl avermectin B_1a and 3"-desmethyl avermectin B_1a. Minor amounts of non-polar conjugates of these two metabolites were also identified in the non-polar fraction of fat tissue.

Oral-Goat

Lactating goats were orally administered ^{3}H-avermectin B_1a at doses of 0.005, 0.05 or 1.0 mg/day for 10 days **(Maynard et al., 1985)**. Unchanged parent avermectin B_1a accounted for 37-99% of the recovered radioactivity, with the 24-hydroxymethyl metabolite ranging from 1-54%. The majority of the excreted radioactivity was in the feces, with less than 1% appearing in the urine. Little radioactivity was detected in the tissues of the low dose group, where most tissue values were at or near the minimum level of quantitation of 0.2 ppb. In the mid- and high-dose groups, the highest residue levels were found in the liver, which was followed by fat, kidney and muscle. At least 84% of the residues were unchanged avermectin B_1a.

Data from the two goats in the high dose group (~20 ug/kg/day) indicate that avermectin B_1a has the potential to partition from the blood into the milk. The mean concentrations measured in the milk of the two animals were approximately 2-3 times higher than the blood concentrations, as early as one day after the initial dosing. The highest mean milk "concentration factor" was 3.5 times on day 4.

A. PHARMACOKINETICS (continued)

Oral-Cow

On the other hand, a feeding study conducted with lactating Holstein dairy cows indicated that avermectin only appeared in the milk of the high dose animals (100 ppb) after day 7 and only at a maximum concentration of 2 ng/ml **(Wehner and Baylis, 1986)**. The plasma concentration of avermectin from days 7 through 28 was 2-3 ng/ml, indicating no increased tendency for the compound to partition into the milk of these animals.

Ivermectin

Oral-Rat

The partitioning from the blood into the milk of lactating rats has also been reported for the structurally similar chemical, ivermectin **(MSD, 1980)**. Sexually mature female rats were given tritium-labelled ivermectin orally at a dose of 2.5 mg/kg/day for 61 days and throughout mating, gestation and lactation until Day 9 postpartum. The concentrations of ivermectin in the milk was 3-4 times higher than maternal plasma concentrations on comparable days postpartum. Plasma levels of ivermectin in the offspring were low on Day 1 postpartum but increased rapidly until, on Days 6 and 10 postpartum, the concentration of ivermectin in the plasma of the pups was approximately 2-3 times greater than that measured in the lactating dam. The results of this study indicate that the high concentration of ivermectin in the milk of lactating dams, who were administered the compound daily for over 60 days, was probably responsible for the acute toxicity observed in the offspring during the neonatal period.

Oral-Human

In contrast to the results from the rat study, clinical studies using human volunteers indicated that ivermectin **(Mectizan)** does not partition into breast milk at therapeutic doses which would be used in the treatment of onchocerciasis **(MSD, 1988)**. A single oral dose of 12 mg **Mectizan** (~ 200 mcg/kg) was administered to 12 lactating women who were not breast feeding or contributing to "milk banks." Breast milk and blood were collected 1, 4, and 12 hours post-treatment and daily thereafter for 14 days for milk samples and for three days for blood samples. The peak mean concentrations of ivermectin in breast milk and plasma occurred four hours following treatment and were approximately 3-times lower in milk than plasma.

Delta 8,9-Isomer

Oral-Rat

The metabolism of the delta-8,9-isomer of avermectin B_1a was determined in rats given a single oral dose of ^{3}H-labeled material at 1.4 mg/kg **(Maynard et al., 1986b)**. Daily urine and fecal samples were collected, and tissues samples were collected at the end of the seven day study. Approximately 94% of the radioactivity was excreted in the feces, and less than 1% was found in the urine. The tissue half-life was approximately 1 day. Two metabolites were identified, 3"-desmethyl-delta-8,9-isomer (3% of dose) and 24-hydroxymethyl-delta-8,9-isomer (<1% of dose).

B. ACUTE TOXICITY

		Ref.
TECHNICAL MATERIAL		
Oral LD_{50} (rat):	8.7 mg/kg (M) 12.8 mg/kg (F)	1
Oral LD_{50} (mouse): (M/F)	13.6 mg/kg (sesame oil) 29.7 mg/kg (methyl cellulose)	2
Dermal LD_{50} (rabbit): (M/F)	2,120 mg/kg	3
Eye Irritation (rabbit):	Slightly irritating (Category III)	4
Dermal Irritation (rabbit):	Non-irritating	5
Dermal Sensitization: (guinea pig)	Negative	6
EMULSIFIABLE CONCENTRATE (1.8%)		
Oral LD_{50}(rat) (M/F)	0.722 ml/kg (0.650 g/kg)	7
Dermal LD_{50} (rabbit): (M/F)	>2.23 ml/kg	8
Inhalation LC_{50} (rat): (M/F)	1.062 mg/L (Category III)	9
Eye Irritation (rabbit):	Slight to moderate (Category III)	10
Dermal Irritation (rabbit):	Slight (Category III)	11
DELTA-8,9-PHOTOISOMER		
Oral LD_{50}(mouse): (M/F)	>80 mg/kg	12
POLAR METABOLITES		
Oral LD_{50}(mouse):	>5000 mg/kg	13

Acute Toxicity Refs: (1) Robertson, 1981a; (2) MSD, 1985; (3) Gordon, 1984a; (4) Robertson 1981b; (5) Robertson, 1983; (6) Gordon, 1983; (7) Everett, 1983; (8) Stolz, 1983a; (9) Terrill, 1984; (10) Stoltz, 1983b; (11) Stoltz, 1983c; (12) Gordon et al., 1986; (13) Gordon et al., 1984.

B. ACUTE TOXICITY (continued)

AVERT FORMULATION

Oral LD_{50} (rat): (M/F)	> 5.0 g/kg (Cat. IV)	(14)
Dermal LD_{50} (rabbit):	> 2.0 g/kg (Cat. III)	(15)
Inhalation LC_{50} :	Particle size not inhalable	(16)
Eye Irritation :	Category III	(17)
Dermal Irritation:	Category IV	(18)
Dermal Sensitization	Negative	(19)

Acute Toxicity Refs.: (14) Biosearch Inc., 1987a; (15) Biosearch Inc., 1987b; (16) Whitmire Research Lab. Inc., 1990; (17) Biosearch Inc., 1987c; (18) Biosearch Inc., 1987d; (19) Biosearch Inc., 1987e.

C. SUBCHRONIC TOXICITY (1.8% Emulsifiable Concentrate)

Several multi-exposure dermal toxicity studies were performed with the 1.8 % emulsifiable concentrate using rabbits **(MITR, 1984)**. The lowest NOEL for mortality and tremors was 125 mg/kg. Possible testicular degeneration was indicated; however, subsequent studies demonstrated that this effect was caused by the stress of restraint methods. No other potential adverse effects were indicated.

D. CHRONIC TOXICITY/ONCOGENICITY

Dietary-Rat

A combined two year chronic toxicity-oncogenicity feeding study with rats was performed using abamectin at dose levels of 0, 0.75, 1.5, or 2.0 mg/kg/day **(Gordon, 1984b)**. The NOEL for tremors was 1.5 mg/kg/day. Oncogenic effects were not found. This 105 week study was considered acceptable based on FIFRA Guidelines.

Dietary-Dog

A one year chronic dog feeding study was performed using abamectin at dose levels of 0, 0.25, 0.5, or 1.0 mg/kg/day **(Gordon, 1984c)**. The NOEL for mydriasis was less than 0.25 mg/kg/day. Animals experienced decreased body weight gain, possibly from inappetence for treated food, slight decreases in serum urea nitrogen in the high dose group, and slight decreases in alkaline phosphatase and alanine aminotransferase activities in the high and middle dose groups. The NOEL for decreased body weight gain and alterations of clinical chemistry was 0.25 mg/kg/day. This study was considered acceptable based on FIFRA Guidelines.

D. CHRONIC TOXICITY (continued)

Dietary-Mouse

A two year combined chronic toxicity-oncogenicity feeding study in mice was performed using avermectin at dose levels of 0, 2, 4, or 8 mg/kg/day **(Gordon,1985)**. The NOEL for increased mortality was 2 mg/kg/day. The NOEL for tremors was less than 2 mg/kg/day. Oncogenic effects were not found. This 94 week study was considered acceptable based on FIFRA Guidelines.

E. GENOTOXICITY

Avermectin

Several genotoxicity studies were conducted in three areas: gene mutation **(Gordon, 1986a; MSD, 1986a; Gordon, 1983b; Gordon, 1986b)**, chromosomal aberration **(Gordon, 1983a; Gordon, 1986c)**, and DNA damage and repair **(Gordon, 1983a)**.

The studies using several strains of Salmonella, with and without metabolic activation, were all negative. The gene mutation study using Chinese hamster V79 cells showed no increase in mutation frequency up to cyctotoxic concentrations.

An in vivo mouse chromosomal aberration study indicated no evidence of an increase in aberrations after male animals were given up to 12 mg/kg by oral gavage. An in vitro study using CHO-WBL cells showed no increase in aberrations with or without metabolic activation at cytotoxic concentrations.

A DNA damage study using rat hepatocytes in vitro, or after oral gavage, showed single strand breaks in DNA at cytotoxic concentrations in vitro, but no effects on the DNA in vivo up to 10.6 mg/kg (the oral LD_{50}).

Delta 8,9-Isomer

Microbial mutagenicity assays using several strains of Salmonella typhimurium or E. coli were conducted with and without metabolic activation **(Gordon, 1988a)**. There was no evidence of an increase in reversion rate in any strain.

Polar Metabolites

Microbial mutagenicity assays using several strains of Salmonella typhimurium or E. coli were conducted with and without metabolic activation **(Gordon, 1988b)**. The results indicated no increase in reversion rate.

F. REPRODUCTIVE TOXICITY

Avermectin

Two supplemental and one definitive rat reproduction studies have been performed using abamectin. The acceptable, definitive study was a two generation, two litter per generation oral gavage study using dose levels of 0, 0.05, 0.12 or 0.40 mg/kg/day **(Hoberman, 1984)**. The parental NOEL was greater than 0.40 mg/kg/day. The reproductive NOEL was 0.12 mg/kg/day and was based on decreased pup survival **(Table 1)**, decreased weight gain and retinal alterations, which were characterized by an increase in retinal folds with pigmented epithelium **(Table 2)**.

Delta 8,9-Isomer

The delta 8,9-isomer of abamectin was administered by oral gavage to groups of 20 Crl:CD (SD) BR female rats at doses of 0, (sesame oil control), 0.06, 0.12 or 0.40 mg/kg/day from 15 days prior to cohabitation through day 20 of lactation (one generation) **(Gordon, 1988c)**. There were no signs indicating that a Maximum Tolerated Dose (MTD) had been achieved during the study, and no treatment-related maternal or reproductive effects were noted, including gross and histo-morphological eye examinations on weanling-aged offspring. The maternal and reproductive NOEL was greater than 0.40 mg/kg/day, the highest dose tested.

Table 1 Post-natal survival of rat pups given abamectin for two generations by oral gavage

Generation		Dosage (mg/kg/day) 0	0.05	0.12	0.40
F1a					
	No. Surviving	221/222	226/226	259/261	117/222
	%	99.5	100	99.2	52.7*
F1b					
	No. surviving	193/197	199/202	237/239	84/140
	%	98.0	98.5	99.2	60.0**
F2a					
	No. surviving	230/230	201/201	216/217	169/180
	%	100	100	99.5	93.9*
F2b					
	No. surviving	174/174	105/106	174/175	129/139
	%	100	99.1	99.4	92.8*

Statistical significance: * $p < 0.05$; ** $p < 0.01$

F. REPRODUCTIVE TOXICITY (continued)

Table 2 Incidence of retinal abnormalities in rat pups given abamectin for two generations by oral gavage

	Dosage (mg/kg/day)							
	0		0.05		0.12		0.40	
Generation								
F1b	M	F	M	F	M	F	M	F
	0/5++	1/5	1/5	0/5	1/5	0/5	3/4*	1/5
F2b	M	F	M	F	M	F	M	F
	3/57++	2/51+++	0/26	1/34	5/88	2/86	10/63a	18/66***

Trend test: ++ $p < 0.01$; +++ $p < 0.001$
Fisher's Exact (Pair-wise): * $p < 0.05$; *** $p < 0.001$
a/ $p = 0.056$

G. DEVELOPMENTAL TOXICITY

Avermectin

Gavage-Rat

A rat teratology study was performed by gavage using dose levels of avermectin b_1a at 0, 0.4, 0.8, or 1.6, mg/kg/day **(Gordon, 1982)**. A pilot study was performed using 2 mg/kg/day as the highest dose. The NOEL for maternal toxicity was estimated to be greater than 1.6 mg/kg/day but less than 2.0 mg/kg/day, based on maternal mortality (1/10 animals) in the pilot study. The NOEL for fetotoxicity was 1.6 mg/kg/day, based on the lack of fetal malformations greater than historical controls.

