UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: October 28, 2004

SUBJECT: Permethrin: HED Chapter of the Reregistration Eligibility Decision Document (RED). PC Code 109701, Case No. 52645-53-1, DP Barcode D298312.

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This document is the Health Effects Division's (HED) Chapter of the Reregistration Eligibility Decision (RED) Document for the chemical permethrin (109701). The document is generated as part of the Phase I of the public participation process. The Health Effects Division chapter reflects the Office of Pesticide Programs (OPP) current policies and guidelines concerning risk assessment. This chapter includes a product chemistry review by Ken Docker, a toxicological profile and endpoint selection by Yung Yang, a residue chemistry review by Sherrie Kinard, a dietary exposure assessment by Samuel Ary, a drinking water exposure assessment by Jose Melendez (Environmental Fate and Effects Division), an occupational and residential exposure assessment by Charles Smith, a review of human health incident data by Jerome Blondell and Monica S. Hawkins, and a review of animal incident data from the use of permethrin products by Virginia Dobozy.

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1.0 Executive Summary

This assessment provides information to support the issuance of a risk management decision document known as a Reregistration Eligibility Decision (RED) Document for permethrin. EPA's pesticide reregistration process provides for the review of older pesticides (those initially registered prior to November 1984) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to ensure that they meet current scientific and regulatory standards. The process considers the human health and ecological effects of pesticides and incorporates a reassessment of tolerances (pesticide residue limits in food) to ensure that they meet the safety standard established by the Food Quality Protection Act (FQPA) of 1996.

Permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] is a broad spectrum, non-systemic, synthetic pyrethroid insecticide registered for use on numerous food/feed crops, livestock and livestock housing, modes of transportation, structures, buildings (including food handling establishments), and for residential uses. Producers supporting the use of permethrin on crops and livestock include FMC Corporation, Syngenta Crop Protection, Inc., and Amvac Chemical Corporation under the trade names Astro®, Pounce® and Ambush®. Permethrin formulations registered by these companies for use on food/feed crops and livestock include emulsifiable concentrates (ECs), wettable powders (WPs), dusts (D), and a granular (G) formulation. These products may be applied to crops as broadcast or banded applications, pre- or post-emergence using ground or aerial equipment. Several of these formulations can also be applied directly to livestock and as surface sprays to livestock housing and premises.

In addition to the pesticidal uses, there is also a non-FIFRA pharmaceutical use of permethrin as a pediculicide for the treatment of head lice and scabies. The Food and Drug Administration (FDA) approves uses of the pesticidal-containing pharmaceutical products under FFDCA. HED is currently working with FDA to derive the appropriate exposure assessment methodology to determine how the pharmaceutical use of permethrin should be considered in EPA's aggregate risk assessment. An independent risk assessment for the pharmaceutical use will be conducted in the future.

Permethrin has a low acute toxicity via the oral, dermal, or inhalation route of exposure. Permethrin is not an eye or skin irritant and not a skin sensitizer. Permethrin is a type I pyrethroid with the primary target organ being the nervous system. The neurotoxic effects are consistently characterized by tremors, hyperactivity, and altered FOB observations. Following oral administration, permethrin is rapidly absorbed, metabolized, and excreted in urine and feces. Developmental and reproductive toxicity studies demonstrated that there is no evidence (qualitative or quantitative) for increased susceptibility of infants and children, and there is no evidence that permethrin induces any endocrine disruption. There is, however, a concern for developmental neurotoxicity based on evidence of neurotoxicity and increased incidence of microscopic lesions associated with neurotoxic effects at high doses in a subchronic neurotoxicity study. A developmental neurotoxicity study (DNT) is required for additional assurance as to the dose-response in characterizing neurotoxic effects. Although a DNT has been required, a dose-analysis with the existing reliable toxicity data for permethrin provided the

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HED with the confidence that the risk assessment conducted with no additional factor will provide reasonable certainty of no harm to the safety of infants and children. A database uncertainty factor (UF_{DB}) is not required for acute and chronic dietary risk assessments or for residential (non-dietary) exposure scenarios. In addition, the permethrin risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the special FQPA SF be reduced to 1x.

An acute dietary endpoint for the general U.S. population including infants and children was selected from a acute neurotoxicity study in rats, based on observations of clinical signs (i.e., aggression, abnormal and or decreased movement) and increased body temperature. No appropriate endpoint attributable to a single dose was identified for the females 13-50 years of age. Chronic dietary, short-term incidental oral, intermediate-term incidental oral, short-term dermal, intermediate-term dermal, and long-term dermal endpoints were also selected from the acute neurotoxicity study in rats and are based on observations of clinical signs (i.e., aggression, abnormal and or decreased movement) and increased body temperature. Short-, intermediate-, and long-term inhalation endpoints were selected from a 15-day inhalation study in rats based on body tremors and hypersensitivity to noise.

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the CARC classified permethrin as **"Likely to be Carcinogenic to Humans"** by the oral route. This classification was based on evidence of two reproducible benign tumor types (lung and liver) in the mouse, equivocal evidence of carcinogenicity in Long-Evans rats, and supportive SAR information. The Committee recommended using a linear low-dose extrapolation approach for the quantification of human cancer risk based on female mouse lung adenoma and/or carcinoma combined tumor rates. The unit risk for permethrin is based on female mouse lung adenoma and/or carcinoma combined tumor rates.

Highly refined acute, chronic, and cancer dietary exposure analyses (food + water) were performed in order to determine the exposure and risks resulting from the registered uses of permethrin. Acute, chronic, and cancer dietary (food and water) risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Permethrin residue estimates used in this assessment include cis- and trans-permethrin calculated as total permethrin along with the percent crop treated (%CT) estimates reported by the Biological and Economic Analysis Division (BEAD). The anticipated residue (AR) estimates are based primarily on the USDA PDP food sampling data. Processing data were also used on a number of crops if available. Acute dietary risk estimates are provided for the general U.S. population and various population subgroups and concludes that for all supported commodities, the acute dietary risk estimates do not exceed HED's level of concern (100% aPAD) at the 99.9th exposure percentile. The most highly exposed population subgroup in the acute dietary exposure analysis is all infants less than 1 year of age (18% aPAD). Chronic dietary risk estimates were also calculated for the U.S. population (total) and various population subgroups. The chronic assessment concludes that for all supported commodities, the chronic dietary risk estimates do not exceed HED's level of concern for the U.S. population and all population subgroups (all

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populataions <1% cPAD). The cancer dietary risk estimated tor the general U.S. population to permethrin exceeds HED's level of concern of 1.0×10^{-6}. The cancer dietary exposure estimate is 2.08×10^{-6} mg/kg/day with the significant contributors identified as spinach, water (direct and indirect all sources), and lettuce.

HED has also considered a number of exposure scenarios for products that can be used in the residential environment representing different segments of the population including toddlers, youth-aged children, and adults. Short-term noncancer MOEs were calculated for all scenarios. The assessment for residential exposure concludes that there are a number of risk concerns for permethrin as it is currently used in residential environments.

Risks exceed HED's level of concern (i.e., the MOEs are less than 100) for exposure to adults contacting treated indoor surfaces, for incidental ingestion of granules by toddlers, for hand-to-mouth and dermal postapplication exposures to toddlers from indoor pesticide treatments, and for toddlers that have contact with pets treated with dust or liquid products. Toddler risks from pet and turf uses and while wearing permethrin impregnated clothing represent total exposures from many pathways. For the pet uses, and wearing impregnated clothing, dermal and hand-to-mouth exposures essentially both equally contribute to the overall estimate. For the turf uses, dermal and hand-to-mouth exposures are also the key contributors to the overall estimates. When wearing impregnated clothing, dermal exposures are the key pathway. Cancer postapplication risks were estimated for the general U.S. population and most were found to be in the 10^{-7} to 10^{-9} range on the day of application (e.g., lawncare, golfing and gardening). Risks exceed HED's level of concern on the day of application for all indoor scenarios and for the pet contact scenario (after a liquid spray). All postapplication cancer risks (except for the impregnated clothing scenario) were estimated based on an annual frequency of 1 exposure-day per year (assuming exposure on the day of application (i.e., day 0).

The acute and long-term (noncancer) aggregate risk estimates include the contribution of risk from dietary (food + drinking water) sources only. Acute and chronic risk estimates from exposures to food and water, associated with the use of permethrin do not exceed the HED's level of concern.

For short-term adult aggregate risk estimates, chronic food and water exposures for the U.S. general population and for females 13-49 years of age were combined with residential handler and postapplication exposures. Short-term aggregate risk estimates exceed HED's level of concern (i.e., the MOEs are less than 100) for some scenarios considered. For short-term child aggregate risk estimates, with the exception of indoor carpet and vinyl sprays, and liquid pet uses, which alone exceed HED's level of concern, combined residues of permethrin from food, drinking water, and residential exposures do not result in short-term aggregate risks of concern.

As mentioned above, cancer exposure to permethrin from dietary (food and water) sources alone exceed HED's level of concern (i.e., 1.0×10^{-6}) , as do the potential risks for exposure from residential uses for eight scenarios. Any aggregation of residential exposures with dietary levels of exposure would only serve to increase the reported risks; therefore, cancer exposure estimates were not aggregated at this time.

Risk assessments have also been completed for occupational handler scenarios as well as occupational postapplication scenarios since there is potential for exposure to permethrin in occupational scenarios from handling permethrin products during the application process (i.e., mixer/loaders, applicators, flaggers, and mixer/loader/applicators) and a potential for postapplication worker exposure from entering into areas previously treated with permethrin. Short-term noncancer MOEs as well as postapplication cancer risks were calculated for all scenarios.

Most short-and intermediate-term postapplication occupational risks do not exceed HED's level of concern (i.e., the MOEs are greater than 100) at day 0, approximately 12 hours following application. In a few cases, postapplication occupational risks from certain high exposure activities exceed HED's level of concern for 1 to 4 days following application. Risks from corn detasseling – the highest exposure activity – exceeds HED's level of concern until 9 days following application. All postapplication long-term exposure scenarios for permethrin-impregnated clothing do not exceed HED's level of concern (i.e., the MOEs are greater than 100).

Postapplicaiton occupational cancer risks were estimated for hired hands (i.e., 10 exposures/year) and commercial/migratory farmworkers (i.e., 30 exposures/year) with the only difference being the annual frequency of exposure days. All of the estimated postapplication cancer risk estimates for both types of farmworkers are less than 1×10^{-4} and most do not exceed HED's level of concern (i.e., 1.0×10^{-6}). Postapplication occupational cancer risks were also estimated for exposure to impregnated clothing. All of the estimated postapplication cancer risk estimates for military personnel and garment workers exposed to permethrin impregnated clothing do not exceed HED's level of concern.

Although this assessment demonstrates risks of concern for residential and occupational exposures, HED is currently attempting to locate a previously unreviewed human dermal permethrin penetration study from California Department of Pesticide Regulation (CDPR) to help further refine this assessment. Upon evaluation of this study, we will compare it with the rat dermal penetration study used to perform the route-to-route extrapolation in the current assessment. If the human study is selected as being more appropriate for risk assessment purposes, residential risks calculated in a future revision to this assessment would no longer be expected to exceed the HED's level of concern; also, numerous aggregate exposure scenarios would no longer be expected to exceed the HED's level of concern since food plus water exposures are relatively small. If this is the case, few, if any additional residential exposure refinements are expected to be necessary in future revisions.

Although perhaps not necessary in future revisions to this assessment, the following may be of use to HED to refine permethrin residential and aggregate exposures and risk: (i) a probabilistic assessment of residential exposures and concomitant risks that HED has been informed is expected to be conducted by permethrin registrants and (ii) permethrin-specific data collected by the Indoor Residential Exposure Joint Venture (IREJV) detailing actual treatment rates, frequency and duration of application, exposure scenarios likely on a given day, etc.

2.0 Ingredient Profile

Product Chemistry Chapter for the Reregistration Eligibility Decision (RED) Document. Ken Dockter. DP Barcode D266247. June 4, 2004.

Permethrin. Residue Chemistry Considerations for Reregistration Eligibility Decision (RED) Document. PC Code: 109701. DP Barcode: D298290. Sherrie Kinard. October 25, 2004.

Permethrin: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. Charles Smith. DP Barcode D298288. October 20, 2004.

Permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] is a broad spectrum, non-systemic, synthetic pyrethroid insecticide registered for use on numerous food/feed crops, livestock and livestock housing, modes of transportation, structures, and buildings (including food handling establishments). Producers supporting the use of permethrin on crops and livestock include FMC Corporation, Syngenta Crop Protection, Inc., and Amvac Chemical Corporation under the trade names Astro®, Pounce® and Ambush®. Permethrin formulations registered by these companies for use on food/feed crops and livestock include emulsifiable concentrates (ECs), wettable powders (WPs), dusts (D), and a granular (G) formulation. These products may be applied to crops as broadcast or banded applications, pre- or post-emergence using ground or aerial equipment. Several of these formulations can also be applied directly to livestock and as surface sprays to livestock housing and premises.

Plant Uses: Permethrin formulations registered by the basic producers for use on food/feed crops include emulsifiable concentrates (ECs), wettable powders (WPs), and a granular (G) formulation. These products may be applied to crop plants as broadcast and banded preemergence applications or foliar applications using ground or aerial equipment.

Livestock Uses: For direct application of permethrin to ruminants and their housing, the available residue data support repeated applications to livestock premises at a rate of 0.21 oz ai/1,000 ft^2 with a 14-day retreatment interval (RTI). The data also support direct applications to ruminants at 950 mg ai/animal (2 mg ai/kg body weight) with a 14-day RTI along with the use of self-oilers containing permethrin at 0.17 oz ai/gal. A 1-day preslaughter interval (PSI) should be specified for ruminants.

For direct application of permethrin to swine and their housing, the available residue data support repeated applications to swine housing at a rate of 0.18 oz ai/1,000 ft^2 with a 14-day RTI. The data also support direct applications to swine at 240 mg ai/animal with a 14-day RTI along with the use of self-oilers containing permethrin at 0.17 oz ai/gal. A 5-day PSI may be specified for swine.

For direct application of permethrin to poultry and their housing, the available residue data support repeated applications to poultry houses at a rate of 0.18 oz ai/1,000 ft^2 with a 14-day RTI. The data also support direct applications to hens at ~20 mg/bird with a 14-day RTI. A 1-day PSI should be specified for poultry.

Non-Agricultural Uses: In addition to agricultural uses, permethrin can be used for non-crop sites such as non-cultivated crop areas, certain recreational, commercial and industrial areas, greenhouses, ornamental areas, animal premises, pet treatment, and wood treatment. Permethrin is used to control many pests including but not limited to mosquitoes, ants, and termites.

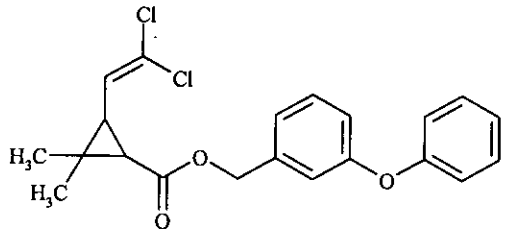
Permethrin can also be used by Public Health Officials and trained personnel in certain districts for mosquito abatement and other mosquito control programs. It can be formulated with piperonyl butoxide and applied by nonthermal ULV by ground or aerial methods.

2.1 Summary of Registered and Proposed Uses

Permethrin is a widely used insecticide in the United States. Permethrin is used in agricultural, commercial, and residential settings. Permethrin is formulated as an emulsifiable concentrate, a wettable powder (including water soluble bags), a granular, a dust, as well as a number of ready to use formulations, such as aerosol cans, foggers, trigger pump sprayers, ear tags, etc. A comprehensive summary of the registered use patterns of permethrin is presented in Appendix A. Conclusions regarding the reregistration eligibility of permethrin uses are based on the use patterns being supported by FMC, Syngenta, and Amvac. When end-use product DCIs are developed, RD should require that all end-use product labels (e.g., MAI labels, SLNs, and products subject to the generic data exemption) be amended such that they are consistent with the basic producer's labels.

RD

2.2 Structure and Nomenclature

Table 2.2. Chemical Structure and Nomenclature of Permethrin.	
Chemical structure	
Common name	Permethrin
Molecular Formula	$C_{21}H_{20}Cl_2O_3$
Molecular Weight	391.3
IUPAC name	3-phenoxybenzyl (1RS)-*cis-trans*-3-(2,2-dichlorovinyl)-2,2- dimethyl cyclopropanecarboxylate
CAS name	(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate
CAS #	52645-53-1
PC Code	109701
Current Food/Feed Site Registration	Numerous food/feed crops, livestock, livestock housing and premises, and food-handling establishments

Permethrin, a racemic mixture of the cis and trans isomers, is a synthetic pyrethroid insecticide. The current registered technical active product has a content of cis isomer ranging from 35% to 55%.

2.3 Physical and Chemical Properties

TABLE 2.3. Physicochemical Properties of Permethrin.		
Parameter	Value	Reference
Boiling point	220 °C (0.05 mm Hg; decomposes)	2001 Farm Chemicals Handbook
Melting point	31 °C 35 °C	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook
pH	4.44 at 20 °C	RD D274107, 7/12/01, S. Mathur
Density, bulk density, or specific gravity	1.229 g/cc 1.190-1.272 specific gravity at 20 °C	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook
Water solubility	0.21 mg/L at 20 °C <1 ppm	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook
Solvent solubility	258 mg/kg in methanol at 25 °C >1000 g/kg in hexane at 25 °C Miscible in most organic solvents except ethylene glycol; soluble in acetone, ethanol, ether, and xylene	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook
Vapor pressure	0.07 mPa at 20 °C <10 Torr at 50 °C	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook

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TABLE 2.3. Physicochemical Properties of Permethrin.		
Parameter	Value	Reference
Dissociation constant, pK_a	Not applicable because permethrin is neither an acid nor a base.	
Octanol/water partition coefficient	log P_{ow} = 4.19 at 20 °C	RD D274107, 7/12/01, S. Mathur
UV/visible absorption spectrum	At pH 7 λmax 1 = 273 nm, 3.22 log ϵ λmax 2 = 207 nm, 4.55 log ϵ At pH <2 λmax 1 = 276 nm, 3.24 log ϵ λmax 2 = 209 nm, 4.43 log ϵ At pH >10 λmax 1 = 272 nm, 3.19 log ϵ λmax 2 = 212 nm, 4.99 log ϵ	RD D274107, 7/12/01, S. Mathur

Permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] is a synthetic pyrethroid insecticide. Permethrin is a racemic mixture of the cis and trans isomers. Permethrin is a colorless crystal to a pale yellow viscous liquid with a melting point of 35°C and a boiling point of 220°C (0.05 mm Hg). Permethrin is soluble in water at less than 1 ppm, and is miscible in most organic solvents except ethylene glycol. Permethrin is soluble in acetone, ethanol, ether, and xylene.

3.0 Metabolism Assessment

Permethrin. Metabolism Assessment Review Committee Memorandum by S. Kinard, Y. Yang, and J. Melendez dated July 6, 2004.

3.1 Comparative Metabolic Profile

The qualitative nature of the residue in plants, livestock, and rotational crops is adequately understood based on soybean, cabbage, sweet corn, livestock (oral and dermal), and rotated crop metabolism data. DCVA, MPBA, and 3-PBA are the major residues (>10% TRR). All submitted rat metabolism studies on permethrin have been classified as unacceptable/guideline based on deficiencies in the level of detail provided which prevent verification/validation of findings (e.g., insufficient data regarding characterization of recovered radioactivity, no dose confirmation, no lot/batch numbers for the test article). However, when considering all rat metabolism studies together, it provides information on absorption, distribution, and excretion which indicated that permethrin is rapidly absorbed, metabolized, and excreted in urine and feces. Most of the urinary metabolites and some fecal metabolites appeared to be hydroxylation products, and glucuronide and sulfate conjugates.

3.2 Nature of the Residue in Foods

MARC had previously concluded that tolerances will be expressed in terms of the parent, *cis*- and *trans*-permethrin only, but that the risk assessment will consider residues of *cis*- and *trans*-DCVA in addition to the parent compound (C. Olinger, 2/1/96). However, based on the weight of all the available evidence, the MARC concluded in a meeting on January 15, 2004 that there are not sufficient grounds to include DCVA in the cancer risk assessment at this time, and that for tolerance expression and risk assessment purposes, parent only is the residue of concern.

3.2.1. Description of Primary Crop Metabolism

The qualitative nature of the residue in plants is adequately understood based on three adequate plant metabolism studies. Plant metabolism studies on cabbage, sweet corn, and soybean indicated that parent, DCVA, and MPBA are major residues (>10% TRR). Multiple applications were made to the sweet corn at a 5X rate. Forage was sampled one day after the third application while the grain was sampled one day after the fifth application. Product labels specify a one-day PHI.

A translocation study was also conducted with soybean plants where foliar and pod applications were made and samples of the plant parts were taken 15 and 45 days post-treatment. Permethrin, *cis*- and *trans*-DCVA, and MPBA were the major metabolites in corn forage and fodder, cabbage, and soybean leaves. Hydroxylated MPBA and MPBAcid were also found in minor amounts.

All three studies demonstrate that the major residue is permethrin when the RAC is harvested soon after treatment (within one day). As the time between treatment and harvest increases, hydrolysis of the ester bond occurs, yielding DCVA and MPBA. Hydroxylation of the alcohol or conversion to the corresponding acid may then occur.

3.2.2 Description of Livestock Metabolism

The qualitative nature of the residue in animals is adequately understood based upon acceptable poultry and ruminant metabolism studies using both oral and dermal dosing of [^{14}C]permethrin.

Oral and dermal metabolism studies have been conducted in ruminants and poultry. All studies were conducted with cyclopropyl- and phenyl-labeled permethrin in separate tests. The ruminant oral study was conducted at an approximately 1x rate, while the poultry oral study was conducted at a 116x rate. Dermal studies were conducted at a 1x rate per application, but with a much shorter retreatment interval. The poultry studies are considered adequate, but additional characterization of two organosoluble unknowns have been requested for the ruminant studies.

Permethrin was the major residue found in fat, muscle, milk, and eggs for orally and dermally dosed animals. Hydrolysis to DCVA and 3-PBA occurred in liver and kidney in the oral and dermal studies; minimal permethrin was found. MPBA was also found in the muscle of hens treated dermally.

3.2.3 Description of Rotational Crop Metabolism, including identification of major metabolites and specific routes of biotransformation

An adequate confined rotational crop study is available. These data indicate that residues of permethrin in rotational crops are qualitatively similar to the residues resulting from the direct application of permethrin to the primary crops. Based on this study and the label-specified 60-day plant-back interval, limited field rotational crop studies are required.

Residues of *cis* and *trans* permethrin and DCVA were each <0.01 ppm (<LOD) in/on all crop samples tested; therefore, tolerances for residues of permethrin in/on rotated crops are not required, provided all labels specify a 60-day plant-back interval.

3.3 Rat Metabolism

All submitted rat metabolism studies on permethrin were classified unacceptable/guideline based on deficiencies in level of detail provided which prevent verification/validation of findings (e.g., insufficient data regarding characterization of recovered radioactivity, no dose confirmation, no lot/batch numbers for the test article). No data on quantification of metabolites are available. Studies indicate that permethrin is rapidly absorbed, metabolized, and excreted in urine and feces. Most of the urinary metabolites and some fecal metabolites appeared to be hydroxylation products, and glucuronide and sulfate conjugates.

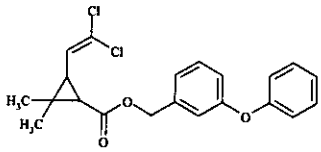
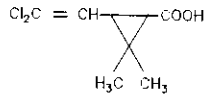
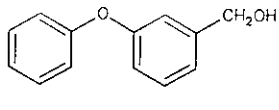
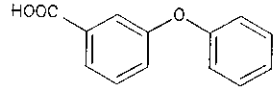
3.4 Environmental Degradation

Permethrin appears to dissipate primarily through binding to the soil, and by soil microbial degradation. It does not degrade through abiotic means (hydrolysis or photolysis).

The moderately high reported half-life for permethrin by aerobic soil metabolism was 37 days. The major degradates reported were $^{14}CO_2$ (34-40% after 6 months), trans-DCVA and 3-(2,2-dichlorovinyl)-2-methylcyclopropane-1,2-dicarboxylic acid, and 3-PBA. In an acceptable aerobic aquatic metabolism study the reported half-life ranged from 38 to 42 days. The half-life in an anaerobic soil metabolism study was 204 days when applied at a rate of 3.2 lb ai/A. The major degradates were trans-DCVA and 3-PBA. The half-life reported for permethrin in an anaerobic aquatic study ranged from 113 days to 175 days which indicates that the degradation is slower as the oxygen levels are reduced.

3.5 Tabular Summary of Metabolites and Degradates

Table 3.5. Tabular Summary of Metabolites and Degradates

Chemical Name	Commodity	Percent TRR		Structure
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
Permethrin	Cabbage	permethrin, DCVA, MPBA	3-PBA, 4'OH MPBA, 2'OH MPBA	
DCVA	Corn, sweet	permethrin, *trans*-DCVA, MPBA	*cis*-DCVA, 4-OH PBA, 3-PBA	
MPBA	Soybean	permethrin, DCVA, MPBA	3-PBA, 4'OH MPBA, 2'OH MPBA	
3-PBA	Rotational Crops	none	permethrin, DCVA	
	Ruminant and Poultry	permethrin, DCVA, OH-DCVA, DCVA-Glucuronide, 3PBA, 4'OH-3-PBA	OH-permethrin, DCVA-lactone	
	Water	permethrin, DCVA, 3PBA, 3PBalcohol	----	

Cabbage; 00025919 and 92142094; 1X rate; 0, 30, and 60 days.
Corn, sweet; 43307801 ; 5X rate; 1 day.
Soybean; 00094393 and 92142095; 1X rate; 30, 50, and 78 days and 15 and 45 days.

Goat (oral); 42410001, 43505201, 43962801, and 44417803; 1X MTDB; days of dosing..
Hen (oral); MRID No. 42503201; 116X MTDB; 7 days.
Cows (dermal); 43713303, 43713304, and 44196102; 2 mg/kg body wt./day; 1X rate; 3 days.
Hen (dermal); 43458802; 10.3 mg/kg body wt./day; 1X rate; 3 days.

Rotational Crops; 43174401, 44428201, 44428202, 44428203; Lettuce, Radish, and Spring Wheat, 1X rate; 60 day PBI.

Rat; No guideline studies available.

3.6 Toxicity Profile of Major Metabolites and Degradates

The HED Metabolism Committee has previously determined tolerances will be expressed in terms of the parent, *cis*- and *trans*-permethrin only, but the risk assessment will consider residues of *cis*- and *trans*-DCVA in addition to the parent compound (CBRS No. 16744, DP Barcode 222362, C. Olinger, 2/1/96); however, in a meeting on January 15, 2004, MARC decided that DCVA will not likely cause the same neurotoxic effects as the parent pyrethriods and, based on the weight of all the available evidence, the MARC concluded there are not sufficient grounds to include DCVA in the cancer risk assessment at this time. The following points were considered in drawing this conclusion.

- Based on the amount and nature of the radioactivity appearing in the urine of rats it is likely that the three pyrethroids permethrin, cypermethrin/zeta-cypermethrin, and cyfluthrin are metabolized to a significant extent by cleavage of the ester linkages with the resulting formation of DCVA. In the case of cypermethrin, similar metabolism and pharmacokinetics are observed in mice and dogs. The results of cancer studies in mice for the three pyrethroids were significantly different. Permethrin is classified as a likely human carcinogen with a q* based on lung adenomas and carcinomas plus liver adenomas in mice. Cypermethrin is a possible human carcinogen without a q* based on lung adenomas plus carcinomas also in mice. Cyfluthrin is classified as not likely to be carcinogenic to humans based on no evidence of carcinogenicity rat or mouse studies. Considering that cyfluthrin and permethrin are both metabolized to a significant extent in mammalian systems to DCVA and the different cancer classifications for the two insecticides, the weight of evidence suggests that DCVA per se does not contribute significantly to the carcinogenic effect.

- Looking at the total human exposure to permethrin related residues from all possible sources, DCVA is expected to be a minor contributor compared to the parent. This conclusion is based on the wide array of residential uses of permethrin, the relative levels of parent and DCVA observed in crops and livestock, and the low absolute levels (ppb) of DCVA anticipated in drinking water.

- It is noted that the above decision is consistent with those made for DCVA as a metabolite of the pyrethroid cyfluthrin (see 6/13/02 memo, D283553, PC code 128831) and for the November 1997 assessment to address expiring tolerances for most of the pyrethroids.

- The salmonella reverse mutation assay (Ames assay) conducted with DCVA indicated that the compound was negative in the presence and absence of metabolic activation in all five tester strains.

3.7 Summary of Residues for Tolerance Expression and Risk Assessment

3.7.1 Tabular Summary

Table 3.7. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent only (both *cis*- and *trans*-)	Parent only (both *cis*- and *trans*-)
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Parent only (both *cis*- and *trans*-)	Parent only (both *cis*- and *trans*-)
	Poultry	Parent only (both *cis*- and *trans*-)	Parent only (both *cis*- and *trans*-)
Drinking Water		Parent only (both *cis*- and *trans*-)	Not Applicable

3.7.2 Rationale for Inclusion of Metabolites and Degradates

MARC has concluded that for tolerance expression and risk assessment, parent only is the residue of concern; therefore, there is no need for the rationale for inclusion of metabolites and degradates. For the rationale on not including DCVA in the risk assessment, please refer to section 3.6 Toxicity Profile of Major Metabolites and Degradates.

4.0 Hazard Characterization and Assessment

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision. Yung Yang, Ph.D. TXR No. 0050721. December 16, 2003.

Third Report of the Hazard Identification Assessment Review Committee. TXR No 0052543. Yung Yang Ph.D. May 12, 2004.

4.1 Hazard and Dose-Response Characterization

4.1.1 Database Summary

4.1.1.1 Studies available and considered (animal, human, general literature)

- Acute - Oral rat neurotoxicity
- Subchronic - Oral rat neurotoxicity
- Chronic - Oral rat neurotoxicity; 2-year rat and mouse cancer studies; 1-year dog
- Repro/developmental - Rat and rabbit developmental; 3-generation reproductive rat
- Other - mutagenicity screens

4.1.1.2 Mode of action, metabolism, and toxicokinetic data

Permethrin is a Type I pyrethroid (i.e., it lacks a cyano group at the α carbon position of the alcohol moiety). This structural group targets sodium channels and affects neuromuscular signal conduction. Permethrin is absorbed by all routes with an estimated dermal absorption factor of 30%. Following oral administration, permethrin is rapidly absorbed, metabolized, and excreted via urine and feces.

4.1.1.3 Sufficiency of studies and data

Data are sufficient for each exposure scenario, FQPA evaluation, and for important endpoints and dose-response evaluation.

4.1.2 Toxicological Effects

Permethrin has a low acute toxicity via the oral, dermal, or inhalation route of exposure. Permethrin is not an eye or skin irritant and not a skin sensitizer. Permethrin is a type I pyrethroid with the primary target organ being the nervous system. The neurotoxic effects are consistently characterized by tremors, hyperactivity, and altered FOB observations. In studies where the liver is affected, it appears to be an adaptive response and is not considered an adverse effect. Following oral administration, permethrin is rapidly absorbed, metabolized, and excreted in urine and feces. Developmental and reproductive toxicity studies demonstrated that there is no evidence (qualitative or quantitative) for increased susceptibility to infants and children following *in utero* and/or pre-/post-natal exposure of permethrin. There is no evidence that permethrin induces any endocrine disruption. However, there is a concern for developmental

neurotoxicity based on evidence of neurotoxicity and increased incidence of microscopic lesions associated with neurotoxic effects at high doses in a subchronic neurotoxicity study. A developmental neurotoxicity study (DNT) is required for additional assurance as to the dose-response in characterizing neurotoxic effects. Although permethrin is not mutagenic, it is classified as **"Likely to be Carcinogenic to Humans"** by the oral route based on evidence of two reproducible benign tumor types (lung and liver) in the mouse, equivocal evidence of carcinogenicity in Long-Evans rats, and supportive SAR information.