Gavage-Rabbit

A rabbit teratology study was performed by gavage using dose levels of avermectin b_1a at 0, 0.5, 1.0, or 2.0 mg/kg **(Gordon, 1982)**. The NOEL for maternal toxicity was 1.0 mg/kg based on decreased body weight. The NOEL for developmental toxicity was 1.0 mg/kg based on skeletal malformations, cleft palate and clubbed foot, which occurred at 2.0 mg/kg/day.

G. DEVELOPMENTAL TOXICITY (continued)

Gavage-Mouse

Two CF_1 mouse teratology studies were performed using the parent avermectin B_1a. In the initial study avermectin B_1a was given by oral gavage to 20 pregnant mice per dose at levels of 0, 0.1, 0.2, 0.4 or 0.8 mg/kg **(MSD, 1986b)**. The NOEL for cleft palate was 0.2 mg/kg; however, maternal toxicity, as indicated by tremors, occurred at the lowest dose tested, 0.1 mg/kg/day **(Table 3)**. A subsequent study was performed in pregnant mice at doses of 0, 0.025, 0.05, 0.075 or 0.1 mg/kg **(MSD, 1986c)**. The NOEL for maternal toxicity was established at 0.05 mg/kg, based on tremors and death at the next highest dose of 0.075 mg/kg **(Table 4)**. In this study at 0.075 mg/kg/day, one out of 20 female mice experienced treatment-related tremors after the second dose (day 2) and was subsequently sacrificed because the animal went into a coma and aborted after the 4th dose (day 4). At the highest dose of 0.1 mg/kg/day, one animal was found dead after the 3rd dose, preceded by severe tremors. Tremors were also observed in two other animals at this dose and time **(Table 4)**.

Table 3 Incidence of severe effects reported in the initial CF-1 mouse teratology study using avermectin B_1a

	Dosage (mg/kg/day)				
	0	0.1	0.2	0.4	0.8
Maternal toxicity (death)	0/40[a]	1/20	0/20	3/20	2/20
Maternal toxicity (tremors)	NR[b]	yes	NR[b]	yes	no
Cleft palate	1/1[c]	1/1	0	4/2	5/2

a/ There were two groups of control animals, 20/group
b/ Not reported
c/ Fetuses/litter

Table 4 Incidence of severe effects reported in the second CF-1 mouse teratology study using avermectin B_1a

	Dosage (mg/kg/day)				
	0	0.025	0.05	0.075	0.10
Tremors associated with death	0/20	0/20	0/20	1/20	1/20
Tremors	0/20	0/20	0/20	0/20	2/20

Delta 8,9-Isomer

Gavage-Mouse

In the mouse developmental toxicity studies using the delta 8,9-photoisomer, the NOEL for maternal toxicity was established at 0.1 mg/kg/day, based on one death at the next highest dose of 0.5 mg/kg/day. The initial study used dose levels of 0, 0.015, 0.03, 0.1 or 0.5 mg/kg/day **(MSD, 1986d)**. The NOEL for teratogenicity, based on exencephaly, was 0.015 mg/kg/day. Cleft palate also occurred with a probable NOEL of 0.015 to 0.03 mg/kg/day **(Table 5)**. A subsequent study using doses of 0, 0.015, 0.03 or 0.06 mg/kg/day again established the NOEL for exencephaly at 0.015 mg/kg/day, but the NOEL for cleft palate was considered to be 0.06 mg/kg **(MSD, 1986e) (Table 6)**. The further review of additional data, which presented the historical incidence of exencephaly in untreated CF-1 mice, lead to the conclusion that exencephaly was not related to treatment with the delta 8,9-photoisomer **(MSD, 1989)**. However, cleft palate was still considered treatment-related with a NOEL of 0.06 mg/kg. EPA concluded that the over-all NOEL for teratogenicity in the mice given the delta 8,9-isomer was 0.06 mg/kg, based on cleft palate.

Gavage-Rat

The delta 8,9-isomer of avermectin b_1 was administered by oral gavage to groups of 25 Crl:CD (SD) BR mated female rats at doses of 0 (sesame oil control), 0.25, 0.5 or 1.0 mg/kg/day on days 6-17 of gestation **(Gordon, 1988d)**. There were no signs indicating that a MTD was achieved during the study. While maternal weight gain was significantly increased at 0.5 and 1.0 mg/kg during the treatment period, there were no adverse treatment-related maternal or developmental effects reported. The maternal and developmental NOEL were equal to or greater than 1.0 mg/kg, the highest dose tested.

G. DEVELOPMENTAL TOXICITY (continued)

Table 5 Incidence of effects reported in the initial CF-1 mouse teratology study using the 8,9-isomer of avermectin B_1

	Dosage (mg/kg/day)				
	0	0.015	0.03	0.1	0.5
Litters exam	23	24	23	24	23
Litters with malformations	1	3	3	2	9
(%)	4	13	13	8	39
Exencephaly	1[a]	1[a]	5[b]	0	1
Open eyelid	1[a]	1[a]	3[b]	1	0
Cleft palate	0	1	1	6/1[c]	24/6[c]
Cleft lip	0	0	0	1	0

a/ same fetus
b/ both findings in 3 fetuses; 5 exencephaly in 2 litters
c/ fetuses/litter

Table 6 Incidence of effects reported in the second CF-1 mouse teratology study using the delta 8,9-isomer of avermectin B_1

	Dosage (mg/kg/day)			
	0	0.015	0.03	0.06
Litters exam.	22	22	23	22
Litters with malformations	1	2	4	2
(%)	5	9	17	9
Exencephaly	0	0	3[a]	3/2[b]
Cleft palate	0	1	0	0

a/ one in a dead fetus, in separate litters
b/ fetuses/litter

G. DEVELOPMENTAL TOXICITY (continued)

Polar Metabolites

Gavage-Mouse

Polar metabolites obtained from thin-film dish photolysis were administered by oral gavage to groups of 25 Crl:CF_1 BR female mice on days 6-15 of gestation at doses of 0 (0.5% methyl cellulose control), 0.25, 0.5 or 1.0 mg/kg/day **(Gordon, 1988e)**. There were no signs indicating that a MTD was achieved in this study. A slight, non-significant increase in cleft palate at the high dose was not considered treatment related. There were no other maternal or developmental observations suggestive of a treatment related effect. The maternal and developmental NOEL was estimated to be equal to or greater than 1.0 mg/kg/day, the highest dose tested.

Polar metabolites, which were derived from citrus, were administered to groups of 25 mated Crl:CF_1 BR female mice by oral gavage on days 6-15 of gestation at 0 (0.5% methyl cellulose control), 0.25, 0.5 or 1.0 mg/kg/day **(Gordon, 1988f)**. At each of the three treatment doses, there was a slight, statistically non-significant decrease in maternal weight gain that was insufficient to establish a MTD. No treatment related developmental effects were observed in this study. The maternal and developmental NOEL were considered to be equal to or greater than 1.0 mg/kg/day, the highest dose tested.

H. NEUROTOXICITY

Since abamectin is not an organophosphate, delayed neuropathy studies are not required for registration. However, several of the studies reported the development of tremors and, in some cases, the loss of righting ability. These effects would be expected from the putative property of avermectin B_1 in enhancing GABA activity. When histological examinations were performed on neural tissue from animals exhibiting CNS toxicity, no morphological alterations were seen.

IV RISK ASSESSMENT

A. HAZARD IDENTIFICATION

Adverse reproductive and developmental effects have been reported in animal studies using the parent compound, avermectin B_1, or the delta-8,9-photoisomer. A two generation rat reproductive study using avermectin B_1 established a NOEL of 0.12 mg/kg based on decreased pup survival, decreased weight gain and retinal alterations. A rat teratology study established the NOEL for both maternal toxicity and teratogenicity at 1.6 mg/kg. The NOEL for maternal toxicity and teratogenicity (skeletal malformations) in a rabbit teratology study was 1.0 mg/kg. In teratology studies using the CF_1 mouse, cleft palate was reported at 0.4 mg/kg, with the NOEL at 0.2 mg/kg. The NOEL for fetotoxicity (lethality) was also 0.2 mg/kg. The lowest dosage producing systemic toxicity, characterized by tremors and/or lethality, in pregnant mice was 0.075 mg/kg, with a NOEL established at 0.05 mg/kg. In the studies using the 8,9-photoisomer, the maternal NOEL for the CF_1 mouse was 0.1 mg/kg, and the NOEL for teratogenicity, based on cleft palate, was 0.06 mg/kg. The lowest NOEL reported from studies using the parent compound or the photoisomer was 0.05 mg/kg and was the value used to evaluate the acute toxicological risk from the residential use of abamectin as the active ingredient in **Avert Prescription Treatment 310.**

The potential long term (chronic) toxicological risk from the residential use of **Avert** was not quantified because: 1) the NOEL used to assess acute risk is 2.4 times lower than the NOEL for chronic risk (i.e. 0.05 mg/kg/day vs. 0.12 mg/kg/day), 2) the potential exposure from repeated use of **Avert** would be equal to or less than the absorbed daily dosage (ADD), depending on the ratio of exposure days/potential exposure days. Therefore, adequate margins of safety under an acute exposure scenario would also be adequate under any potential long term exposure. In addition, a combined occupational and chronic dietary assessment was not conducted since a previous chronic dietary assessment **(CDFA, 1991)** indicated MOSs of at least 30,000 for all population subgroups from the potential combined consumption of the commodities considered in the present acute dietary assessment.

B. EXPOSURE ASSESSMENT

Residential

An estimate of potential human exposure was provided by the Worker Health and Safety Branch of the Department of Pesticide Regulation (See Appendix B). The primary concern was the exposure to small children who could potentially come in contact with the bait through crawling activities. Additionally, an estimate of exposure for a commercial applicator was developed using surrogate data from the use of carbaryl, as a dust formulation, on homegrown vegetables.

B. EXPOSURE ASSESSMENT (continued)

The individual and combined dosage from oral, dermal and inhalation routes were calculated for a 9 kg infant using the following exposure scenarios:

Equilibrium Model: This model assumes that the residue on a surface comes to equilibrium with the residue on the body; therefore, the dermal exposure is equal to the body surface area exposed. It is assumed that a 9 kg infant has a body surface area of ~3900 cm^2 (See Table 1, Appendix B).

Transfer Factor Model: This model provides the best estimate of potential human exposure through contact with household surfaces. The estimated transfer factor for an infant is ~ 800 cm^2/hr., based on a 3500 cm^2/hr. transfer factor for an adult, multiplied by the ratio of the infant/adult body surface areas (See Table 2, Appendix B).

The potential daily exposure and estimated absorbed daily dosage for a 9 kg infant using the equilibrium and transfer factor models are presented in **Table 7**. The potential exposure and dosage for the crawling infant were calculated as an average of the potential exposures for day 1 and day 2 after application (See Tables 1 and 2, Appemdix B). The justification for using a two day average, rather than the highest single day value immediately after application (i.e. day 1), was based on the time after treatment of pregnant mice required to observe the response used to set the NOEL of 0.05 mg/kg/day. The first reported appearance of tremors in the pregnant mice at the LOEL dosage of 0.075 mg/kg/day was on day 2 of treatment with abamectin.

Table 7 Potential Infant Exposure to Abamectin from the Residential Use of **Avert**

	Potential Exposure (ug/infant/day)	Absorbed Daily Dosage[b] (ug/kg/day)
Equilibrium Model	2.64[a]	0.147
Transfer Factor Model	2.39[a]	0.087

a/ Two day average combined oral, dermal and inhalation exposure. See Tables 1 and 2 in Appendix B for exposures from specific routes.

b/ Infant body weight is 9 kg; dermal absorption is 1% **(MSD, 1986f)**; breathing rates are 4.2 liters/min. (light activity) and 1.5 liters/min.(resting); inhalation absorption is 50%; oral absorption is 100%

B. EXPOSURE ASSESSMENT (continued)

Commercial Applicator

The combined dermal and respiratory exposure for a commercial applicator was estimated assuming a 6-hr. work day during which 12 containers of **Avert** would be used (See Table 3, Appendix B). The resulting absorbed daily dosage (ADD) was 0.082 ug/kg/day for a 70 kg male. Although potential exposure and an absorbed daily dosage for a female applicator was not quantified, the exposure estimates for the male applicator would likely be greater since breathing rates for males are generally higher than for females and approximately 82% of the total potential exposure was from the respiratory route. Significant gender differences with regard to potential dermal exposure are unlikely since the ratios of body surface area to body weight are comparable for males and females[1].

Dietary

Residue Data

The commodities and corresponding residues used to assess the dietary exposure to abamectin are presented in **Table 8**. These residue levels had been used in previous dietary exposure assessments. Tolerances currently exist for cottonseed and resulting by-products for the use of abamectin on cotton under the Section 3 registration. The other commodities have an action level under a current or pending Section 18 registration.

Dietary Assessment

An acute dietary exposure analysis was conducted using the software program, Exposure-4 (EX-4, Detailed Distributional Dietary Exposure Analysis) developed by Technical Assessment Systems, Inc. **(TAS, 1990)**. The Ex-4 program estimates the distribution of single day dietary exposures for the overall U.S. Population and various subgroups, including infants and small children. The program utilizes the actual individual food consumption data, as reported by respondants in the 1987-88 U.S. Department of Agriculture (USDA) Nationwide Food Consumption Survey, which included all seasons of the year and all regions of the continental United States **(USDA, 1987-88)**. The foods and food-forms used in the dietary assessment are presented in Appendix D.

Potential acute dietary exposures from the consumption of all the commodities in **Table 8** were determined for several population subgroups (Appendix D) but specifically for non-nursing infants (<1 yr.) and for male adults (20 yrs.), so that these dietary exposure estimates could be combined with the potential residential exposure for crawling infants and applicators from the residential use of **Avert**.

1/ Male breathing rate is 29 L/min.; female breathing rate is 16 L/min. (U. S. EPA, 1987). Male body surface area/body wt. ratio is 277 cm^2/kg (19,400 cm^2/70 kg); female ratio is 307 cm^2/kg (16,900 cm^2/55 kg) (U.S. EPA, 1985)

B. EXPOSURE ASSESSMENT (continued)

Table 8 Commodities and Residue Levels Used to Assess Potential Dietary Exposure to Abamectin

Commodity	Residue (ppb)	Reference
Cottonseed (oil/meal)	5[a]	CDFA, 1990a
Strawberries	20[b]	CDFA, 1990b
Head lettuce	50[b]	CDFA, 1990c
Celery	50[b]	CDFA, 1990d; DPR, 1992
Pears		
RAC	20[b]	
Processed	2[c]	CDFA, 1991

a/ minimum quantifiable level
b/ action level established under Section 18
c/ minimum detection level

The potential exposures to abamectin from **Avert**, dietary sources and a combination of both are presented in **Table 9**. Only the ADD from the Equilibrium Model is presented since this model represents the highest potential exposure.

The crawling infants had the highest potential residential exposure (0.147 ug/kg/day) but the lowest combined exposure (0.200 ug/kg/day). The commercial applicator the highest potential dietary exposure (0.138 ug/kg/day) and the highest combined exposure (.220 ug/kg/day).

Table 9 Potential acute exposure for infants and adults (commercial applicator) to abamectin from residential use of Avert and from dietary sources

Subgroup	Absorbed Daily Dosage (ug/kg/day)		
	Residential	Dietary[a]	Combined
Infant (<1 yr.)	0.147[b]	0.053	0.200
Commercial applicator	0.082[c]	0.138	0.220

a/ Based on 99.5th percentile of user-days. See Appendix D for additional exposure percentiles
b/ From Equilibrium Model, Table 7
c/ Based on 70 kg body weight from Table 3, Appendix B

C. RISK CHARACTERIZATION

Margins of safety (MOS) were calculated for infants (<1 yr.) and a commercial (male, 20+ yrs.) as the ratio of the NOEL (50 ug/kg/day) and the Absorbed Daily Dosages presented in **Table 9**, (MOS = NOEL/ADD). These MOSs are presented in **Table 10** for potential exposures to abamectin from the residential use of **Avert**, from dietary sources and from the combination of residential and dietary sources.

Table 10 Margins of safety for infants and adults (commercial applicator) from residential use of Avert and from dietary sources

Subgroup	Margins of Safety[a]		
	Residential	Dietary	Combined
Infant (<1 yr.)	340	943	250
Commercial applicator	610	362	227

a/ Calculated as the ratio of the acute NOEL (50 ug/kg/day)/ADD from Table 9

Infants had the lowest MOS from potential exposure to abamectin from the residential use of Avert (MOS = 340) but the highest combined MOS from both residential and potential dietary sources (MOS = 250). The male commercial applicator had the lowest MOS from potential dietary sources of abamectin and from combined sources.

V RISK APPRAISAL

A margin of safety of 100 is generally considered to indicate an adequate level of health protectiveness between a NOEL for the test animal and the potential human exposure. In this risk assessment all margins of safety were at least 227 for combined residential and dietary exposures. Information presented in this section suggest that primates do not exhibit the same toxicity to treatment with abamectin or ivermectin as reported for rodents; therefore, humans may not be susceptible to the overt adverse effects of these chemicals that has sufficiently characterized the acute toxicity in the mouse.

Residential

Margins of safety were considered adequate for the crawling infant and the commercial applicator based on the methods used to estimate exposure from the use of **Avert** as a crack and crevice insecticide.

Dietary

Margins of safety were considered adequate for both infants and male/female adults from potential dietary exposure to abamectin from currently (and pendidng) registered uses of abamectin.

Combined Residential/Dietary

Margins of safety were considered adequate for infants and male/female adults from the potential combined exposure to abamectin from the residential use of **Avert** and from potential dietary sources.

Discussion

When using a MOS of 100 as an acceptable benchmark in risk assessment, the underlying inference is that humans are 10-times more susceptible to the chemical toxicity at the NOEL established in the animal species, and that there is a 10-fold range in the dose/response within the human population. Since abamectin is not used in human medicine, there are no controlled clinical studies which characterize the variability of response in the human population. However, studies in which monkeys were exposed to abamectin (or ivermectin) demonstrate considerable inter-species variability, both qualitatively and quantitatively. Signs, such as tremors, coma and death, which characterize the response of both abamectin and ivermectin in rodents and were the endpoints used to calculate a margin of safety for potential acute human exposure, do not appear in monkeys given abamectin or ivermectin, nor in humans treated with ivermectin. For example, a child survived an accidental dose of ivermectin of approximately 7-8 mg/kg and exhibited signs of toxicity (e.g. emesis, mydriasis, sedation) similar to those observed in rhesus monkeys at similar dosages **(Lankas and Gordon, 1989)**. A dosage of 8 mg/kg of ivermectin is approximately 40-times greater than the lowest minimum effect level (e.g. 0.2 mg/kg) and 80-fold

greated than the NOEL (e. g. 0.1 mg/kg) for maternal toxicity (e.g. tremors, death) seen in the ivermectin mouse studies. In addition, the human therapeutic dosage of ivermectin in the treatment of onchocerciasis is 0.15 to 0.2 mg/kg, as a single dose. Dosages up to 0.25 mg/kg have been used in humans to characterize the pharmacokinetics of ivermectin. Therefore, the therapeutic dosage of 0.2 mg/kg in humans is equivalent to the minimum effect level for tremors and death in the mouse, supporting the contention of a lower human sensitivity to ivermectin than rodents.

Additionally, 103 children, 5-12 years old and infected with the microfilaria causing onchocerciasis, were treated with ivermectin (0.15 mg/kg), as part of an experimental clinical trial **(MSD, no date)**. Forty seven clinically adverse reactions were reported in 36 children and included headache (23%), myalgia (9%), edema (5-10%), vomiting (1%), vertigo (1%) and abdominal pain (1%). These are similar side effects reported by adults treated with ivermectin for onchocerciasis. Only one case (edema) was considered serious, and all but one experience (vomiting) were considered to be hypersensitivity reactions from dead or dying microfilaria. This study indicated that, in general, young children do not exhibit the overt toxicity seen in the ivermectin mouse studies at comparable dosages.

In monkey studies comparing the effects of abamectin and ivermectin at dosages from 0.2 to 24 mg/kg, the NOEL for both compounds (i.e. no signs of toxicity) was 1 mg/kg. The most sensitive endpoint was emesis, and the minimum effect level for both compounds was 2 mg/kg (i.e. ~10x greater than the therapeutic dosage of ivermectin for river blindness and ~40x greater than the NOEL for maternal toxicity of 0.05 mg/kg in the mouse developmental toxicity study). At 24 mg/kg, the highest dose tested, marked mydriasis occurred, as well as slight sedation and emesis. Recovery from these effects was complete by 48 hours for both ivermectin and abamectin-treated monkeys. No tremors or convulsions were observed, and all animals survived at the highest dose, where plasma levels of ivermectin were ~34-fold greater than the average human therapeutic plasma level of 20 ng/ml. The plasma data indicate that the tolerance by the monkeys to the high doses of ivermectin is not due to a decrease in absorption with increasing dose.

In general, the currently available scientific information indicates that the acute adverse effects reported in humans given ivermectin and in monkeys exposed to either ivermectin or abamectin are qualitatively different than in rodents and occur at higher doses.

Recommendation:

Registration of **Avert Prescription Treatment 310** is recommended.

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VII APPENDICES

A. APPENDIX A

TOXICOLOGY SUMMARRIES

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

AVERMECTIN B1

SB 950-non-assigned, Tolerance # 50406

March 16, 1987
Revised November 22, 1988; June 16, 1989; March 14, 1990

I. DATA GAP STATUS

Combined Rat: (Chronic + Onco)	No data gap, no adverse effect
Chronic Dog:	No data gap, no adverse effect
Combined Mouse: (Chronic + Onco)	No data gap, possible adverse effect (not onco)
Repro Rat:	No data gap, possible adverse effect
Terato Rabbit:	No data gap, no adverse effect
Terato Mouse:	No data gap, possible adverse effect
Gene Mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect
DNA Damage:	No data gap, no adverse effect
Neurotox:	Not required at this time

Note, Toxicology one-liners are attached

** indicates acceptable study
indicates study on file, not yet reviewed
Bold face indicates possible adverse effect
File name: T900314
Revised by G. Chernoff, 3/14/90

Record numbers through 086100, and Volumes through 147, listed by the Pesticides Registration Library as of 3/14/90, have been rectified with those listed in the Toxicology Summary.

3/16/90

3/14/90

II. TOXICOLOGY SUMMARY

COMBINED (CHRONIC/ONCOGENICITY) TOXICITY, RAT

**013, 016-025; 046635, 046641-046650, "MK-0936: 105 Week Carcinogenicity and Toxicity Study in Rats with 53 Week Interim Necropsy", (Merck, Sharp and Dohme Research Labs., Report TT#82 099 0 - interim report, pilot study, final report - Vol. 8, 5/29/85). Abamectin (Avid), 89-91%; 0 (acetone), 0(acetone), 0.75, 1.5, 2.0 (increased to 2.5 at week 11 and decreased to 2.0 at week 13) mg/kg, 65/sex/group, two control groups; few animals with tremors at >2.0 mg/kg. NOEL = 1.5 mg/kg based on tremors at the next highest dose level. Originally evaluated as unacceptable but upgradeable. (Hathaway, 8/7/86). Additional data (056 052064) supplied and study considered ACCEPTABLE. (Hathaway, 1/7/87).

056 052064, Dietary analysis, statistical analysis of food consumption, organ weight and clinical parameters and GLP statement provided. (Hathaway, 1/7/82).

CHRONIC TOXICITY, DOG

**012 046634, "Fifty-three Week Dietary Toxicity Study in Dogs", (Merck Sharp & Dohme Research Laboratories, TT #82-104-0, 5/23/84). Abamectin (at least 89% avermectin B1a and avermectin B1b; MK-0936 identified as L-676,863-00V54); 0 (acetone), 0.25, 0.50, 1.0 mg/kg/day by feeding to 6 males and 6 females per group for 52 weeks. No adverse effects. NOEL = 0.25 mg/kg/day (mydriasis). ACCEPTABLE. Davis 8/7/86, 11/14/88.

015 046637, Twelve-Week Oral Range-Finding Study in Dogs - Pilot study for 012 046634. No review.

010 046627, "Eighteen Week Oral Toxicity Study in Dogs," (Merck Sharp & Dohme Research Laboratories, Report TT 76 073 0, no date). A Subchronic Oral Toxicity Study. Avermectin B1a, purity not indicated; 0 (sesame oil), 0.25, 0.5, 2.0, 8.0 mg/kg/day by gavage to 3 males and 3 females per group for 17 to 17.5 weeks. Adverse effects: whole body muscular tremors, ataxia, mydriasis, ptyalism, tonic convulsions, emesis, body weight decreases, and among animals which died or sacrificed prior to schedule termination, hepatocellular vacuolation and gallbladder edema. NOEL = 0.25 mg/kg/day. Supplemental. (BKDavis, 8/6/86).