4.1.3 Dose-response

The critical effect (neurotoxicity) for the overall risk assessment is based on the most sensitive species, rats. The oral exposure limits for all durations were based on an acute neurotoxicity study in rats. The effects of permethrin in several species are early in onset and short-term, without indications that incidence or severity of effects would increase based on metabolism studies that permethrin is rapidly absorbed, metabolized, and almost completely eliminated from the body within a short period of time. This finding that permethrin does not bioaccumulate is supported by a close range of NOAEL and LOAEL among acute, subchronic, and chronic toxicity studies associate with clinical signs of neurotoxicity.

The dermal exposure limits for all durations were based on an acute neurotoxicity study. This oral study with an absorption factor (30%) is being used for short-, intermediate- and long-term dermal exposure because the endpoints of concern (i.e., FOB parameters indicative of neurotoxicity) was not measured in the 21-day dermal toxicity study in rats.

The inhalation exposure limits for all durations were based on a rat 15-day inhalation study. The selected dose/endpoint is appropriate for the route of exposure.

Quantification of cancer risk will use a Q_1^*(mg/kg/day)$^{-1}$ of 9.567 x 10^{-3} in human equivalents based on female mouse lung adenoma and/or carcinoma combined tumor rates

The uncertainty factors used in determining RfD exposure limits were 100 (10x for intraspecies variation and 10x for interspecies extrapolation).

4.1.4 FQPA

The database is adequate in terms of endpoint studies and dose response information to characterize any potential for prenatal or postnatal risk for infants and children. There is no evidence (qualitative or quantitative) for increased susceptibility following *in utero* and/or pre-/post-natal exposure in the developmental toxicity studies in rats and rabbits and multi-generation reproduction studies in rats. Since there is no developmental or reproductive toxicity observed in the developmental studies in rats and rabbits or reproduction study in rats, the HIARC concluded that there are no concerns or residual uncertainties for pre- and post-natal toxicity.

The HIARC also concluded that there is a concern for developmental neurotoxicity resulting from exposure to permethrin based on the weight of evidence. A revised dose analysis that included an evaluation of the acute and subchronic neurotoxicity studies in addition to the 3-generation reproduction study indicated that a database uncertainty factor (UF_{DB}) is not required for acute and chronic dietary risk assessments or for residential (non-dietary) exposure scenarios.

Table 4.1.4.1. Acute Toxicity Profile on Permethrin*

OPPTS Guideline	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute oral toxicity in Rats	242899	LD_{50} = 3580 mg/kg (M) 2280 mg/kg (F)	III
870.1200	Acute dermal toxicity in Rabbits in Rats	242899 099258	LD_{50} >2000 mg/kg	III
870.1300	Acute inhalation toxicity in Rats	096692	LC_{50} >23.5 mg/L	IV
870.2400	Acute eye irritation in Rabbits	242899 099258	No corneal opacity or conjunctival irritation	IV
870.2500	Acute dermal irritation in Rabbits	242899 096692	All irritation cleared by 48 hrs	IV
870.2600	Skin sensitization in Guinea Pigs	099258 099263	Non-sensitizer	N/A**

* Data extracted from HED Doc. No. 008216.
** N/A: Not Applicable.

Table 4.1.4.2. Subchronic, Chronic and Other Toxicity Profile on Permethrin		
Guideline No./ StudyType/	**MRID Nos. Doses/Classification**	**Results**
870.3200 21-Day dermal toxicity - Rat	41143801,42653301 Ph III Summ: 92142030 0, 50, 150, 500 mg/kg/day Acceptable/guideline	The systemic NOAEL was 500 mg/kg/day (the highest dose tested), the systemic LOAEL was not established. The dermal LOAEL was 50 mg/kg/day based on skin irritation. A dermal NOAEL was not identified.
870.3465, 82-4 15-Day inhalation toxicity - Rat	00096713 0, 0.0061, 0.042, 0.583 mg/L Acceptable/non-guideline	The LOAEL is 0.583 mg/L in male and female rats based on body tremors and hypersensitivity to noise. The NOAEL is 0.042 mg/L.
870.3700a Prenatal developmental - Rat	40943603 0, 15, 50, 150 mg/kg/day Acceptable/Guideline	The maternal toxicity LOAEL is 150 mg/kg/day based on clinical signs of toxicity and decreased body weight gain and food consumption. The maternal toxicity NOAEL is 50 mg/kg/day.the developmental toxicity LOAEL is 150 mg/kg/day based on decrease in fetal body weights and an increase in the incidence rate of short length extra ribs. The developmental toxicity NOAEL is 50 mg/kg/day.
870.3700b Prenatal developmental - Rabbit	92142091,40943602, 92142036 0, 600, 1200, 1800 mg/kg/day Acceptable/guideline	The maternal toxicity LOAEL is estimated to be <600 mg/kg/day based on decreased body weight gain. The maternal toxicity NOAEL is not identified. The developmental toxicity LOAEL is 1200 mg/kg/day based on increased post-implantation loss, greater numbers of early and late resorptions and an equivocal decrease in ossification of the fore- and hind-limbs. The developmental toxicity NOAEL is 600 mg/kg/day.
870.3800 Reproduction and fertility effects - Rat	00102108 00120271 92142092 92142037 0, 500,1000,2500 ppm (0, 25,50,125 mg/kg/day) Acceptable/guideline	The LOAEL for systemic toxicity is 2500 ppm (125 mg/kg/day) based on tremors observed in the F_0 females, and the F_1 and F_2 males and females. The systemic toxicity NOAEL is 1000 ppm (50 mg/kg/day). The reproductive toxicity NOAEL is ≥2500 ppm (125 mg/kg/day) and the reproductive toxicity LOAEL is not identified. The NOAEL for offspring growth and development is ≥2500 ppm (125 mg/kg/day) and the offspring LOAEL is not identified.
870.4300 Chronic toxicity -Rat	92142123 0, 500, 1000, or 2500 ppm 0, 19.4, 36.9, 91.5 mg/kg/day (M) 0, 19.1, 40.2, 104 mg/kg/day (F) Acceptable/guideline	The chronic toxicity LOAEL is 2500 ppm (91.5 mg/kg/day for males and 104 mg/kg/day for females), based on tremors and hypersensitivity. The NOAEL is 500 ppm (36.9 mg/kg/day for males and 19.4 mg/kg/day for females). No tumor
870.4100b Chronic toxicity - dog	00129600 0,5,100,1000 mg/kg/day (capsule) Acceptable/Guideline	The systemic toxicity LOAEL is 1000 mg/kg/day based on clinical neurotoxic signs and decreased body weight gain and food consumption. The NOAEL is 100 mg/kg/day.
870.4200b Carcinogenicity - mouse	00062806, 92142033 0, 3, 71, 286 mg/kg/day (M) 0, 3, 357, 714 mg/kg/day (F) Acceptable/guideline	There were statistically significant increases in liver adenoma at all doses for males and at mid- and high-doses for females with a significant dose-related trend in both sexes.

Table 4.1.4.2. Subchronic, Chronic and Other Toxicity Profile on Permethrin		
Guideline No./ StudyType/	**MRID Nos. Doses/Classification**	**Results**
870.4200b Carcinogenicity - mouse	00102110, 92142032 0, 26.9, 110.5, 287.2 mg/kg/day (M). 0, 29.8, 124.2, 316.1 mg/kg/day (F) Acceptable/guideline	There was no evidence of significant increase in unusual tumor types. A non-significant increase in lung adenomas in males and in lung adenomas plus carcinomas in females was seen at the highest dose.
870.4200b Carcinogenicity - mouse	45597105 0, 5000 ppm (Females only) (0, 780-807 mg/kg/day) Acceptable/non-guideline	There were significant increases in the incidences of lung bronchioloalveolar adenomas in mice. The increased incidences of basophilic hepatocellular adenoma did not show a relationship to the treatment duration. No progression to carcinoma was observed in the lung or liver.
870.5100 Gene mutation Salmonella typhimurium	41031107 Acceptable/guideline	There were no evidence of increased revertant colonies above control in 5 Salmonella strains up to 5000 µg/plate (solubility limit).
870.5550 Unscheduled DNA	40943604 Acceptable/guideline	There was no evidence of unscheduled DNA synthesis above control up to 10^{-4} M and possibly 10^{-2} M Limits of cytotoxicity).
870.5395 Mouse Bone Marrow Micronucleus	42723302 Acceptable/guideline	There was no evidence that permethrin is clastogenic in the bone marrow cells of mice.
870.6200 Acute Neurotoxicity - Rat	43046301 45657401 Acceptable when considered together	NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
870.6200 Subchronic neurotoxicity - Rat	00071952 2500,3000,3750,4500, 5000, 7500 ppm Acceptable/nonguideline	The systemic and neuro- toxicity LOAEL is 2500 ppm (125 mg/kg) based on clinical signs of toxicity and decreases in body weight gain and food consumption. The systemic and neuro- toxicity NOAEL was not identified for this preliminary study.
870.6200b Subchronic neurotoxicity -Rat	40766807 0, 100, 200, 400 mg/kg/day Acceptable/nonguideline	The systemic LOAEL is 200 mg/kg/day based on tremors and irritability. The systemic NOAEL is 100 mg/kg/day. The NOAEL is > 400 mg/kg/day with respect to morphological and histological changes.
870.6100b Delayed Neurotox - Hen	00112933 approx. 9000 mg/kg (94.9% a.i.) cis:trans 36:58.9 Acceptable/guideline	Oral administration of permethrin does not produce delayed neuropathy in the hen.
870.6100b Delayed Neurotox - Hen	00097426 0, 2000,4000 mg/kg cis:trans 25:75 Acceptable/guideline	Oral administration of permethrin up to 4000 mg/kg does not produce delayed neuropathy in the hen.

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

The HIARC concluded that the toxicology database for permethrin is adequate for FQPA considerations.

- Acute neurotoxicity study in hens (acceptable).
- Acute and subchronic neurotoxicity studies in rats (acceptable).
- Developmental toxicity studies in rats and rabbits (acceptable).
- Three generation reproduction study in rats (acceptable).

4.2.2 Evidence of Neurotoxicity

The HIARC concluded that there is a concern for neurotoxicity resulting from exposure to permethrin based on neurotoxic effects characterized by tremors, hyperactivity, and altered FOB observations.

4.2.2.1 Acute Neurotoxicity

Executive Summary: In an acute neurotoxicity study (MRID 43046301), permethrin (95.3% a.i., Lot # PL90-269, cis:trans 50:50) was administered by gavage to Sprague-Dawley rats (4/sex/group) at dose levels of 0, 10, 150, or 300 mg/kg in corn oil. Following administration, the rats were assessed for clinical signs daily. FOB and motor activity assessments were made pre-test and at day 0, (at estimated time of peak effect) and days 7 and 14. After day 14, the rats were sacrificed and the nervous system assessed histopathologically.

Reactions to treatment were noted in the 300 mg/kg treated males and females only. The reactions attributed to treatment included one death (a female), tremors (all animals), staggered gait and gait impairment (8/sex), splayed hindlimbs (2 males, 6 females),decreased forelimb grip strength (21% decrease in males, 13.5% decrease in females) as well as other symptoms occurring in 2 or fewer animals but not in the controls (convulsion, ataxia, exaggerated hindlimb flexion, increased auditory response, uncoordinated landing). No evidence of compound related neurohistopathology was noted in tissues from animals perfused in vivo. **The LOAEL was 300 mg/kg based on tremors and gait impairment. The NOAEL was 150 mg/kg.**

This acute neurotoxicity study was classified **unacceptable/guideline** because the study was determined to have used inappropriate dose levels and dosing volume of corn oil. A pilot study was reported to indicate clinical signs due to treatment with 50 mg/kg of permethrin when administered as a 10% corn oil solution. The main study was assessed using a 1% corn oil solution and the LOAEL was determined to be 300 mg/kg or 4 times greater. The 1% corn oil solution required dosing the rats with 30 ml/kg for the control and high dose groups and 15 ml/kg for the mid-dose group and 1 ml/kg for the low-dose group. It is considered that dosing with volumes greater than 10 ml/kg results in confounding the interpretation of the study data

because of potential effects on compound absorption.

However, the Toxicology Branch has determined that the requirement for an acute neurotoxicity screen study has been satisfied when taken together with another acute oral neurotoxicity study (MRID 45657401, McDaniel and Moser, Neurotoxicology and Teratology 15:71-83, 1993). An executive summary of this study is as follows.

Executive Summary: In a published literature study (MRID 45657401), permethrin (95%, a.i., cis:trans 50:50) was administered by gavage to Long-Evans rats (8/sex/group) at dose levels of 0, 25, 75, or 150 mg/kg in corn oil. FOB and motor activity were assessed prior to dosing and at 2, 4, 24 and 48 hours after dosing.

At 75 mg/kg, the rats displayed a general pattern of increased excitability and aggressive behavior. Some of the more pronounced responses included abnormal motor movement (3/8, both sexes) decreased grip strength for forelimb (males) and hindlimb (males and females), motor activity (males), and increased body temperature (males). At 150 mg/kg, arousal score (males), righting reflex (males) and approach response score (females) were affected and 7/8 of both sexes had abnormal motor movement and motor activity was further decreased and body temperature was increased >2°C. Slight decreases in body weight (3-4%) were evident. Recovery from the symptoms was within 24 hours. **The LOAEL is 75 mg/kg based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature. The NOAEL is 25 mg/kg.**

The study is classified as **acceptable/nonguideline.** Study is in the form of a literature reprint and was not designed to meet a specific guideline protocol.

4.2.2.2 Acute Delayed Neurotoxicity

Executive Summary: In a delayed neurotoxicity study (MRID 00097426), a group of 10 domestic hens were administered 0, 2000, or 4000 mg/kg of permethrin (Lot No.: ZJ; isomer ratio 25 cis:75 trans) in corn oil by oral gavage. An additional group of 10 birds was given 500 mg tri-*ortho*-cresyl-phosphate (TOCP)/kg as the positive control. All birds were given a single oral dose on study day 0 and observed for 21 days. Birds in the permethrin and negative control groups were redosed on study day 21 and observed for an additional 21 days. Toxicity assessments were limited to clinical observations, assessment of ataxia, body weight measurements, and microscopic evaluation of the spinal cord and sciatic nerve. Acetylcholinesterase and neurotoxic esterase activities were not measured.

No treatment-related clinical signs of toxicity and no effects on body weights or food consumption were observed in birds administered permethrin. Ataxia was not seen in birds treated with the test article and no treatment-related lesions were observed on microscopic examination of the nervous tissues.

Following treatment with TOCP, clinical signs and neurohistopathological lesions indicative of delayed neuropathy were observed in these birds.

Therefore, under the conditions of this study, oral administration of permethrin up to 4000 mg/kg does not produce delayed neuropathy in the hen.

This study is classified **acceptable/guideline** and does satisfy the requirements for a delayed neurotoxicity study [OPPTS 870.6100 (81-7)] in hens. Although a deficiency was that AChE and NTE activities were not measured, the study is considered sufficient for determining the potential of permethrin to produce delayed neurotoxicity in the hen. This study was conducted prior to initiation of current guidelines.

Executive Summary: In a delayed neurotoxicity study (MRID 00112933), a group of 15 domestic hens were administered 15 mL of permethrin (Lot No.: not given; isomer ratio 36 cis:58.9 trans, 94.9% a.i.) by oral gavage. Based on a specific gravity of 1.2, mean body weight on study day 0, and not correcting for purity of the test article, the dose to the hens was approximately 9000 mg/kg. Additional groups were given water as the negative control (n = 10) or 500 mg TOCP/kg as the positive control. All birds were given a single oral dose on study day 0 and observed for 21 days. Birds in the permethrin and negative control groups were redosed on study day 21 and observed for an additional 21 days. Prior to redose, birds in the permethrin group were protected with 10 mg atropine/kg and 50 mg 2-PAM/kg given by intramuscular injection.

Toxicity assessments were limited to clinical observations, assessment of ataxia, measurements of body weights and food consumption, and microscopic evaluation of the brain, spinal cord, and sciatic nerve. Acetylcholinesterase and neurotoxic esterase activities were not measured.

No treatment-related clinical signs of toxicity and no effects on body weights or food consumption were observed in birds administered permethrin. Ataxia was not seen in birds treated with the test article and no treatment-related lesions were observed on microscopic examination of the nervous tissues.

Following treatment with TOCP, clinical signs and neurohistopathological lesions indicative of delayed neuropathy were observed in these birds.

Therefore, under the conditions of this study, oral administration of permethrin does not produce delayed neuropathy in the hen.

This study is classified **acceptable/guideline** and does satisfy the requirements for a delayed neurotoxicity study [OPPTS 870.6100 (§81-7)] in hens. Although a major deficiency was that AChE and NTE activities were not measured, the study is considered sufficient for determining the potential of permethrin to produce delayed neurotoxicity in the hen. This study was conducted prior to implementation of current guidelines.

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4.2.2.3 Subchronic Neurotoxicity

Executive Summary: In a subchronic neurotoxicity study (MRID 42933701), permethrin (95.3% a.i., Lot# PL90-269, cis:trans 50:50) was administered via diet to Sprague-Dawley rats (10/sex/group) at dose levels of 0, 250, 1500, or 2500 ppm (0, 15.49, 91.51, or 150.35 mg/kg/day for males and 0, 18.66, 111.37, or 189.63 mg/kg/day for females, respectively) for 13 weeks. Assessments for clinical signs were made daily and FOB and motor activity assessments were made at pretest, and 4, 8, and 13 weeks of the study. Following sacrifice, the control and high dose group rats were perfused and subjected to histopathological assessment.

Reactions to treatment noted in the 1500 ppm dose group included tremors (in 3 males and 5 females), staggered and/or impaired gait, splayed hindlimbs, increased landing feet splay and abnormal posture and decreased grip strength. Only splayed hindlimb and staggered gait were noted in the FOB battery at 1500 ppm. At 2500 ppm, all of the rats had tremors, staggered gait and splayed hindlimbs. Staggered gait and splayed hindlimbs started later. No effects on motor activity or neurohistopathological lesions were noted. Body weight in the high dose group males was 5% decreased and a corresponding slight decrease in food consumption was also noted for this group. **The LOAEL for neurotoxicity is 1500 ppm (91.51 mg/kg/day in males) based on clinical signs (tremors and staggered gait). The NOAEL is 250 ppm (15.49 mg/kg/day).**

This subchronic neurotoxicity study is classified **acceptable/guideline** and satisfied guideline requirement for a subchronic neurotoxicity study.

Executive Summary: In a preliminary subchronic oral neurotoxicity study (MRID 00071952), groups of 10 male Wistar rats were administered 2500, 3000, 3750, 4500, 5000, or 7500 ppm of permethrin (PP 557) in the diet for 14 days. The isomeric ratio of the test article (Batch No. P48; 90.4% a.i.) was 39.9% cis and 60.1% trans. Based on a food factor of 0.05 for the rat, doses for the treated groups were 125, 150, 187.5, 225, 250, and 375 mg/kg, respectively. Each treated group had a paired control group consisting of litter mates with similar body weights. Toxicity assessments were limited to clinical observations, measurements of body weights and food consumption, and light and electron microscopic evaluation of the sciatic nerve.

At 7500 ppm six rats were found dead on day 1 and the remainder were sacrificed *in extremis* on day 1 or 2. Prior to sacrifice the animals were observed with convulsive tremors and excessive salivation and those animals for which data were available showed marked weight loss and decreased food consumption. In the 5000-ppm group, two rats were found dead on day 1 and six were sacrificed on day 2; convulsive tremors were observed in one animal prior to death.

Slight to moderate whole body tremors were observed initially in all animals in the 2500 and 3000 ppm groups but almost complete remission occurred by day 5. Moderate tremors were seen in most animals of the 3750 and 4500 ppm groups which lessened during the study but were still evident on day 14. Also at 3750 and 4500 ppm hyperactivity and hypersensitivity to noise were observed mainly during the first 7 days. In the two surviving 5000-ppm animals, slight to moderate tremors were observed until day 10.

Mean absolute body weights of the 3000-, 3750-, and 4500-ppm groups were significantly ($p \leq 0.05$ or 0.01) less than their paired control group weights beginning on day 1 and continuing until termination. Body weights of the surviving 5000-ppm animals were also clearly less than the control. Body weight gains by the 2500-, 3000-, 3750-, 4500-, and 5000-ppm groups were 81%, 60%, 61%, 28%, and 22%, respectively, of their control group level during the first week. However, during the second week body weight gains by all treated groups were 98-104% of the control levels with the exception of the 5000-ppm group which was 83% of the controls.

Food consumption for the first week was significantly ($p \leq 0.01$) reduced in all treated groups to 67-84% of their paired control group levels. Consequently, food utilization was increased in a dose-related manner for all treated groups as compared with the control groups.

The number of rats with degenerating nerve fragments in the treated and paired control groups was 5/10 each at 2500 ppm, 8/10 and 2/9, respectively, at 4500 ppm, and 6/10 and 2/10, respectively, at 5000 ppm. The number of fragments per nerve ranged from 1-5 for animals in the control, 2500-, and 4500-ppm groups and for animals in the 5000 ppm group that died or were killed intercurrently. In contrast, the two surviving rats in the 5000 ppm group had 19 and 44 fragments respectively.

Nerves from rats in the 2500- and 5000-ppm groups were also examined by electron microscopy. No treatment-related abnormalities were observed in the 2500-ppm group. At 5000 ppm, the ultrastructural changes observed were similar in animals that died and in the two rats that survived to scheduled termination. In the unmyelinated nerves, 7/7 rats given 5000 ppm had degenerative changes including axonal swelling, disorganization of the neurofilaments, an increase in multivesicular-type and vesicular structures, and vacuolation. Only a minimal increase in vesicular structures was observed in 3/7 paired controls. Mild to marked vacuolation of the Schwann cell cytoplasm was seen in 5/7 rats treated with 5000 ppm and mild vacuolation was seen in 2/7 controls. Also in the Schwann cells, dense bodies occurred in the cytoplasm of 6/7 treated rats vs. 0/7 controls and hypertrophy and increased nuclear chromatin with multiple nucleoli were seen in 5/7 treated and 1/7 control rats. Intercellular vacuolation was observed in 4/7 treated and 1/7 control rats.

Therefore, the systemic and neurotoxicity LOAEL is 2500 ppm (125 mg/kg) based on clinical signs of toxicity and decreases in body weight gain and food consumption. The systemic and neurotoxicity NOAEL was not identified for this preliminary study.

This study is classified **acceptable/nonguideline** and does not satisfy the requirements for a subchronic oral neurotoxicity study [OPPTS 870.6200 (§82-7)] in rats. The study is sufficient for the purposes for which it was intended, as an evaluation of the effects of feeding high concentrations of PP 557 to male rats on body weights, food consumption, clinical signs, and microscopic lesions in the sciatic nerve.

Executive Summary: In a subchronic oral neurotoxicity study (MRID 40766807), Sprague-Dawley rats (10/sex/group) were administered Permethrin (98%, 40:60 cis/trans, Lot No. PL85-216) in acetone at concentrations of 0, 100, 200, or 400 mg/kg/day in the diet for 90 days (main study). Two control groups were included, one was an untreated control group and the other was a vehicle (acetone treated diet) control group. After the 90 days, the rats in the main study were sacrificed by a special procedure designed to allow for fixation of the nervous system *in situ*. The experiment also included a special recovery component that consisted of 10 male and 10 female rats in the 400 mg/kg/day and untreated control groups; these animals were sacrificed 6 weeks after the completion of dosing after being maintained on untreated control diet. Neurological tissues from control and high-dose animals were examined microscopically. Functional observational battery (FOB) and motor activity testing were not performed.

There were no treatment-related deaths. Clinical signs included hyperexcitability, intermittent tremors, and irritability in mid-dose males during the first 3 weeks of treatment and intermittent tremors in mid-dose females during the first week of treatment. High-dose rats exhibited hyperexcitability, intermittent and continuous tremors, twitching, nystagmus (males only) and combativeness (males only) throughout the treatment period. Body weight gain was decreased 6 to 13% in high-dose males from treatment week 11 to post-dosing week 2; and 5 to 9% in high-dose females compared to controls from weeks 3 to 13. No treatment-related food consumption effects were noted. There were no gross lesions associated with treatment and there were no microscopic observations indicative of a neurotoxic effect.

The systemic LOAEL is 200 mg/kg/day based on tremors and irritability. The systemic NOAEL is 100 mg/kg/day. The NOAEL is > 400 mg/kg/day with respect to morphological and histological changes.

This study is classified **acceptable/nonguideline**. The data provide useful information suggesting no morphological or histological effects in rats fed 400 mg/kg/day in the diet for 90 days.

Executive Summary: In a nonguideline repeated dose oral neurotoxicity study (MRIDs 00059066 and 00070627), groups of 10-16 Sprague-Dawley rats/sex/dose were administered 700, 2000 or 6000 ppm of NRDC 143 (Lot No.: 60307, 93.3% a.i.; 45 *cis*:55 *trans*) in the diet for 8 days. Additional groups of 8-10 animals/sex served as controls. Doses for the treated groups were 57, 160 or 454 mg/kg/day, respectively, males and 58, 198 or 453 mg/kg/day, respectively, females. Toxicity assessments were limited to clinical observations, body weights, food consumption and microscopic evaluation of the brain, spinal cord and sciatic nerve. In addition, groups of 16 Sprague-Dawley rats/sex/dose group were treated with three other synthetic pyrethroids: NRDC 149 at 500, 1500 or 3000 ppm (average daily dose levels 42, 72 or 126 mg/kg/day, males and 37, 80 or 115 mg/kg/day, females); S3206 at 1000 ppm (77 mg/kg/day, males or 58 mg/kg/day, females) and S5602 at 3000 ppm (146 mg/kg/day, males or 142 mg/kg/day, females) and were similarly evaluated.

At 6000 ppm permethrin, a total of 3 males and 2 females died during the study; one each on day 5 and the remainder on day 6. In addition, 4 moribund high-dose rats of each sex were sacrificed on day 7 and again on day 8. Clinical signs of toxicity, including severe tremor and muscle twitch, were reported in high-dose males and females beginning on day 1, but the frequency of these signs was not given. Body weight gains by the high-dose males and females (taken on day 7) were -74% and -58% lower than their respective control group levels (mean body weights were about -8.4% below controls, both sexes).

Food consumption was not affected at any dietary concentration. No clinical signs of toxicity or mortalities and no effects on body weight gains occurred in the low- and mid-dose groups. Very slight or slight swelling of the sciatic nerve fibers was seen in 5/5 high-dose males and females, but only very slight swelling was observed in 6/15 control males, 5/13 control females, 1/8 low-dose males and 1/9 mid-dose females. No abnormalities were noted in the brains or spinal cords from any high-dose or control animal. Findings in the brains and spinal cords from the low- and mid-dose groups were not reported. **The LOAEL is 6000 ppm (453 mg/kg/day, females; 454 mg/kg/day, males) based on mortality, clinical signs of toxicity, decreased body weight gain and microscopic lesions in the sciatic nerve. The NOAEL is 2000 ppm (160 mg/kg/day, males; 198 mg/kg/day, females).**

Similar clinical findings (mortality, clinical signs in addition to tremor including hindlimb ataxia, erratic jumping and hypersensitivity) and neuropathology (sciatic nerve swelling, fiber disintegration and/or occasional nodal demyelination) were observed at variable incidence with NRDC 149 (3000 ppm), S3206 (1000 ppm)and S5602 (3000 ppm). Body weight/weight gain decreases were observed in all groups. Effects at 1500 ppm NRDC 149 included slight hypersensitivity, decreased body weight/weight gain and in females, very slight sciatic nerve fiber swelling and disintegration. No findings were reported at 500 ppm NRDC 149. NOAELs were not established for S3206 or S5602 in these studies.

This study is classified **unacceptable/nonguideline (upgradable)** and does not satisfy the requirements for a subchronic oral neurotoxicity study [OPPTS 870.6200 (§82-7)] in rats. These studies were performed as a comparative evaluation of neurobehavioral observations and neuropathology. The study was not conducted to fulfill a guideline requirement and a new study is not required. However, this study may be upgraded to acceptable if the deficiencies listed in the Discussion section of this review can be satisfactorily addressed.

4.2.3 Developmental Toxicity Studies

4.2.3.1 Developmental Toxicity Study in Rats

Executive Summary: In a developmental toxicity study (MRID 40943603), 24 presumed pregnant Wistar rats per group were administered 0, 15, 50, or 150 mg/kg/day of permethrin (93.9% a.i.; 38 cis:62 trans isomers; Reference No. RS 78/E) by gavage on gestation days (GD) 7-16, inclusive. The vehicle was corn oil. On GD 22, all surviving dams were sacrificed and all fetuses were weighed, sexed, and examined for external malformations/variations. All fetuses

were examined for visceral anomalies and the heads cut along the fronto-parietal suture line. All carcasses were processed for skeletal examination.

All animals survived to scheduled termination and no treatment-related abnormalities were noted at gross necropsy. No maternal effects on clinical signs of toxicity, body weight gains, or food consumption were observed in the low- or mid-dose groups. In the high-dose group, clinical signs of toxicity seen between GD 8-19 included tremors in 21/24 rats and head flicking in 6/24 rats. Body weight gains by the high-dose dams were significantly ($p \leq 0.05$ or 0.01) less than that of the controls throughout the dosing interval. For GD 7-10, 10-13, and 13-16, body weight gains were decreased by 88%, 32%, and 18%, respectively, as compared with the controls. Food consumption by the high-dose group was significantly ($p \leq 0.05$ or 0.01) less than that of the controls during the dosing interval.

Therefore, the maternal toxicity LOAEL is 150 mg/kg/day based on clinical signs of toxicity and decreased body weight gain and food consumption. The maternal toxicity NOAEL is 50 mg/kg/day.

No dose- or treatment-related effects were observed on gravid uterine weights, fetal sex ratios, pre- or post-implantation losses, or numbers of corpora lutea/dam or live fetuses/dam. Mean fetal body weight of the high-dose group was 3.2% ($p \leq 0.05$) less than that of the controls. However, mean litter weight of the high-dose group was 3% (n.s.) greater than that of the controls. Therefore, the reduced fetal body weights were considered a questionable toxic response.

No treatment-related external or visceral fetal malformations/variations were noted. The fetal and litter incidence rates of short length extra ribs were significantly ($p \leq 0.05$ or 0.01) increased in the high-dose group as compared with the controls. Short length extra ribs were observed in 31% of the high-dose fetuses vs. 11% of the control fetuses and in 87% of high-dose litters vs. 57% of control litters.

Therefore, the developmental toxicity LOAEL is 150 mg/kg/day based on decrease in fetal body weights and an increase in the incidence rate of short length extra ribs. The developmental toxicity NOAEL is 50 mg/kg/day.

This study is classified as **acceptable/guideline** and does satisfy the requirements for a developmental toxicity study [OPPTS 870.3700 (83-3a)] in rats.

4.2.3.2 Developmental Toxicity Study in Rabbits

Executive Summary: In a developmental toxicity study (MRID 92142091), presumed pregnant Dutch rabbits were administered 0, 600, 1200, or 1800 mg/kg/day of permethrin (92.5% a.i.; 32.3 cis:60.2 trans isomers; Batch No. D108136E) by gavage on gestation days (GD) 6-18, inclusive. The number of does mated for each group was 19, 21, 20, and 23, respectively. The vehicle was 0.5% aqueous Tween 80. On GD 29, all surviving does were sacrificed and all

fetuses were weighed and examined for external malformations/variations. Approximately one-half of the fetuses was processed for skeletal examination and the remaining one-half was fixed and examined for visceral anomalies. Maternal food consumption was not measured.

A total of 0, 5, 5, or 4 does died or were sacrificed moribund in the control, low-, mid-, or high-dose groups, respectively. Due to the lack of a dose-response, the deaths could not be definitively attributed to test article administration. Clinical signs of toxicity included body tremors observed in 5 of the high-dose animals only. Little or no feces or urine was noted on at least one occasion for 2/19 (11%), 4/21 (19%), 6/20 (30%), and 8/23 (35%) animals in the control, low-, mid-, and high-dose groups, respectively.

Absolute body weights were similar between the treated and control groups throughout the study. However, after examining the replotted body weight data, there was a sharp drop in weight for the low, mid, and high dose groups after day 6 and only a slight drop for the control that was noticeable after day 12. Body weight gain by the low-, mid-, and high-dose groups was 21%, 50%, and 9%, respectively, of the control level during GD 0-18 with statistical significance ($p \leq 0.05$) attained for the low- and high-dose groups. During the post-dosing interval, recovery of body weights was noted for the low- and mid-dose groups, but not for the high-dose group.

The maternal toxicity LOAEL is estimated to be <600 mg/kg/day based on decreased body weight gain. The maternal toxicity NOAEL is not identified.

The number of live fetuses and mean litter size was decreased for all dose groups compared to the control group (110(15), 80(13), 69(14), and 72(13) for control, low-, mid-, and high-dose groups, respectively). However, no dose-response was evident or statistical significance noted.

Post-implantation loss was significantly ($p \leq 0.05$) increased in the mid- and high-dose groups to 155% and 248% of the control level. Correspondingly, the number of early and late resorptions were higher in these groups as compared to the control group values (statistical significance was not reported). Mean fetal body weights in the high-dose group were slightly (-9%; n.s.) less than that of the controls and attributed to maternal body weight decreases. No dose-related or statistical differences were observed between the treated and control groups for number of fetuses/litter or mean gravid uterine weights.

No treatment-related external or visceral fetal malformations/variations were noted. In the mid- and high-dose groups, reduced ossification of the fore- and hind-limbs was indicated by slightly (n.s.) greater ossification scores as compared with the controls. Mean scores for the control, low-, mid-, and high-dose groups were 1.92, 1.99, 2.00, and2.25, respectively, for the forelimb and 1.65, 1.56, 1.89, and 1.90, respectively, for the hindlimb.

Therefore, the developmental toxicity LOAEL is 1200 mg/kg/day based on increased post-implantation loss, greater numbers of early and late resorptions and an equivocal decrease in ossification of the fore- and hind-limbs. The developmental toxicity NOAEL is 600 mg/kg/day.

This study is classified as **acceptable/guideline** and does satisfy the guidelines for a developmental toxicity study [OPPTS 870.3700 (83-3b)] in rabbits. It should be noted that this study was conducted prior to implementation of the current guidelines. Because the mid- and high-doses exceeded the limit dose of 1000 mg/kg/day, the study is considered sufficient for determining the developmental toxicity potential of permethrin in the rabbit even though a maternal toxicity NOAEL was not identified.

4.2.4 Reproductive Toxicity Study

Executive Summary: In a three generation reproduction study (MRID 92142092, 120271, 92142037), permethrin, PP557, (purity, 94.0-98.8%; cis:trans 40:60) was administered to groups of 12 male and 24 female Wistar rats in the diet at concentrations of 0, 500, 1000, or 2500 ppm (0, 25, 50, and 125 mg/kg/day, respectively, using a standard conversion factor of 0.05). Two litters were produced by each generation. F_0, F_1, and F_2 parental animals received test or control diet for 12 weeks post weaning and were then paired for mating to produce the A litters. After various rest periods, the F_0, F_1, and F_2 parental animals were remated to produce the B litters. Test diets were administered during mating, gestation and lactation for three successive generations throughout the study. The F_2 parents were mated for a third time, using the same breeding pairs as for the B litters, producing the C litters for a developmental toxicity evaluation. Ten males of the F_1 generation were maintained on experimental diets until they were 54-55 weeks old and were submitted for microscopic examination of selected neurological tissues.

No animals of the parental generations died during the study, although a few were killed because of conditions not related to administration of PP557. There were no dose- or treatment-related effects on body weights, body weight gains, food consumption, or food efficiency.

Treatment-related clinical signs in high-dose parental animals were limited to whole body tremors, occurring in all parental generations (exception: tremors were not observed in the F_0 males) during the first few days of the premating period. In the 2500-ppm groups, the incidence rates for the tremors were 20/24 (F_0 females), 11/12 and 24/24 (F_1 males and females, respectively), and 12/12 and 24/24 (F_2 males and females, respectively). Tremors were also observed in pregnant and lactating females exposed to 2500 ppm PP557. There were no tremors at 0 ppm in any generation. The tremors were intermittent and transient. Neuropathy was not observed in a special microscopic examination of selected neurological tissues from F_1 males continued on test for one year. Gross examination at necropsy did not reveal any dose- or treatment-related findings, nor did microscopic examination of grossly abnormal tissues from all parents surviving to scheduled termination and of reproductive tissues from animals suspected of infertility.

Therefore, the LOAEL for systemic toxicity is 2500 ppm (125 mg/kg/day) based on tremors observed in the F_0 females, and the F_1 and F_2 males and females. The systemic toxicity NOAEL is 1000 ppm (50 mg/kg/day).

Mating performance, fertility, and pup growth and survival were not affected by PP557 treatment in the F_1, F_2, and F_3 generations.

In the F_3C litters, there were no developmental effects associated with the administration of PP557 over three generations. The percentages of male fetuses of the 1000- and 2500-ppm groups (39.0 and 44.7%, respectively) were lower than the control value (53.2%), but the effect was not associated with increased resorptions and was not dose-related. Also, no consistent effect on sex ratios was observed in other litters or generations of the study and the effect is not considered to be treatment-related.

Therefore, the reproductive toxicity NOAEL is >2500 ppm (125 mg/kg/day) and the reproductive toxicity LOAEL is not established.

Microscopic examination of F_3B weanlings revealed dose-related increases in centrilobular hypertrophy of the liver. The incidences of slight and moderate centrilobular hypertrophy were dose-related, ranging from 0 to 80% for the males and from 10 to 100% for the females. The HIARC determined that the hypertrophy of the liver is an adaptive and reversible effect and is not considered as an adverse effect. This conclusion is supported by a 90-day rat feeding study (MRID 00054737) where the hepatocellular hypertrophy was observed at 185 mg/kg/day with a NOAEL of 92.9 mg/kg/day. In addition, similar findings might have been observed if histopathological examinations were conducted during the parental evaluation.

The NOAEL for offspring toxicity is >2500 ppm (125 mg/kg/day). The offspring LOAEL is not established.

The study is classified as **acceptable/guideline** and satisfies the requirements for a reproduction study (OPPTS 870.3800 [§83-4a]) in rats.

4.2.5 Additional Information from Literature Sources

A literature search was conducted and found a few studies on the neurotoxicity of permethrin. The information is summarized as follows.

The effects of permethrin on schedule-controlled behavior were investigated in rats following oral doses of 100-400 mg/kg (Peele and Crofton, 1987). Animals had been trained to respond for food according to a multiple schedule consisting of four different variable-interval schedules. A monotonic dose-dependent decrease in response rate was observed with a calculated ED_{50} of 350 mg/kg. Statistically significant decreases in response occurred at doses of 300 and 400 mg/kg as compared to vehicle controls. In a similar study, rats injected i.p. with 15-60 mg permethrin/kg showed a dose-related decrease in operant response rate and significantly decreased total food intake at the highest dose (Bloom et al., 1983).

Male and female rats were dosed by gavage with 400, 800, or 1200 mg/kg/day for 7 days. Clinical signs in all groups included hyperexcitability, ataxia, and tremor and 30% of high-dose males died. All groups showed a significant transient functional impairment on the inclined plane test with maximal effect at the end of the dosing period. Significant increases in β-glucuronidase and β-galactosidase activities in the distal section of the sciatic/posterior tibial nerve were found 3-4 weeks postdosing. The study authors concluded that there was no correlation between neuromuscular dysfunction and neurobiochemical changes (Rose and Dewar, 1983).

Tremors and hypersensitivity to noise were observed during the first 2 weeks of a 2-year study in rats fed 2500 ppm (Ishmael and Litchfield, 1988). Male Wistar rats treated by gavage with 300 mg permethrin/kg/day for 5 days had tremors and convulsions (incidence and severity not stated); microscopic examination revealed segmental demyelination in a cervical nerve and inflammatory and degenerative changes in the diaphragm muscle (Cavaliere et al., 1990).

4.2.6 Pre- and/or Postnatal Toxicity

4.2.6.1 Determination of Susceptibility

The HIARC determined that there is no evidence (qualitative or quantitative) for increased susceptibility following *in utero* and/or pre-/post-natal exposure in the developmental toxicity studies in rats and rabbits and multi-generation reproduction studies in rats.

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

Since there is no developmental or reproductive toxicity observed in the developmental studies in rats and rabbits or reproduction study in rats, the HIARC concluded that there are no residual uncertainties for pre- and post-natal toxicity.

4.3 Recommendation for a Developmental Neurotoxicity Study

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity Study

- Evidence of neurotoxicity was shown in the acute and subchronic neurotoxicity studies and other subchronic and chronic toxicity studies in dogs and rats.
- The subchronic neurotoxicity studies showed increased incidence of microscopic lesions associated with neurotoxic effects at high doses.

4.3.2 Evidence that supports not requiring for a Developmental Neurotoxicity Study

1. No evidence of increased susceptibility (qualitative or quantitative) following *in utero* and/or pre-/post-natal exposure in the developmental toxicity studies in rats and rabbits.

4.3.3 Rationale for the UF_{DB} (when a DNT is recommended)

On September 9, 2003, the Hazard Identification Assessment Review Committee (HIARC) recommended a 10X Database Uncertainty Factor (UF_{DB}) to account for the lack of a developmental neurotoxicity study (DNT) in rats. The 10X UF_{DB} was determined based on a dose analyses as described in the HIARC report dated May 12, 2004 (TXR No. 0052543).

The Health Effects Division, since then, has revised the dose analyses procedure to determine the need for and size of the UF_{DB} to account for the lack of a DNT. This revised procedure was based on an analysis of the DNT data submitted and reviewed to date (Hot Sheet # 24).

The Reregistration Branch, using the above procedure, re-analyzed the size of the UF_{DB} for the lack of the DNT for permethrin. The re-analysis indicates that a UF_{DB} is not required for the DNT data gap. This decision is based on the following considerations:

- The dose levels tested in the subchronic neurotoxicity study (0, 15, 92 or 150 mg/kg/day) is lower than the doses tested in the three generation reproduction study (25, 50 or 125 mg/kg/day). Therefore, it is assumed that the doses used in a DNT study may be similar to those used in the subchronic neurotoxicity study in rats. The NOAEL in the subchronic study was 15 mg/kg/day and the LOAEL was 92 mg/kg/day..

- It is presumed that the offspring NOAEL in the DNT would be the lowest dose tested (i.e, 15 mg/kg/day).

- The results of the DNT would have no impact on the risk assessment because: 1) the endpoint of concern (neurotoxicity) is used for overall risk assessments; 2) the DNT is not likely to identify new hazard at a lower dose since the potential NOAEL (i.e, 15 mg/kg/day) from that study is comparable to the current dose (25 mg/kg/day) used for dietary (acute and chronic), non-dietary (incidental oral and dermal), and inhalation (11 mg/kg/day) exposure risk assessments; 3) because of the wide gap in the candidate study (i.e, subchronic neurotoxicity), the true NOAEL could have been higher than the one that was established (i.e, higher than the 15 mg/kg/day; 4) the DNT is being requested as a "confirmatory" data due to clinical signs seen at high doses (125-450 mg/kg/day) in adult animals and there is a large margin of safety between these doses and the doses used for risk assessment; and 4) it is also worth reiterating that there is no evidence (quantitative or qualitative) of increased susceptibility in the pre-natal developmental or the two generation reproduction study.

Therefore, HED is confident that although a DNT has been required, the existing toxicity data for permethrin provided the Agency with the confidence that the risk assessment conducted with no additional factor will provide reasonable certainty of no harm to the safety of infants and children.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD) - Females age 13-49

Since there is no developmental or reproductive toxicity of concern for permethrin, no appropriate endpoint or study is selected for the female (13-49) group. The selected dose/endpoint for general population would provide adequate protection for females 13-49 years old.

4.4.2 Acute Reference Dose (aRfD) - General Population

Study Selected: Acute Neurotoxicity Study in Rats § 870.6200a

MRID No.: 45657401

Executive Summary: In a published literature study (MRID 45657401), permethrin (95%, a.i., cis:trans 50:50) was administered by gavage to Long-Evans rats (8/sex/group) at dose levels of 0, 25, 75, or 150 mg/kg in corn oil. FOB and motor activity were assessed prior to dosing and at 2, 4, 24 and 48 hours after dosing.

At 75 mg/kg, the rats displayed a general pattern of increased excitability and aggressive behavior. Some of the more pronounced responses included abnormal motor movement (3/8, both sexes) decreased grip strength for forelimb (males) and hindlimb (males and females), motor activity (males), and increased body temperature (males). At 150 mg/kg, arousal score (males), righting reflex (males) and approach response score (females) were affected and 7/8 of both sexes had abnormal motor movement and motor activity was further decreased and body temperature was increased >2°C. Slight decreases in body weight (3-4%) were evident. Recovery from the symptoms was within 24 hours. **The LOAEL is 75 mg/kg based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature. The NOAEL is 25 mg/kg.**

The study is classified as **acceptable/nonguideline.**

Dose and Endpoint for Establishing aRfD: 25 mg/kg (NOAEL) based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature at 75 mg/kg (LOAEL).

Uncertainty Factor (UF): 100 (10x for interspecies extrapolation, 10x for intraspecies variations).

Comments about Study/Endpoint/Uncertainty Factor: The study is appropriate for a single dose exposure with the effects of concern via the oral route and length of exposure for an acute dietary endpoint. The endpoints for risk assessment are based on clinical signs of neurotoxicity.

Acute RfD (General Population) = $\frac{25 \text{ mg/kg/day}}{100}$ = **0.25 mg/kg/day**

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: Acute Neurotoxicity Study in Rats §870.6200a

MRID No.: 45657401

Executive Summary: See acute RfD.

Dose and Endpoint for Establishing cRfD: 25 mg/kg (NOAEL) based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature at 75 mg/kg (LOAEL).

Uncertainty Factor(s): 100 (10x for interspecies extrapolation, 10x for intraspecies variations).

Comments about Study/Endpoint/Uncertainty Factor: Previously, the HED TES Committee has established a RfD for permethrin at 0.05 mg/kg/day based on increased liver weight in several chronic rat and mouse studies (HED Doc. 013494). This HIARC determined that the increased liver weight and hypertrophy observed in the liver are adaptive and reversible effects and are not considered adverse effects. Therefore, liver weight increase is not an appropriate endpoint to be selected for a chronic RfD of permethrin. The HIARC concluded that a dose and endpoints based on clinical signs of neurotoxicity are more appropriate for risk assessment on permethrin.

A metabolism study indicated that permethrin is rapidly absorbed and excreted (HED Doc. No. 001660). The World Health Organization report (1990) also suggested that permethrin administration to mammals was rapidly metabolized and almost completely eliminated from the body within a short period of time. This finding that permethrin does not bioaccumulate is supported by a close range of NOAEL and LOAEL among acute, subchronic , and chronic toxicity studies associate with clinical signs of neurotoxicity. Ranges of NOAEL/LOAEL (mg/kg/day) are: 25/75 in an acute neurotoxicity in rats (MRID 45657401), 15.5/91.5 in a subchronic neurotoxicity study in rats (MRID 42933701), 92.9/185 in a subchronic oral toxicity in rats (MRID 00054737), 50/150 in a developmental toxicity study in rats (MRID 40943603), 50/125 in a 3-generation reproduction study in rats (MRID 92142037), and 40.2/104 in a 2-year chronic feeding study in rats (MRID 92142123), respectively. Base on the dose spacing of these studies, the HIARC determined that a NOAEL/LOAEL of 25/75 based on clinical signs of neurotoxicity from the acute neurotoxicity study in rats is appropriate for the dose/endpoint

selection for chronic RfD. In addition, since long-term studies do not indicate that neurotoxic effects are cumulative, an additional uncertainty factor for using a short-term study for a long-term risk assessment is not required.

Chronic RfD = $\frac{25 \text{ mg/kg/day}}{100}$ = **0.25 mg/kg/day**

4.4.4 Incidental Oral Exposure: Short-Term (1-30 days)

Study Selected: Acute Neurotoxicity Study in Rats § 870.6200a

MRID No.: 45657401

Executive Summary: See acute RfD.

Dose and Endpoint for Risk Assessment: 25 mg/kg (NOAEL) based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature at 75 mg/kg (LOAEL).

Comments about Study/Endpoint: This dose/endpoint is appropriate for the population of concern (infants and children). Also see comment under chronic RfD.

4.4.5 Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: Acute Neurotoxicity Study in Rats § 870.6200a

MRID No.: 45657401

Executive Summary: See acute RfD.

Dose and Endpoint for Risk Assessment: 25 mg/kg (NOAEL) based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature at 75 mg/kg (LOAEL).

Comments about Study/Endpoint: This dose/endpoint is appropriate for the population (infants and children) and duration of concern.

4.4.6 Dermal Absorption

Dermal Absorption Factor: 30%

An acceptable rat dermal absorption study (MRID 43169001) was conducted at dose levels of 9.1, 0.86, 0.08, or 0.004 mg/rat with exposure durations of 0.5, 1, 2, 4, 10, and 24 hours per dose. The reviewer noted that the mass absorption increased with duration of exposure and dose up to 24 hours without an indication of a plateau. Thus, exposure to permethrin for period of longer than 24 hours may result in higher percentage of the exposed dose being absorbed. The largest portion of the retained dose was found in the corneum as may be expected by the solubility of the test compound. Absorption in corneum at 24 hours was 3.66, 10.25, 31.40, or 14.92% at the respective dose level. A dermal absorption factor of 30% is selected; however, it is considered to be a conservative estimate because neurotoxicity signs were not observed in a 21-day dermal toxicity study at doses up to 500 mg/kg/day whereas they were observed in the acute or subchronic neurotoxicity studies at a dose level of 75 or 100 mg/kg/day, respectively.

4.4.7 Dermal Exposure: (All Durations)

Study Selected: Acute Neurotoxicity Study in Rats § 870.6200a

MRID No.: 45657401

Executive Summary: See acute RfD.

Dose and Endpoint for Risk Assessment: 25 mg/kg (NOAEL) based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature at 75 mg/kg (LOAEL).

Comments about Study/Endpoint: The HIARC determined that an oral study is appropriate for short-, intermediate- and long-term dermal exposure because the endpoints of concern (i.e., FOB parameters indicative of neurotoxicity) was not measured in the 21-day dermal toxicity study in rats. See chronic RfD section for rationale of using a short-term study for all exposure durations.

4.4.8 Inhalation Exposure: (All Durations)

Study Selected: 15-Day Inhalation Study in Rats §870.3465

MRID No.: 00096713

Executive Summary: In a 15-day inhalation toxicity study (MRID 00096713), permethrin (94.7% a.i., Lot # ZJ, cis:trans 25.2:69.5) was administered to groups of 5 male and 5 female Charles River rats/concentration by dynamic whole-body inhalation exposure at concentrations of 0, 6.1, 42.2, or 583 mg/m^3 (0.0061, 0.042, or 0.583 mg/L) for 15 exposures (6 hours/day for 2 days during week 1, 5 days during weeks 2 and 3, and 3 days during week 4).

There was no test material-related effect on mortality, body weight or weight gain, food consumption, hematology, organ weights, or gross pathology. Weight gain was actually greater in all treated groups than in the respective control groups. Clinical signs were observed in the treated groups. Two female rats in the 0.0061 mg/l group were observed to have slightly labored breathing 30 minutes into the first exposure but not subsequently. In the 0.042 mg/l (MCT) group, licking of the inside of the mouths became more extensive then in the low-treatment group and involved most of the rats. All 5 females were observed to have slightly labored breathing during the first exposure but not subsequently. Labored breathing was not observed in male rats in either the 0.0061 or 0.042 mg/L groups. All rats in the 0.042 mg/L group appeared more alert than in the control and low-dose groups and adopted a hunched posture with open eyes during the early part of some exposures. The 0.583 mg/L group (HCT) demonstrated less activity, greater response to auditory or touch stimuli, and more extensive licking behavior than the other groups. Body tremors were observed in this group beginning with 3 females during the last hour of the first exposure and in 3 males during the second exposure. In both instances, tremors continued post exposure. The tremors reached a peak incidence, 5 males and 4 females, during the 5th exposure (3rd day of the second week) and declined thereafter, with only 1 male and 1 female showing tremors on exposure day 15 (2nd exposure of week 4). Slightly labored breathing was recorded in 1 male and 1 female in this group.

The hypersensitivity to noise or touch became evident in the 0.583 mg/L (HCT) group following the second exposure and involved 5 males and 5 females. This sign tapered off with continued exposures, but was still displayed by 3 females following the 7th exposure. Rales, poor grooming, and crusty brown staining around the nose were observed occasionally in the 0.583 mg/L group, with incidences higher in females than in males. **The LOAEL is 0.583 mg/L in male and female rats based on body tremors and hypersensitivity to noise. The NOAEL is 0.042 mg/L.** Microscopic pathology on the lungs showed focal to diffuse pneumonitis and perivascular inflammation - although to some degree more severe in the treated groups, could not be clearly distinguished from the respiratory infection present in all animals.

The HIARC determined that the dose/endpoint can be used for risk assessment purpose because the clinical signs of neurotoxicity were observed in the first day of exposure. This 15-day inhalation toxicity study in the rat is classified **acceptable/non-guideline** and does not satisfy the guideline requirement for a subchronic inhalation study OPPTS 870.3465.

Dose/Endpoint for Risk Assessment: NOAEL of 11 mg/kg/day (0.042 mg/L) based on body tremors and hypersensitivity to noise in male and female rats at a LOAEL of 154 mg/kg/day (0.583 mg/L).

Comments about Study/Endpoint: The selected dose/endpoint is appropriate for the route of exposure. See chronic RfD section for rationale of using a short-term study for all exposure durations.

4.4.9 Margins of Exposure

Table. 4.4.9. Levels of Concern (LOC) Summary (MOEs) for Risk Assessment			
Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	N/A
Dermal	100	100	100
Inhalation	100	100	100

The MOEs for dermal and inhalation exposures may be combined for occupational exposure risk assessment because the toxicity endpoints for these routes of exposure are the same.

4.4.10 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows: for short-, intermediate- and long-term aggregate exposure risk assessments, the oral, dermal (oral equivalent) and inhalation routes can be combined because of the common toxicity endpoints (clinical signs of neurotoxicity) via these routes.

4.4.11 Classification of Carcinogenic Potential

4.4.11.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

Executive Summary: In a chronic oral toxicity/oncogenicity study (MRID 92142123), Permethrin was administered to Wistar rats (60/sex/group) in the feed at doses of 0, 500, 1000, or 2500 ppm. The mean estimated compound intake for males was 0, 19.4, 36.9, or 91.5 mg/kg/day, respectively, and for females was 0, 19.1, 40.2, or 104 mg/kg/day. Of these animals, 12/sex/group were sacrificed at 52 weeks and the surviving rats were sacrificed at 104 weeks' exposure.

No treatment-related effect on mortality was observed during the study. No treatment-related effects were seen on tumor induction. During the first two weeks of the study, treatment-related tremors and hypersensitivity were observed in both the high-dose male and female groups. No

other treatment-related clinical effects were observed. There were no toxicologically significant effects on body weight, body weight gain, food consumption, or food efficiency. There were no treatment-related effects on ophthalmologic endpoints, hematologic endpoints, clinical chemistry or urinalysis parameters.

Liver changes suggestive of adaptive hypertrophy included increased aminopyrine-N-demethylase activity in all male treatment groups, in the mid- and high-dose female at 52 weeks, and in the high-dose male and female groups at 104 weeks. This was coupled with modestly increased absolute and relative liver weights in the high-dose males and high and low-dose females at 52 weeks and in all male treatment groups and mid-dose females at 104 weeks. Further evidence for adaptive changes included hypertrophy of centrilobular hepatocytes with increased cytoplasmic eosinophilia in the mid- and high-dose male and females at 104 weeks' exposure and increased smooth endoplasmic reticulum proliferation in all treatment groups except low-dose males at 52 weeks and high-dose groups at 104 weeks. Electron microscopy evaluation on the liver showed fatty vacuoles in the mid- and high-dose males at both 52 and 104 weeks and in the high-dose females at 104 weeks.

Under the conditions of this study, the chronic toxicity LOAEL is 2500 ppm (104 mg/kg/day) based on tremors and hypersensitivity. The NOAEL is 1000 ppm (40.2 mg/kg/day).

At the doses tested, permethrin did not affect the incidence of tumor-bearing animals or the incidence of any specific tumor type in either sex. Permethrin was not carcinogenic to the rat. Dosing was considered adequate based on tremors and hypersensitivity as well as liver effects.

This chronic toxicity/oncogenicity study in the rat is **acceptable/guideline** and satisfies the guideline requirements for a chronic toxicity/oncogenicity oral study [OPPTS 870.4300 (§83-5a)] in the rat.

Discussion of Tumor Data : There are no treatment-related changes in incidence of tumors of any type in male or female rats.

Adequacy of the Dose Levels Tested: Dosing was considered adequate based on tremors and hypersensitivity as well as liver effects in rats.

Executive Summary: In a combined chronic toxicity/carcinogenicity study (MRID 97441), permethrin (technical grade, purity not specified, Batch No. 533/17/x) was administered to groups of Wistar strain rats (specific-pathogen free) (60/sex/group) at dietary concentrations delivering doses of 0, 10, 50, or 250 mg/kg/day for up to 104 weeks. Additional groups of 15 male and female rats were included for clinical pathology studies (satellite study).

No treatment-related or biologically significant effects were observed on body weight, weight gain, food consumption, food efficiency, hematology, clinical chemistry, urinalysis parameters, eyes, organ weights (females only), or gross lesions in male and female rats fed permethrin at doses up to 250 mg/kg/day. The only noteworthy clinical sign was tremors observed in ten males and five females in the high dose group for a 2-week period after week 90. The mortality rates in male rats at study termination were 58%, 78% ($p<0.05$), 67%, and 80% ($p<0.01$) at 0, 10, 50, and 250 mg/kg/day. The lack of a clear dose-related trend and treatment-related cause of death indicate that the increased mortality may not be treatment related. No treatment-related mortality was observed in females. The absolute liver weight of high-dose male rats was elevated by 19% ($p<0.05$) compared with the controls, and the relative liver weight was also slightly increased. Mid- and high-dose male and female rats had significantly increased incidences of periacinar hepatocyte hypertrophy in the liver. The incidence of hepatocyte fatty vacuolation in the liver (all locations combined) was 9/59, 16/56 ($p=0.07$), 17/58 ($p<0.05$), and 22/52 ($p<0.01$) for the control, low-, mid-, and high-dose male rats, respectively. In addition, 9/52 ($p<0.05$) high-dose male rats had hyperplasia of the pelvic epithelium in the kidney compared with 2/59 for controls and 6/52 ($p<0.05$) high-dose male rats had erythrocytes and erythrophagocytosis in the sinus of the thymic lymph nodes compared with 1/59 control. High-dose females had no other lesions that occurred with statistically significant increased incidences compared with the control incidences. These liver effects were considered adaptive effects and were not considered adverse effects.

The LOAEL for permethrin is 250 mg/kg/day in males and females based on clinical signs of neurotoxicity (tremors); the NOAEL is 50 mg/kg/day.

There were no treatment related increases in tumor incidences at any dose of the test material compared with control incidences. Dosing was considered adequate based on clinical signs of neurotoxicity at the high dose and the increased incidence of hepatocyte fatty vacuolation and periacinar hepatocyte hypertrophy at the mid- and high-dose levels.

This chronic/carcinogenicity study in the rat is **unacceptable/guideline (upgradeable)**. The study may be upgraded upon submission of data listing on the study deficiencies section. It should be noted that this study was conducted before Subdivision F or OPPTS 870.4300 guidelines were established.

Discussion of Tumor Data: There were no treatment related increases in tumor incidences at any dose of the test material compared with control incidences.

Adequacy of the Dose Levels Tested: Dosing was considered adequate based on clinical signs of neurotoxicity at the high dose and the increased incidence of hepatocyte fatty vacuolation and periacinar hepatocyte hypertrophy at the mid- and high-dose levels.

4.4.11.2 Carcinogenicity Study in Mice

Executive Summary: In a carcinogenicity study (MRID 00062806, 92142033) FMC 33297 (permethrin, % a.i. not specified, Lot #s MR176 and MR807) was administered to Charles River CD-1 mice (75/sex/dose) in the diet at dose levels of 0, 20, 500, or 2000 ppm for males (equivalent to 0, 3, 71, or 286 mg/kg/day, respectively) and 0, 20, 2500, or 5000 ppm for females (equivalent to 0, 3, 357, or 714 mg/kg/day, respectively) for 24 months.

Mortality was significantly increased in high-dose males after 75 weeks of treatment, but was not significantly different from the control group after 104 weeks. Clinical signs consisting of distended abdomens, ano-genital staining, and alopecia were increased in treated males compared to the control during the first year of treatment, but were not dose-related at 24 months.

Insufficient data were provided on body weights (with the exception of final body weights for females), body weight gains, organ weights (with the exception of brain weights of females at study termination), hematology parameters, and gross and microscopic changes for the reviewer to evaluate. An 8% increase in final female body weight was not considered a biologically significant effect. Although difficult to evaluate in the absence of summary data, the effects listed by the study author - transient increased body weights, decreased leucocyte counts and liver and kidney inflammatory changes - do not appear to be toxicologically significant.

A NOAEL and LOAEL for FMC 33297 (permethrin) in mice could not be determined in this study due to major study deficiencies including failure to include summaries of numbers of animals with clinical signs and data on body weights, body weight gains, organ weights, hematology parameters, and gross and microscopic necropsy findings.

A joint FDA-EPA audit of this study conducted in late 1980 at Bio/Dynamics and FMC facilities did not reveal any inadequacies in the conduct or reporting of this study serious enough to compromise the usefulness of these study results for oncogenic evaluation. However, the audit concluded that this study was not useful for assessment of chronic toxicity (HED Doc. #004204).

On December 12, 1988 the HED Cancer Peer Review Committee reviewed the study and concluded that there were statistically significant increases in liver adenoma at all doses for males and at mid- and high-doses for females with a significant dose-related trend in both sexes. Combined liver adenoma/carcinoma also showed statistically significant increases at mid- and high-doses for male and female mice. Statistically significant increases in lung adenomas and combined adenoma/carcinoma at all doses were observed in females only. Carcinoma were increased at all doses but only at HDT that the increase was statistically significant. The incidences of adenoma and carcinoma at mid- and high-doses were outside historical control ranges. There were also significant dose-related trends for lung adenomas, carcinomas and combined adenoma/carcinomas in females. The incidences of lung tumors in male mice (adenoma or carcinoma, or combined) were not statistically significant at any dose, nor was there

a dose-related trend for any of them.

This carcinogenicity study in mice is classified as **acceptable/guideline (OPPT 870.4200b; §832b)** for evaluation of carcinogenicity. However, this study may not be used for regulatory purpose on assessment of chronic toxicity.