ONCOGENICITY, RAT

See Combined Chronic/Onco above

COMBINED (CHRONIC/ONCOGENICITY), MOUSE

**026-031; 046651-046656, "MK-0936: Ninety-Four Week Carcinogenicity and Toxicity Study in Mice", (Merck, Sharp & Dohme Research Laboratories, antemortem report, tables, methods, etc., 6-20-86). Abamectin, 89.0 - 91.1%, 0 (acetone), 0 (acetone), 2, 4, & 8 mg/kg/day, 50/sex/group, 2 control groups plus 12/sex/group for 6 and 12 month sacrifices. Possible adverse effect - Increased mortality at 4 and 8 mg/kg/day. NOEL = 2 mg/kg/day. Originally

3/16/90 3/16/90

reviewed as unacceptable but upgradeable. (Carlisle, 8/13/86). Additional data (056, #052069), supplied and study considered ACCEPTABLE. (Carlisle, 1/6/87).

056 052069, Missing pages (2301 - 2305), indicates Good Laboratory Practices compliance. (JCC, 1-6-87).

REPRODUCTION. RAT

****014 046636,** "Reproductive Effects of MK 0936 Administered Orally by Gavage to Crl:COBS CD (SD)BR Rats for Two Generations", (Argus Research Laboratories, report TT #82-901-0, 1984). Avermectin, no purity stated; 30/sex/group were given 0 (sesame oil), 0.05, 0.12 or 0.40 mg/kg/day by oral gavage for 2 generations, 2 litters per generation. Parental NOEL > 0.4 mg/kg, Repro NOEL = 0.12 mg/kg (pup survival and weight). Originally reviewed as unacceptable, JGee, 8/12/86 and JAParker, 8/25/86. Additional data supplied, (056 #052066 and 058 # 052590, 052591) and study now ACCEPTABLE. **Possible adverse effect.** (JGee, 1/8/87, 2/26/87; JAParker, 2/26/87).

011 046633, Summary of 014 046636.

056 052066; 058 052590, supplementary information: Necropsy on F0 adults, clinical observations for F0, F1 males and females, eyes - clarified, and test substance purity and stability information. (JGee, 1/8/87 and JAParker, 2/26/87).

NOTE: The next three (3) studies are preliminary studies to study 014 046636 and should be considered supplemental, not unacceptable as previously noted. (JAParker, 8/10/88)

015 046639, "MK-0936: Oral Range-Finding Study (Multigeneration) in Rats", (Merck, Sharp and Dohme Research Laboratories, TT #82-707-0, 1-6-84). Avermectin, 94%, 12 females/group were given 0 (aqueous 1% v/v propylene glycol plus 0.6% v/v dicotyl sodium sulfosuccinate), 0.15, 0.5, 1.5, or 5.0 mg/ml in drinking water for 15 days before mating through day 21 of lactation. Nominal maternal NOEL = 1.5 mg/ml; nominal neonatal NOEL = 1.5 mg/ml (neonatal weight gain and mortality). (Gee, 8/11/86).

009 046626, "C-076 (B1a): Oral Reproduction Study in Rats", (Merck, Sharp and Dohme Research Laboratories, no date, TT #77-712-0). Avermectin B1a, lot 00P22, no purity stated, 12 females/group (2 control groups) were given 0 (sesame oil), 0.1, 0.2, or 0.4 mg/kg/day by gavage 14 days before mating through day 21 post partum; maternal NOEL = 0.4 mg/kg (HDT); Repro NOEL = 0.1 mg/kg (spastic movements of pups); no histology, (JGee, JAParker, 8/8/86).

009 046625, "C-076(B1a): Oral Reproduction Study in Rats", (Merck, Sharp and Dohme Research Laboratories, no date, TT# 77-706-0). Avermectin B1a, lot P-20 (no purity stated); 12 females/group (2 control groups) were given 0 (sesame oil), 0.5, 1.0, or 2.0 mg/kg by gavage for 15 days before start of mating; 2.0 mg/kg reduced to 1.5 mg/kg after 5 doses; maternal NOEL = 1.0 mg/kg; Repro NOEL < 0.5 mg/kg (pup weight and survival). (Gee, Parker, 8/8/86).

REPRODUCTION, RAT
DELTA 8,9-ISOMER OF AVERMECTIN B1

120 071744, "Delta 8,9-Isomer of Avermectin B. Single Generation Study in Rats", (Merck Sharp and Dohme, TT #87-716-0, 6/7/88). L-652,280-000N, 91.6% pure, Lot # L-652,280-000N005, was administered by oral gavage to groups of 20 Crl:CD (SD) BR female rats at doses of 0, (sesame oil vehicle control), 0.06, 0.12, and 0.40 mg/kg/day from fifteen days prior to cohabitation through day 20 of lactation. There were no signs indicating a MTD was achieved during the course of this study, and no treatment related maternal or reproductive findings, including gross and histomorphological eye examinations on weanling-aged offspring, were reported. The maternal and reproductive NOEL = 0.40 mg/kg/day (HDT). Supplementary study with no adverse health effects noted (G. Chernoff, 3/7/90).

REPRODUCTION, RAT
IVERMECTIN

146 085374, "MK-933: Multigeneration Study in Rats", (Merck Sharp and Dohme, TT #78-713-0/-1, 11/11/80). MK-933 (lot #'s 00W03, 00W08, 00W12, 00W19, and 00W40, >98% purity) was administered by oral intubation to groups of 20 female and 10 male CRCD rats at doses of 0 (sesame oil vehicle control), 0.4, 1.2, and 3.6 mg/kg/day. The study, which was designed for continuous treatment throughout production of two litters in each of three generations, was terminated early (at weaning of the F-1a litters for the high dose group, and following production of the F-2a litters for the 0.4 and 1.2 mg/kg groups) because of high neonatal mortality. A NOEL could not be determined. Supplemental study with possible adverse health effects (neonatal mortality) noted (G. Chernoff, 3/8/90).

146 086098, "MK-933: Multigeneration Study in Rats", (Merck Sharp and Dohme, TT #78-724-0, 11/11/80). MK-933 (lot #'s 00W12, 00W19, and 00W40, >98% purity) was administered by oral intubation to groups of 20 female and 10 male CRCD rats at doses of 0 (sesame oil vehicle control), and 2.0 mg/kg/day for 20 weeks, beginning 11 weeks prior to mating and continuing through weaning of 1 litter (F-1a). The study, which was designed for continuous treatment throughout production of two litters in each of three generations, was terminated early because of high neonatal mortality in a concurrent MK-933 reproduction study (CDFA Record No. 085374) utilizing similar dose levels. In the study under review, increased neonatal mortality was observed in the treatment group, and a NOEL could not be determined. Supplemental study with a possible adverse health effect (increased neonatal mortality) noted (G. Chernoff, 3/8/90).

147 085375, "MK-933: Multigeneration Study in Rats", (Merck Sharp and Dohme, TT #79-706-0/-1, 11/11/80). MK-933 (lot # L-640,471-00W51, >97.78% purity) was administered by oral intubation to groups of 20 female and 10 male CRCD rats at doses of 0 (sesame oil vehicle control), 0.05, 0.1, 0.2, and 0.4 mg/kg/day for 70 days prior to mating, and continuing through 2 generations, 2 litters per generation. Pre-mating maternal weight gains were reduced in high dose group females; in the F-2 offspring, neonatal mortality was increased at 0.2 and 0.4 mg/kg and pre-weaning mortality was increased at the high dose. A treatment-related increase in MK-933 residues was found in both the plasma and liver. The systemic NOEL = 0.2 mg/kg/day (reduced pre-mating weight gain); and the reproductive NOEL = 0.1 mg/kg/day (increased neonatal mortality). Supplemental study with a possible adverse health effect (increased neonatal mortality) noted (G. Chernoff, 3/12/90).

145 085373, "MK-933: Multigeneration Study in Rats", (Merck Sharp and Dohme, TT #79-706-2, 6/18/81). In this continuation of the multigeneration study reported in CDFA Record No. 085375, MK-933 (lot # L640,471-00W51, >97% pure) was administered by oral intubation to groups of 20 female and 10 male F-2b CRCD rats at doses of 0 (sesame oil vehicle control), 0.05, 0.1, 0.2, and 0.4 mg/kg/day (corresponding to their parents dosages) from weaning through the production and weaning of 2 litters (F-3a & F-3b). Pre-mating parental weight gains were reduced in the mid and high dose groups; mean live litter size and pup survivability were decreased, and kidney cysts increased in the high dose group offspring; and a treatment-related increase in MK-933 residues was observed in the plasma and liver. The systemic NOEL = 0.1 mg/kg/day (reduced pre-mating weight gain); and the reproductive NOEL = 0.2 mg/kg/day (decreased litter size and increased neonatal mortality). Supplemental study with a possible adverse health effect noted (G. Chernoff, 3/8/90).

147 086099, "MK-933: Cross-Fostering Study in Rats", (Merck Sharp and Dohme, TT #79-710-0, 11/11/80). MK-933 (lot # L-640,471-00W51, >97.78% purity) was administered by oral intubation to groups of 40 female CRCD rats at doses of 0 (sesame oil vehicle control), or 2.4 mg/kg/day for 61 days prior to mating, and continuing through day 20 postpartum. Within 24 hours of birth, all the litters were cross-fostered into 1 of four groups: group 1 from treated dams to treated dams (treated → treated); group 2 control → treated; group 3 control → control; and group 4 treated → control. The study was terminated 13 weeks postpartum. Pup mortality was significantly increased between days 8 and 14 postpartum in groups 1 and 2 and pup body weights were decreased. Body weights through week 13 were also decreased in groups 1 and 2, as well as in group 4. The results of this study indicate that the neonatal mortality observed in the other rat reproduction studies may be attributed to postnatal exposure to the test compound through maternal milk. A reproductive NOEL cannot be established from this study. Supplemental study with a possible adverse health effect (increased pup mortality) noted (G. Chernoff, 3/12/90).

147 086100, "MK-933: Metabolism Study in the Rat", (Merck Sharp and Dohme, TT #79-711-0, 11/11/80). Tritium labeled MK-932 (lot # L-638,709-11X0, 97.6% purity, specific activity of 0.2 mCi/mg) was administered by oral intubation to 2 groups of 6 female CRCD rats at doses of 2.5 mg/kg/day. Treatment was administered to a chronic group 61 days prior to mating through day 9 postpartum, and to an acute group from days 1 through 9 postpartum. In the chronic group, MK-932 plasma levels increased until treatment day 10, after which time they remained relatively constant except on postpartum day 1, when they were significantly higher. Throughout the study period, erythrocyte levels were one-half to one-third the plasma levels. In the acute group, plasma levels increased with length of treatment, and reached chronic levels on postpartum day 10. MK-932 tissue levels were highest in the kidneys from chronic group females, and were lowest in brains from both groups of females. Milk levels from both groups were 2 to 3 times higher than the corresponding maternal plasma levels on day 4, 6 and 10 postpartum, and pup consumption approached the LD-50. Pup plasma levels increased dramatically from days 1-6 postpartum, and were approximately 3 times higher than the maternal plasma level by day 6. Both liver and brain MK-932 levels paralleled the increase in pup plasma levels, with the brain reaching its highest concentration on day 6 postpartum, after which time it dropped to approximately one third the plasma level. Supplemental study (G. Chernoff, 3/12/90).

144 085366, "Developmental Changes in Metabolism and Transport Properties of Capillaries Isolated from Rat Brain", A.L. Betz and G.W. Goldstein, J. Physiol. (1981), 312:365-376. Capillaries were isolated from the cerebral cortices of an unspecified number of SD rats, at 1, 5, 10, 15, 21, 30, and 45

days of age, and investigated for the time in development of metabolic and transport aspects of the blood-brain barrier. The results indicated that various aspects of brain capillary functions showed distinct developmental patterns which may be related to changes in blood-brain barrier permeability during development. Supplemental journal article (G. Chernoff, 3/13/90).

144 085367, "Ontogeny of the Blood-Brain Barrier", N.R. Saunders, Exp. Eye Res. (1977), Suppl:523-550. The morphology of development of the blood-brain and blood-CSF barriers, the development of the blood-brain barrier to non electrolytes, the penetration of protein from plasma into CSF and brain in fetal sheep, and the effects of adverse conditions on barrier permeability during development, are all reviewed in this article. Among the many conclusions reached, is that the critical period for the development of a number of different blood-brain barrier mechanisms occurs between 50 and 70 days gestation in sheep, and during the neonatal period in rats. Supplemental journal article (G. Chernoff, 3/13/90).