Discussion of Tumor Data: There were statistically significant increases in liver adenoma at all doses for males and at mid- and high-doses for females with a significant dose-related trend in both sexes.

Adequacy of the Dose Levels Tested : Adequate

Executive Summary: In a carcinogenicity study (MRID 00102110, 92142032) PP557 (94.0-98.9 % a.i., batch/lot #'s P24, P34, P35, P36, P44, P52, BX4, and BX6; cis:trans 40:60) was administered to pathogen free Alderley Park mice (70/sex/dose) in the diet at dose levels of 0, 250, 1000, or 2500 ppm (equivalent to 0, 26.9, 110.5, or 287.2 mg/kg/day for males and 0, 29.8, 124.2, or 316.1 mg/kg bw/day for females) for up to 98 weeks. Ten males and females per group were set aside for each of 26- and 52-week interim studies during which necropsies were done and hematology, and clinical chemistry parameters were measured.

No significant compound-related effects on mortality or clinical signs were noted. Transient decreases occurred in body weight gain in high-dose males and high-dose females, but at study termination (98 weeks), the final body weight and body weight gain for male mice in the high-dose group were reduced by only 5 and 12%, respectively and the final body weight and body weight gain in females in the high-dose group were unaffected. Food consumption was decreased in the high-dose groups relative to controls during the first week of the study, but was increased at most time points thereafter. No treatment-related changes were seen in hematology or clinical chemistry parameters. Increases of 31 to 48% were seen in liver weights and liver weights corrected for body weight in high-dose males and females compared to the controls. Centrilobular hepatocellular eosinophilia was increased in high-dose males and high-dose females at 52 and 98 weeks compared to the controls. Other liver effects included smooth endoplasmic reticulum proliferation, increased nuclear microbodies, and increased aminopyrine-N-demethylase activity in high-dose animals of both sexes compared to the respective controls. Kidney weights were decreased by 21% in high-dose males, but were slightly increased in high-dose females. Proximal tubular epithelium vacuolation was decreased in number and incidence in high-dose males.

A LOAEL for Permethrin is established at 2500ppm (287.2 mg/kg/day for males and 316.1 mg/kg/day for females) based on increased liver weight, induction of microsomal enzyme activity, electron microscope evidence of increased smooth endoplasmic reticulum, and hepatocyte eosinophilia. The NOAEL is 1000 ppm (110.5 mg/kg/day for males and 124.2 mg/kg/day for females).

At the doses tested, there was no evidence compared to controls of a significant increase in unusual tumor types or in tumor bearing animals. A non-significant increase in lung adenomas in male mice and in lung adenomas plus carcinomas in female mice at the highest dose (2500 ppm in the diet) was not considered evidence of a carcinogenic effect in light of the high incidences in the control groups of both sexes. In addition to the lungs, major organs examined included liver, kidney, testes, ovary, bladder, brain, and thyroid. The dosing based on toxic response was marginal in both males and females. However, the dosing is considered adequate because higher doses would have resulted in a significant weight deficit in male mice.

This carcinogenicity study in mice is classified **acceptable/guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice.

Executive Summary: In a nonguideline mouse carcinogenicity study (MRID 45597105), Permethrin technical (lot no. PL95-329, 94.7% a.i.) was administered to groups of 50 to 109 Crl:CD-1®(ICR)BR female mice in the diet at 0 or 5000 ppm (equivalent to 780 - 807 mg/kg bw/day) for 39, 52, 65, or 78 weeks. Groups of mice from all treatment groups were examined immediately after treatment and at weeks 79 and 101. Matching groups of untreated control mice were examined at each interval.

There were no compound-related effects on mortality or body weight. Body weight gain was slightly less in mice treated for 65 or 78 weeks and allowed to recover to week 101 (both 86% of the control weight). The overall food consumption was slightly decreased by 2-3% in some treated groups. The overall food efficiency in the pooled 52-week treatment groups was about 5% less than that of the controls.

At the end of each treatment period, the absolute liver weights were increased by about 44-53% compared to the control groups regardless of the treatment duration. Liver centrilobular hypertrophy and karyomegaly occurred in 87-100% and Kupffer cell hypertrophy was seen in 43-61% of treated animals compared to the controls (0-5%). Centrilobular hypertrophy and Kupffer cell hypertrophy at all dose durations was reversed to or near control levels during the recovery periods. Karyomegaly incidences were reduced by about 11-70% according to the length of the respective recovery periods, but were still present in 25-75% of the treated animals at the 101-week recovery. Inflammatory liver changes were seen in 75-95% of treated animals compared to 37-63% in the controls. The inflammatory liver changes increased in the control mice as a function of age; therefore, recovery was only seen in the treated groups allowed to recover to week 79. Amyloid deposits were increased in treated animals immediately after treatment, and continued to increase during the recovery period. Incidences of eosinophilic foci were significantly increased in the livers of treated groups only after the recovery periods and appeared to be related to the length of the treatment period. The activities of cytochrome P450 (CYP) mixed function oxidases in the livers of animals treated for 52 weeks were expressed both as specific activity (nmol/mg microsomal protein) and the total enzyme activity per liver. Specific activities of total CYP, CYP1A, CYP2B, CYP2E1, and CYP3A were unaffected by treatment, whereas, the specific activity of CYP4A was increased 3-fold. The total enzyme

activities per liver of total CYP, CYP1A, CYP2B, CYP2E1, and CYP3A2 were increased in treated animals by 142-283%, and the activity of CYP4A was increased by 829% compared to the control values.
The incidences of Clara cell hyperplasia were increased in the lungs of all treated animals, and the incidences were significantly decreased during the recovery periods to weeks 79 and 101. The specific activities of CYP2B, CYP2E1, and CYP4A in animals sacrificed after 52 weeks of treatment were unaffected by treatment. The total enzyme activities of CYP2E1 and CYP4A expressed as activity/g lung were increased to only 133% and 125%, respectively, of controls.

Significant increases were seen in the incidences of basophilic and eosinophilic hepatocellular adenomas in female mice administered 5000 ppm in the diet for 39, 52, or 78 weeks followed by recovery to week 101 (7% to 10% compared to 1% in controls). The increased incidences were not treatment-duration (dose) related; treatment for 65 weeks resulted in no basophilic adenomas. Eosinophilic adenomas were increased after 78 weeks of treatment and after the recovery period (both 10% compared to 1-2% in controls). The incidences did not increase during the recovery period. No increases in hepatocellular carcinoma incidences were seen and the time to tumor onset for the adenomas was not different in treated animals compared to the controls. Lung bronchioloalveolar adenoma incidences increased immediately after treatment and continued to increase during the recovery periods compared to the controls. The incidences were 14%, 43%, 47%, 49%, and 49% for the control and 39, 52, 65, and 78 weeks exposure followed by recovery to week 101 ($p<0.01$). The lung adenomas did not occur any earlier in the treated animals than in the control groups, and there was no increase in lung carcinomas in treated animals.

This mouse carcinogenicity study is designed to test the progression and possible reversal of toxic effects including benign liver and lung tumors and is classified as **acceptable/non-guideline**.

Discussion of Tumor Data: There were significant increases in the incidences of lung bronchioloalveolar adenomas in mice. The increased incidences of basophilic hepatocellular adenoma did not show a relationship to the treatment duration. No progression to carcinoma was observed in the lung or liver.

Adequacy of the Dose Levels Tested: Only one dose was tested.

4.4.11.3 Classification of Carcinogenic Potential

The Cancer Assessment Review Committee met on August 21, 2002 to re-evaluate the carcinogenic potential of Permethrin (CARC Report, 10/23/02, TXR No. 0051220). In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the CARC classified permethrin as **"Likely to be Carcinogenic to Humans"** by the oral route. This classification was based on evidence of two reproducible benign tumor types (lung and liver) in the mouse, equivocal evidence of carcinogenicity in Long-Evans rats, and supportive SAR

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information. The Committee recommended using a linear low-dose extrapolation approach for the quantification of human cancer risk based on female mouse lung tumors (combined adenomas and carcinomas) using the data from the PWG assessment. The unit risk, Q_1^*(mg/kg/day)$^{-1}$ for Permethrin is 9.6×10^{-3} based on female mouse lung adenoma and/or carcinoma combined tumor rates (Memo, L. Brunsman, 9/25/02, TXR No. 0051166).

4.4.12 Mutagenicity

The HIARC concluded that there is no concern for mutagenicity resulting from exposure to permethrin.

4.4.12.1 Gene Mutation

Salmonella/mammalian reverse gene mutation assay (MRID 41031107): there were no evidence of increased revertant colonies above control in 5 Salmonella strains up to 5000 µg/plate (solubility limit).

4.4.12.2 Chromosome Aberrations

Mouse bone marrow micronucleus assay (MRID 42723302): five CD-1 mice/sex/harvest time were treated once each orally with permethrin (Batch No.: P58/D7534/30, 93.1% a.i., w/w) in corn oil at a dose of 200 mg/kg for males and 320 mg/kg for females. Bone marrow cells were harvested at 24 and 48 hours post-treatment.

The MPE/PE ratio (micronuclated polychromatic erythrocytes/1000 polychromatic erythrocytes) at 24 hours was increased for male (2.6 ± 1.1 vs 1.2 ± 1.6) and female (2.0 ± 1.6 vs 1.0 ± 2.2) mice dosed with permethrin relative to the solvent control value; however, the increases were not statistically significant. The ratio at 48 hours was less than the solvent control values in either sex. Data on the mean percentage of polychromatic erythrocytes in males and females indicated no statistical differences between the animals treated with permethrin and the solvent controls at either time interval. The solvent control and the cyclophosphamide positive control induced the appropriate responses. **Based on these data, there is no evidence that permethrin is clastogenic in the bone marrow cells of mice in this study.**

This study is classified as **acceptable/guideline**. It satisfies the requirement for FIFRA Test Guideline OPPTS 870.5395 [§84-2] for *in vivo* cytogenetic mutagenicity data.

4.4.12.3 Other Mutagenic Mechanism

Unscheduled DNA synthesis (UDS) in primary male rat hepatocytes assay (MRID 40943604): There was no evidence of unscheduled DNA synthesis above control up to 10^{-4} M and possibly 10^{-2} M Limits of cytotoxicity).

Dominant Lethal Test (MRID 40943604): No evidence of increased dominant lethal effects up to 150 mg/kg/day (oral dose administered daily for 5 days to males).

Table 4.3 Summary of Toxicological doses and endpoints for Permethrin for Use in Human Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	**Acute RfD** = No applicable	An appropriate endpoint attributable to a single dose was not identified.	
Acute Dietary (General population including infants and children	NOAEL = **25** mg/kg/day UF = **100** **Acute RfD** = 0.25 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.25 mg/kg/day	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
Chronic Dietary (All populations)	NOAEL= **25** mg/kg/day UF = **100** **Chronic RfD** = 0.25 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.25 mg/kg/day	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
Short-Term Incidental Oral (1 - 30 Days)	NOAEL = 25 mg/kg/day	**Residential** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
Intermediate-Term Incidental Oral (1 - 6 Months)	NOAEL = 25 mg/kg/day	**Residential** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.

Table 4.3 Summary of Toxicological doses and endpoints for Permethrin for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Short-Term Dermal (1 - 30 days)	Oral study NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
Intermediate-Term Dermal (1 - 6 Months)	Oral study NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
Long-Term Dermal (> 6 Months)	Oral NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
Short-Term Inhalation (1 - 30 days)	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.
Intermediate-Term Inhalation (1 - 6 Months)	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.
Long-Term Inhalation (>6 Months)	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.
Cancer (Oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" based on female mouse lung adenoma and/or carcinoma combined tumor rates. Q_1^* $(mg/kg/day)^{-1} = 9.567 \times 10^{-3}$		

NOTE:* The Special FQPA Safety Factor recommended by the HIARC **assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

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4.5 Special FQPA Safety Factor

Based on the hazard data, there are no concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. Although a DNT has been required, a dose-analysis with the existing reliable toxicity data for permethrin provided the Agency with the confidence that the risk assessment conducted with no additional factor will provide reasonable certainty of no harm to the safety of infants and children. In addition, the permethrin risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the special FQPA SF be reduced to 1x. The recommendation is based on the following:

- The dietary food exposure assessment demonstrates that acute and chronic exposures do not underestimate the risk and are not of concern.
- The residential exposure assessment is based on reliable data and is unlikely to underestimate exposure and risk.

4.6 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administration may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and FFDCA authority to require wildlife evaluations, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on permethrin, there was no toxicologically significant evidence of endocrine disruptor effects. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, permethrin may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

5.1 Human Incident Reports

Review of Permethrin Incident Reports. Jerome Blondell and Monica S. Hawkins. DP Barcode DP298313. June 25, 2004.

It is likely that most poisonings due to permethrin resulted from misuse or inadvertent exposures. The large majority of cases resulted in minor effects to the skin (primarily rash, irritation, itching), eyes (redness, pain, burning), headache, dizziness, nausea, vomiting, and shortness of breath or difficulty breathing. Loss of consciousness appears to occur only in cases of ingestion involving 700 mg/kg body weight or more (Yang et al. 2002). Persons handling permethrin directly are the most likely to experience symptoms. Permethrin does not appear to pose significant risks from exposure to residues or drift, based upon a relatively small number of documented cases. Compared to other pesticides, permethrin is much less likely to result in serious or persistent medical outcome/condition. Even ingestion of suicidal/potentially lethal doses can be resolved within a few days with medical treatment. The only death reported was due to pneumonitis likely due to the xylene solvent rather than the permethrin. Though a relatively safe product, permethrin can readily cause problems to skin and eyes and inhalation may lead to headache, dizziness, and difficulty breathing. A number of the data sources reviewed for the permethrin human incident report suggest permethrin can aggravate asthma or lead to asthma like symptoms. Ingestion or inhalation has led to nausea and vomiting.

There are a number of different datasets from which HED compiles a human exposure incident report. The OPP Incident Data system items are anecdotal or represent allegations only. Information in this system comes from registrants, other federal and state health and environmental agencies and individual consumers. The most prevalent complaints reported by ten or more individuals included: headache (43 cases); rash (32 cases); tingling/burning skin (29 cases); nausea (22cases); difficulty breathing/shortness of breath/asthma (17 cases); eye irritation (15 cases); itching (14 cases); dizziness (13 cases); and vomiting (12 cases). Note that 20 of the 29 case of tingling or burning skin were tingling, a symptom known to be associated with exposure to the class of pesticides, pyrethroids. Other dermal symptoms including burning, itching, and irritation to skin are known to be related to exposure to pyrethroids (Reigart and Roberts 1999 summarized by Blondell and Hawkins, 2004).

EPA also accesses Poison Control Center Data (1993-1998) to examine poisoning information noted in occupational cases, non-occupational cases involving adults and older children, and for cases involving children under the age of six. In this data set, the ratio of the percent of cases involving permethrin and the percent of cases for all other pesticides is compared using several severity metrics, *e.g.*, symptomatic cases and cases seen at an intensive care facility. The non-occupational category is probably the most representative of general population exposure to permethrin pesticides because the children were much more likely exposed to head lice control products regulated by the Food and Drug Administration (FDA). Note, that 84% of the permethrin exposure to children identified by specific products, were products for the control of

head lice. Ten or more people reported eye (40 persons) or skin (26 persons) irritation and/or pain. Other dermal symptoms included edema (15 persons), erythema/flushed (21 persons), hives/welts (11 persons), pruritus (itching - 22 persons), and rash (18 persons). Tingling is not a choice coded by Poison Control Centers, but may indeed be present in the cases. Neurological symptoms reported in ten or more people included dizziness/vertigo (21 persons) and headache (18 persons). Gastrointestinal symptoms reported in ten or more people included nausea (25 persons), vomiting (23 persons), and diarrhea (15 persons). Respiratory symptoms were reported by10 persons with broncho spasm, 16 with cough/choke, and 32 person with dyspnea (difficulty breathing). The relatively high occurrence of dyspnea (second most common symptom among Poison Center cases and fifth most common among cases reported to the Incident Data System) suggests that permethrin may pose a hazard of asthma-like reactions in sensitive individuals.

Detailed descriptions of 432 cases submitted to the California Pesticide Illness Surveillance Program (1982-2001) were also reviewed to prepare the permethrin incident report. In 79 of these cases, permethrin was used alone or was judged to be responsible for the health effects reported. Permethrin ranked 58th as a cause of systemic poisoning in this states. According to the above activity categories, routine indoor use was associated with more exposures than any other category. Outside handlers, applicators and mixer/loaders accounted for the next largest group. Together, indoor and outdoor handlers accounted for two-thirds of the illnesses reported. The most prevalent symptoms in ten or more individuals were eye irritation (including burning, pain, redness, and swelling), rash, headache, dizziness, nausea, and shortness of breath or difficulty breathing.

The National Pesticide Information Center receives calls concerning human incidents of pesticide exposure. There were 220 calls received concerning exposure to permethrin. Of this number, 36 vases were considered probable cases of permethrin exposure incidents. Nearly half of these cases had skin complaints (e.g., rash, itching, pain or burning sensation) and nearly half also report effects to the eyes (e.g., pain, irritation, tearing). Headache, dizziness, or light-headedness were reported by nearly half the cases and respiratory problems such as tight chest or difficulty breathing were reported by 22% of the probable cases. Six (17%) reported asthma or asthma-like symptoms and 6 cases reported problems with the permethrin product used for termite treatment.

The National Institute of Occupational Safety and Health manages a program called SENSOR - Sentinel Event Notification *System for Occupational Risk.* Through this program, from 1998 through 2002, seven NIOSH SENSOR states received 40 reports of exposure to permethrin in a single product, 22 of which were from states other than California. Because California pesticide poisoning incidents have already been discussed, an analysis of the other cases is presented here. Eighteen of the non-California cases were reported as having minor effects and four were classified as moderate. Three cases were classified as definite, three probable, 13 as possible, and 3 as suspicious. Dermal symptoms were most common reported in 10 of 22 cases. Ocular symptoms were reported in six cases, respiratory and gastrointestinal symptoms in 9 cases each,

and neurological symptoms in 7 cases.

A review of the scientific literature indicates symptoms similar to those already reported are common in study groups. Reported symptoms included eye irritation, itching, nasal secretions, headache (Kolomodin-Hedman et al., (1982) as reported by Blondell and Hawkins, 2004). Notably, Edling et al. (1985)) reported numbness in the lips as an effect. Also, the World Health Organization published a summary of the literature and noted a study of 23 laboratory workers involved in field trials. In this study, the most frequent symptom was a facial sensation described as tingling or burning. This did not occur when permethrin alone was involved but when exposures included cypermethrin, fenvalerate, or fenpropathrin. These findings correlate with the results of animal studies used in this assessment. The general symptoms reported also suggests that permethrin products are more likely to cause a direct irritative effect rather than an allergic reaction. The World Health Organization reported another study cited tested permethrin impregnated clothing on 10 male volunteers and they did not complain of any irritation. A third study tested permethrin for up to nine days using a patch test and 2 out of 17 volunteers developed mild erythema (flushing). A test of permethrin against head lice in 10 adults found 3 with mild, patchy erythema which faded away after 4-7 days. *The overall reported adverse effect rate is 2.5 per 1,000 patients.*

5.2 Animal Incident Reports

Review of Domestic Animal Incident Data for Reregistration Eligibility Decision (RED). V. Dobozy. DP Barcode D279521. TXR 0050902. July 9, 2002.

HED performed an animal incident data review in 2002 and reviewed that database again in April 2004 to note any changes or additions. This section reflects the most updated information concerning animal incident data from use of permethrin. (Internal communication: Kit Farwell, April 2004.) Permethrin is registered for use on many species of domestic animals (dogs, cats, cattle, horses, swine) for control of a variety of insects, including fleas, ticks, lice, mites, etc. Single ingredient products contain 0.25-65% active ingredient. Multiple ingredient products contain permethrin combined with other insecticides, insect growth regulators and synergists. Formulations include sprays, dusts, shampoos, dips, collars, concentrated spot-on preparations, pour-ons and ear tags. Concentrated (45%-65%) permethrin spot-on preparations are registered for use only on dogs; there are extremely toxic to cats.

HED requests that the registrants submit aggregate incident summary reports concerning injury/poisoning to domestic animals for individual permethrin products. Incidents reported are categorized in a range of severity from domestic animal death (DA) to clinical signs are unknown or not specified. Registrants are only required to report the number of animals in each category, however, if OPP has concern about the number of incidents reported for a products, the Agency may request more detailed information. For Permethrin containing products, there were 18,466 incidents involving domestic animals reported from April 1, 1998 to March 31, 2002. The products included in this data base were both those used directly on animals and for other uses such as household ant or roach killer. A review of the data showed there three products

were responsible for the majority of the incidents with domestic animals: Ortho Ant Killer spray (239-2678), Hartz One Spot Repellant for Dogs (2596-137), and, Hartz Control One Spot for Dogs and Puppies (2596-146).

There is evidence that a majority of the incidents for Hartz Control One Spot for Dogs and Puppies involve cats. Care reports for the incidents recorded for this product show that the majority of domestic animal deaths reported for this product, 59%, involved cats which were accidently or intentionally treated with the product and some of the deaths of cats (7%) involved exposure to treated dogs. Symptoms in cats reported before death include tremors, seizures and ataxia. Exposure of cats to permethrin can cause life-threatening toxicosis because cats, as compared to other domestic animals, are relatively deficient in their ability to conjugate xenobiotics with glucuronic acid, which is the most important step in the metabolism of certain substances. Therefore, they metabolize many chemicals more slowly than other species.

EPA/RD has previously suggested label changes to make it more clear to domestic animal owners/caretakers of the potential for adverse affects occurring to cats as a result of either direct or indirect permethrin exposure. At the time of this writing, the suggested label changes have not been made by the registrants. As a result, HED has the following recommendations regarding the conclusions of the domestic animal incident report:

1. Some permethrin products for use on domestic animals may have been registered prior to the uniform requirement of a companion animal safety study. It is recommended that these studies be required for the reregistration of such products.

2. The number and severity of the incidents reported for the Ortho-Ant Killer Spray (239-2678) are surprising. There were a total of 2629 incidents with 162 deaths and 274 major events reported from April 1, 1998 to March 31, 2002. It is recommended that the registrant review the incidents and provide OPP with an analysis of the specifics involved, the types of adverse reactions and a determination of causality for the cases of domestic animal death and major effect.

3. Severe adverse reactions, including deaths, in cats intentionally or mistakenly exposed directly to concentrated (45 and 65%) permethrin products or secondarily exposed to treated dogs are a major concern. HED recommends that OPP consult with the ASPCA/APCC about the overall magnitude of permethrin toxicity in cats and whether label revisions are a reasonable solution both to direct and secondarily exposures.

6.0 Exposure Assessment and Characterization

6.1 Dietary Exposure Pathway

6.1.1 Residue Profile

Permethrin. Residue Chemistry Considerations for Reregistration Eligibility Decision (RED) Document. PC Code: 109701. DP Barcode: D298290. Sherrie Kinard. October 25, 2004.

The qualitative nature of permethrin residues in plants and animals is adequately understood based on the adequate soybean, cabbage, and sweet corn metabolism studies and the oral and dermal ruminant and poultry metabolism studies. In the most recent review of metabolism data, the Metabolism Assessment Review Committee (MARC memo by S. Kinard, Y. Yang, and J. Melendez dated July 6, 2004) concluded that the residues of concern in plants and animals include *cis*- and *trans*-permethrin for purposes of both tolerance reassessment and risk assessment.

With the exception of cottonseed, tolerances for permethrin residues in/on plant raw agricultural commodities (RACs) are currently expressed in terms of the combined residues of permethrin and its metabolites, 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid (DCVA) and (3-phenoxyphenyl) methanol (MPBA) [40 CFR §180.378 (b) and (d)]. Tolerances for residues of permethrin in/on cottonseed (0.5 ppm) are expressed in terms of permethrin *per se* [40 CFR §180.378 (a)]. Tolerances for permethrin residues in/on animal RACs are currently expressed in terms of the combined residues of permethrin, DCVA, MPBA, and 3-phenoxybenzoic acid (3-PBA) [40 CFR §180.378 (c)].

Adequate GC electron capture detection (GC/ECD) methods are available for enforcing tolerances of permethrin *per se* and are listed in PAM Vol. II (Section 180.378). Method I is a GC/ECD method for determining permethrin in plant matrices and has a limit of quantitation (LOQ) of 0.05 ppm for each isomer. Method II is a GC/ECD method for determining permethrin in animal matrices that has a LOQ of 0.01 ppm for each isomer. In addition, permethrin is completely recovered using FDA Multiresidue Methods (PAM Vol. I Sections 302 and 304).

In addition to the uses on crops and livestock, permethrin is registered for use in food-handling establishments. Although residue data on representative foods have not been submitted to support this use, the current label restrictions for uses in food-handling establishments are such that residues of permethrin are unlikely to occur in/on food commodities when permethrin is applied in accordance with the amended label directions. However, confirmatory food residue data are still required at the present time to ensure no detectable residues in food when permethrin is applied in residential areas while food is present. The registrant should submit a protocal on the determination of residues in food when permethrin is applied at maximum application rates to areas containing uncovered and covered food products.

Reregistration requirements for magnitude of the residues in animals are fulfilled provided

supporting storage stability data for representative animal commodities are submitted and deemed adequate. Data are available from studies depicting residues in animal commodities following direct treatment of cattle, swine, and poultry and their premises with permethrin. Data are also available from several cattle and poultry feeding studies. Based upon residue data from these studies, dietary exposure to permethrin residues is the route that can result in the highest potential residues in animal commodities. Therefore, data from the ruminant and poultry feeding studies were used as the basis for reassessing tolerances for animal commodities. Based on the reassessed tolerances for livestock feed items, the maximum theoretical dietary burdens (MTDB) of permethrin residues for livestock are 34.1 ppm for beef cattle, 40.3 ppm for dairy cattle, 4.56 ppm for poultry, and 0.06 ppm for swine.

Reregistration requirements for magnitude of the residue in plants are fulfilled for the following crops: alfalfa, almonds, apples, artichokes, asparagus, avocados, broccoli, Brussels sprouts, cauliflower, celery, cherries, corn, cucurbit vegetables, filberts, horseradish, lettuce (head), onions (dry bulb), papayas, peppers (bell), pistachios, potatoes, spinach, turnips, and walnuts. Adequate field trial data depicting permethrin residues following applications made according to the maximum use patterns have been submitted for these crops. Although complete sets of data are not available on all crops depicting use of permethrin formulated as a WP, these data are not required as bridging data from side-by-side trials using EC and WP formulations indicate that permethrin residues resulting from application of an EC are consistently higher or no different than permethrin residues resulting from application of a WP.

The adequate data from bell peppers will be translated to supplement the residue data on eggplants. Adequate data are also available on soybeans, provided use directions for soybeans are amended to specify a minimum volume of 2 gal/A for aerial applications; otherwise, residue data supporting ULV applications to soybeans are required. Additional field trail data are required on cabbage, collards, grasses (rangeland), leaf lettuce, tomatoes and sweet corn (FL only), and information is also required to upgrade the existing mushroom, peach, and pear field trials.

The reregistration requirements for magnitude of the residue in processed food/feed commodities are also fulfilled for apple, corn, potatoes, soybeans, and tomatoes. Based on the available processing studies, tolerances for permethrin are not required on apple, corn (field), potato, soybean, and tomato processed commodities. However, data from the corn grain processing study indicate that a separate tolerance is necessary for aspirated grain fractions. Residues of permethrin concentrated by 19.3x in corn aspirated grain fractions. Based on the highest average field trial (HAFT) residues for field corn grain and the above concentration factor, the maximum expected residues in corn aspirated grain fractions would be 0.386 ppm.

Adequate confined and limited field rotational crop studies are available for assessing the potential of inadvertent residues occurring in rotational crops following applications of permethrin to primary crops totaling 2.0 lb ai/A/season, which is 1x the maximum seasonal use rate on any rotated crops. The metabolism in rotational crops is similar to the primary crops.

For purposes of tolerance enforcement and risk assessment the residues of concern consist of the *cis*-and *trans*-permethrin isomers. The limited rotational field trial data indicate that tolerances for residues of permethrin in rotational crops are not required, provided labels specify a 60-day plant-back interval (PBI) for crops not listed on the labels.

6.1.2 Acute and Chronic Dietary Exposure and Risk

Permethrin. Acute, Chronic, and Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision (RED) Document. PC Code: 109701. DP Barcode: D298311. Samuel Ary. October xx, 2004.

Quantitative Usage Analysis. David Widawsky. Permethrin 109701. October 23, 1998.

Acute, chronic, and cancer dietary (food and water) risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The acute and chronic dietary risk assessments were conducted for all supported permethrin food uses and were performed to support the reregistration eligibility decision.

Highly refined acute (probabilistic), chronic, and cancer dietary exposure assessments were conducted to estimate the dietary risks associated with the reregistration of permethrin. Permethrin residue estimates used in these assessments include cis- and trans-permethrin calculated as total permethrin along with the percent crop treated (%CT) estimates reported by the Biological and Economic Analysis Division (BEAD). The anticipated residue (AR) estimates are based primarily on the USDA PDP food sampling data. Processing data was also used on a
number of crops if available.

The estimated surface drinking water concentrations (EDWCs) for permethrin were calculated using Tier II PRZM (Pesticide Root Zone Model) and EXAMS (Exposure Analysis Modeling System) for use in the human health risk assessment. The EDWCs for permethrin were calculated based on a maximum application rate of 2.0 lb ai/A and were incorporated into the DEEM-FCID analyses.

Acute dietary risk estimates are provided for the general U.S. population and various population subgroups, with the major emphasis placed on the exposure estimates for infants and children. This assessment concludes that for all supported registered commodities, the acute risk estimates do not exceed HED's level of concern (less than 100%) at the 99.9th exposure percentile for the U.S. population (7% aPAD) and all population subgroups, with the highest exposed population subgroup being infants at 18% aPAD.

Chronic dietary risk estimates are provided for the general U.S. population and various population subgroups, with the major emphasis placed on the exposure estimates for infants and children. This assessment also concludes that for all supported registered commodities,

the chronic risk estimates do not exceed HED's level of concern for the U.S. population and all population subgroups (all populations were less than 1% cPAD).

Cancer dietary risk estimates are provided for the general U.S. population and resulted in a estimated cancer risk of 2.08×10^{-6}. The estimated dietary cancer risk for the general U.S. population is above the Agency's level of concern (greater than 1.0×10^{-6}). The significant cancer risk contributors have been identified as spinach, water (direct and indirect, all sources), and lettuce (leaf and head).

Table 6.1. Summary of Food and Water Dietary Exposure and Risk for Permethrin.

Population Subgroup	Acute Dietary (99.9th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.014613	5.85	0.000217	0.1	**0.000217**	**2.08×10^{-6}**
All Infants (< 1 year old)	**0.043546**	**17.42**	**0.000422**	**0.2**	N/A	N/A
Children 1-2 years old	0.031640	12.66	0.000348	0.1		
Children 3-5 years old	0.018751	7.50	0.000313	0.1		
Children 6-12 years old	0.010467	4.19	0.000202	0.1		
Youth 13-19 years old	0.015206	6.08	0.000163	0.1		
Adults 20-49 years old	0.012961	5.18	0.000195	0.1		
Adults 50+ years old	0.015868	6.35	0.000236	0.1		
Females 13-49 years old	N/A	N/A	0.000209	0.1		

6.2 Water Exposure Pathway

Tier II Estimated Drinking Water Concentrations of Permethrin (PC Code # 109701; DP Barcode D298743). José Luis Meléndez . July 16, 2004.

This assessment presents Tier II Estimated Surface Drinking Water Concentrations (EDWCs) , calculated using PRZM/EXAMS (surface water) and employing the Index Reservoir (IR) water body with a Percent Crop Area (PCA) adjustment. Ground water concentrations were estimated using the Tier 1 model SCIGROW.