144 085371, "Effects of Ivermectin on Reproduction and Neonatal Toxicity in Rats", (G.R. Lankas, D.H. Minsker, and R.T. Robertson; submitted for publication in Food and Chemical Toxicology, no date given). This article, submitted for publication, is based on 6 studies (CDFA Record Nos. 085373-085375, and 086098-086100) listed above. This is supplemental information and no worksheet has been provided (G. Chernoff, 3/14/90).

SUMMARY of Ivermectin Rat Reproduction Studies: Combining the data provided in CDFA Records 085375 and 085373 and considering the collective data from 3 generations (2 litters per generation), the reproductive NOEL = 0.2 mg/kg/day, and an adverse health effect (increased neonatal mortality) is noted. The cross-fostering study in CDFA Record 086099 indicates that the adverse effect is a postnatal event, occurring in the early stages of lactation. The metabolism study in CDFA Record 086100 demonstrates that the level of Ivermectin in maternal milk is approximately 3 times higher than in the maternal plasma, suggesting that the perinatal pups are consuming quantities of Ivermectin in the LD-50 range. Since the blood-brain barrier is not fully developed in the neonatal rat (CDFA Record 085367), it is hypothesized that the Ivermectin in the lactating dams milk passes to the neonatal pup and enters the brain, thereby, resulting in the observed neonatal mortality (G. Chernoff, 3/14/90).

TERATOLOGY, RAT

**032 046659, "I. Oral Range-finding Study in Pregnant Rats and Oral Teratogenic Study in Rats", (Merck, Sharp and Dohme Research Laboratories, reports TT #82-705-1, #82-705-0 11-10-82). Avermectin, 94%, pilot study with 10/group at 0 (sesame oil), 0.25, 0.5, 1.0, and 2.0 mg/kg by gavage days 6 - 17, 1 death at 2.0 mg/kg. Full Study with 25/group at 0 (sesame oil), 0.4, 0.8, 1.6 mg/kg by oral gavage days 6 - 19; nominal maternal NOEL = 1.6 mg/kg, nominal terato/feto NOEL = 1.6 mg/kg/day. Originally reviewed as unacceptable but upgradeable, JGee, 3/8/86 and JAParker, 3/28/86. Additional data received (057 # 052070 and 058 # 052581) made study ACCEPTABLE. No adverse effect. (JAParker, 2/26/87).

057 052070, Supplemental information: Individual fetal data by dam and individual clinical observations for pilot study TT 82-705-1 and for study TT 82-705-0. (Parker, 2-26-87).

058 052581, Analysis of dosing suspension for Teratogenic study in rats (032 046659). (Parker, 2-26-87)

032 046657, "Exploratory Teratology Studies in the Rat," (Merck, Sharp and Dohme Research Laboratories, report TT 77-701-0" 4-21-82). Avermectin B1a (no purity stated), range-finding study, 20 females/group (2 controls) given 0 (sesame oil), 0.8, 1.6 or 3.2 mg/kg/day by oral gavage on days 6 - 15; 3 deaths at the high dose, maternal NOEL = 1.6 mg/kg, Teratogenic NOEL not established since only control and high dose fetuses were examined for visceral and skeletal findings, External teratogenic NOEL = 1.6 mg/kg. Supplemental. (JG 8-8-86, JAP 8-28-86).

010 46628, Fourteen-Week Oral Toxicity Study in Rats Following <u>In Utero</u> Exposure. Supplemental histology. No review/worksheet. (Kishiyama, 11/14/88).

TERATOLOGY, RAT
DELTA 8,9-ISOMER OF AVERMECTIN B1

120 071743, "Delta 8, 9-Isomer, Avermectin B, Oral Developmental Toxicity Study in Rats", (Merck Sharp and Dohme, TT #87-715-0, 6/7/88). L-652,280-000N, Lot # L-652,280-000N005, 91.6% pure, was administered by oral gavage to groups of 25 Crl:CD (SD) BR mated female rats at doses of 0 (sesame oil vehicle control), 0.25, 0.5, and 1.0 mg/kg/day on day 6-17 of gestation. There were no signs indicating a MTD was achieved during the study. While maternal weight gain was significantly increased at 0.5 and 1.0 mg/kg during the treatment period, there were no adverse treatment related maternal or developmental effects reported. Maternal and developmental NOEL = 1.0 mg/kg (HDT). Supplemental study with no adverse health effects noted (G. Chernoff, 3/7/90).

TERATOLOGY, RABBIT

**032 046660, "II. Oral Range-finding Study in Pregnant Rabbits and Teratogenic Study in Rabbits", (Merck, Sharp and Dohme Research Laboratories, report TT #82-706-1, #82-706-0, 11-10-82, Range-finding at 0 (sesame oil), 0.5, 1.0, 2.0 or 3.0 mg/kg/day by gavage on days 6-18. Full study at 0, 0.5, 1.0, or 2.0 mg/kg/day by gavage on days 6-27. Maternal NOEL = 1.0 mg/kg/day, Teratogenic NOEL = 1 mg/kg/day. Originally reviewed as unacceptable but upgradeable, (JG, 8-8-86, JAP, 8-28-86). Additional data were supplied (057 # 052071 and 058 # 052581) and the study is considered ACCEPTABLE. No adverse effect. (Parker, 2/26/87).

057 052071, Supplemental information: Individual fetal data by dam and workbook pages with clinical observations and food consumption data. (Parker, 2/26/86)

058 052581, Dosing solution analytical results. (Parker, 2/26/86).

032 046658, "Oral Range-finding Exploratory Teratology Studies of Avermectin B1a in the Rabbit ", (Merck, Sharp and Dohme Research Laboratories, report TT 76-724, 77-702-0/1", 4/21/82). Avermectin B1a (no purity stated, no lot number), Pilot at 0 (sesame oil), 0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg/day. Full study (2 studies with a combined total of 25/dose group, 2 control groups) given 0, 0.25, 0.5, or 1.0 mg/kg/day by gavage on days 7 - 16. Apparent maternal NOEL = 1.0 mg/kg, apparent developmental NOEL = 1.0 m/kg. (JGee, 8-8-86, JAParker, 8-28-86).

TERATOLOGY, MICE, CF-1 strain

009 046622, "Oral Teratogenic Evaluation in Mice", (Merck Sharp and Donme, report TT #76-723-0,1/2/3, no date given). Avermectin B1a and B2 (no purity given), 2 replicate studies, with 10 and 15 /group = 25 total. Given 0 (sesame oil), 0.1, 0.2, 0.4, or 0.8 mg/kg/day by gavage on days 6 - 15. For B1a, Maternal NOEL < 0.1 mg/kg (mortality), Teratogenic NOEL = 0.2 mg/kg. For B2, Maternal NOEL < 0.1 mg/kg, Teratogenic NOEL = 0.1 mg/kg. Tremors at all doses, no repro effects noted. Cleft palate seen in fetuses. Range finding studies conducted to 8.0 mg/kg/day with tremors, coma and death as the signs of maternal toxicity. **Adverse effect.** Initially reviewed as unacceptable: Gee, 8/6/86, JAParker, 8/28/86. Additional data submitted, 057, # 052072 (individual fetal observations and clinical observations). Analysis of dosing solutions was not performed. Study STILL NOT ACCEPTABLE. (JAParker, 1/12/87).

057 052072, Supplemental information: individual fetal observations and clinical observations. (Parker, 1-12-87).

009 046623, "Oral Teratogenic Evaluation in Mice", (Merck, Sharp and Donme, report TT #77-705-0", no date); Avermectin B_{1a} (no purity stated); 20/group (2x20 for controls) were given 0 (sesame oil), 0.1, 0.2, 0.4 or 0.8 mg/kg days 6-15 by oral gavage; Maternal NOEL < 0.1 mg/kg (tremors); Terat NOEL = 0.2 mg/kg (cleft palate) **adverse effect.** Upgradeable. Initially reviewed as unacceptable; Gee, 8/6/86, Parker, 8/28/86. Additional data submitted, 010, #046629 (fetal observations). Analysis of dosing solutions was not performed. Study still NOT ACCEPTABLE. (Parker, 1/12/87).

009 046624, "Ten-day Oral Toxicity Study in Pregnant Mice", (Merck, Sharp and Donme report TT #77-717-1", no date). Avermectin B_{1a}, no purity stated; 20 per group given 0 (sesame oil), 0.025, 0.050, 0.075 or 0.10[d] mg/kg by oral gavage days 6-15; low pregnancy rate; maternal NOEL = 0.05 mg/kg; no data on fetuses - no terat NOEL available due to lack of data. Supplemental. (Gee, 8/6/86, 8/13/87 and Parker 8/13/87).

010 046630, "Ten-day Dietary Maternotoxicity Study in Mice", (Merck, Sharp, and Donme, report TT 83-705-1, 1984). Avermectin approximately 88% (Tritiated at > 98%), nominal 0 (acetone), 0.1, 0.3, or 0.6 mg/kg/day, days 6-15 in the diet: NOEL = 0.1 mg/kg/day (actually, 0.06 due to diet intake and content). Supplemental. (Gee, 8/7/86).

TERATOLOGY, MOUSE CF-1 Strain
DELTA 8,9 ISOMER OF AVERMECTIN B1

036 046683, "8,9 Isomer of Avermectin B1 Maternotoxicity and Teratology Studies", (Merck, Sharp & Donme, report TT 84-722-0, 1-8-86). (8, 9-Avermectin B_1a, 99%, L-652,280-00N); 8-13 Females per group given 0 (sesame oil), 1.5, 3.0, 6.25, 25.0, or 50 mg/kg/day, 6-15 of gestation; no survivors in ≥ 3 mg/kg; NOEL s not establisned; 24/83 fetuses in 4/7 litters had cleft palate in 1.5 mg/kg (adverse effect**), 0 in control; originally reviewed as unacceptable. Gee, 8/8/86, Parker, 8/28/86. Additional data supplied, analysis of dosing solutions, 058 # 052592, and study now ACCEPTABLE. (JAP 8/13/87).

**036 046684, "Oral Maternotoxicity Study in Mice", (Merck Sharp and Donme, report TT 84-722-1; 1/8/86). (8,9 Isomer of avermectin B_1, 99%); 12 females per group were given 0 (sesame oil), 0.05, 0.10, 0.50 or 1.0[d] mg/kg by oral

gavage days 6 - 15 . Terato NOEL = 0.05 mg/kg (Cleft Palate)(adverse effect); maternal NOEL = 0.10 mg/kg; ORIGINALLY reviewed as unacceptable (missing data, animal number). Gee, 8/8/86, Parker, 8/28/86. Additional data received, 058 # 052592, analysis of dosing solutions and study now ACCEPTABLE. (JAP 3/13/87).

**046685, "8,9 Isomer of Avermectin B_1 (L-552,280-00N) III Oral Teratology Study in Mice, TT #85-710-0." (Merck, Sharp and Dohme, 1/8/86). Avermectin, 8,9 isomer of B_1, 99% purity, 25 females per group were given 0 (sesame oil), 0.015, 0.03 or 0.06 (nominal) mg/kg/day, day 6-15; by oral gavage; study to confirm NOEL values; maternal NOEL $\geq$ 0.06 mg/kg, developmental NOEL $\geq$ 0.06 mg/kg; initially reviewed as unacceptable but upgradeable with a possible adverse effect of exencephaly and a NOEL of 0.015. Incidences of cleft palate were 0/22, 1/22, 0/23 and 0/22 for control through high dose. Gee, 8/8/86, Parker, 8/28/86. Additional data received -analysis of dosing solutions, 058 # 052592, and study now ACCEPTABLE. (Parker 3/13/87). Record 073797 in -139 contains historical control data for exencephaly and cleft palate by litter and by fetus. Reconsideration of the study finds the exencephaly not clearly treatment related and there was no adverse effect at the doses tested. (Gee, 6/15/89)

**036 046686, "Oral Teratology Study in Mice", (Merck Sharp and Dohme, report TT 85-710-1, 1/18/86). Avermectin, 8, 9 isomer of B1, 99%; 25 females per group given 0 (sesame oil), 0.015, 0.03, 0.1 or 0.5 mg/kg/day by oral gavage, days 6-15; maternal NOEL = 0.1 mg/kg (nominal) (1 death at 0.5 mg/kg), Developmental NOEL = 0.03 mg/kg (nominal)(adverse effect of cleft palate); initially reviewed as unacceptable but upgradeable. Gee, 8/8/86, Parker, 8/28/86. Additional data received, 058 052592, analysis of dosing solutions, and study now ACCEPTABLE. (Parker 3/13/87). Initial review indicated a NOEL of 0.015 mg/kg based on exencephaly. Submission of 073797 on -139 contains historical control data for exencephaly and cleft palate in CF1 mice. Rereview finds that the exencephaly is not dose related and the incidence falls within historical control range. The cleft palate remains as treatment-related adverse effect. (Gee, 6/16/89) [NOEL corrected to 0.03 (Gee, 5/8/92)]

058 052592, Analytical results for mouse teratology studies conducted with delta 8,9 isomer of Avermectin B1 (TT 84-722-0, TT 84-722-1, TT 85-710-0 and TT 85-710-1). This information is sufficient to upgrade the studies to ACCEPTABLE. (Parker and Gee, 3/13/87)

057 052073, Merck Sharp and Dohme discussion of exencephaly and cleft palate in mice treated with delta 8,9 isomer of Avermectin B1. Selected journal articles. No Worksheet. (Parker, 1/12/87).