The EDWCs for permethrin were calculated based on a maximum application rate of 2.0 lb a.i./A. The acute concentration in surface water is 5.50 ppb[1] of permethrin. The cancer/chronic concentration is 2.99 ppb, using the Maine potatoes scenario. These values represent the mean value over a 30-year period. Several other scenarios were also explored (CA almonds, FL peppers, GA onions, CA onions, ID potatoes), but they consistently yielded lower EDWCs. The SCIGROW generated EDWC for lettuce, almond or onion (highest application rate) is 0.012 ppb of permethrin, which is recommended for use, both for acute and chronic exposures.

These values generally represent upper-bound estimates of the concentrations that might be found in surface water and groundwater due to the use of permethrin on almonds, peppers, onions, and potatoes which represent the scenarios with the highest application rates, and with the lowest intervals between applications. Both models provide estimates suitable for screening purposes.

Table 6.2. Summary of Estimated Surface and Ground Water Concentrations for Permethrin

Exposure Duration	Permethrin	
	Surface Water Conc., ppb[a]	Ground Water Conc., ppb[b]
Acute	5.50	0.012
Chronic (non-cancer)	2.99	0.012
Chronic (cancer)	2.99	0.012

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on a maximum application rate of 2.0 lb a.i./A.
[b] From the SCI-GROW model assuming a maximum seasonal use rate of 2.0 lb ai/A, a K_{oc} of 170,000, and a half-life of 37 days.

[1] Actual modeled value was 11.22 ppb, but the reported one is 5.50 ppb, which is the solubility limit of permethrin.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

Permethrin: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. Charles Smith. DP Barcode D298288. October 20, 2004.

At this time, products containing permethrin are intended for both occupational and non-occupational uses. Residential homeowners may use permethrin in a variety of indoor and outdoor residential environments including: lawns, gardens, indoor surfaces and spaces, ornamentals, and on pets. Due to this use profile, adult residential homeowners may experience exposure to permethrin during application of the chemical (i.e., residential handler exposures). Adults and children may experience exposure to permethrin when contacting permethrin-treated areas (i.e., residential postapplication exposure). Risk assessments presented in this section reflect potential exposures to adult residential handlers and potential postapplication exposure to adults and children of varying ages.

In addition to homeowner uses in residential settings, permethrin is labeled for mosquito adulticide use, which is applied by occupational handlers, but may result in postapplication exposures in residential settings. These potential postapplication exposures to adults and children also have been considered in this assessment.

Short-term exposures (defined as exposures from 1 to 30 days in duration) may occur for residents applying permethrin products and for residents exposed to permethrin following applications in residential settings. Intermediate- and long-term exposures are not anticipated for residential handling or postapplication exposures, due to the episodic nature of the applications. The HIARC selected short-term dermal (25 mg/kg/day) and inhalation (11 mg/kg/day) endpoints of concern for permethrin. The short-term dermal (noncancer) endpoint for permethrin is from an oral study, therefore, a dermal absorption factor must be used. The HIARC report, dated October 8, 2003, states that a dermal absorption factor of 30% should be used to assess dermal risks.

6.3.1 Home Uses

The permethrin assessment reflects HED's current approaches for completing residential exposure assessments based on the guidance provided in the OPPTS Harmonized Guidelines, Series 875: Occupational and Residential Exposure Test Guidelines, Group B: Postapplication Exposure Monitoring Test Guidelines, the Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment, and the Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments.

6.3.1.1 Residential Handlers - Noncancer

Scenarios used to define risks are based on the *U.S. EPA Guidelines For Exposure Assessment* (U.S. EPA; Federal Register Volume 57, Number 104; May 29, 1992). Assessing exposures and risks resulting from residential uses is very similar to assessing occupational exposures and risks, with the following exceptions: 1) residential handler exposure scenarios are considered to be short-term only, due to the infrequent use patterns associated with homeowner products, 2) homeowner handler assessments are based on the assumption that individuals are wearing shorts, short-sleeved shirts, socks, and shoes [no personal protective equipment (PPE)], and 3) homeowner handlers are expected to complete all tasks associated with the use of a pesticide product including mixing/ loading, if needed, as well as the application.

The anticipated use patterns and current labeling indicate several likely residential handler exposure scenarios, based on the types of equipment and techniques that can potentially be used to apply permethrin in residential settings. Due to the scope of the various permethrin residential uses (there are over 900 permethrin products registered), it is extremely difficult to assess each individual exposure scenario. Therefore, HED selected representative exposure scenarios to reflect the major ways in which permethrin can be applied in the residential environment. HED believes this approach is protective of public health as the scenarios likely to result in the greatest exposure are considered. Anticipated use pattern and current labeling indicate 23 likely residential exposure scenarios based on the types of equipment and techniques that can potentially be used to make permethrin applications. Scenarios in this document include the following (scenarios denoted with a "*" could not be evaluated quantitatively, because applicable unit exposure data are not available):

Residential Mixer/Loader/Applicators:

(1) Liquid: Low Pressure Handwand;
(2) Liquid: Backpack Sprayer;
(3) Liquid: Hose-End Sprayer;
(4) Liquid: Watering Can;
(5) Liquid: Paint Brush;
(6) Liquid: Sponge;
(7) Granulars: Push Type Spreader;
(8) Granulars: Belly Grinder;
(9) Granulars: Spoon or Cup;
(10) Dusts: Spoon or Cup;
(11) Dusts: Shaker Can;
(12) Dusts: Rotary Duster/Dust Gun*;
(13) Dusts: FPO Puffer Can*;
(14) RTU Liquids: Pour-on (using PHED liquid mixing/loading data);
(15) RTU Cream: Applicator Tube*;
(16) RTU Shampoos: Hands*;
(17) RTU Wipe Applications (using CMA data);

(18) RTU: Trigger Pump Sprayer Applications;
(19) RTU: Aerosol Cans;
(20) RTU: Fogger (using PHED aerosol can data);
(21) RTU Tubes (for use on lawns)*;
(22) RTU Chair and Table Coasters*;
(23) RTU Protective Flanges*.

A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below. In addition to these factors, unit exposure values were used to calculate risk estimates. Unit exposure values were derived from the following exposure data:

- the Pesticide Handler Exposure Database (PHED);
- the Outdoor Residential Task Force (ORETF) studies;
- the Non-Dietary Exposure Task Force (NDETF) Studies;
- the Chemical Manufacturers Association (CMA) Antimicrobial Exposure Assessment Study; and
- three proprietary exposure studies reflecting the following scenarios-
  - handlers applying dusts via shaker can or by hand (MRID # 444399-01),
  - handlers applying granulars via spoon and cup (MRID # 452507-02), and
  - handlers applying liquids via trigger sprayer (MRID # 410547-01).

The noncancer residential handler exposure and risk calculations are included in Table 6.3.1.1. Scenarios that could not be evaluated quantitatively are not presented in the table. The results indicate that all of the residential handler risks do not exceed HED's level of concern [i.e., MOEs are all greater than 100]. Due to the number of registered residential uses of permethrin, only the worst case scenarios are presented in this chapter. For the complete short-term residential handler noncancer exposure and risk assessment, see *Permethrin: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. Bill Smith. October 27, 2004.* In order to refine this residential handler risk assessment, more data on actual use patterns including rates, timing, and areas treated would better characterize permethrin risks.

Table 6.3.1.1. Summary of Short-Term Permethrin Residential Handler Noncancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai)	Dose (mg/kg/day)		Baseline MOEs		
						Dermal	Inhalation	Dermal	Inhalation	Combined
Mixing/Loading/Applying Emulsifiable Concentrates with Low Pressure Handwand (1)	outdoor surfaces	0.046 lb ai/gallon	5 gallons	56	3.8	0.055	0.000012	450	880000	**450**
	fire ant mounds	0.1 lb ai/mound	5 mounds	56	3.8	0.12	0.000027	210	410000	**210**
	animal: dogs, horses	0.00075 lb ai/animal	2 animals	56	3.8	0.00036	0.000000081	69000	140000000	**69000**
Mixing/Loading/Applying Emulsifiable Concentrates with Backpack Sprayer (2)	outdoor surfaces	0.046 lb ai/gallon	5 gallons	5.1	30	0.005	0.000099	5000	110000	**4800**
	fire ant mounds	0.1 lb ai/mound	5 mounds	5.1	30	0.011	0.00021	2300	51000	**2200**
	animal: dogs, horses	0.00075 lb ai/animal	2 animals	5.1	30	0.000033	0.00000064	760000	17000000	**730000**
Mixing/Loading/Applying Emulsifiable Concentrates with Hose-End Sprayer (ORETF data) (3)	turf	0.087 lb ai/acre	0.5 acres	11	17	0.0021	0.000011	12000	1000000	**12000**
	ornamentals: outdoor trees	0.043 lb ai/gallon	100 gallons	11	17	0.2	0.001	120	11000	**120**
Mixing/Loading/Applying Emulsifiable Concentrates with a Watering Can (using ORETF residential hose-end data) (4)	fire ant mounds	0.1 lb ai/mound	5 mounds	11	17	0.024	0.00012	1100	91000	**1000**
	stored lumber, wood piles	0.04 lb ai/gallon	5 gallons	11	17	0.0094	0.000049	2700	230000	**2600**
Mixing/Loading/Applying Emulsifiable Concentrates with a Paint Brush (5)	outdoor wood surfaces; outdoor surfaces	0.04 lb ai/gallon	1 gallon	230	284	0.039	0.00016	630	68000	**630**
Mixing/Loading/Applying Emulsifiable Concentrates via Sponge (CMA data) (6)	horses	0.005 lb ai/animal	2 animals	2870	27700	0.12	0.004	200	2800	**190**
Loading/Applying Granulars via Push Type Spreader (ORETF data) (7)	turf	0.65 lb ai/acre	0.5 acres	0.68	0.91	0.00095	0.0000042	26000	2600000	**26000**
	perimeter treatment	0.08 lb ai/1000 sq ft	1000 sq ft	0.68	0.91	0.00023	0.000001	110000	11000000	**110000**
Loading/Applying Granulars via Belly Grinder (8)	turf	0.65 lb ai/acre	0.5 acres	110	62	0.15	0.00029	160	38000	**160**
	perimeter treatment	0.08 lb ai/1000 sq ft	1000 sq ft	110	62	0.038	0.000071	660	160000	**660**
Loading/Applying Granulars via Spoon or Cup (MRID 452507-01) (9)	fire ant mounds	0.00125 lb ai/mound	5 mounds	1.98	45	0.000053	0.000004	470000	2700000	**400000**
Loading/Applying Dusts via Spoon or Cup (MRID 444598-01) (10)	fire ant mounds	0.00156 lb ai/mound	5 mounds	148	870	0.0049	0.000097	5100	110000	**4800**
Mixing/Loading/Applying Dusts via Shaker Can (MRID 444598-01) (11)	indoor surfaces	0.05 lb ai/1000 sq ft	1000 sq ft	148	870	0.032	0.00062	790	18000	**750**
	various crops [c]	0.0025 lb ai/1lb container	1 lb container	148	870	0.0016	0.000031	16000	350000	**15000**
	animal: dogs, cats	0.00016 lb ai/animal	2 animals	148	870	0.0002	0.000004	5500	96000	**5200**

Table 6.3.1.1. Summary of Short-Term Permethrin Residential Handler Noncancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai)	Dose (mg/kg/day)		Baseline MOEs		
						Dermal	Inhalation	Dermal	Inhalation	Combined
Applying Ready to Use Formulations via Pour-on (using PHED liquid mixer/loader data) (14)	animal: horses	0.005 lb ai/animal	2 animals	2.9	1.2	0.00012	0.00000017	200000	64000000	**200000**
	clothing: personal	0.002 lb ai/gallon	1 container	2.9	1.2	0.000025	0.000000034	1000000	320000000	**1000000**
Applying Ready to Use Formulations via RTU Wipe (CMA data) (17)	animal: dogs & horses	0.0062 lb ai/animal	2 animals	2870	27700	0.15	0.0049	160	2200	**150**
Applying Ready to Use Formulations via Trigger-Pump Sprayer (using Propoxur study) (18)	ornamentals: outdoors; indoor surfaces	0.043 lb ai/gallon	1 gallon	13.5	123	0.0025	0.000076	10000	150000	**9400**
	animal: dogs	0.00034 lb ai/ounce	8 ounces (assume ½ 16 oz bottle)	13.5	123	0.00016	0.0000048	160000	2300000	**150000**
	animal: horses, foals	0.016 lb ai/animal	2 animals	13.5	123	0.0019	0.000056	14000	200000	**13000**
Applying Ready to Use Formulations with Aerosol Cans (19)	outdoor & indoor surfaces	0.00438 lb ai/16 oz can	1 sixteen-ounce aerosol can	220	2400	0.0041	0.00015	6100	73000	**5600**
	animal: dogs & cats; animal premises: dogs and cats	0.000538 lb ai/16 oz can	0.5 sixteen-ounce aerosol cans	220	2400	0.00025	0.0000092	99000	1200000	**91000**
Applying Ready to Use Formulations with Foggers (using PHED aerosol data) (20)	indoor spaces	0.002 lb ai/6 oz fogger	2 animals	220	2400	0.0043	0.00016	5800	70000	**5300**

Footnotes

a Application rates are the maximum application rates for permethrin.

b Amount handled per day values are HED estimates of area treated, or gallons applied, or other area/volume treated Exposure SAC SOP #11 "Standard Operating Procedures for Residential Assessments," industry input, and HED estimates.

c Crops include apples, asparagus, broccoli, brussel sprouts, cauliflower, cabbage, celery, cucumber, eggplant, garlic, head & leaf lettuce, muskmelon, onion: dry bulb, parsley, peaches, pepper: bell, potato, pumpkin, rhubarb, spinach, squash, sweet corn, tomato, walnuts, watermelon, ornamentals: outdoor, and roses: outdoor.

6.3.1.2 Residential Handlers - Cancer

The residential handler exposure and cancer risk calculations are presented in this section. Cancer risk estimates were calculated using a linear, low-dose extrapolation approach (Q_1*). The same scenarios, assumptions, and unit exposures were used as in the noncancer assessment. HED estimated cancer risk assuming estimates for an annual a maximum of 1 day of exposure per year. In addition, HED calculated the maximum number of days of exposure per year that still would result in cancer risks less than or equal to $1x10^{-6}$ (HED's level of concern for residential cancer).

The cancer risk calculations for residential permethrin handlers completed in this assessment are included in Table 6.3.1.2. There are 24 scenarios where up to 5 exposure-days per year would result in risks at or below $1x10^{-6}$. For all but eight scenarios, estimated cancer risks are less than $1x10^{-6}$ (most are in the 10^{-7} to 10^{-9} range) when a single day of exposure per year is evaluated. The eight scenarios where cancer risk estimates are more than $1x10^{-6}$ when a single day of exposure per year is evaluated include:

- mixing/loading/applying emulsifiable concentrates with low pressure handwand to outdoor surfaces (0.046 lb ai/gallon),
- mixing/loading/applying emulsifiable concentrates with low pressure handwand to outdoor trees (0.043 lb ai/gallon),
- mixing/loading/applying emulsifiable concentrates with low pressure handwand to outdoor wood surfaces and for perimeter treatments (0.04 lb ai/gallon),
- mixing/loading/applying emulsifiable concentrates with low pressure handwand to fire ant mounds (0.01 lb ai/mound),
- mixing/loading/applying emulsifiable concentrates with hose-end sprayer to outdoor trees (0.043 lb ai/acre),
- mixing/loading/applying emulsifiable concentrates with hose-end sprayer to stored lumber and wood piles (0.04 lb ai/gallon)
- mixing/loading/applying emulsifiable concentrates with hose-end sprayer to ornamentals outdoors (0.02 lb ai/gallon),
- applying to dogs or horses using a ready-to-use wipe (0.0062 lb ai/wipe)

Due to the number of registered residential uses of permethrin, only the worst case scenarios are presented. Scenarios that could not be evaluated quantitatively are not presented in the table. For the complete handler cancer risk estimate table, see *Permethrin: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. Bill Smith. October 27, 2004.* In order to refine this residential risk assessment, more data on actual use patterns including rates, timing, and areas treated would better characterize permethrin risks.

Table 6.3.1.2. Summary of Permethrin Residential Handler Cancer Risk Esimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai)	Daily Total Dose (mg/kg/day)	Total LADD (mg/kg/day)	Residential Applicator Baseline Cancer Risk [c]	Allowed Days per Year[d]
Mixing/Loading/Applying Emulsifiable Concentrates with Low Pressure Handwand (1)	outdoor surfaces	0.046 lb ai/gallon	5 gallons	56	3.8	0.099	1.9e-04	1.8E-06	<1
	ornamentals: outdoor trees	0.043 lb ai/gallon	5 gallons	56	3.8	0.092	1.8e-04	1.7E-06	<1
	perimeter treatment, outdoor wood surfaces	0.04 lb ai/gallon	5 gallons	56	3.8	0.086	1.7e-04	1.6E-06	<1
	ornamentals: outdoor	0.02 lb ai/gallon	5 gallons	5.1	30	0.043	8.4e-05	8.0E-07	1
	fire ant mounds	0.1 lb ai/mound	5 mounds	5.1	30	0.21	4.2e-04	4.0E-06	<1
	animal: dogs, horses	0.00075 lb ai/animal	2 animals	5.1	30	0.00064	1.3e-06	1.2E-08	83
Mixing/Loading/Applying Emulsifiable Concentrates with Backpack Sprayer (2)	outdoor surfaces	0.046 lb ai/gallon	5 gallons	5.1	30	0.0051	1.0e-05	9.6E-08	10
	fire ant mounds	0.1 lb ai/mound	5 mounds	5.1	30	0.011	2.2e-05	2.1E-07	4
	animal: dogs, horses	0.00075 lb ai/animal	2 animals	5.1	30	0000033	6.5e-08	6.3E-10	365
Mixing/Loading/Applying Emulsifiable Concentrates with Hose-End Sprayer (ORETF data) (3)	turf	0.087 lb ai/acre	0.5 acres	11	17	0.0021	4.0e-06	3.9E-08	25
	ornamentals: outdoor trees	0.043 lb ai/gallon	100 gallons	11	17	0.2	4.0e-04	3.8E-06	<1
	stored lumber, wood piles	0.04 lb ai/gallon	100 gallons	11	17	0.19	3.7e-04	3.5E-06	<1
	ornamentals: outdoor	0.02 lb ai/gallon	100 gallons	11	17	0.095	1.9e-04	1.8E-06	<1
	almonds, filberts, pears, pistachios	0.004 lb ai/gallon	100 gallons	11	17	0.019	3.7e-05	3.5E-07	2
Mixing/Loading/Applying Emulsifiable Concentrates with a Watering Can (using ORETF residential hose-end data) (4)	fire ant mounds	0.1 lb ai/mound	5 mounds	11	17	0.024	4.6e-05	4.4E-07	2
	stored lumber, wood piles	0.04 lb ai/gallon	5 gallons	11	17	0.0095	1.9e-05	1.8E-07	5
Mixing/Loading/Applying Emulsifiable Concentrates with a Paint Brush (5)	outdoor wood surfaces; outdoor surfaces	0.04 lb ai/gallon	1 gallon	230	284	0.04	7.7e-05	7.4E-07	1
Mixing/Loading/Applying Emulsifiable Concentrates via Sponge (CMA data) (6)	horses	0.005 lb ai/gallon	2 animals	2870	27700	0.13	2.5e-04	2.4E-06	2
Loading/Applying Granulars via Push Type Spreader (ORETF data) (7)	turf	0.65 lb ai/acre	0.5 acres	0.68	0.91	0.00095	1.9e-06	1.8E-08	56
	perimeter treatment	0.08 lb ai/1000 sq ft	1000 sq ft	0.68	0.91	0.00023	4.6e-07	4.4E-09	228
Loading/Applying Granulars via Belly Grinder (8)	turf	0.65 lb ai/acre	0.5 acres	110	62	0.15	3.0e-04	2.9E-06	2
	perimeter treatment	0.08 lb ai/1000 sq ft	1000 sq ft	110	62	0.038	7.4e-05	7.1E-07	2
Loading/Applying Granulars via Spoon or Cup (MRID 452507-01) (9)	fire ant mounds	0.00125 lb ai/mound	5 mounds	1.98	45	0.000057	1.1e-07	1.1E-09	365
Loading/Applying Dusts via Spoon or Cup (MRID 444598-01) (10)	fire ant mounds	0.00156 lb ai/mound	5 mounds	148	870	0.005	9.9e-06	9.4E-08	10

Table 6.3.1.2. Summary of Permethrin Residential Handler Cancer Risk Esimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai)	Daily Total Dose (mg/kg/day)	Total LADD (mg/kg/day)	Residential Applicator Baseline Cancer Risk [c]	Allowed Days per Year[d]
Mixing/Loading/Applying Dusts via Shaker Can (MRID 444598-01) (11)	indoor surfaces	0.05 lb ai/1000 sq ft	1000 sq ft	148	870	0.032	6.3e-05	6.1E-07	1
	various crops [e]	0.0025 lb ai/1lb container	1 lb container	148	870	0.0016	3.2e-06	3.0E-08	33
	animal: dogs, cats	0.00016 lb ai/animal	2 animals	148	870	0.00021	4.0e-07	3.9E-09	258
Applying Ready to Use Formulations via Pour-on (using PHED liquid mixer/loader data) (14)	animal: horses	0.005 lb ai/animal	2 animals	2.9	1.2	0.00012	2.4e-07	2.3E-09	365
	clothing: personal	0.002 lb ai/gallon	1 container	2.9	1.2	0.000025	4.9e-08	4.7E-10	365
Applying Ready to Use Formulations via RTU Wipe (CMA data) (17)	animal: dogs & horses	0.0062 lb ai/animal	2 animals	2870	27700	0.16	3.1e-04	2.9E-06	<1
Applying Ready to Use Formulations via Trigger-Pump Sprayer (using Propoxur study) (18)	ornamentals: outdoors; indoor surfaces	0.043 lb ai/gallon	1 gallon	13.5	123	0.0026	5.0e-06	4.8E-08	20
	animal: dogs	0.00034 lb ai/ounce	8 ounces (assume ½ 16 oz bottle)	13.5	123	0.00016	3.2e-07	3.0E-09	329
	animal: horses, foals	0.016 lb ai/animal	2 animals	13.5	123	0.0019	3.7e-06	3.6E-08	27
Applying Ready to Use Formulations with Aerosol Cans (19)	outdoor & indoor surfaces	0.00438 lb ai/16 oz can	1 sixteen-ounce aerosol can	220	2400	0.0043	8.4e-06	8.0E-08	12
	animal: dogs & cats; animal premises: dogs and cats	0.000538 lb ai/16 oz can	0.5 sixteen-ounce aerosol cans	220	2400	0.00026	5.1e-07	4.9E-09	203
Applying Ready to Use Formulations with Foggers (using PHED aerosol data) (20)	indoor spaces	0.002 lb ai/6 oz fogger	2 animals	220	2400	0.0045	8.8e-06	8.4E-08	11

Footnotes

a Application rates are the maximum application rates for permethrin in all cases; typical rates were not available.

b Amount handled per day values are HED estimates of area treated, or gallons applied, or other area/volume treated Exposure SAC SOP #11 "Standard Operating Procedures for Residential Assessments," industry input, and HED estimates.

c Cancer risk estimates were calculated assuming one day of exposure per year.

d HED calculated the maximum number of days of exposure per year that still would result in cancer risks less than or equal to a $1x10^{-6}$.

e Crops include apples, asparagus, broccoli, brussel sprouts, cauliflower, cabbage, celery, cucumber, eggplant, garlic, head & leaf lettuce, muskmelon, onion: dry bulb, parsley, peaches, pepper: bell, potato, pumpkin, rhubarb, spinach, squash, sweet corn, tomato, walnuts, watermelon, ornamentals: outdoor, and roses: outdoor.

Table 6.3.1.3.3. Toddler Residential Risk Estimates for Postapplication Exposure to Permethrin			
Exposure Scenario	Route of Exposure	Application Rate	MOE at Day 0
Outdoors			
Hand to Mouth Activity on Turf	Oral	0.87 lb ai/acre	15,000
Object to Mouth Activity on Turf	Oral	0.87 lb ai/acre	250,000
Incidental Soil Ingestion	Oral	0.87 lb ai/acre	570,000
Incidental Ingestion of Granules	Oral	0.65 lb ai/acre	250
Residential Turf (High Contact Activities)	Dermal	0.87 lb ai/acre	2,000
Mosquitos (ULV Truck Fogger)	Inhalation	0.1 lb ai/acre	1700
Indoors			
Hand to Mouth Activity on Indoor Surfaces (Carpet)	Oral	0.0001 lb ai/sq ft	68
Hand to Mouth Activity on Indoor Surfaces (Vinyl)	Oral	0.0001 lb ai/sq ft	130
Indoor Surfaces (High Contact Activities) - Spray (Carpet)	Dermal	0.0001 lb ai/sq ft	12
Indoor Surfaces (High Contact Activities) - Spray (Vinyl)	Dermal	0.0001 lb ai/sq ft	79
Indoor Surfaces (High Contact Activities) - Fogger (Carpet)	Dermal	0.0023 lb ai/6 oz fogger	130
Indoor Surfaces (High Contact Activities) - Fogger (Vinyl)	Dermal	0.0023 lb ai/6 oz fogger	680
Pets			
Hand to Mouth Activity on Pets - Dusts	Oral	0.00016 lb ai/animal	1,300
Hand to Mouth Activity on Pets - Liquid	Oral	0.0014 lb ai/animal	44
Pet Contact Activities - Dusts	Dermal	0.00016 lb ai/animal	270
Pet Contact Activities - Liquid	Dermal	0.0014 lb ai/animal	31
Clothing			
Impregnated Clothing	Dermal	0.125 mg ai/cm^2	440
Object to Mouth Activity on Impregnated Clothing	Oral	0.125 mg ai/cm^2	24,000

Combined Risk Assessment for Residential Scenarios

HED combines risks resulting from different exposure pathways when logically they can co-occur. For permethrin, HED has combined risks to residential children from exposures to treated lawns (i.e., dermal, hand-to-mouth, object-to-mouth, and soil ingestion), from hugging treated companion animals, (i.e., dermal and hand-to-mouth), and from wearing impregnated clothing scenarios (i.e., dermal and object-to-mouth). Table 6.3.1.3.4 presents a summary of the combined risk estimates.

The combined risks for the turf spray scenario, the pet-dust scenario, and the impregnated clothing scenario are 1700, 220, and 430, respectively and do not exceed HED's level of concern. The combined risks (MOE = 26) exceed HED's level of concern for the pet-shampoo

scenario.

Table 6.3.1.3.4. Permethrin Residential Scenarios for Combined Risk Estimates				
Postapplication Exposure Scenario			Margins of Exposure (MOEs) (UF=100)	
			Short-Term Oral (Non-Dietary)	Total Non-Dietary Risk
Toddler	Turf - sprays (0.87 lb ai/acre)	Dermal	2,000	1,700
		Hand to Mouth	15,000	
		Object to Mouth	250,000	
		Incidental Soil Ingestion	570,000	
Toddler	Pet - shampoo	Hand to Mouth	150	26
		Dermal	31	
Toddler	Pet - dusts	Hand to Mouth	1,300	220
		Dermal	270	
Toddler	Impregnated Clothing	Object to Mouth	24,000	430
		Dermal	440	

6.3.1.4 Residential/Recreational Cancer Postapplication Exposures and Risks

The residential postapplication exposure and cancer risk calculations are presented in this section. Postapplication cancer risk estimates were calculated using a linear, low-dose extrapolation approach (Q_1*). The same scenarios, assumptions, and unit exposures were used as in the noncancer postapplication assessment. HED estimated cancer risk assuming a maximum of 1 day of exposure per year. In addition, HED calculated the maximum number of days of exposure per year that still would result in cancer risks less than or equal to $1x10^{-6}$ (HED's level of concern for residential cancer).

Table 6.3.1.4 below summarizes the postapplication risk estimates calculated for adults after applications of permethrin. It should be noted that these estimates represent one day of postapplication exposure per year and exposure on the day of application (i.e., day 0) for each year of a 50-year exposure period. HED lacks data to further refine postapplication cancer assessments in residential settings. The postapplication cancer risk estimates indicate that:

- for all scenarios on turf, home gardening, and mosquitos, cancer risk estimates are in the 10^{-7} to 10^{-8} range or less when a single reentry event per year is evaluated and entry on the day of the application (i.e., day 0) is assumed.

- for all indoor scenarios, estimated risks are in the 10^{-5} to 10^{-6} range and exceed HED's level of concern when a single reentry event per year is evaluated and entry on the day of application (i.e., day 0) is assumed.

- for the pet scenarios, estimated risks do not exceed HED's level of concern for postapplication dermal exposure to pets after dust applications when a single exposure event per year is evaluated and exposure on the day of application (i.e., day 0) is assumed. However, estimated risks exceed HED's level of concern for

postapplication dermal exposure to pets after spray applications when a single exposure event per year is evaluated and exposure on the day of application (i.e., day 0) is assumed.

- for the impregnated clothing scenarios, estimated cancer risks (in the 10^{-7} range) do not exceed HED's level of concern when a single exposure event per year is evaluated. HED believes that individuals will wear permethrin impregnated clothing more than one time a year. If multiple exposure events per year are considered, then estimated cancer risks exceed HED's level of concern.

Table 6.3.1.4. Summary of Permethrin Postapplication Residential Cancer Risks For Adults

Exposure Scenario	Route of Exposure	Application Rate[a, b]	Cancer Risk at Day 0[c]	Days/Year to Reach LOC[d]
Outdoors				
Residential Turf (High Contact Activities)	Dermal	0.87 lb ai/acre	1.4×10^{-7}	7
Residential Turf (Mowing)	Dermal	0.87 lb ai/acre	4.9×10^{-9}	205
Home Garden (Fruit and Nut Tree)	Dermal	0.4 lb ai/acre	3.6×10^{-8}	28
Home Garden (Vegetables)	Dermal	0.23 lb ai/acre	2.1×10^{-8}	48
Mosquitos (ULV Truck Fogger)	Dermal/ Inhalation	0.1 lb ai/acre	3.9×10^{-8}	25
Indoors				
Indoor Surfaces (High Contact Activities) - Spray	Dermal	0.0001 lb ai/sq ft	2.6×10^{-5}	<1
Indoor Surfaces (High Contact Activities) - Fogger	Dermal	0.0023 lb ai/6 oz fogger	2.4×10^{-6}	<1
Pets				
Pet Contact Activities - Dust	Dermal	0.00016 lb ai/animal	3.7×10^{-7}	2
Pet Contact Activities - Liquid	Dermal	0.0014 lb ai/animal	3.2×10^{-6}	<1
Clothing				
Impregnated Clothing	Dermal	0.125 mg ai/cm^2	7.4×10^{-7}	1

Footnotes

a Application rates are the maximum application rates for permethrin in all cases; typical rates were not available.

b Amount handled per day values are HED estimates of area treated, or gallons applied, or other area/volume treated based on Exposure SAC SOP #11 "Standard Operating Procedures for Residential Assessments," industry input, and HED estimates.

c Cancer risk estimates were calculated assuming one day of exposure per year.

d HED calculated the maximum number of days of exposure per year that still would result in cancer risks less than or equal to a 1×10^{-6}.

6.3.2 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for permethrin. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State

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Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of the U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticide applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures (oral, dermal, and inhalation exposures). In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

In general, exposures from various sources (routes) are aggregated only when the toxic effects, determined by the endpoint selected for that route, are the same. In this case, a screening level aggregate assessment was performed using high-end exposures and conservative (lowest) endpoints. Further refinements would have been incorporated into the assessment if it had showed risks of concern.