096 No record number: Merck, Sharp & Dohme Letter 8/19/87. EPA appraisal of teratogenic response. No change in status. No worksheet. (Parker, 11/22/88).

139 073797, Rebuttal and historical control data for exencephaly and cleft palate by litter and by fetus. Document contains a letter from Dr. William J. Scott, Jr., University of Cincinnati, giving his opinion of the results of the mouse studies. He agreed with Merck scientists that the exencephaly did not appear to be treatment related but the cleft palates were due to avermectin exposure. No worksheet. CDFA response in R890616. Gee, 6/16/89.

SUMMARY: CDFA has examined EPA's discussion and the historical control values previously submitted. CDFA still maintained the developmental NOEL of the delta 8,9 isomer is 0.015 mg/kg/day based on exencephaly (Parker, 11/22/88).

With the submission of much more complete historical control data covering 1978 to 1985, by individual study, a reevaluation of the exencephaly incidence was made. CDFA now concurs that the results are equivocal at best and no dose response was found. In addition, examination of the historical control data indicates the percentage of litters with exencephaly is within the range. EPA also concluded that the exencephaly was not treatment related - see 096 (Gee, 6/16/89).

TERATOLOGY, MICE
POLAR DEGRADATES OF ABAMECTIN

120 071746, "L-930,406 (Polar Degradates From Thin Film Disp Photolysis, Oral Developmental Toxicity Study in Mice", (Merck Sharp and Dohme, TT #87-717-0, 6/7/88). L-930,406, Lot # L-930,406-0ON001, purity not determined, was administered by oral gavage to groups of 25 Crl:CF-1 BR female mice on days 6-15 of gestation at doses of 0 (vehicle control - 0.5% methylcellulose), 0.25, 0.5, and 1.0 mg/kg/day. There were no signs indicating a MTD was achieved during the course of the study. A slight, non-significant increase in cleft palate at the high dose was not considered to be treatment related. There were no other maternal or developmental observations suggestive of a treatment related effect. Maternal and developmental NOEL = 1.0 mg/kg/day (HDT). Supplemental study with no adverse health effects noted (G. Chernoff, 3/7/90).

121 071747, "Oral Developmental Toxicity in Mice, L-930,463 (Citrus Derived Abamectin Polar Degradates)", (Merck Sharp and Dohme, TT #88-713-0, 11/1/88). L-930,463, Lot # L-930,463-000S001, purity not determined, was administered to groups of 25 mated Crl:CF-1 BR female mice by oral gavage on days 6-15 of gestation at 0 (vehicle control of 0.5% methylcellulose), 0.25, 0.5, and 1.0 mg/kg/day (containing concentrated methanol washings from the surface of vehicle tested citrus, L-930,462 carrier vehicle, at doses of 50, 100 and 200 mg/kg, respectively). Two additional control groups treated with 100 and 200 mg/kg L-930,462 carrier vehicle were also tested. At each of the three treatment doses tested, there was a slight non-significant decrease in maternal weight gain. This was not sufficient evidence to establish a MTD. No treatment related developmental findings were observed. Maternal and Developmental NOEL = 1.0 mg/kg/day (HTD). Supplemental study with no adverse health effects noted (G. Chernoff, 3/7/90).

121 071748, "Abamectin Polar Degradates Derived from Citrus Fruits for use in Toxicity (Teratology) Testing", (Merck Sharp and Dohme Research Laboratories, PLM#-3,-4, 11/8/88). Three reports describing the generation and isolation of polar degradates of Abamectin in citrus, which were used for the teratology study in CDFA Record No. 071747. Supplemental information, no worksheet provided (G. Chernoff, 3/14/90).

GENE MUTATION

009 046621, "Salmonella", (Merck Sharp and Dohme 1976). Avermectin B, no purity stated, ± rat liver activation - aroclor or phenobarbital-induced; lot 00P02 at 0, 1, 10, or 100 ug/plate, lot 00P08 at 0, 20, 200, or 2000 ug/plate; strains TA1537, TA92, TA98 and TA100; UNACCEPTABLE and NOT UPGRADEABLE (Gee, 8/5/86).

033 046663, "Salmonella Strains TA1535, TA1537, TA1538, TA98 and TA100", (Merck Sharp & Dohme - 1982). Avermectin, 94% purity, ± rat liver activation; 0, 100, 300, 1000, 3000 or 10,000 ug/plate in triplicate, 1 trial;

ppt at 3000 and 10,000 ug/plate; no evidence of increased reversion rate. incomplete (no individual plate counts); UNACCEPTABLE (Gee, 8/1/86).

**033 046664, "Chinese Hamster V79 Cells", (Merck Sharp and Dohme - 1983; 8-1-86). Avermectin, 94% purity, + S-9, rat liver, two trials; 0, 0.03, 0.04, 0.045; 0.05 mM + S-9; 0, 0.002, 0.004, 0.005 and 0.006 mM,-S9; no increase in mutation frequency to cytotoxic concentrations; ACCEPTABLE. (Gee, 8/1/86).

033 046667, "Salmonella, 5 Strains", (Merck Sharp & Dohme - 1986). Avermectin, 89% purity, TA1535, TA1537, TA1538, TA98, TA100 - No activation; 0, 100, 300, 1000, 3000 or 10,000 ug/plate; no increased reversion rate; UNACCEPTABLE and NOT UPGRADEABLE. (Gee, 8/4/86).

**033 046668, "Salmonella", (Merck Sharp & Dohme - 1986). Avermectin, 94% purity, TA1535, TA1537, TA1538, TA98, and TA100 ± rat liver activation at 0, 3, 10, 30, 100, or 1000 ug/plate in triplicate; no evidence of increased reversion rate. Considered ACCEPTABLE along with other studies in Salmonella. (Gee, 8/5/86).

GENE MUTATION
DELTA 8,9-ISOMER of AVERMECTIN

120 071742, "L-652,280 (Delta 8, 9-Isomer, Avermectin B.) Microbial Mutagenesis Assay", (Merck Sharp and Dohme, TT #87-8046, 6/7/88). Delta 8,9 isomer of MK-0936, 91.6%; tested with Salmonella typhimurium strains TA1535, TA97a, TA98 and TA100 and with Escherichia coli strains WP2, WP2 uvrA, WP2 uvrA pKM101; tested with and without Aroclor 1254-induced rat liver activation; at 0 (DMSO), 10, 30, 100, 300, 1000 or 3000 g/plate, triplicate plates; precipitate formed at 3000 g/plate; no individual plate counts, mean only; no evidence of an increase in reversion rate in any strain. Supplemental study on isomer. (Gee, 3/12/90)

GENE MUTATION
POLAR DEGRADATES OF ABAMECTIN

120 071745, "L-930,406 (Polar Degradates From Thin Film Dish Photolysis) Microbial Mutagenesis Assay", (Merck Sharp and Dohme, TT #87-8047 & #87-8058, 6/7/88). L-930,406-000N001, polar degradates from MK-0936; tested with Salmonella typhimurium strains TA1535, TA97a, TA98 and TA100 and with Escherichia coli strains WP2, WP2 uvrA and WP2 uvrA pKM101; with and without Aroclor 1254-induced rat liver activation; concentrations of 0 (DMSO), 100, 300, 1000, 3000 or 10,000 g/plate, triplicate plates, 48 hour incubation; precipitation at the highest concentration but no evidence of cytotoxicity; two trials with activation; positive controls gave expected results without activation but not with activation in trial 1, hence the repeat; no clear increase in reversion rate. No individual plate counts. Supplemental study. (Gee, 3/12/90)

CHROMOSOME EFFECTS

033 046666, "Chromosome-in vivo Mouse Chromosomal Aberrations", (SRI-1983). Avermectin, 94% purity, 0, 1.2, 4.0 or 12.0 mg/kg by oral gavage to 12 (control) or 8 (test group) male mice; sacrificed at 6, 24 or 48 hours; no evidence of increase in aberrations; pilot study included; UNACCEPTABLE but UPGRADEABLE. (Gee, 8/4/86).

**033 046669, "Chromosome-in vitro Aberrations", (Merck Sharp & Dohme-1986). Avermectin, 94% purity, CHO-WBL cells; ± rat liver activation -beta-Naphthaflavone and phenobarbital induced; 0, 0.01, 0.015, and 0.02 mM scored at 10.5 and 24 hours -S9; 0, 0.005, 0.010, 0.015 or 0.02 at 10.5 hours +S9; 3 hour exposure; no evidence for increased aberrations to cytotoxic levels; ACCEPTABLE. (Gee, 8/5/86).

DNA DAMAGE

**033 046665, "844 MUTA-DNA; Alkaline Elution with Rat Hepatocytes", (Merck Sharp & Dohme, in vitro (TT82 8520, TT82 8523, TT82 8525 and TT82 8526 - 1982 and in vivo (TT83 8302 - 1983)). Avermectin, 4 in vitro trials at 0 to 0.6 mM; 1 in vivo trial in rats; at 10.6, 3.5, or 1.06 mg/kg/male rat by oral gavage; 3 hours exposure in both types; no increase in SS breaks without increased cytotoxicity in vitro; no effects in vivo; ACCEPTABLE. (Gee, 8/1/86).

NEUROTOXICITY

Not required at this time.

OTHER
CLINICAL, IVERMECTIN

144 085368, "The Chemotherapy of Onchocerciasis X. An assessment of four single dose treatment regimes of MK-933 (Ivermectin) in human onchocerciasis", (K. Awadzi, K.Y. Dadzie, H. Shulz-Key, D.R.W. Haddock, H.M. Gilles, and M.A. Aziz; Annals of Tropical Medicine and Parasitology, 79 (1):63-78, 1985). A publication with supplemental clinical information. No worksheet provided (G. Chernoff, 3/14/90).

144 085369, "The Effects of Ivermectin on Transmission of Onchocerca volvulus", (E.W. Cupp, M.J. Bernardo, A.E. Kiszewski, R.C. Collins, H.R. Taylor, M.A. Aziz, and B.M. Greene; Science, 231:740-742, 1986). A publication with supplemental clinical information. No worksheet provided (G. Chernoff, 3/14/90).

144 085370, "Comparison of Ivermectin and Diethylcarbamazine in the Treatment of Onchocerciasis", (B.M. Greene, H.R. Taylor, E.W. Cupp, R.P. Murphy, A.T. White, M.A. Aziz, H. Shulz-Key, S.A. D'Anna, H.S. Newland, L.P. Goldschmidt, C. Auer, A.P. Hanson, S.V. Freeman, E.W. Reber, and P.N. Williams; New England Journal of Medicine, 313 (3):133-138, 1985). A publication with supplemental clinical information. No worksheet provided (G. Chernoff, 3/14/90).

144 085372, "Mectizan (Ivermectin, MSD)", (Merck Sharp and Dohme Product Monograph). Supplemental clinical information. No worksheet provided (G. Chernoff, 3/14/90).

B. APPENDIX B

EXPOSURE ASSESSMENT

ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO THE PESTICIDE PRODUCT AVERT PRESCRIPTION TREATMENT 310

BY

Tareq A. Formoli, Associate Pesticide Review Scientist

October 2, 1991
Revised March 11, 1992
Revised May 25, 1993

California Environmental Protection Agency
Department of Pesticide Regulation
Worker Health and Safety Branch
1220 N Street P.O. Box 942871
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ABSTRACT

Avert Prescription Treatment 310 is a dust formulation that contains 0.05% abamectin B_1. It is recommended for use by commercial applicators to treat homes, and commercial and industrial buildings to control roaches. In addition to the applicators, the residents, especially children could be exposed to abamectin B_1 following residential application. Two scenarios have been used to estimate exposure to children. Applicator exposure was estimated using surrogate data.

This report was prepared to be included as an exposure assessment in the Department's risk characterization document for Avert Prescription Treatment 310.

Exposure Assessment for Avert Prescription Treatment 310

October 2, 1991
Revised March 11, 1992
Revised May 25, 1993

Introduction:

The subject product is a dust formulation that contains 0.05% abamectin B_1. It is labeled for crack and crevice uses in homes, and non-food/feed areas of commercial and industrial buildings. The label specifies "Do not apply where children are likely to come in frequent contact with treated areas. Any powder visible after application is complete should be brushed into cracks and crevices or removed. No generalized dusting should be done in household areas accessible to children or pets". Studies have shown that not only the applicators but the residents, especially children, are also exposed to pesticide residues following residential application of pesticides (1, 2).

Estimate of Infant Exposure:

Indoor residue monitoring has shown 42 ng, 3 ng, and 3 ng abamectin per 100 cm^2 on horizontal surfaces immediately, 24, and 72 hours respectively after application of Avert Prescription Treatment 310 (3).

Children spend much of their time on the floor and their tendencies of hand to mouth contact and pica are a recognized potential route of exposure (4). A model that has been used to estimate dermal exposure from indoor surface pesticides in the absence of any data is the equilibrium model (5). It assumes pesticide residues on a surface come to equilibrium with residues on the body, so that dermal exposure is equal to the human body surface area exposed. Based on this scenario, the estimate of unclothed infant's dermal exposure to abamectin will be 1.64 ug the day of application and 0.12 ug the following day. Considering infants' (9-10 months old) movement and pica behaviors, it is conceivable that 50% of the dermal exposure would occur on hands and eventually be swallowed each day. The remaining 0.82 ug and 0.06 ug abamectin residues on the skin on the day and on the following day of application could be absorbed at a dermal absorption rate of 1% (6).

Indoor ambient air monitoring immediately, 24 and 72 hours after application of a 0.05% abamectin dust have demonstrated 0.9 ug/m^3, 0.3 ug/m^3, and 0.1 ug/m^3 residues in the air, respectively (3). Infant respiratory exposure was calculated based on average residues of 0.6 ug/m^3 in the air on the day of application and 0.25 ug/m^3 on the following day. Breathing rates were assumed to be 4.2 liters/minute during light activity and 1.5 liters/minute during rest periods (7).

Estimated oral, dermal, and respiratory exposure of infants to abamectin as a result of residential use of Avert Prescription Treatment 310 is summarized in Table 1.

Table 1

Route of Exposure	potential Exposure (ug/infant/day)		Absorbed Daily Dosage (ug/kg/day)	
	Day 1	Day 2	Day 1	Day 2
Oral	0.82	0.06	0.09	0.007
Dermal	0.82	0.06	0.001	0.0001
Respiratory	2.50	1.03	0.14	0.057
Total	4.14	1.15	0.23	0.064
Two-day Average	**2.64**		**0.147**	

Based on: Infant body surface area of ~3900 cm^2 (7), body weight of 9 kg (1), 100% surface residue transfer to skin, 1% dermal absorption (6), oral absorption of 100%, respiratory uptake of 50%, 12 hours of light activity and 12 hours of rest.

Formoli, WH&S, 1993

The most refined estimate of human exposure to surface residues comes from work done with adult humans who's exposures were measured after defined contact with a pesticide treated carpet (8). From this work it was possible to estimate transfer factors for pesticide residues from treated carpets to individual's bodies. The estimated transfer factor for infants is approximately 800 cm^2/hour based on 3500 cm^2/hour transfer factor for adults multiplied by the ratio of infant to adult body surface area (3900/17,700 cm^2). Assuming daily six hours of continual moving contact with the treated surface yields a potential dermal exposure for an infant of 2.02 ug on the day of application and 0.14 ug on the following day. In the human experiment with dermal absorption, the hands contributed 14% of the total dermal exposure (Ross et al., 1990). If all hand residues were solvated in the mouth, the oral exposure would be 0.28 ug, and 0.02 ug on the day of application and on the following day, respectively. Estimates of exposure by all routes using this model are shown in Table 2.

Table 2

Route of exposure	Potential exposure (ug/infant/day)		Absorbed Daily Dosage (ug/kg/day)	
	Day 1	Day 2	Day 1	Day 2
Oral	0.28	0.02	0.03	0.002
Dermal	1.70	0.12	0.002	0.0001
Respiratory	1.88	0.78	0.10	0.043
Total	3.86	0.92	0.13	0.045
Two-day Average	**2.39**		**0.087**	

Based on: Body weight of 9 kg, 1% dermal absorption, 6 hours of light activity and 18 hours of rest.

Formoli, WH&S, 1993

Estimate of Commercial Applicator Exposure:

The product label recommends the use of this product by commercial applicators. This label does not apparently preclude homeowner application. No residential applicator exposure data are available for a dust formulation

that is used in the manner of Avert Prescription Treatment 310. A home gardener exposure study with carbaryl has shown 0.46 mg to 0.57 mg of carbaryl exposure for each gram active ingredient used for an applicator wearing clothing such as a T-shirt, shorts, and shoes (9). The applicators used a 5% dust formulation to treat corn and green beans. This could be used as a conservative estimate of exposure for a person applying Avert Prescription Treatment 310 which is a 0.05% dust formulation. Assuming that a commercial applicator uses a dozen containers (30 g/container) in a 6-hour work day, the estimated dermal exposure would be 0.103 mg abamectin/person/day. Applicator's respiratory exposure can be extrapolated from levels of abamectin residues found in the air of treated mess halls (reference 3) immediately after application.

Estimates of potential exposure and absorbed daily dosage for a commercial applicator are summarized in Table 3.

Table 3

Route of Exposure	Potential Exposure (ug/person/day)	Absorbed Daily Dosage (ug/kg/day)
Dermal	103.0	0.015
Respiratory	9.4	0.067
Total Exposure	**112.4**	**0.082**

Based on:
Dermal absorption of 1%, respiratory uptake of 50%, breathing rate of 29 liters/minute, body weight of 70 kg, and a 6-hour work day.

Formoli, WH&S, 1991

References

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2. Roberts, J.W. and D.E. Carmann. 1989. Pilot study of cotton glove press test for assessing exposure to pesticides in house dust. Bull. Environ. Contam. Toxicol. 43:717-724.

3. Whitmire Research Laboratories, Inc. 1991. Abamectin movement study at Ft. Bragg. Whitmire Research Laboratories, Inc., Saint Louis, Missouri. CDFA Registration Doc. No. 50406-167.

4. Van Wijen, J.H., P. Clausing and B. Brunekreef. 1990. Estimated soil ingestion by children. Environmental Research 51:147-162.

5. Fong, H.R., R.K. Brodberg, T.A. Formoli, J.R. Sanborn, T. Thongsinthusak and J. Ross. 1990. Estimation of exposure of persons in California to pesticide products that contain malathion. Worker Health and Safety Branch, California Department of Food and Agriculture, Sacramento, CA. HS-1569

6. Thongsinthusak, T. et. al. 1990. Estimation of exposure of a person in California to pesticide products that contain abamectin. Worker Health and Safety Branch, California Department of Food and Agriculture, Sacramento, CA. HS-1567.

7. Snyder, S. et. al. 1974. Report of the task group on reference man. The International Commission on Radiological Protection, Pergamon Press, New York.

8. Ross, J., et al. 1990. Measuring potential dermal transfer of surface pesticide residues generated from fogger use: An interim report. Chemosphere 20(3/4):349-360. HS-1581.

9. Kurtz, D.A. and W.M. Bode. 1985. Application exposure to the home gardener. American Chemical Society Symposium Series 273:139-161.

C. APPENDIX C

PRODUCT LABEL

AVERT®

Prescription Treatment® 310

- Contains approximately 200 bait placements
- Crack and Crevice® Bait
- Kills cockroaches

Whitmire

KILLS: Cockroaches (including carbamate, organophosphate and organochlorine resistant strains).

For use in: Garages, Homes, and the non-food/feed areas of Hospitals and Nursing Homes (non-patient areas), Hotels, Motels, Transportation Equipment (Buses, Boats, Ships, Trains, Planes), Utilities, Warehouses, and other commercial and industrial buildings.

Not for Use in USDA Inspected Meat and Poultry Plants

ACTIVE INGREDIENT: Abamectin B1[A mixture of avermectins containing 80% avermectin B1a(5-0-demethyl avermectin A1a and 20% avermectin B1b (5-0-demethyl-25-de(1-methylpropyl-25-(1-methylethyl) avermectin A1a)] 0.05%

INERT INGREDIENTS: 99.95%

EPA Reg. No. 499-294

EPA Est. No. 9113-WI-01

Recommended for Use
by Commercial Applicators

KEEP OUT OF REACH OF CHILDREN
CAUTION

STATEMENT OF PRACTICAL TREATMENT

IF SWALLOWED: Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person. Get medical attention.

IF INHALED: Remove patient to fresh air. Apply artificial respiration if indicated. Seek medical attention.

IF ON SKIN: Wash with soap and warm water. Seek medical attention if irritation persists.

IF IN EYES: Flush with plenty of water. Seek medical attention if irritation persists.

See Side Panel for Additional Precautionary Statements

Net Weight: 30g

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

CAUTION

Harmful if swallowed, inhaled or absorbed through the skin. Do not breathe dust. Do not allow to contact skin, eyes or clothing. If contact occurs, wash skin with soap and warm water, or eyes with clean water.

Wash hands and exposed skin before eating, drinking or smoking and after handling. Wash all contaminated clothing thoroughly before reuse.

Do not apply where children (or domestic animals) are likely to come in frequent contact with treated areas. Any powder visible after application is complete should be brushed into cracks or crevices or removed. No generalized dusting should be done in household areas accessible to children or pets.

ENVIRONMENTAL HAZARDS: This pesticide is toxic to fish and wildlife. Do not apply directly to water. Do not contaminate water by cleaning of equipment or disposal of equipment washwaters.

This product is highly toxic to bees exposed to direct treatment or residues on blooming crops or weeds. Do not apply this product or allow it to drift to blooming crops or weeds if bees are visiting the treatment areas.

PRECAUTIONS: Do not use on or contaminate fruit, vegetables or other food or feed crops.

Do not apply to humans, animals, clothing or bedding.

Do not contaminate feed or food products or food preparation surfaces; dishes, kitchen utensils and food containers.

IMPORTANT NOTICE

Do not dispense this product with power dusters in confined areas (i.e. attics, hot water heater closets, furnace rooms, etc.) in the presence of open flames, such as pilot lights.

(See reverse side for Directions for Use)

AVERT®

Prescription Treatment® 310

- Contains approximately 200 bait placements
- Crack and Crevice® Bait
- Kills cockroaches

Whitmire

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

PT® 310 is intended for application with the supplied hand duster to hiding and runway areas and those places where pests are found. Apply insecticide directly into cracks and crevices. Apply lightly and uniformly to infested areas. Pay particular attention to cracks and crevices; service ducts; false floors and ceilings; wall voids; around electrical and telephone fittings and equipment; around water and sewer pipes; under and behind cabinets, refrigerators and sinks; around window and door frames; and in attics and crawl spaces. The amount to be applied will vary with the site. Concentrate treatment at insect activity sites. For light infestations, a minimum of 4 - 6 bait points is recommended per 100 sq. feet of treatment area. For heavy infestations, a minimum of 12 - 24 bait points is recommended per 100 sq. feet of treatment area. Repeat treatments as necessary to maintain adequate control.

Do not use in the food/feed areas of food/feed handling establishments, restaurants or other areas where food/feed is commercially prepared or processed. Do not use in serving areas while food/feed is exposed. (Serving areas are considered areas where prepared foods are served, such as dining rooms, but exclude areas where foods may be produced or held.) In the home, all food processing surfaces and utensils should be covered and surfaces washed following treatment. Cover exposed food or remove from premises.

Examples of nonfood areas in food/feed handling establishments are garbage rooms, lavatories, floor drains (to sewers), entries and vestibules, offices, locker rooms, garages, mop closets, and storage (after canning and bottling).

Cockroaches (including carbamate, organophosphate and organochlorine resistant strains). Apply thoroughly to all areas where these pests crawl and hide, especially in cracks and crevices and hidden surfaces around sinks and storage areas, behind baseboards, around doors and windows, behind and under cabinets, stoves, behind refrigerators and in attics and crawl spaces.