7.1 Acute Aggregate Risk

The acute aggregate risk estimate includes the contribution of risk from dietary (food + drinking water) sources only. Acute risk estimates from exposures to food and water, associated with the use of permethrin do not exceed HED's level of concern. The estimated acute dietary risk for the general U.S. population is <7 %, with the highest exposed population subgroup being infants at 18% aPAD (see Section 4.4).

Drinking water expected concentrations (DWECs) were calculated from models, for risk assessment purposes, based on maximum application rates. The deterministic DWECs were combined directly with the acute dietary exposure assessment for all populations to calculate aggregate dietary (food + water) risk. The advantage of this approach, for any population subgroup, is that the actual individual body weight and water consumption data from the CSFII are used, rather than assumed weights and consumption for broad age groups. Surface water DWECs were combined with estimated food exposure for aggregate risk assessment purposes since the calculated surface water estimates exceed the calculated ground water estimates and therefore, are more conservative.

7.2 Short-Term Aggregate Risk

Aggregate short-term risk estimates include the contribution of risk from chronic dietary sources (food + water) and short-term residential sources. There are a number of exposure scenarios that could be aggregated. For purposes of this assessment, exposure scenarios that were not of concern on their own and might occur during the same time-frame were combined to provide a conservative (high-end) estimate of aggregate risk.

Adult Aggregate Risk: Chronic food and water exposures for the U.S. general population and for females 13-49 years of age were combined with residential handler and postapplication exposures. Residential handler exposures for mixing/loading/applying emulsifiable concentrates with a hose-end sprayer at 0.043 lb ai/gal (max rate) to ornamental outdoor trees, dermal and inhalation, were combined, by route, with postapplication exposures (dermal) for indoor surface vinyl spray, considered a high contact activity, performed at 0.0001 lb ai/sq ft. Residential handler exposures for mixing/loading/applying emulsifiable concentrates with a hose-end sprayer at 0.043 lb ai/gal (max rate) to ornamental outdoor trees, dermal and inhalation, were also combined, by route, with postapplication exposures (dermal) for indoor carpet fogger, considered a high contact activity, performed at 0.0001 lb ai/sq ft and then with impregnated clothing at 0.125 mg ai/cm^2. To calculate the route-specific MOEs the dose/endpoints used were; oral and dermal 25 mg/kg/day; and inhalation 11 mg/kg/day.

Child/Toddler Aggregate Risk: Chronic food and water exposures for children 1-2 years of age were combined with postapplication residential hand to mouth activity on pets plus residential pet contact plus residential mosquito exposures resulting from applications of permethrin to pets at 0.00016 lb ai/animal and applications of permethrin via ULV truck fogger at 0.1 lb ai/acre, respectively. To calculate the route-specific MOEs the dose/endpoints used were; oral and dermal 25 mg/kg/day.

With the exception of indoor carpet and vinyl sprays, and liquid pet uses, which alone exceed HED's Level of concern, HED can conclude that combined residues of permethrin from food, drinking water, and other potential residential exposures do not result in short-term aggregate risks of concern to population subgroups.

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Table 7.2. Short-Term Aggregate Risk

Population	Residential Scenarios Included in Aggregate	Short-Term Scenario					
		HED's Aggregate LOC[1]	MOE food + water[2]	MOE incid oral[3]	MOE dermal[4]	MOE inhalation[5]	Aggregate MOE (food and residential)[6]
U.S. Pop.	Orn. Outdoor Trees, Indoor Vinyl Spray	100	115,207	NA	62	11,000	62
	Orn. Outdoor Trees, Indoor Carpet Fog	100	115,207	NA	79	11,000	78
	Orn. Outdoor Trees, Impregnated Clothing	100	115,207	NA	101	11,000	101
Adult Female	Orn. Outdoor Trees, Indoor Vinyl Spray	100	119,617	NA	62	11,000	62
	Orn. Outdoor Trees, Indoor Carpet Fog	100	119,617	NA	79	11,000	78
	Orn. Outdoor Trees, Impregnated Clothing	100	119,617	NA	101	11,000	100
Child	Pet Dust, Mosquito	100	59,242	1,300	270	1,700	197

[1] *Level of Concern (LOC) is 100 based on 10X for inter-species extrapolation and 10X for intra-species variation.*

[2] MOE food + water = [(short-term oral NOAEL 25 mg/kg/day)/(chronic dietary exposure)]
Chronic dietary exposure: U.S. Pop.=0.000217 *mg/kg/day; Females 13-49 yrs* = 0.000209 *mg/kg/day; All Infants <1 yr* = 0.000422 *mg/kg/day*.

[3] MOE incidental oral = [(short-term incidental oral NOAEL 25 mg/kg/day)/(child residential exposure)]
Child residential exposure: Hand-to-mouth = 0.019231mg/kg/day; Pet Contact = 0.1mg/kg/day; Mosquito = 0.002273 mg/kg/day

[4] MOE dermal = [(short-term dermal NOAEL 25 mg/kg/day)/(high-end dermal residential exposure)]
Dermal exposure: Adults = handler 0.208333 mg/kg/day + postapp 0.192308 mg/kg/day; Child = 0.0925925 mg/kg/day

[5] MOE inhalation = [(inhalation NOAEL 11mg/kg/day)/(high-end inhalation residential exposure)]
Inhalation exposure: Adult = handler 0.002273mg/kg/day

[6] Aggregate MOE (food + water + residential) = 1÷[[(1÷MOE food+water) + (1÷MOE incidental oral) + (1÷MOE dermal) + (1÷MOE inhalation)]]

7.3 Intermediate-Term Aggregate Risk

All residential/recreational exposures are expected to be short-term in duration.

7.4 Long-Term Aggregate Risk

Aggregate long-term (noncancer) risk estimates include the contribution of risk from chronic dietary sources (food + water) and residential sources. However, based on the labeled uses, no long-term or chronic residential exposures are expected. Chronic risk estimates from exposures to food and water, associated with the use of permethrin do not exceed HED's level of concern for the U.S. population and all population subgroups (all populations were less than 1% cPAD).

As in the acute aggregate assessment, surface water DWECs were calculated by EFED to estimate the potential contribution to the chronic exposure from drinking water, and the DWECs were combined with chronic food exposures to estimate potential long-term aggregate risks from the uses of permethrin.

7.5 Cancer Risk

Exposures to permethrin from dietary (food and water) sources alone exceed HED's level of concern. As mentioned earlier in the residential exposure/risk discussion, the potential risks for exposures from residential uses, are also of concern for eight scenarios. Any aggregation of residential exposures with dietary levels of exposure would only serve to increase the reported risks.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to permethrin and any possibly associated substances. For the purposes of this risk assessment, therefore, EPA has not assumed that permethrin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

Permethrin: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. Charles Smith. DP Barcode D298288. October 20, 2004.

There is a potential for exposure to permethrin in occupational scenarios from handling permethrin products during the application process (i.e., mixer/loaders, applicators, flaggers, and mixer/loader/applicators) and a potential for postapplication worker exposure from entering into areas previously treated with permethrin. As a result, risk assessments have been completed for occupational handler scenarios as well as occupational postapplication scenarios.

9.1 Short- and Intermediate-Term Noncancer Handler Risk

Exposure scenarios categorize the exposures that occur during the use of a chemical. The use of scenarios in exposure assessments is common and is described in the *U.S. EPA Guidelines For Exposure Assessment* (U.S. EPA; Federal Register Volume 57, Number 104; May 29, 1992). Information from the current labels, use and usage information, toxicology data, and exposure data were all key components in developing the exposure scenarios. For exposure and risk assessment purposes, pesticide handling tasks associated with occupational pesticide use are categorized as one of the following:

- **Mixers and/or Loaders:** these individuals perform tasks in preparation for an application. For example, prior to application, mixer/loaders would mix the permethrin and load it into the holding tank of the airplane or groundboom.

- **Applicators:** these individuals operate application equipment during the release of a pesticide product into the environment. These individuals can make applications using equipment such as airplanes or groundboom sprayers.

- **Mixer/Loader/Applicators and or Loader/Applicators:** these individuals are involved in the entire pesticide application process (i.e., they do all job functions related to a pesticide application event). These individuals would transfer permethrin into the application equipment and then also apply it.

- **Occupational Flaggers:** these individuals guide aerial applicators during the release of a pesticide product onto an intended target.

The risk assessors must understand how exposures to permethrin occur (i.e., frequency and duration) and how the patterns of these occurrences can cause the effects of the chemical to differ (referred to as dose response). Wherever possible, use and usage data determine the appropriateness of certain types of risk assessments. Other parameters are also defined from use and usage data such as application rates and application frequency. HED always completes non-cancer risk assessments using maximum application rates for each scenario because what is possible under the label (the legal means of controlling pesticide use) must be evaluated in order

to ensure there are no concerns for each specific use.

The frequency and duration of pesticide handlers' exposures must also be estimated in order to determine the which toxicological endpoints of concern are applicable to a handler exposure scenario. HED believes that occupational permethrin exposures can occur over a single day or up to weeks at a time for many use-patterns and also anticipates intermittent exposures can occur over several weeks. Custom or commercial applicators may apply permethrin over a period of weeks completing applications for a number of different clients. HED classifies exposures up to 30 days as short-term and exposures greater than 30 days up to several months as intermediate-term. HED completes both short- and intermediate-term assessments for occupational scenarios in essentially all cases, because these kinds of exposures are likely and often reliable use/usage data are not available to justify deleting intermediate-term scenarios. Long-term handler exposures are not expected to occur for permethrin. The same toxicological endpoint (25 mg/kg/day from an oral study) of concern was selected for short- and intermediate-term dermal permethrin exposures, therefore the risk results for all dermal durations of exposure are numerically identical. The HIARC report, dated October 8, 2003, states that a dermal absorption factor of 30% should be used to assess dermal risks, since the dermal noncancer θ endpoint for permethrin is from an oral study. The same toxicological endpoint (11 mg/kg/day from an inhalation study) of concern has been selected for short- and intermediate-term inhalation exposures to permethrin, therefore the risk results for all inhalation durations of exposure are numerically identical. Since the inhalation endpoint of concern is from an inhalation study, no inhalation absorption factor is necessary.

Occupational handler exposure assessments are completed by HED using different levels of personal protection. HED typically evaluates all exposures with a tiered approach. The lowest tier is represented by the baseline exposure scenario (i.e., long-sleeve shirt, long pants, shoes, socks, and no respirator) followed by increasing the levels of personal protective equipment or PPE (e.g., gloves, double-layer body protection, and respirators), and then by engineering controls (e.g., enclosed cabs and closed mixing/loading systems). This approach is always used by HED in order to be able to define label language using a risk-based approach. In addition, the minimal level of adequate protection for a chemical is generally considered by HED to be the most practical option for risk reduction (i.e., over-burdensome risk mitigation measures are not considered a practical alternative).

The anticipated use patterns and current labeling indicate several likely occupational handler exposure scenarios, based on the types of equipment and techniques that can potentially be used to apply permethrin. Due to the scope of the various permethrin occupational uses (there are over 900 permethrin products registered), it would be difficult to assess each individual exposure scenario. Therefore, HED selected representative worse-case exposure scenarios to represent the major ways permethrin can be handled in the occupational environment. HED believes this approach is protective of public health as the scenarios likely to result in the greatest exposure are considered. Anticipated use pattern and current labeling indicate 37 likely occupational exposure scenarios, based on the types of equipment and techniques that can potentially be used to make permethrin applications. Scenarios in this document include: (Note: scenarios denoted

with a "*" could not be evaluated quantitatively, because applicable unit exposure data are not available.)

Mixer/Loaders:

(1a) Liquids for Aerial Applications;
(1b) Liquids for Groundboom Applications;
(1c) Liquids for Airblast Applications;
(1d) Liquids for Truck Mounted ULV Applications;
(1e) Liquids for Dip Applications*;
(2a) Wettable Powder for Aerial Applications;
(2b) Wettable Powder for Groundboom Applications;
(2c) Wettable Powder for Airblast Applications;
(2d) Dusts for Mechanical Duster Applications (using PHED WP mixer/loader data);
(2e) Dusts for Dust Bag Applications (using PHED WP mixer/loader data);
(3a) Granulars for Aerial Applications;
(3b) Granulars for Tractor Drawn Spreader Applications;

Applicators:

(4) Aerial Applications (Sprays);
(5) Groundboom Applications;
(6) Airblast Applications;
(7) Truck Mounted ULV Applications;
(8) Dip Applications*;
(9) Aerial Applications (Granulars)
(10) Tractor Drawn Spreader Applications (Granulars);
(11) Mechanical Duster Applications*;
(12) Dust Bag Applications*;

Flaggers:

(13) Flagging for Aerial- Sprays;
(14) Flagging for Aerial-Granulars;

Mixer/Loader/Applicators:

(15) Liquid: Low Pressure Handwand Sprayer;
(16) Liquid: Handgun Sprayer;
(17) Liquid: High Pressure Handwand Sprayer;
(18) Liquid: Termiticide Injector;
(19) Liquid: Foam Applicator Equipment (using ORETF low pressure handwand data);
(20) Liquid: Watering Can (using ORETF residential hose end sprayer data);
(21) Liquid: Backpack ULV Sprayer (using ORETF low pressure handwand data);
(22) Liquid: Paint Brush;
(23) Wettable Powder: Low Pressure Handwand Sprayer;
(24) Wettable Powder: Handgun Sprayer;
(25) Wettable Powder: High Pressure Handwand Sprayer*;

(26) Water Soluble Bag: Handgun Sprayer;
(27) Dusts: Shaker Can;
(28) Microencapsulated Liquid: Fogger/Mist Generator*;
(29) RTU Liquid: Pour On Applications (using PHED mixing/loading liquid data);
(30) RTU Ear Tag Applications*;
(31) RTU: Hand Applications (Shampoos);
(32) RTU: Wipe Applications;
(33) RTU: Trigger Pump Sprayer Applications;
(34) RTU: Aerosol Cans;
(35) RTU: Fogger (using PHED aerosol can data);
(36) RTU Protective Flanges*;
(37) RTU Vapor Recovery System Tubes*.

Unit exposure values from the following sources were used to calculate risk estimates:

- the Pesticide Handler Exposure Database (PHED);
- the Outdoor Residential Task Force (ORETF) studies;
- the Chemical Manufacturers Association (CMA) Antimicrobial Exposure Assessment Study; and
- two proprietary exposure studies reflecting the following scenarios:
  - handlers applying shampoo to dogs (MRID # 446584-01), and
  - handlers applying liquids via trigger sprayer (MRID # 410547-01).

The noncancer occupational handler exposure and risk calculations are included in Table 9.1. Scenarios that could not be evaluated quantitatively are not presented in the table. The results indicate that for most scenarios, risks do not exceed HED's level of concern (i.e., the MOEs are greater than 100) at some level of risk mitigation. The following occupational scenarios have short- and intermediate-term risks that exceed HED's level of concern (i.e., the MOEs are less than 100) for handlers at all levels of risk mitigation:

Scenario 17: Mixing/Loading/Applying Liquids via High Pressure Handwand (PHED data)
- mushroom houses at 1000 gallons per day (0.267 lb ai/gallon)

Scenario 27: Loading/Applying Dusts via Shaker Can (ORETF data)
- poultry at 4,000 animals per day (0.0025 lb ai/animal)

Scenario 31: Applying Ready-to-Use Shampoo Formulations via Hands (using EPA MRID 446584-01)
- dogs at 8 animals per day (0.00621 lb ai/animal)

Scenario 32: Applying Ready-to-Use Formulations via Wipe (using CMA)

- dogs and horses at 8 animals per day (0.00621 lb ai/animal)

Scenario 33: Applying Ready-to-Use Formulations via Trigger Pump Sprayer (using EPA MRID 410547-01)

- horses and foals at 400 animals per day (0.016 lb ai/animal)

Due to the number of registered occupational uses of permethrin, only the worst-case scenarios are presented in this chapter. For the complete short-term occupational handler noncancer exposure and risk assessment (ORE), see *Permethrin: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. Bill Smith. October 27, 2004.* A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed in the permethrin ORE document. In order to refine this occupational handler risk assessment, more data on actual use patterns including rates, timing, and areas treated would better characterize permethrin risks.

Table 9.1. Summary of Short- and Intermediate-Term Permethrin Occupational Handler Non-cancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Combined MOEs [c]							
				Base	G - NR	PPE-G, DL - NR	G - 80% R	G - 90% R	G,DL - 80% R	G,DL - 90% R	Eng Cont
Mixer/Loader											
Mixing/Loading Emulsifiable Concentrates for Aerial Applications (1a)	pine seed orchard	1.2 lb ai/acre	100 acres	17	**1500**	1900	2000	2100	2700	2800	5300
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	350 acres	14	**1300**	1600	1800	1800	2300	2400	4500
	corn: sweet (FL only)	0.25 lb ai/acre	1200 acres	6.7	**610**	750	820	830	1100	1100	2100
	rose: field grown	0.2 lb ai/acre	60 acres	**170**	15000	19000	20000	21000	27000	28000	53000
Mixing/Loading Emulsifiable Concentrates for Groundboom Applications (1b)	artichokes, garlic, onions: dry bulb	0.3 lb ai/acre	80 acres	**84**	**7600**	9300	10000	10000	14000	14000	26000
	corn: sweet (FL only)	0.25 lb ai/acre	200 acres	40	**3600**	4500	4900	5000	6600	6700	13000
	chrysanthemum, roses: field grown	0.2 lb ai/acre	40 acres	**250**	23000	28000	31000	31000	41000	42000	79000
Mixing/Loading Emulsifiable Concentrates for Airblast Applications (1c)	pine seed orchard	1.2 lb ai/acre	20 acres	84	**7600**	9300	10000	10000	14000	14000	26000
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	40 acres	**130**	11000	14000	15000	16000	20000	21000	39000
Mixing/Loading Emulsifiable Concentrates with Truck Mounted ULV Sprayer (using PHED airblast data) (1d)	outdoor spaces	0.05 lb ai/acre	3000 acres	13	**1200**	1500	1600	1700	2200	2200	4200
Mixing/Loading Emulsifiable Concentrates via Dip (1e)	animal: livestock (beef and dairy cattle), horses, swine	0.0023 lb ai/animal	400 animals	**2200**	200000	240000	270000	270000	360000	360000	690000
	animal: dogs	0.005 lb ai/gal	10 gallons	**40000**	3600000	4500000	4900000	5000000	6600000	6700000	13000000
Mixing/Loading Wettable Powders for Aerial Applications (2a)	pine seed orchard	1.2 lb ai/acre	100 acres	12	98	**110**	240	260	310	340	ND
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	350 acres	10	84	91	**210**	230	260	290	ND
	corn: sweet (FL only)	0.25 lb ai/acre	1200 acres	4.8	39	43	98	**110**	120	130	ND
	rose: field grown	0.2 lb ai/acre	60 acres	**120**	980	1100	2400	2600	3100	3400	ND

Table 9.1. Summary of Short- and Intermediate-Term Permethrin Occupational Handler Non-cancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Combined MOEs [c]							
				Base	G - NR	PPE-G, DL - NR	G - 80% R	G - 90% R	G,DL - 80% R	G,DL - 90% R	Eng Cont
Mixing/Loading Wettable Powders for Groundboom Applications (2b)	artichokes, garlic, onions: dry bulb	0.3 lb ai/acre	80 acres	60	**490**	530	1200	1300	1500	1700	ND
	corn: sweet (FL only)	0.25 lb ai/acre	200 acres	29	**240**	260	590	630	740	810	ND
	chrysanthemum, roses: field grown	0.2 lb ai/acre	40 acres	**180**	1500	1600	3700	4000	4600	5100	ND
Mixing/Loading Wettable Powders for Airblast Applications (2c)	pine seed orchard	1.2 lb ai/acre	20 acres	60	**490**	530	1200	1300	1500	1700	ND
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	40 acres	91	**740**	800	1800	2000	2300	2500	ND
	conifers (field grown), ornamental nursery stock	0.2 lb ai/acre	20 acres	**360**	2900	3200	7300	7900	9200	10000	ND
Loading Dusts via Mechanical Duster (using PHED wettable powders data) (2d)	animal: dairy and beef cattle, horses	0.000031 lb ai/animal	400 animals	**120000**	950000	1000000	2400000	2600000	3000000	3300000	ND
	animal: poultry	0.0025 lb ai/animal	100000 animals	5.8	47	51	**120**	130	150	160	ND
Loading Dusts via Dust Bag (using PHED wettable powders data) (2e)	animal: dairy and beef cattle, horses	0.000031 lb ai/animal	400 animals	**120000**	950000	1000000	2400000	2600000	3000000	3300000	ND
Loading Granulars for Aerial Applications (3a)	almonds, pistachios	0.4 lb ai/acre	350 acres	**2000**	2100	2600	5200	5600	9200	11000	98000
	alfalfa; corn: field, sweet-fresh & processed; corn: field-preplant	0.2 lb ai/acre	1200 acres	**1100**	1200	1500	3000	3300	5400	6100	56000
Loading Granulars for Tractor Drawn Spreader Applications (3b)	almonds, pistachios	0.4 lb ai/acre	80 acres	**8600**	9200	11000	23000	24000	40000	46000	430000
	alfalfa, corn (field, sweet-fresh & processed), corn: field (preplant)	0.2 lb ai/acre	200 acres	**6900**	7400	9000	18000	20000	32000	37000	340000
Applicator											
Applying Liquid Sprays via Aerial Equipment (4)	pine seed orchard	1.2 lb ai/acre	100 acres	ND	ND	ND	ND	ND	ND	ND	**8800**
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	350 acres	ND	ND	ND	ND	ND	ND	ND	**7500**
	corn: sweet (FL only)	0.25 lb ai/acre	1200 acres	ND	ND	ND	ND	ND	ND	ND	**3500**
	rose: field grown	0.2 lb ai/acre	60 acres	ND	ND	ND	ND	ND	ND	ND	**88000**
Applying Liquid Sprays via Groundboom Equipment (5)	artichokes, garlic, onions: dry bulb	0.3 lb ai/acre	80 acres	**12000**	12000	15000	17000	17000	21000	22000	46000
	corn: sweet (FL only)	0.25 lb ai/acre	200 acres	**6000**	6000	7000	8000	8200	10000	10000	22000
	chrysanthemum, roses: field grown	0.2 lb ai/acre	40 acres	**37000**	37000	44000	50000	51000	63000	65000	140000
Applying Liquid Sprays via Airblast Equipment (6)	pine seed orchard	1.2 lb ai/acre	20 acres	**620**	890	960	1000	1000	1100	1100	11000
	almonds, apples, filberts, pears (dormant	0.4 lb ai/acre	40 acres	**930**	1300	1400	1500	1500	1600	1600	16000

Table 9.1. Summary of Short- and Intermediate-Term Permethrin Occupational Handler Non-cancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Combined MOEs [c]							
				Base	G - NR	PPE-G, DL - NR	G - 80% R	G - 90% R	G,DL - 80% R	G,DL - 90% R	Eng Cont
	& prebloom combo), pistachios, walnuts										
	conifers (field grown), ornamental nursery stock	0.2 lb ai/acre	20 acres	**3700**	5300	5700	6000	6000	6500	6600	65000
Applying Liquid Sprays with Truck Mounted ULV Sprayer (using PHED airblast data) (7)	outdoor spaces	0.05 lb ai/acre	3000 acres	99	**140**	150	160	160	170	180	1700
Applying Granulars via Aerial Equipment (9)	almonds, pistachios,	0.4 lb ai/acre	350 acres	ND	ND	ND	ND	ND	ND	ND	**3600**
	alfalfa, corn: field, corn: sweet (fresh & processed), corn: field (preplant)	0.2 lb ai/acre	1200 acres	ND	ND	ND	ND	ND	ND	ND	**2100**
Applying Granulars via Tractor Drawn Spreader (10)	almonds, pistachios,	0.4 lb ai/acre	80 acres	**9600**	11000	14000	23000	24000	36000	40000	49000
	alfalfa, corn: field, corn: sweet (fresh & processed), corn: field (preplant)	0.2 lb ai/acre	200 acres	**7700**	9000	11000	18000	19000	29000	32000	39000
Flagger											
Flagging for Liquid Sprays via Aerial Equipment (13)	pine seed orchard	1.2 lb ai/acre	100 acres	**3600**	ND	3800	ND	ND	4800	4800	89000
	almonds, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	350 acres	**3100**	ND	3300	ND	ND	4100	4100	77000
	rose: field grown	0.2 lb ai/acre	60 acres	**36000**	ND	38000	ND	ND	48000	48000	890000
Flagging for Granulars via Aerial Equipment (14)	almonds, pistachios,	0.4 lb ai/acre	350 acres	**11000**	ND	15000	ND	ND	25000	25000	24000
	alfalfa, corn: field, corn: sweet (fresh & processed), corn: field (preplant)	0.2 lb ai/acre	350 acres	**21000**	ND	30000	ND	ND	49000	51000	48000
Mixer/Loader/Applicator											
Mixing/Loading/Applying Emulsifiable Concentrates with Low Pressure Handwand (15)	mushroom houses	0.267 lb ai/gallon	40 gallons	5.4	**410**	430	1100	1200	1200	1300	NF
	termites	33.2 lb ai/1000 linear feet	1000 linear feet	1.8	**130**	140	340	3900	390	430	NF
	animal: livestock (beef and dairy cattle), goats, horses, sheep, swine	0.0023 lb ai/animal	400 animals	63	**4700**	5000	12000	14000	14000	15000	NF
Mixing/Loading/Applying Emulsifiable Concentrates with a Handgun Sprayer (ORETF data) (16)	turf	0.87 lb ai/acre	5 acres	ND	**2900**	5100	3000	3000	5300	5400	NF
	conifers (field grown)	0.2 lb ai/gallon	1000 gallons	ND	63	**110**	65	65	120	120	NF

Table 9.1. Summary of Short- and Intermediate-Term Permethrin Occupational Handler Non-cancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Combined MOEs [c]							
				Base	G - NR	PPE-G, DL - NR	G - 80% R	G - 90% R	G,DL - 80% R	G,DL - 90% R	Eng Cont
Mixing/Loading/Applying Emulsifiable Concentrates with a High Pressure Handwand (only study in PHED is for greenhouse use) (17)	mushroom houses	0.267 lb ai/gallon	1000 gallons	ND	6.4	8.7	8.5	8.6	13	13	NF
	rose: field grown	0.02 lb ai/gallon	1000 gallons	ND	86	**120**	110	110	170	180	NF
	animal: poultry	0.00027 lb ai/animal	4000 animals	ND	**1600**	2200	2100	2100	3200	3300	NF
Mixing/Loading/Applying Emulsifiable Concentrate with an Injector (18)	termites	0.08 lb ai/gallon	2000 gallons (Carbaryl)	ND	97	**140**	100	100	140	150	NF
Mixing/Loading/Applying Emulsifiable Concentrates via Foam Applicator Equipment (using ORETF low-pressure handwand) (19)	termites	4.25 lb ai/1000 sq ft	1000 sq ft	14	**2100**	2300	3100	3100	3500	3600	NF
Mixing/Loading/Applying Emulsifiable Concentrates with a Watering Can (using ORETF residential hose-end data) (20)	fire ant mounds	0.04 lb ai/gallon	10 gallons	**2500**	ND	ND	ND	ND	ND	ND	NF
Mixing/Loading/Applying Emulsifiable Concentrates with Backpack ULV Sprayer (using PHED backpack data) (21)	outdoor spaces	0.1 lb ai/acre	5 acres	ND	**4300**	6400	4600	4600	7200	7200	NF
Mixing/Loading/Applying Emulsifiable Concentrates with a Paint Brush (22)	indoor surfaces	0.08 lb ai/gallon	5 gallons	80	**560**	600	600	610	660	660	NF
Mixing/Loading/Applying Wettable Powders with Low Pressure Handwand (23)	conifers (field grown)	0.2 lb ai/gallon	40 gallons	ND	43	50	78	81	**110**	110	NF
	rose: field grown	0.02 lb ai/gallon	40 gallons	ND	**430**	500	780	810	1100	1100	NF

Table 9.1. Summary of Short- and Intermediate-Term Permethrin Occupational Handler Non-cancer Risk Estimates											
Exposure Scenario	**Crop or Target**	**Application Rate [a]**	**Area Treated Daily [b]**	**Combined MOEs [c]**							
				Base	**G - NR**	**PPE-G, DL - NR**	**G - 80% R**	**G - 90% R**	**G,DL - 80% R**	**G,DL - 90% R**	**Eng Cont**
Mixing/Loading/Applying Wettable Powders with a Handgun Sprayer (ORETF data) (24)	conifers (field grown)	0.2 lb ai/gallon	40 gallons	ND	23	32	35	36	62	65	NF
	rose: field grown	0.02 lb ai/gallon	40 gallons	ND	**230**	320	350	360	620	650	NF
Mixing/Loading/Applying Water Soluble Bags with Handgun Sprayer (ORETF data) (26)	conifers (field grown)	0.2 lb ai/gallon	40 gallons	ND	42	69	45	78	45	78	NF
	rose: field grown	0.02 lb ai/gallon	40 gallons	ND	**420**	690	450	780	450	780	NF
Applying Dusts via Shaker Can (MRID 444598-01) (27)	animal: poultry	0.0025 lb ai/animal	4000 animals	7.2	ND	ND	ND	ND	ND	ND	NF
	animal: swine	0.00016 lb ai/animal	400 animals	**1100**	ND	ND	ND	ND	ND	ND	NF
	animal: dogs, cats	0.00016 lb ai/animal	8 animals	**56000**	ND	ND	ND	ND	ND	ND	NF
Applying Ready to Use Formulations via Pour-on (using PHED mix/load liquid) (29)	animal: horses	0.005lb ai/animal	400 animals	**1000**	91000	110000	120000	120000	160000	170000	NF
	clothing: personal	0.002 lb ai/6 oz container	1 container	**1000000**	91000000	110000000	120000000	120000000	160000000	170000000	NF
	deer (ticks)	0.0092 lb ai/per post (240 lbs corn consumed per week)	40 posts (per treatment device)	**5400**	490000	610000	670000	680000	890000	910000	NF
Applying Ready to Use Formulations via RTU Ear-Tag (30)	animal	0.0044 lb ai/2 ear tags	400 cattle (2 tags/cattle)	ND	ND	ND	ND	ND	ND	ND	NF
Applying Ready to Use Shampoo Formulations via Hands (MRID 446584-01) (31)	animal: dogs	0.0062 lb ai/animal	8 animals	65	ND	ND	ND	ND	ND	ND	NF
Applying Ready to Use Formulations via RTU Wipe (32)	animal: dogs and horses	0.0062 lb ai/animal	8 animals	38	ND	ND	ND	ND	ND	ND	NF
Applying Ready to Use Formulations via Trigger-Pump Sprayer (using Propoxur Trigger Pump study) (33)	indoor surfaces; animal: cattle, goats, sheep, swine	0.043 lb ai/gallon	2 gallons	**4700**	ND	ND	ND	ND	ND	ND	NF
	animal: horses, foals	0.61 lb ai/gallon	2 gallons	**330**	ND	ND	ND	ND	ND	ND	NF

Table 9.1. Summary of Short- and Intermediate-Term Permethrin Occupational Handler Non-cancer Risk Estimates											
Exposure Scenario	**Crop or Target**	**Application Rate [a]**	**Area Treated Daily [b]**	**Combined MOEs [c]**							
				Base	**G - NR**	**PPE-G, DL - NR**	**G - 80% R**	**G - 90% R**	**G,DL - 80% R**	**G,DL - 90% R**	**Eng Cont**
Applying Ready to Use Formulations with Aerosol Cans (34)	outdoor surfaces	0.00438 lb ai/16 oz can	2 sixteen-ounce aerosol cans	**3300**	7300	9000	8100	8200	10000	10000	NF
Applying Ready to Use Formulations with Foggers (using PHED aerosol data) (35)	indoor spaces	0.0016 lb ai/6 oz fogger	4 six ounce fogger treats 6000 cubic feet	**4600**	10000	12000	11000	11000	14000	14000	NF

Footnotes

* MOEs shown in bold indicate the lowest risk mitigation level that does not exceed HED's level of concern.