OUTDOOR USE: Use for control of cockroaches. Inject into cracks and crevices around windows and doors, porches, screens, eaves, patios, garages, under stairways and in crawl spaces and other areas where pests hide, such as tree holes and cracks in fences.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

STORAGE: Store in a tightly closed container in a cool, dry place.

PESTICIDE DISPOSAL: Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility.

CONTAINER DISPOSAL: Do not reuse empty container. Wrap container and put in trash.

LIMITATION OF LIABILITY

Manufacturer warrants that this product conforms to the chemical description on the label. Buyer assumes all risks of use in handling which are at variance in any way with the directions on the label. MANUFACTURER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY OR ANY OTHER EXPRESS OR IMPLIED WARRANTY. IN NO CASE SHALL MANUFACTURER BE LIABLE FOR CONSEQUENTIAL, SPECIAL OR INDIRECT DAMAGES RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT. DAMAGES CAUSED BY THIS PRODUCT ARE LIMITED TO REPLACEMENT OF THE PRODUCT OR RETURN OF THE PURCHASE PRICE.

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Part No. 17-0405

D. APPENDIX D

DIETARY ASSESSMENT

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY
EPA REFERENCE DOSE = 0.0004 MG/KG BODY WT/DAY
COMMENT 1: Values based on U.S. EPA action levels or anticipated residues
COMMENT 2: Cottonseed, head lettuce, celery, strawberries, and pears

RESIDUE FILE LISTING

TAS CODE	CROP GRP	FOOD NAME	RESIDUE (PPM)	ADJ FACT	SOURCE CODE[1]
17	N	STRAWBERRIES	0.020000	1.00	EPA
56	L	PEARS			
		Raw	0.020000	1.00	EPA
		Cooked	0.020000	1.00	EPA
		Baked	0.020000	1.00	EPA
		Canned: Cooked	0.002000	1.00	REG
57	L	PEARS-DRIED	0.020000	6.25	EPA
166	E	CELERY	0.050000	1.00	EPA
192	E	LETTUCE-HEAD VARIETIES	0.050000	1.00	EPA
290	A	COTTONSEED-OIL	0.005000	1.00	EPA
291	A	COTTONSEED-MEAL	0.005000	1.00	EPA
318	X	MILK-NONFAT SOLIDS	0.000040	1.00	REG
319	X	MILK-FAT SOLIDS	0.000040	1.00	REG
320	X	MILK SUGAR (LACTOSE)	0.000040	1.00	REG
321	U	BEEF-MEAT BYPRODUCTS	0.000040	1.00	REG
322	U	BEEF(ORGAN MEATS)-OTHER	0.000380	1.00	REG
323	U	BEEF-DRIED	0.000040	1.00	REG
324	U	BEEF(BONELESS)-FAT	0.000240	1.00	REG
325	U	BEEF(ORGAN MEATS)-KIDNEY	no consumption in survey		
326	U	BEEF(ORGAN MEATS)-LIVER	0.000380	1.00	REG
327	U	BEEF(BONELESS)-LEAN (FAT/FREE)	0.000040	1.00	REG
384	E	CELERY JUICE	0.050000	1.00	EPA
404	L	PEARS-NECTAR			
		Raw	0.020000	1.00	EPA
		Canned: Cooked	0.002000	1.00	REG
416	N	STRAWBERRIES-JUICE	0.020000	1.00	EPA
467	A	CELERY SEED	0.050000	1.00	EPA

1/ EPA = U.S. EPA tolerance
REG = Registrant-supplied residue data

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY
EPA REFERENCE DOSE = 0.0004 MG/KG BODY WT/DAY
COMMENT 1: Values based on U.S. EPA action levels or anticipated residues
COMMENT 2: Cottonseed, head lettuce, celery, strawberries, and pears
Initial estimate of user-days as % of person-days in survey = 100.00%

U.S. POP - ALL SEASONS

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.5%	0.000014	3488

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	194623	20.0	0.000024	2052
80.0	0.000001	97312	10.0	0.000047	1066
70.0	0.000001	64874	5.0	0.000068	735
60.0	0.000001	48656	2.5	0.000094	534
50.0	0.000001	38925	1.0	0.000131	381
40.0	0.000004	12873	0.5	0.000170	293
30.0	0.000011	4351	0.0	0.001006	50

WESTERN REGION

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.6%	0.000016	3165

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	166552	20.0	0.000028	1755
80.0	0.000001	83276	10.0	0.000050	1003
70.0	0.000001	55517	5.0	0.000071	704
60.0	0.000001	41638	2.5	0.000096	522
50.0	0.000002	33310	1.0	0.000132	378
40.0	0.000007	7540	0.5	0.000154	324
30.0	0.000014	3500	0.0	0.000546	92

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY

HISPANICS

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.1%	0.000014	3641

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	193512	20.0	0.000023	2153
80.0	0.000001	96756	10.0	0.000042	1191
70.0	0.000001	64504	5.0	0.000072	697
60.0	0.000001	48378	2.5	0.000090	558
50.0	0.000001	38702	1.0	0.000124	402
40.0	0.000006	8627	0.5	0.000155	322
30.0	0.000013	3834	0.0	0.000272	183

NON-HISPANIC WHITES

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.6%	0.000015	3280

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	178253	20.0	0.000027	1873
80.0	0.000001	89126	10.0	0.000049	1014
70.0	0.000001	59418	5.0	0.000071	706
60.0	0.000001	44563	2.5	0.000097	515
50.0	0.000001	35651	1.0	0.000136	368
40.0	0.000005	9511	0.5	0.000170	294
30.0	0.000013	3792	0.0	0.001006	50

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY

NON-HISPANIC BLACKS

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY	
	MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.1%	0.000009	5702

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	360841	20.0	0.000009	5377
80.0	0.000000	180420	10.0	0.000028	1794
70.0	0.000000	120280	5.0	0.000051	987
60.0	0.000001	90210	2.5	0.000075	665
50.0	0.000001	72168	1.0	0.000120	415
40.0	0.000001	60140	0.5	0.000158	316
30.0	0.000003	19155	0.0	0.000306	163

NON-HISPANIC OTHER

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY	
	MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.6%	0.000013	3770

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	208155	20.0	0.000019	2588
80.0	0.000000	104077	10.0	0.000045	1102
70.0	0.000001	69385	5.0	0.000066	759
60.0	0.000001	52039	2.5	0.000088	566
50.0	0.000001	41631	1.0	0.000132	380
40.0	0.000002	21351	0.5	0.000179	280
30.0	0.000008	5932	0.0	0.000514	97

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY

FEMALES (13+/PREG/NOT NSG)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.6%	0.000012	4091

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	231853	20.0	0.000025	2002
80.0	0.000000	115926	10.0	0.000044	1137
70.0	0.000001	77284	5.0	0.000057	884
60.0	0.000001	57963	2.5	0.000069	721
50.0	0.000001	46371	1.0	0.000082	608
40.0	0.000003	16882	0.5	0.000100	498
30.0	0.000011	4632	0.0	0.000223	224

FEMALES (13+/NURSING)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
100.0%	0.000016	3207

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	176648	20.0	0.000020	2514
80.0	0.000001	88324	10.0	0.000057	881
70.0	0.000001	58883	5.0	0.000076	654
60.0	0.000001	44162	2.5	0.000109	458
50.0	0.000002	24800	1.0	0.000123	406
40.0	0.000007	7213	0.5	0.000128	391
30.0	0.000011	4680	0.0	0.000133	377

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY

NURSING INFANTS (<1 YEAR)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
83.0%	0.000002	21412

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	1356920	20.0	0.000001	99475
80.0	0.000000	678460	10.0	0.000010	5009
70.0	0.000000	453938	5.0	0.000015	3283
60.0	0.000000	360696	2.5	0.000024	2056
50.0	0.000000	299232	1.0	0.000030	1681
40.0	0.000000	255666	0.5	0.000031	1612
30.0	0.000000	190622	0.0	0.000032	1549

NON-NURSING INFANTS (<1)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
90.4%	0.000003	15617

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	363510	20.0	0.000001	40068
80.0	0.000000	181755	10.0	0.000008	6145
70.0	0.000000	134799	5.0	0.000024	2107
60.0	0.000000	111215	2.5	0.000032	1560
50.0	0.000001	94655	1.0	0.000044	1125
40.0	0.000001	82387	0.5	0.000053	951
30.0	0.000001	56504	0.0	0.000073	685

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY

MALES (13-19 YEARS)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
100.0%	0.000011	4477

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	253694	20.0	0.000019	2625
80.0	0.000000	126847	10.0	0.000037	1346
70.0	0.000001	84565	5.0	0.000055	909
60.0	0.000001	63424	2.5	0.000077	646
50.0	0.000001	50739	1.0	0.000106	472
40.0	0.000002	32620	0.5	0.000122	408
30.0	0.000009	5359	0.0	0.000261	191

FEMALES (13-19 YRS/NP/NN)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.8%	0.000014	3573

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	229003	20.0	0.000022	2272
80.0	0.000000	114502	10.0	0.000046	1099
70.0	0.000001	76334	5.0	0.000069	722
60.0	0.000001	57251	2.5	0.000105	475
50.0	0.000001	45801	1.0	0.000151	331
40.0	0.000002	26418	0.5	0.000190	264
30.0	0.000010	5067	0.0	0.000264	190

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY

CHILDREN (1-6 YEARS)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY	
	MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.9%	0.000016	3150

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	191827	20.0	0.000012	4050
80.0	0.000001	95914	10.0	0.000046	1082
70.0	0.000001	63942	5.0	0.000098	508
60.0	0.000001	47957	2.5	0.000148	338
50.0	0.000001	38365	1.0	0.000211	237
40.0	0.000002	28878	0.5	0.000265	189
30.0	0.000003	16688	0.0	0.001006	50

CHILDREN (7-12 YEARS)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY	
	MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.9%	0.000015	3243

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	179826	20.0	0.000022	2276
80.0	0.000001	89913	10.0	0.000054	918
70.0	0.000001	59942	5.0	0.000079	630
60.0	0.000001	44957	2.5	0.000111	451
50.0	0.000001	35965	1.0	0.000160	312
40.0	0.000003	19608	0.5	0.000201	249
30.0	0.000009	5814	0.0	0.000514	97

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY

MALES (20+ YEARS)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.5%	0.000014	3688

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	198568	20.0	0.000024	2047
80.0	0.000001	99284	10.0	0.000043	1150
70.0	0.000001	66189	5.0	0.000063	793
60.0	0.000001	49642	2.5	0.000085	585
50.0	0.000001	39714	1.0	0.000118	425
40.0	0.000006	8352	0.5	0.000138	361
30.0	0.000012	4038	0.0	0.000281	178

FEMALES (20+ YEARS/NP/NN)

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY: MG/KG BODY WT/DAY	MEAN DAILY EXPOSURE PER USER-DAY: MARGIN OF SAFTEY
99.5%	0.000015	3263

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	177340	20.0	0.000029	1713
80.0	0.000001	88670	10.0	0.000051	982
70.0	0.000001	59113	5.0	0.000070	715
60.0	0.000001	44335	2.5	0.000093	538
50.0	0.000001	35468	1.0	0.000126	398
40.0	0.000006	8343	0.5	0.000145	346
30.0	0.000015	3426	0.0	0.000378	132

ACUTE EXPOSURE (EX4) ANALYSIS FOR Avermectin; Section 3 REGISTRATION
RESIDUE FILE NAME: AVERT1A (NFCS87/88 DATA) ANALYSIS DATE: 12-09-1992
DPR NOEL = 0.05 MG/KG BODY WT/DAY

CUSTOM DEMOGRAPHICS 1: Seniors 55+ Years
All Seasons All Regions Sex: M F-all
All Races Age-Low: 55 yrs High: 110 yrs

ESTIMATED PERCENT OF PERSON-DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE PER USER-DAY	
	MG/KG BODY WT/DAY	MARGIN OF SAFTEY
99.8%	0.000015	3263

ESTIMATED PERCENTILE OF POPULATION USER-DAYS EXCEEDING CALCULATED EXPOSURE IN MG/KG BODY WT/DAY AND CORRESPONDING MARGIN OF SAFETY (MOS)

PERCENTILE	EXPOSURE	MOS	PERCENTILE	EXPOSURE	MOS
90.0	0.000000	182235	20.0	0.000030	1692
80.0	0.000001	91118	10.0	0.000049	1012
70.0	0.000001	60745	5.0	0.000068	734
60.0	0.000001	45559	2.5	0.000090	554
50.0	0.000001	36447	1.0	0.000121	414
40.0	0.000007	7511	0.5	0.000136	366
30.0	0.000016	3137	0.0	0.000378	132