ND No Data

NF Not Feasible

a Application rates are the maximum application rates determined from EPA registered labels for permethrin.

b Amounts handled per day are HED estimates of acres, square feet, or cubic feet treated or gallons applied based on Exposure SAC SOP #9 "Standard Values for Daily Acres Treated in Agriculture," industry sources, and HED estimates.

c
- Baseline: Long-sleeve shirt, long pants, no gloves, and no respirator.
- PPE-G-NR: Baseline plus chemical-resistant gloves, and no respirator.
- PPE-G,DL-NR: Coveralls worn over long-sleeve shirt and long pants, chemical-resistant gloves, and no respirator.
- PPE-G-80% R: Baseline plus chemical-resistant gloves and an 80% PF (quarter-face dust/mist) respirator.
- PPE-G,DL-80% R: Coveralls worn over long-sleeve shirt and long pants, chemical-resistant gloves, and an 80% PF (quarter-face dust/mist) respirator.
- PPE-G-90% R: Baseline plus chemical-resistant gloves and a 90% PF (half-face dust/mist) respirator.
- PPE-G,DL-90% R: Coveralls worn over long-sleeve shirt and long pants, chemical-resistant gloves, and a 90% PF (half-face dust/mist) respirator.
- Eng Controls: Closed mixing/loading system, enclosed cab, or enclosed cockpit.

9.2 Short- and Intermediate-Term Cancer Handler Risk

The occupational handler exposure and cancer risk calculations are presented in this section. Cancer risk estimates were calculated using a linear, low-dose extrapolation approach (Q_1*). The same scenarios, assumptions, and unit exposures were used as in the noncancer assessment. HED estimated cancer risk assuming estimates for an annual maximum of 10 days of exposure per year. This number is based on a Biological & Economic Analysis Division (BEAD) memo dated March 24, 2004 (Brassard). This memo provided information on the number of days permethrin is applied annually by applicators. The information in this memo showed that for most crops and use-patterns, occupational handlers apply permethrin less than ten days per year. As a result, HED considered one handler population (small, medium, and large scale growers as well as commercial applicators) for the cancer risk assessment.

HED has defined a level of concern range for cancer risk estimates based on a policy memorandum issued in 1996 by then Office of Pesticide Programs (OPP) director, Mr. Dan Barolo. This memo refers to a predetermined quantified "level of concern" for occupational carcinogenic risk. In summary, this policy memo indicates occupational carcinogenic risks that are 1×10^{-6} or lower require no risk management action. For those chemicals subject to reregistration, HED is to carefully examine uses with estimated risks in the 10^{-6} to 10^{-4} range to seek ways of cost-effectively reducing risks. If estimated cancer risks are in this range for occupational handlers, increased levels of personal protection would be warranted as is commonly applied with non-cancer risk estimates (e.g., additional PPE or engineering controls). Cancer risk estimates that remain above 1.0×10^{-4} at the highest level of mitigation appropriate for that scenario remain a concern.

Estimated permethrin cancer risks for handlers are summarized below in Table 9.2. In most scenarios, estimated cancer risks are below OPP's target level of concern (i.e., risks are below 1×10^{-6}) at some level of risk mitigation. For the most part, cancer risk estimates are below OPP's level of concern for cancer risks (i.e., risks are below 1×10^{-4}) with the single layer clothing, gloves, and no respirator level of personal protection. Cancer risk estimates for handlers are greater than OPP's level of concern (i.e., risks are at or above 1.0×10^{-4}) at maximum feasible mitigation for the following handler scenario:

Scenario 17: Mixing/Loading/Applying Liquids via High Pressure Handwand (PHED data)

- mushroom houses at 1000 gallons per day (0.267 lb ai/gallon)

Due to the number of registered occupational uses of permethrin, only the worst-case scenarios are presented. Scenarios that could not be evaluated quantitatively are not presented in the table. For the complete occupational handler cancer risk estimate table, see *Permethrin: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. Bill Smith. October 27, 2004.* In order to refine this occupational risk assessment, more data on actual use patterns including rates, timing, and areas treated would better characterize permethrin risks.

Table 9.2. Summary of Permethrin Occupational Handler Cancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Cancer Risk Estimates							
				Baseline	PPE-G-NR	PPE-G, DL-NR	PPE-G-80% R	PPE-G, DL- 80% R	PPE-G- 90% R	PPE-G, DL- 90% R	Eng Cont
Mixer/Loader											
Mixing/Loading Emulsifiable Concentrates for Aerial Applications (1a)	pine seed orchard	1.2 lb ai/acre	100 acres	2.0E-04	1.8E-06	1.4e-06	1.6E-06	1.2E-06	1.6E-06	1.2E-06	6.0E-07
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	350 acres	2.3E-04	2.1E-06	1.7e-06	1.9E-06	1.4E-06	1.8E-06	1.4E-06	7.0E-07
	corn: sweet (FL only)	0.25 lb ai/acre	1200 acres	4.9E-04	4.5E-06	3.5e-06	4.0E-06	3.0E-06	3.9E-06	2.9E-06	1.5E-06
	rose: field grown	0.2 lb ai/acre	60 acres	2.0E-05	1.8E-07	1.4e-07	1.6E-07	1.2E-07	1.6E-07	1.2E-07	6.0E-08
Mixing/Loading Emulsifiable Concentrates for Groundboom Applications (1b)	artichokes, garlic, onions: dry bulb	0.3 lb ai/acre	80 acres	3.9E-05	3.6E-07	2.8e-07	3.2E-07	2.4E-07	3.2E-07	2.3E-07	1.2E-07
	corn: sweet (FL only)	0.25 lb ai/acre	200 acres	8.2E-05	7.6E-07	5.9e-07	6.7E-07	5.0E-07	6.6E-07	4.9E-07	2.5E-07
	chrysanthemum, roses: field grown	0.2 lb ai/acre	40 acres	1.3E-05	1.2E-07	9.4e-08	1.1E-07	8.0E-08	1.1E-07	7.8E-08	4.0E-08
Mixing/Loading Emulsifiable Concentrates for Airblast Applications (1c)	pine seed orchard	1.2 lb ai/acre	20 acres	3.9E-05	3.6E-07	2.8e-07	3.2E-07	2.4E-07	3.2E-07	2.3E-07	1.2E-07
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	40 acres	2.6E-05	2.4E-07	1.9e-07	2.1E-07	1.6E-07	2.1E-07	1.6E-07	8.0E-08
Mixing/Loading Emulsifiable Concentrates with Truck Mounted ULV Sprayer (using PHED airblast data) (1d)	outdoor spaces	0.05 lb ai/acre	3000 acres	2.4E-04	2.3E-06	1.8e-06	2.0E-06	1.5E-06	2.0E-06	1.5E-06	7.5E-07
Mixing/Loading Emulsifiable Concentrates via Dip (1e)	animal: livestock (beef and dairy cattle), horses, swine	0.0023 lb ai/animal	400 animals	1.5E-06	1.4E-08	1.1e-08	1.2E-08	9.2E-09	1.2E-08	9.0E-09	4.6E-09
	animal: dogs	0.005 lb ai/gal	10 gallons	8.2E-08	7.6E-10	5.9e-10	6.7E-10	5.0E-10	6.6E-10	4.9E-10	2.5E-10
Mixing/Loading Wettable Powders for Aerial Applications (2a)	pine seed orchard	1.2 lb ai/acre	100 acres	2.6E-04	2.1E-05	1.8e-05	1.3E-05	1.1E-05	1.2E-05	9.7E-06	7.1E-07
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	350 acres	3.0E-04	2.5E-05	2.1e-05	1.6E-05	1.2E-05	1.4E-05	1.1E-05	8.3E-07
	corn: sweet (FL only)	0.25 lb ai/acre	1200 acres	6.5E-04	5.3E-05	4.6e-05	3.3E-05	2.7E-05	3.1E-05	2.4E-05	1.8E-06
	rose: field grown	0.2 lb ai/acre	60 acres	2.6E-05	2.1E-06	1.8e-06	1.3E-06	1.1E-06	1.2E-06	9.7E-07	7.1E-08
Mixing/Loading Wettable Powders for Groundboom Applications (2b)	artichokes, garlic, onions: dry bulb	0.3 lb ai/acre	80 acres	5.2E-05	4.2E-06	3.7e-06	2.7E-06	2.1E-06	2.5E-06	1.9E-06	1.4E-07
	corn: sweet (FL only)	0.25 lb ai/acre	200 acres	1.1E-04	8.8E-06	7.7e-06	5.6E-06	4.5E-06	5.2E-06	4.1E-06	3.0E-07
	chrysanthemum, roses: field grown	0.2 lb ai/acre	40 acres	1.7E-05	1.4E-06	1.2e-06	8.9E-07	7.1E-07	8.3E-07	6.5E-07	4.8E-08
Mixing/Loading Wettable Powders for Airblast Applications (2c)	pine seed orchard	1.2 lb ai/acre	20 acres	5.2E-05	4.2E-06	3.7e-06	2.7E-06	2.1E-06	2.5E-06	1.9E-06	1.4E-07
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	40 acres	3.5E-05	2.8E-06	2.5e-06	1.8E-06	1.4E-06	1.7E-06	1.3E-06	9.5E-08
	conifers (field grown), ornamental nursery stock	0.2 lb ai/acre	20 acres	8.6E-06	7.0E-07	6.1e-07	4.5E-07	3.6E-07	4.1E-07	3.2E-07	2.4E-08

Table 9.2. Summary of Permethrin Occupational Handler Cancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Cancer Risk Estimates							
				Baseline	PPE-G-NR	PPE-G, DL-NR	PPE-G-80% R	PPE-G, DL-80% R	PPE-G-90% R	PPE-G, DL-90% R	Eng Cont
Loading Dusts via Mechanical Duster (using PHED wettable powders data) (2d)	animal: dairy and beef cattle, horses	0.000031 lb ai/animal	400 animals	2.7E-08	2.2E-09	1.9e-09	1.4E-09	1.1E-09	1.3E-09	1.0E-09	ND
	animal: poultry	0.0025 lb ai/animal	100000 animals	5.4E-04	4.4E-05	3.8e-05	2.8E-05	2.2E-05	2.6E-05	2.0E-05	ND
Loading Dusts via Dust Bag (using PHED wettable powders data) (2e)	animal: dairy and beef cattle, horses	0.000031 lb ai/animal	400 animals	2.7E-08	2.2E-09	1.9e-09	1.4E-09	1.1E-09	1.3E-09	1.0E-09	ND
Loading Granulars for Aerial Applications (3a)	almonds, pistachios	0.4 lb ai/acre	350 acres	1.1E-06	9.9E-07	7.1e-07	6.3E-07	3.6E-07	5.9E-07	3.1E-07	2.2E-08
	alfalfa; corn: field, sweet-fresh & processed; corn: field-preplant	0.2 lb ai/acre	1200 acres	1.9E-06	1.7E-06	1.2e-06	1.1E-06	6.1E-07	1.0E-06	5.3E-07	3.8E-08
Loading Granulars for Tractor Drawn Spreader Applications (3b)	almonds, pistachios	0.4 lb ai/acre	80 acres	2.5E-07	2.3E-07	1.6e-07	1.4E-07	8.1E-08	1.3E-07	7.1E-08	5.1E-09
	alfalfa, corn (field, sweet-fresh & processed), corn: field (preplant)	0.2 lb ai/acre	200 acres	3.2E-07	2.8E-07	2.0e-07	1.8E-07	1.0E-07	1.7E-07	8.9E-08	6.4E-09
Applicator											
Applying Liquid Sprays via Aerial Equipment (4)	pine seed orchard	1.2 lb ai/acre	100 acres	ND	ND	ND	ND	ND	ND	ND	3.5E-07
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	350 acres	ND	ND	ND	ND	ND	ND	ND	4.1E-07
	corn: sweet (FL only)	0.25 lb ai/acre	1200 acres	ND	ND	ND	ND	ND	ND	ND	8.8E-07
	rose: field grown	0.2 lb ai/acre	60 acres	ND	ND	ND	ND	ND	ND	ND	3.5E-08
Applying Liquid Sprays via Groundboom Equipment (5)	artichokes, garlic, onions: dry bulb	0.3 lb ai/acre	80 acres	2.2E-07	2.2E-07	1.8e-07	2.0E-07	1.5E-07	1.9E-07	1.5E-07	6.9E-08
	corn: sweet (FL only)	0.25 lb ai/acre	200 acres	4.6E-07	4.6E-07	3.8e-07	4.1E-07	3.2E-07	4.0E-07	3.2E-07	1.4E-07
	chrysanthemum, roses: field grown	0.2 lb ai/acre	40 acres	7.4E-08	7.4E-08	6.1e-08	6.5E-08	5.2E-08	6.4E-08	5.1E-08	2.3E-08
Applying Liquid Sprays via Airblast Equipment (6)	pine seed orchard	1.2 lb ai/acre	40 acres	5.1E-06	3.4E-06	3.2e-06	3.3E-06	3.0E-06	3.3E-06	3.0E-06	1.9E-06
	almonds, apples, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	40 acres	3.4E-06	2.3E-06	2.1e-06	2.2E-06	2.0E-06	2.2E-06	2.0E-06	1.3E-06
	conifers (field grown), ornamental nursery stock	0.2 lb ai/acre	20 acres	8.4E-07	5.7E-07	5.3e-07	5.5E-07	5.0E-07	5.4E-07	5.0E-07	3.2E-07
Applying Liquid Sprays with Truck Mounted ULV Sprayer (using PHED Airblast data) (7)	outdoor spaces	0.05 lb ai/acre	3000 acres	3.2E-05	2.1E-05	2.0e-05	2.0E-05	1.9E-05	2.0E-05	1.9E-05	1.2E-05
Applying Granulars via Aerial Equipment (9)	almonds, pistachios,	0.4 lb ai/acre	350 acres	ND	ND	ND	ND	ND	ND	ND	4.7E-07
	alfalfa, corn: field, corn: sweet (fresh & processed), corn: field (preplant)	0.2 lb ai/acre	1200 acres	ND	ND	ND	ND	ND	ND	ND	8.1E-07

Table 9.2. Summary of Permethrin Occupational Handler Cancer Risk Estimates											
Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Cancer Risk Estimates							
				Baseline	PPE-G-NR	PPE-G, DL-NR	PPE-G-80% R	PPE-G, DL- 80% R	PPE-G- 90% R	PPE-G, DL- 90% R	Eng Cont
Applying Granulars via Tractor Drawn Spreader (10)	almonds, pistachios,	0.4 lb ai/acre	80 acres	2.5E-07	2.0E-07	1.5e-07	1.4E-07	9.0E-08	1.4E-07	8.3E-08	5.1E-08
	alfalfa, corn: field, corn: sweet (fresh & processed), corn: field (preplant)	0.2 lb ai/acre	200 acres	3.1E-07	2.5E-07	1.8e-07	1.8E-07	1.1E-07	1.7E-07	1.0E-07	6.4E-08

Table 9.2. Summary of Permethrin Occupational Handler Cancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Cancer Risk Estimates							
				Baseline	PPE-G-NR	PPE-G, DL-NR	PPE-G-80% R	PPE-G, DL- 80% R	PPE-G- 90% R	PPE-G, DL- 90% R	Eng Cont
Flagger											
Flagging for Liquid Sprays via Aerial Equipment (13)	pine seed orchard	1.2 lb ai/acre	100 acres	8.2E-07	ND	7.5e-07	ND	6.9E-07	ND	6.8E-07	3.5E-07
	almonds, filberts, pears (dormant & prebloom combo), pistachios, walnuts	0.4 lb ai/acre	350 acres	9.6E-07	ND	8.8e-07	ND	8.0E-07	ND	8.0E-07	4.0E-07
	rose: field grown	0.2 lb ai/acre	60 acres	8.2E-08	ND	7.5e-08	ND	6.9E-08	ND	6.8E-08	3.5E-08
Flagging for Granulars via Aerial Equipment (14)	almonds, pistachios,	0.4 lb ai/acre	350 acres	2.6E-07	ND	1.7e-07	ND	1.3E-07	ND	1.3E-07	2.2E-07
	alfalfa, corn: field, corn: sweet (fresh & processed), corn: field (preplant)	0.2 lb ai/acre	350 acres	1.3E-07	ND	8.3e-08	ND	6.7E-08	ND	6.5E-08	1.1E-07
Mixer/Loader/Applicator											
Mixing/Loading/Applying Emulsifiable Concentrates with Low Pressure Handwand (15)	mushroom houses	0.267 lb ai/gallon	40 gallons	6.0E-04	3.2E-06	2.8e-06	2.7E-06	2.3E-06	2.6E-06	2.3E-06	NF
	termites	33.2 lb ai/1000 linear feet	1000 linear feet	1.9E-03	9.9E-06	8.8e-06	8.4E-06	7.3E-06	8.2E-06	7.1E-06	NF
	animal: livestock (beef and dairy cattle), goats, horses, sheep, swine	0.0023 lb ai/animal	400 animals	5.2E-05	2.7E-07	2.4e-07	2.3E-07	2.0E-07	2.3E-07	2.0E-07	NF
Mixing/Loading/Applying Emulsifiable Concentrates with a Handgun Sprayer (ORETF data) (16)	turf	0.87 lb ai/acre	5 acres	1.7e-06	1.2e-06	6.2e-07	1.2e-06	6.1e-07	1.2e-06	6.1e-07	NF
	conifers (field grown)	0.2 lb ai/gallon	1000 gallons	7.8e-05	5.4e-05	2.9e-05	5.4e-05	2.8e-05	5.4e-05	2.8e-05	NF
Mixing/Loading/Applying Emulsifiable Concentrates with a High Pressure Handwand (only study in PHED is for greenhouse use) (17)	mushroom houses	0.267 lb ai/gallon	1000 gallons	ND	4.3E-04	3.0e-04	3.9E-04	2.5E-04	3.8E-04	2.5E-04	NF
	rose: field grown	0.02 lb ai/gallon	1000 gallons	ND	3.3E-05	2.2e-05	2.9E-05	1.9E-05	2.9E-05	1.8E-05	NF
	animal: poultry	0.00027 lb ai/animal	4000 animals	ND	4.4E-05	3.0e-05	3.9E-05	2.5E-05	3.9E-05	2.5E-05	NF
Mixing/Loading/Applying Emulsifiable Concentrate with an Injector (18)	termites	0.08 lb ai/gallon	2000 gallons (Carbaryl)	ND	3.3E-05	2.3e-05	3.2E-05	2.3E-05	3.2E-05	2.3E-05	NF
Mixing/Loading/Applying Emulsifiable Concentrates via Foam Applicator Equipment (using PHED low-pressure handwand) (19)	termites	4.25 lb ai/1000 sq ft	1000 sq ft	2.4E-04	1.3E-06	1.1e-06	1.1E-06	9.3E-07	1.1E-06	9.1E-07	NF
Mixing/Loading/Applying Emulsifiable Concentrates with a Watering Can	fire ant mounds	0.04 lb ai/gallon	10 gallons	2.5E-06	ND	ND	ND	ND	ND	ND	NF

Table 9.2. Summary of Permethrin Occupational Handler Cancer Risk Estimates											
Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Cancer Risk Estimates							
				Baseline	PPE-G-NR	PPE-G, DL-NR	PPE-G-80% R	PPE-G, DL- 80% R	PPE-G- 90% R	PPE-G, DL- 90% R	Eng Cont
(using ORETF residential hose-end data) (20)											

Table 9.2. Summary of Permethrin Occupational Handler Cancer Risk Estimates

Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Cancer Risk Estimates							
				Baseline	PPE-G-NR	PPE-G, DL-NR	PPE-G-80% R	PPE-G, DL- 80% R	PPE-G- 90% R	PPE-G, DL- 90% R	Eng Cont
Mixing/Loading/Applying Emulsifiable Concentrates with Backpack ULV Sprayer (using PHED backpack data) (21)	outdoor spaces	0.1 lb ai/acre	5 acres	ND	7.3E-07	4.8e-07	7.1E-07	4.5E-07	7.0E-07	4.5E-07	NF
Mixing/Loading/Applying Emulsifiable Concentrates with a Paint Brush (22)	indoor surfaces	0.08 lb ai/gallon	5 gallons	4.1E-05	5.6E-06	5.2e-06	5.4E-06	5.0E-06	5.4E-06	5.0E-06	NF
Mixing/Loading/Applying Wettable Powders with Low Pressure Handwand (23)	conifers (field grown)	0.2 lb ai/gallon	40 gallons	ND	5.5E-05	4.4e-05	4.2E-05	3.1E-05	4.0E-05	3.0E-05	NF
	rose: field grown	0.02 lb ai/gallon	40 gallons	ND	5.5E-06	4.4e-06	4.2E-06	3.1E-06	4.0E-06	3.0E-06	NF
Mixing/Loading/Applying Wettable Powders with a Handgun Sprayer (ORETF data) (24)	conifers (field grown)	0.2 lb ai/gallon	40 gallons	1.3E-04	1.0E-04	6.6e-05	8.6E-05	4.7E-05	8.3E-05	4.5E-05	NF
	rose: field grown	0.02 lb ai/gallon	40 gallons	1.3E-05	1.0E-05	6.6e-06	8.6E-06	4.7E-06	8.3E-06	4.5E-06	NF
Mixing/Loading/Applying Water Soluble Bags with Handgun Sprayer (ORETF data) (26)	conifers (field grown)	0.2 lb ai/gallon	1000 gallons	4.7E-06	3.3E-06	1.8e-06	3.2E-06	1.7E-06	3.2E-06	1.7E-06	NF
	rose: field grown	0.02 lb ai/gallon	1000 gallons	2.8E-06	2.0E-06	1.1e-06	1.9E-06	1.0E-06	1.9E-06	9.9E-07	NF
Applying Dusts via Shaker Can (MRID 444598-01) (27)	animal: poultry	0.0025 lb ai/animal	4000 animals	8.5E-04	ND	ND	ND	ND	ND	ND	NF
	animal: swine	0.00016 lb ai/animal	400 animals	5.4E-06	ND	ND	ND	ND	ND	ND	NF
	animal: dogs, cats	0.00016 lb ai/animal	8 animals	1.1E-07	ND	ND	ND	ND	ND	ND	NF
Applying Ready to Use Formulations via Pour-on (using PHED mix/load liquid) (29)	animal: horses	0.005lb ai/animal	400 animals	3.3E-06	3.0E-08	2.4e-08	2.7E-08	2.0E-08	2.6E-08	2.0E-08	NF
	clothing: personal	0.002 lb ai/6 oz container	1 container	3.3E-09	3.0E-11	2.4e-11	2.7E-11	2.0E-11	2.6E-11	2.0E-11	NF
	deer: ticks	40	posts (per treatment device)	6.0E-07	5.6E-09	4.3e-09	4.9E-09	3.7E-09	4.8E-09	3.6E-09	NF
Applying Ready to Use Formulations via Hands (MRID 446584-01) (31)	animal: dogs	0.0062 lb ai/animal	8 animals	5.0E-05	ND	ND	ND	ND	ND	ND	NF

Table 9.2. Summary of Permethrin Occupational Handler Cancer Risk Estimates											
Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Cancer Risk Estimates							
				Baseline	PPE-G-NR	PPE-G, DL-NR	PPE-G-80% R	PPE-G, DL- 80% R	PPE-G- 90% R	PPE-G, DL- 90% R	Eng Cont
Applying Ready to Use Formulations via Trigger-Pump Sprayer (using Propoxur Trigger Pump study) (33)	indoor surfaces; animal: cattle, goats, sheep, swine	0.043 lb ai/gallon	2 gallons	6.7E-07	ND	ND	ND	ND	ND	ND	NF
	animal: horses, foals	0.61 lb ai/gallon	2 gallons	9.5E-06	ND	ND	ND	ND	ND	ND	NF

Table 9.2. Summary of Permethrin Occupational Handler Cancer Risk Estimates											
Exposure Scenario	Crop or Target	Application Rate [a]	Area Treated Daily [b]	Cancer Risk Estimates							
				Baseline	PPE-G-NR	PPE-G, DL-NR	PPE-G-80% R	PPE-G, DL- 80% R	PPE-G- 90% R	PPE-G, DL- 90% R	Eng Cont
Applying Ready to Use Formulations with Aerosol Cans (34)	outdoor surfaces	0.00438 lb ai/16 oz can	2 sixteen-ounce aerosol cans	9.6E-07	4.2E-07	3.4e-07	4.0E-07	3.2E-07	4.0E-07	3.2E-07	NF
Applying Ready to Use Formulations with Foggers (using PHED aerosol data) (35)	indoor spaces	0.0016 lb ai/6 oz fogger	4 six ounce fogger treats 6000 cubic feet	7.0E-07	3.1E-07	2.5e-07	2.9E-07	2.3E-07	2.9E-07	2.3E-07	NF

Footnotes

ND No Data

NF Not Feasible

a Application rates are the maximum application rates for permethrin in all cases. Typical rates provided by BEAD differed very little from the maximum rates.

b Amount handled per day values are HED estimates of acreage treated or gallons applied based on Exposure SAC SOP #9 "Standard Values for Daily Acres Treated in Agriculture," industry input, and HED estimates.

Baseline:	Long-sleeve shirt, long pants, no gloves, and no respirator.
PPE-G-NR:	Baseline plus chemical-resistant gloves, and no respirator.
PPE-G,DL-NR:	Coveralls worn over long-sleeve shirt and long pants, chemical-resistant gloves, and no respirator.
PPE-G-80% R:	Baseline plus chemical-resistant gloves and an 80%PF (quarter-face dust/mist) respirator.
PPE-G,DL-80% R:	Coveralls worn over long-sleeve shirt and long pants, chemical-resistant gloves, and an 80%PF (quarter-face dust/mist) respirator.
PPE-G-90% R:	Baseline plus chemical-resistant gloves and a 90% PF (half-face dust/mist) respirator.
PPE-G,DL-90% R:	Coveralls worn over long-sleeve shirt and long pants, chemical-resistant gloves, and a 90% PF (half-face dust/mist) respirator.
Eng Controls:	Closed mixing/loading system, enclosed cab, or enclosed cockpit.

9.3 Short- and Intermediate-Term Noncancer Postapplication Risk

HED uses the term "postapplication" to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide (also referred to as reentry exposure). HED believes that there are distinct job functions or tasks related to the kinds of activities that occur in previously treated areas. Job requirements (e.g., the kinds of jobs to cultivate a crop), the nature of the crop or target that was treated, and the how chemical residues degrade in the environment can cause exposure levels to differ over time. Each factor has been considered in this assessment.

9.3.1 Agricultural Scenarios

To assess postapplication exposures and risks, HED attempts to identify the types of tasks and activities that postapplication workers will be performing in permethrin-treated areas. Examples include: agricultural harvesters, scouting activities in agriculture, crop maintenance tasks (e.g., irrigating, hoeing and weeding), and turf maintenance (golf course mowing). Then HED uses a *transfer coefficient* (cm^2/hr) to estimate the amount of contact with a treated surface a person likely would have while doing a specific postapplication task or activity. HED has developed a series of standard *transfer coefficients* that are unique for variety of job tasks or activities that are used in lieu of chemical- and scenario-specific data.

HED estimates the amount of pesticide residue that can transfer from different treated surfaces to a person's skin using techniques that specifically determine the amount of residues on treated surfaces (e.g., foliage, fruit), rather than the total residues on the surface and absorbed into treated plants. These surface- available residues are called *transferable residues* or *dislodgeable foliar residues*. In order to estimate the transferable residues to which individuals can be exposed, HED relies, whenever possible, on chemical- and crop-specific studies as described in HED guidelines for exposure data collection (*Series 875, Occupational and Residential Exposure Test Guidelines: Group B - Postapplication Exposure Monitoring Test Guidelines*). Permethrin-specific studies measured initial transferable surface residues and subsequent surface residue dissipation over time following applications to cotton, peaches, and turfgrass. The DFR/TTR component of those studies has been extracted for chemical-specific use in this risk assessment. More detailed information is provided in *Permethrin: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. Bill Smith. October 27, 2004*. The studies which have been used in this assessment are identified below followed by a brief summary of each:

- **"Dislodgeable Insecticide Residues on Cotton Foliage: Fenvalerate, Permethrin, Sulprofos, Chloryrifos, Methyl Parathion, EPN, Oxamyl, and Profenofos"** MRID 455705-25; Report dated 1980. Authors N.A. Buck, B.J. Estesen, and G.W. Ware; Submitted by Dow Chemical Company U.S.A.

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- **"Dissipation of Dislodgeable Foliar Residues of Permethrin Applied to Orchards (Peaches)"** EPA MRID 437557-01; Report dated July 20, 1995; Authors; Tami Belcher, Larissa Schuster; Sponsor: Zeneca Ag Products, Inc.: C/O permethrin Task Force; Performing Laboratories: Analytical - ABC Laboratories, Pan-Ag Division.

- **"Transferable Turf Residue Study: Permethrin Residues in Turf Following Application of Dragnet SFR Insecticide"** EPA MRID 449555-01; Report dated October 1, 1999; Author; Jill C. Holihan; Sponsor: FMC Corporation: Agricultural Products Group; Performing Laboratories: Analytical - FMC Corporation and Maxim Technologies, Inc.

In cases where no chemical-specific residue dissipation data are available, HED typically uses a generic dissipation model to complete risk calculations. In this case, HED determined that it is more appropriate, however, to extrapolate using permethrin-specific dissipation data in the risk assessment for other currently labeled crops than it is to use the generic dissipation model. This approach is consistent with current HED policies for generating transferable/dislodgeable residue data. The existing residue data were extrapolated to each of the currently labeled crops. This extrapolation was completed because of similarities in application methods between the study and selected crop groups, the crop canopy, and application rates (i.e., between the study and current labels). (Note: agronomic crop groups are defined in HED's revised transfer coefficient policy 003)

- **Cotton DFR Data:** These data have been used to complete assessments for low/medium field/row crop, tall field/row crop, cucurbit vegetable, fruiting vegetable, head and stem vegetable, leafy vegetable, root vegetable, stem and stalk vegetable, and cut flowers.

- **Peach DFR Data:** These data have been used to complete assessments for tree fruit (deciduous and evergreen), nut crop, and ornamentals.

The frequency and duration of occupational postapplication exposures must also be estimated in order to determine the which toxicological endpoints of concern are applicable to each postapplication scenario. Two dermal non-cancer risk calculations were required for each postapplication scenario: short-term (≤30 days) and intermediate-term (30 days up to several months). In addition, long-term exposures were determined for persons wearing or working with permethrin-impregnated fabric. Since the short-, intermediate-, and long-term dermal toxicological endpoints of concern are the same endpoint, short-, intermediate-, and long-term dermal risks for a specific postapplication scenario are numerically identical. Inhalation exposures are thought to be negligible in outdoor postapplication scenarios because of the low vapor pressure and due to the infinite dilution expected outdoors. As such, inhalation postapplication exposures are not considered in this assessment.

The use of personal protective equipment or other types of equipment to reduce exposures for postapplication workers is not considered a viable alternative for the regulatory process. This is described in some detail in EPA's Worker Protection Standard (40CFR170). As such, an administrative approach is used by HED to reduce the risks and is referred to as the *Restricted Entry Interval* or REI. The REI is time period follow a pesticide application during which entry into the treated area is restricted. At this time, the REI on the permethrin labels is 12 hours set by the highest acute toxicity category among acute dermal toxicity, eye irritation potential, or skin irritation potential) of the active ingredient.

For all, but a few, agricultural postapplication exposure scenarios in some crop groupings, postapplication occupational risks are below HED's level of concern (i.e., the MOEs are greater than 100) on day 0 – approximately 12 hours following application. In a few cases, postapplication occupational risks from certain high exposure activities do not fall below HED's level of concern for 1 to 4 days following application. Risks from corn detasseling – the highest postapplication exposure activity – did not fall below HED's level of concern until 9 days following application. A summary of the results for each crop/activity combination considered for each time-frame is also provided in Table 9.3.1.

Table 9.3.1. Summary of Permethrin Non-cancer Postapplication Worker Risk Estimates from Agricultural Scenarios

Crop	Activity	TC cm^2/hr	Maximum Application Rate (lb ia/A)	DAT (days)	DFR ug/cm^2 normalized	Short/ Intermediate-Term MOE
Occupational Postapplication Non-cancer Risks Calculated with Peach DFR Study (MRID # 437557-01)						
conifer seed orchard	seed cone harvesting	3000	1.2	1	2.44	**100**
apples, pears	thinning	3000	0.4	0	0.85	**290**
	hand-harvesting, hand-pruning, propping, training	1500	0.4	0	0.85	**570**
	hand-weeding, irrigating, scouting	1000	0.4	0	0.85	**860**
almonds, filberts, pistachios, walnuts	hand-harvesting, hand-pruning	2500	0.4	0	0.85	**340**
	irrigating, scouting, thinning	500	0.4	0	0.85	**1,700**
cherries: sweet and sour, nectarines, peaches	thinning	3000	0.3	0	0.64	**380**
	hand-harvesting, hand-pruning	1500	0.3	0	0.64	**760**
	hand-weeding, irrigating, scouting	1000	0.3	0	0.64	**1,100**
avocados, conifer (field grown-Christmas trees), papayas	thinning	3000	0.2	0	0.43	**570**
	hand-pruning	1500	0.2	0	0.43	**1,100**
	hand-weeding, scouting	1000	0.2	0	0.43	**1,700**
ornamentals	hand-pruning	400	0.2	0	0.43	**4,300**
	hand-pinching	175	0.2	0	0.43	**9,800**
	hand-harvesting	110	0.2	0	0.43	**16,000**
Occupational Postapplication Non-cancer Risks Calculated with Cotton DFR Study (MRID # 455705-25)						
alfalfa, soybeans	hand-harvesting	2500	0.20	1	0.13	**160**
	irrigating, scouting (full development)	1500	0.20	0	0.22	**160**
	irrigating, scouting (min development)	100	0.20	0	0.22	**2,400**
corn	detasseling, hand-harvesting	17000	0.20	9	0.028	**110**
	irrigating, scouting (full development)	1000	0.20	0	0.22	**240**
	scouting (min development)	400	0.20	0	0.22	**590**
cucurbits	hand-harvesting, hand-pruning	2500	0.20	1	0.13	**160**
	irrigating, scouting	1500	0.20	0	0.22	**160**
	thinning	500	0.20	0	0.22	**470**

Table 9.3.1. Summary of Permethrin Non-cancer Postapplication Worker Risk Estimates from Agricultural Scenarios

Crop	Activity	TC cm^2/hr	Maximum Application Rate (lb ia/A)	DAT (days)	DFR ug/cm^2 normalized	Short/ Intermediate-Term MOE
onions: dry bulb, garlic	hand-harvesting	2500	0.30	1	0.19	**110**
	hand-weeding, irrigating, scouting, thinning (full development)	1500	0.30	0	0.32	**100**
	hand-weeding, irrigating, scouting, thinning (min development)	300	0.30	0	0.32	**520**
potatoes	hand harvesting	2500	0.20	1	0.13	**160**
	hand-weeding, irrigating, scouting, thinning (full development)	1500	0.20	0	0.22	**160**
	hand-weeding, irrigating, scouting, thinning (min development)	300	0.20	0	0.22	**790**
turnips	hand-harvesting	2500	0.10	0	0.11	**190**
	hand-weeding, irrigating, scouting, thinning (full development)	1500	0.10	0	0.11	**310**
	hand-weeding, irrigating, scouting, thinning (min development)	300	0.10	0	0.11	**1,600**
eggplant, peppers: bell, tomatoes	hand-harvesting, hand-pruning	1000	0.20	0	0.22	**240**
	irrigating, scouting	700	0.20	0	0.22	**340**
	hand-weeding, thinning	500	0.20	0	0.22	**470**
cabbage	hand-harvesting, hand-pruning, irrigating	5000	0.20	3	0.08	**120**
	scouting	4000	0.20	3	0.08	**150**
	hand-weeding	2000	0.20	0	0.22	**120**
broccoli, Brussel sprouts, cauliflower, Chinese broccoli	hand-harvesting, hand-pruning, irrigating	5000	0.10	1	0.06	**160**
	scouting	4000	0.10	0	0.11	**120**
	hand-weeding	2000	0.10	0	0.11	**240**
collards	hand-harvesting	2500	0.10	0	0.11	**190**
	irrigating, scouting (all at medium development)	1500	0.10	0	0.11	**310**
	irrigating, scouting, thinning (all at min development)	500	0.10	0	0.11	**940**
Chinese cabbage, leafy vegetables	hand-harvesting	2500	0.20	1	0.13	**160**
	irrigating, scouting (all at medium development)	1500	0.20	0	0.22	**160**
	irrigating, scouting, thinning (all at min development)	500	0.20	0	0.22	**470**
artichokes	hand-harvesting, hand-pruning	1000	0.30	0	0.32	**160**
	irrigating, scouting (all at medium development)	500	0.30	0	0.32	**310**
	irrigating, scouting, thinning (all at min development), hand weeding	300	0.30	0	0.32	**520**
cut flowers	Old Brouwer data - for comparative purposes only	7000	0.30	6	0.073	**100**
	cut roses	2600	0.30	1	0.19	**100**
	all other cut flowers	500	0.30	0	0.32	**310**
Occupational Postapplication Non-cancer Risks Calculated with Turf TTR Study MRID# 449555-01						
turf	mowing	500	0.87	0	0.06	**1,400**

9.3.2 Impregnated Clothing Scenarios

HED estimated exposures to permethrin-impregnated clothing occur by considering exposure frequency and duration, as well as degree of contact. HED identified two types of occupational postapplication exposures:

- military personnel who *wear* battle dress impregnated with permethrin on a daily basis (i.e., approximately 250 days/year) and
- factory workers who *work with* fabric or clothing after impregnation during making of garments or packaging of clothing on a work-day basis (i.e., 250 days per year).

Since both postapplication occupational exposures are more than 180 days per year, the duration of exposure considered for this noncancer assessment is long-term. Inhalation exposures are thought to be negligible for postapplication scenarios involving exposure to permethrin-impregnated clothing because of the low vapor pressure. As such, inhalation postapplication exposures are not considered in this assessment.

To assess postapplication exposures to impregnated clothing, HED used the latest EPA Antimicrobial Division (AD) approaches for estimating similar postapplication exposures. The data required for estimating postapplication potential doses via AD's methods include the:

- clothing residue concentration (assumed to be equivalent to the application rate on a mass per area basis, as determined from the label),
- surface area of the skin that is in contact with the fabric,
- transfer factor, and
- body weight.

Dermal exposures to military personnel are based on the clothing contact surface area of adults exposed to permethrin-impregnated clothing (0.85 m^2). This number is based on the assumption that military personnel wear briefs and undershirts underneath the battle dress and therefore the surface area of arms and legs (but not the torso) for an adult are used. Dermal exposures to garment workers are based on the contact surface area of adults exposed to permethrin impregnated clothing in a factory after the impregnation process (0.22 m^2). This number is based on the hands and forearms of an adult garment worker.

All postapplication exposure scenarios for permethrin-impregnated clothing are below HED's level of concern (i.e., the MOEs are greater than 100). A summary of the results for each population considered is provided in Table 9.3.2.

Table 9.3.2. Summary of Permethrin Long-Term Non-cancer Postapplication Worker Risk Estimates from Impregnated Clothing Scenarios

Population	Clothing residue (mg ai/cm2)	Surface area (m2/day)	Transfer factor (%/day)	PDR (mg ai/kg/day)	Long-Term MOE
Military adults	0.125	0.85	0.49%	0.022	**1,100**
Garment workers	0.125	0.221	0.49%	0.006	**4,300**

9.4 Short- and Intermediate-Term Cancer Postapplication Risk

The occupational postapplication worker exposure and cancer risk calculations are presented in this section. Postapplication cancer risk estimates were calculated using a linear, low-dose extrapolation approach (Q_1*).

9.4.1 Agricultural Scenarios

Cancer risk estimates for the agricultural scenarios are summarized in Table 9.4.1 below. Two different occupational postapplication exposure scenarios were assessed – individuals employed solely by one establishment (i.e., "hired hands") were assumed to be exposed 10 days per year and individuals employed by multiple establishments (i.e., commercial or migratory farmworkers) were assumed to be exposed 30 days per year. Within each crop group, separate transfer coefficients were used to represent various types of cultural practices. Data from the permethrin-specific studies were used along with the transfer coefficients to calculate the LADDs. For specific crop groupings, permethrin-specific DFRs or TTRs were averaged over time depending on the retreatment interval listed on the labels. These averages were calculated beginning the day after the postapplication non-cancer risk exceeded HED's level of concern of 100 up to the day when it was possible to retreat the crop. For example, conifer seed orchards can be treated every 30 days and the non-cancer postapplication risk for conifer seed orchards exceeded HED's level of concern on Day 1. Thus, an average of the permethrin-specific data from day 2 through day 28 (the last day of the study) was calculated and this average was used as the DFR value in the postapplication cancer calculations for conifer seed orchards. All of the postapplication cancer risk estimates for both "hired hands" and commercial/migratory farmworkers are less than 1 x 10^{-4} and most are in the 10^{-6} to 10^{-7} range.

Table 9.4.1. Summary of Permethrin Cancer Postapplication Worker Risk Estimates for Agricultural Scenarios

Crop	Activity	TC cm^2/hr	Maximum Application Rate	DAT (days)	DFR ug/cm^2 normalized	10 Days per Year		30 Days per year	
						LADD (mg/kg/day)	Cancer risk	LADD (mg/kg/day)	Cancer risk
Occupational Postapplication Cancer Risk Estimates Calculated with Peach DFR Study (MRID # 437557-01)									
conifer seed orchard	seed cone harvesting	3000	1.2	AVG DAT 2-28	1.44	2.0e-03	1.9e-05	6.1E-03	5.8e-05
apples, pears	thinning	3000	0.4	AVG DAT 1-7	0.71	1.0e-03	9.6e-06	3.0E-03	2.9e-05
	hand-harvesting, hand-pruning, propping, training	1500	0.4	AVG DAT 1-7	0.71	5.0e-04	4.8e-06	1.5E-03	1.4e-05
	hand-weeding, irrigating, scouting	1000	0.4	AVG DAT 1-7	0.71	3.3e-04	3.2e-06	1.0E-03	9.6e-06
almonds, filberts, pistachios, walnuts	hand-harvesting, hand-pruning	2500	0.4	AVG DAT 1-7	0.71	8.3e-04	8.0e-06	2.5E-03	2.4e-05
	irrigating, scouting, thinning	500	0.4	AVG DAT 1-7	0.71	1.7e-04	1.6e-06	5.0E-04	4.8e-06
cherries: sweet and sour, nectarines, peaches	thinning	3000	0.3	AVG DAT 1-7	0.53	7.5e-04	7.2e-06	2.2E-03	2.2e-05
	hand-harvesting, hand-pruning	1500	0.3	AVG DAT 1-7	0.53	3.7e-04	3.6e-06	1.1E-03	1.1e-05
	hand-weeding, irrigating, scouting	1000	0.3	AVG DAT 1-7	0.53	2.5e-04	2.4e-06	7.5E-04	7.2e-06

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Table 9.4.1. Summary of Permethrin Cancer Postapplication Worker Risk Estimates for Agricultural Scenarios

Crop	Activity	TC cm^2/hr	Maximum Application Rate	DAT (days)	DFR ug/cm^2 normalized	10 Days per Year		30 Days per year	
						LADD (mg/kg/day)	Cancer risk	LADD (mg/kg/day)	Cancer risk
avocados, conifer (field grown-Christmas trees), papayas	thinning	3000	0.2	AVG DAT 1-7	0.35	5.0e-04	4.8e-06	1.5E-03	1.4e-05
	hand-pruning	1500	0.2	AVG DAT 1-7	0.35	2.5e-04	2.4e-06	7.5E-04	7.2e-06
	hand-weeding, scouting	1000	0.2	AVG DAT 1-7	0.35	1.7e-04	1.6e-06	5.0E-04	4.8e-06
ornamentals	hand-pruning	400	0.2	AVG DAT 1-7	0.35	6.7e-05	6.4e-07	2.0E-04	1.9e-06
	hand-pinching	175	0.2	AVG DAT 1-7	0.35	2.9e-05	2.8e-07	8.7E-05	8.4e-07
	hand-harvesting	110	0.2	AVG DAT 1-7	0.35	1.8e-05	1.8e-07	5.5E-05	5.3e-07
Occupational Postapplication Cancer Risk Estimates Calculated with Cotton DFR Study (MRID # 455705-25)									
alfalfa, soybeans	hand-harvesting	2500	0.20	DAT AVG 2-7	0.07	8.2e-05	7.9e-07	2.5e-04	2.4e-06
	irrigating, scouting (full development)	1500	0.20	DAT AVG 1-7	0.08	5.7e-05	5.4e-07	1.7E-04	1.6e-06
corn	detasseling, hand-harvesting	17000	0.20	DAT AVG 5-14	0.03	2.4e-04	2.3e-06	7.3e-04	7.0e-06
	irrigating, scouting (full development)	1000	0.20	DAT AVG 1-7	0.08	3.8e-05	3.6e-07	1.1E-04	1.1e-06
cucurbits	hand-harvesting, hand-pruning	2500	0.20	DAT AVG 2-7	0.07	8.2e-05	7.9e-07	2.5E-04	2.4e-06
	irrigating, scouting	1500	0.20	DAT AVG 1-7	0.08	5.7e-05	5.4e-07	1.7e-04	1.6e-06
	thinning	500	0.20	DAT AVG 1-7	0.08	1.9e-05	1.8e-07	5.7E-05	5.4e-07
onions: dry bulb, garlic	hand-harvesting	2500	0.30	DAT AVG 2-7	0.11	1.2e-04	1.2e-06	3.7E-04	3.5e-06
	hand-weeding, irrigating, scouting, thinning (full development)	1500	0.30	DAT AVG 1-7	0.12	8.5e-05	8.2e-07	2.6E-04	2.4e-06
potatoes	hand-harvesting	2500	0.20	DAT AVG 2-7	0.13	1.5e-04	1.5e-06	4.6E-04	4.4e-06
	hand-weeding, irrigating, scouting, thinning (full development)	1500	0.20	DAT AVG 1-7	0.08	5.7e-05	5.4e-07	1.7E-04	1.6e-06
turnips	hand-harvesting	2500	0.10	DAT AVG 1-7	0.04	4.7e-05	4.5e-07	1.4E-04	1.4e-06
	hand-weeding, irrigating, scouting, thinning (full development)	1500	0.10	DAT AVG 1-7	0.04	2.8e-05	2.7e-07	8.5E-05	8.1e-07
eggplant, peppers: bell, tomatoes	hand-harvesting, hand-pruning	1000	0.20	DAT AVG 1-7	0.08	3.8e-05	3.6e-07	1.1E-04	1.1e-06
	irrigating, scouting	700	0.20	DAT AVG 1-7	0.08	2.7e-05	2.5e-07	8.0E-05	7.6e-07
	hand-weeding, thinning	500	0.20	DAT AVG 1-7	0.08	1.9e-05	1.8e-07	5.7E-05	5.4e-07
cabbage	hand-harvesting, hand-pruning, irrigating	5000	0.20	DAT AVG 4-7	0.05	1.3e-04	1.2e-06	3.9E-04	3.7e-06
	scouting	4000	0.20	DAT AVG 4-7	0.05	1.0e-04	9.9e-07	3.1E-04	3.0e-06
	hand-weeding	2000	0.20	DAT AVG 1-7	0.08	7.6e-05	7.2e-07	2.3E-04	2.2e-06

Table 9.4.1. Summary of Permethrin Cancer Postapplication Worker Risk Estimates for Agricultural Scenarios

Crop	Activity	TC cm^2/hr	Maximum Application Rate	DAT (days)	DFR ug/cm^2 normalized	10 Days per Year		30 Days per year	
						LADD (mg/kg/day)	Cancer risk	LADD (mg/kg/day)	Cancer risk
broccoli, Brussel sprouts, cauliflower, Chinese broccoli	hand-harvesting, hand-pruning, irrigating	5000	0.10	DAT AVG 2-7	0.04	8.2e-05	7.9e-07	2.5E-04	2.4e-06
	scouting	4000	0.10	DAT AVG 1-7	0.04	7.6e-05	7.2e-07	2.3E-04	2.2e-06
	hand-weeding	2000	0.10	DAT AVG 1-7	0.04	3.8e-05	3.6e-07	1.1E-04	1.1e-06
collards	hand-harvesting	2500	0.10	DAT AVG 1-7	0.04	4.7e-05	4.5e-07	1.4E-04	1.4e-06
	irrigating, scouting, thinning (all at medium development)	1500	0.10	DAT AVG 1-7	0.04	2.8e-05	2.7e-07	8.5E-05	8.1e-07
Chinese cabbage, leafy vegetables	hand-harvesting	2500	0.20	DAT AVG 2-7	0.07	8.2e-05	7.9e-07	2.5E-04	2.4e-06
	irrigating, scouting, thinning (all at medium development)	1500	0.20	DAT AVG 1-7	0.08	5.7e-05	5.4e-07	1.7e-04	1.6e-06
artichokes	hand-harvesting, hand-pruning	1000	0.30	DAT AVG 1-7	0.12	5.7e-05	5.4e-07	1.7E-04	1.6e-06
	irrigating, scouting, thinning (all at medium development)	500	0.30	DAT AVG 1-7	0.12	2.8e-05	2.7e-07	8.5E-05	8.1e-07
cut flowers	Old Brouwer data - for comparative purposes only	7000	0.30	DAT AVG 5-7	0.07	2.4e-04	2.3e-06	7.3E-04	7.0e-06
	cut roses	2600	0.30	DAT AVG 2-7	0.11	1.3e-04	1.2e-06	3.8E-04	3.7e-06
	all flowers	500	0.30	DAT AVG 1-7	0.12	2.8e-05	2.7e-07	8.5E-05	8.1e-07
Occupational Postapplication Cancer Risks Calculated with Turf TTR Study (MRID # 449555-01)									
turf	mowing	500	0.87	DAT AVG 1-14	0.03	6.3e-06	6.1e-08	1.9e-05	1.8e-07

9.4.2 Impregnated Clothing Scenarios

Cancer risk estimates for impregnated clothing scenarios are summarized in Table 9.4.2 below. HED identified two types of occupational postapplication exposures:

- military personnel who *wear* battle dress impregnated with permethrin on a daily basis (i.e., approximately 250 days/year) and
- factory workers who *work with* fabric or clothing after impregnation during making of garments or packaging of clothing on a work-day basis (i.e., 250 days per year).

Dermal exposures to military personnel are based on the clothing contact surface area of adults exposed to permethrin-impregnated clothing (0.85 m^2). This number is based on the assumption that military personnel wear briefs and undershirts underneath the battle dress and therefore the surface area of arms and legs (but not the torso) for an adult are used. Dermal exposures to garment workers are based on the contact surface area of adults exposed to permethrin impregnated clothing in a factory after the impregnation process (0.22 m^2).

This number is based on the hands and forearms of an adult garment worker. All of the postapplication cancer risk estimates for both populations are less than 1 x 10^{-4}, but greater than 1 x 10^{-6}.

Table9.4.2. Summary of Permethrin Cancer Postapplication Worker Risk Estimates for Impregnated Clothing Scenarios

Population	Clothing residue (mg ai/cm2)	Surface area (m2/day)	Transfer factor (%/day)	Exposure duration (years)	Exposure Frequency (days/year)	Averaging time (years)	LADD (mg ai/kg/day)	Cancer Risk
Miltary personnel	0.125	0.85	0.49%	10	250	70	0.0022	2.09E-05
Garment workers	0.125	0.221	0.49%	35	250	70	0.002	1.90E-05

10.0 Data Needs and Label Requirements

10.1 Toxicology

870.6300(83-6) (dev neurotox) 120

- A developmental neurotoxicity study (DNT) is required for additional assurance as to the dose-response in characterizing neurotoxic effects.

10.2 Residue Chemistry

860.1200: Directions for Use

- Current use directions on apple allow for foliar applications at up to 0.4 lb ai/A with a seasonal maximum use rate of 0.8 lb ai/A. The available residue data will allow for an increase in the maximum seasonal use rate to 1.2 lb ai/A/season without impacting the current tolerance.

- The higher use rate allowed on sweet corn grown in FL (0.25 lb ai/A/application; 2.0 lb ai/A/season) is not supported by the available residue data. This use should either be deleted from the EP labels, or the registrants should provide data from at least two field trials in FL supporting the higher application rate to sweet corn.

- Adequate data have been submitted supporting the use of permethrin on papayas grown in HI (the current use on papayas is restricted to FL). However, the use rate proposed for HI is lower, allowing for up to only 4 applications at 0.1 lb ai/A/application, for a total of 0.4 lb ai/A/crop cycle, with a 1-day PHI. Labels may be amended to include the use on papayas grown in HI at the lower rate.

- Use directions for tomatoes on FMC's EP labels include the use on tomatillo. However, the use directions for tomatoes also include a prohibition against applying to tomato cultivars that are smaller than 1 inch in diameter. As many tomatillo cultivars are less than 1 inch in diameter at maturity, this label prohibition is in conflict with a use on tomatillos. The use on tomatillos should be deleted from FMC labels. Alternatively, new field trials are being required to support the current use pattern on tomatoes of up to 6 applications at 0.2 lb ai/A/application (1.2 lb ai/A/season, 0-day PHI). If the requested field trials include applications to cherry tomato cultivars, than the use on tomatillos can remain and the restriction against the use on smaller tomato cultivars can be deleted.

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860.1340: Residue Analytical Methods-Animals

- Descriptions of the residue analytical methodology used in the analysis of peach samples are required to upgrade the peach field trials.

860.1380: Storage Stability

- Data depicting the stability of permethrin in frozen mushrooms and representative animal commodities are required to upgrade the existing animal feeding studies and mushroom studies.

860.1500: Magnitude the Residue in Crop Plants

- Additional field trial data are required to support the existing uses of permethrin on cabbage, collards, grasses (rangeland), leaf lettuce, and tomatoes.
- Additional field trial data on sweet corn are also required to support the use of a higher application rate (0.25 lb ai/A) for sweet corn grown in FL.
- Information on sample storage intervals and conditions is required to upgrade pear and older tomato field studies.

10.3 Occupational and Residential Exposure

Occupational Handler:

Several data gaps were identified for permethrin in many different use areas that include:

- dip treatments to animals and clothing;
- dust treatments via mechanical duster or dust bags on animals in agriculture;
- wettable powder treatments using backpack and high-pressure handwand sprayers; and
- microencapsulated liquids using fogger/mist generator equipment.

There are also several data gaps that were identified for permethrin such as the various specialized uses (i.e., ear tags, protective flanges, and vapor recovery system tubes), however, HED believes that the other assessed scenarios are protective of these specialized uses.

Occupational Postapplication:

HED has used the latest information to complete this postapplication risk assessment for permethrin. Several data gaps exist such as a lack of postapplication studies in different crop groupings (e.g., cole crops, tall field crops) and lack of exposure data on mechanized or partially mechanized cultural practices where there is a potential for exposure. Additionally, because of the number and breadth of permethrin uses, there may be many exposure pathways where the transfer coefficient is not an appropriate model (e.g., working with treated animals or wearing treated clothing such as military uniforms) that have not been quantitatively addressed due to a lack of data.

Residential Handler:

No key data gaps have been identified by HED at this time for residential handlers. However, there were some scenarios that remain unaddressed by HED at this time due to a lack of data or other information:

- rotary duster/dust gun applications,
- puffer-can applications, and
- the use of RTU furniture coasters and protective flanges.

HED believes that the shaker can scenario is representative of the rotary duster/dust gun scenario and thus it can be considered not of concern.

Residential Postapplication:

No key data gaps have been identified by HED at this time for residential postapplication exposures.

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Permethrin. Residue Chemistry Considerations for Reregistration Eligibility Decision (RED) Document. PC Code: 109701. DP Barcode: D298290. Sherrie Kinard. October 25, 2004.

Permethrin. Acute, Chronic, and Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision (RED) Document. PC Code: 109701. DP Barcode: D298311. Samuel Ary. October xx, 2004.

Appendices

1.0 TOXICOLOGY DATA REQUIREMENTS

The requirements (CFR 158.340) for food use of permethrin are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1. Data requirements (CFR 158.340) for food use of permethrin

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes[1]
870.3150	Oral Subchronic (nonrodent)	yes	yes[1]
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	NA
870.3465	90-Day Inhalation	no	NA
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	yes
870.6100b	90-Day Neurotoxicity (hen)	no	no
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	yes	no[2]
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	no
	Subchronic Oral (rat)	no	no
	Six-month Oral (dog)	no	no

1. Requirements are satisfied by chronic oral toxicity studies.
2. The HIARC determined that a developmental neurotoxicity study is required (Data gap).

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2.0 NON-CRITICAL TOXICOLOGY STUDIES

Executive summaries for studies not used for toxicity endpoint selection or FQPA assessment are as follows.

2.1 21/28-Day Dermal Toxicity – Rat (870.3200)

In a 21-day repeated dose dermal toxicity study (MRIDs 41143801, 42653301), groups of Wistar Alpk:Apfsd SPF rats (5/sex/group) were treated with undiluted Permethrin (95.6%, Batch No. Y00040/85, RS/38F). Animals were treated by dermal occlusion for 6 hours/day for 21 days at doses of 0, 50, 150, or 500 mg/kg/day.

There were no treatment-related deaths and no effects on body weight, food consumption, hematology, clinical chemistry, or gross or microscopic lesions. Increases in absolute ($p<0.05$; 10.3% increase) and relative ($p<0.05$; 10.6% increase) liver weight were noted in high-dose females only. No histopathological evidence of adaptive liver change was seen in any treatment group. Therefore, the increase of liver weight in females was not considered biologically significant. Skin irritation was observed at the application site of all treatment groups.

The systemic NOAEL was 500 mg/kg/day (the highest dose tested), the systemic LOAEL was not established. The dermal LOAEL was 50 mg/kg/day based on skin irritation. A dermal NOAEL was not identified.

This study is classified as **Acceptable/Guideline** and does satisfy the guideline requirements for a repeated-dose dermal study [OPPTS 870.3200 (§82-2)] in rats.

2.2 Chronic Toxicity - Dog (870.4100b)

In a chronic oral toxicity study (MRID 00129600), permethrin (92.5%, a.i., cis/trans 32.3/60.2) was administered to beagle dogs (6/sex/group) in corn oil by gelatin capsule at dose levels of 0, 5, 100, or 1000 mg/kg/day for one year. The high dose was lowered from 2000 mg/kg/day after 2 days due to overt toxic reaction to the test material.

There were no mortalities. Neurological clinical signs (tremors, uncoordinated gait, nervousness and convulsions, also excessive salivation and vomiting) were observed in the high-dose group. At the high-dose, decreased body weight gain (37% for males and 33% for females less than control, respectively), decreased food consumption (increased food left uneaten), increased liver weight (+30% and +36% for males and females, respectively) and alkaline phosphatase level (+377% and +220% for males and females, respectively) were reported. At mid-dose, increased liver weight (+25% both sexes) and alkaline phosphatase levels (+134% for males and +99% for females) were observed. Microscopic evaluation of the adrenals showed focal degeneration and necrosis in the cortex with variable inflammatory cell infiltration along with swelling and vacuolization of the cells in the inner cortex at high-dose males and females and at mid-dose males. The liver also showed hepatic cellular swelling at mid- and high-dose males and females.

On April 18, 2002, the HIARC evaluated the toxicology database of permethrin and determined that the

observations of increased liver weight, alkaline phosphatase levels, and hepatic cellular swelling are adaptive and reversible effects and are not considered adverse effects (HED Doc# 0050731). **Therefore, the systemic toxicity LOAEL is 1000 mg/kg/day based on clinical neurotoxic signs and decreased body weight gain and food consumption. The NOAEL is 100 mg/kg/day.**

This one-year dog study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity study in dogs.

2.3 Metabolism - Rat (870.7485)

(1) In a series of metabolism and disposition experiments (MRID 00089006, 00054719, and MRID 92142041 [summary of MRID 00089006], and MRID 92142042 [summary of MRID 00054719]), male and female Wistar-derived rats were placed on various oral treatment regimens with [^{14}C-alcohol]permethrin ([^{14}C-cyclopropyl]permethrin) or [^{14}C-acid]permethrin ([^{14}C-benzyl]permethrin). For MRID 00054719, [^{14}C-acid]permethrin (>98% purity, 53:47, cis trans ratio; no lot or batch no.) or [^{14}C-alcohol]permethrin (99% purity, 40.5:59.5 cis:trans ratio; no lot or batch no.) were diluted as needed with nonlabeled permethrin (93.6% purity, 40.5:59.5, cis:trans ratio; no lot or batch no.) and given by gavage to two male and two female rats at a dose of 6.5 mg/kg for quantitative and qualitative assessment of excretion. In MRID 00089006, tissue distribution and blood kinetics were assessed in male and female Wistar-derived rats given repeated or single oral doses of [^{14}C-acid]permethrin (>98% purity; 53:47, cis:trans ratio; no lot or batch no.) or [^{14}C-alcohol]permethrin (99% purity, 38:62 cis:trans ratio; no lot or batch no.)

These studies provided information on the excretion and tissue burdens of permethrin in rats following single or multiple oral doses of either alcohol ([^{14}C-cyclopropyl]permethrin) or acid [^{14}C-benzyl]permethrin). Based upon a limited number of rats, overall recovery was 93.7% to 101% regardless of label position. Following a single oral dose of 6.5 mg/kg, most radioactivity (58-65%) from a single dose of the [^{14}C-alcohol] permethrin was eliminated via the urine over a 7-day period with much of the remainder (29-43%) being excreted in the feces. Urinary excretion of radioactivity following a single dose of [^{14} C-acid] permethrin was slightly less and fecal excretion correspondingly greater. Results of tissue distribution and autoradiographic experiments showed that most radioactivity was associated with adipose tissue and, initially, with the gastrointestinal tract and organs/tissue associated with excretory function. Following oral administration to rats, most permethrin-associated radioactivity appears to be excreted within 48 hours. Following multiple doses, radioactivity in adipose tissue appears to be greater for [^{14}C-alcohol] permethrin than for [^{14}C-acid] permethrin. This is also consistent with blood kinetics data showing lower radioactivity (C_{max}) in the blood of rats receiving [^{14}C-acid] permethrin. Upon cessation of dosing, radioactivity levels in adipose tissues declined. There was no attempt to identify the metabolites in these studies.

This metabolism study in the rat is classified **Unacceptable/Guideline** and does not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. The unacceptability is the result of deficiencies in level of detail provided which prevent verification/validation of findings (e.g., unreadable data, environmental conditions not reported, no dose confirmation, no lot/batch numbers for the test article).

(2) In a metabolism study (MRID 00102185), male Wistar-derived rats were given a single low dose (2.0 mg/rat) or single high dose (20 mg/rat) of permethrin ([^{14}C-cyclopropane]permethrin, 40:60 cis-trans ratio and

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non-labeled permethrin, 38.2:59.3 cis-trans ratio; no purity or lot/batch nos. for either) intragastrically. Feces and urine collected one day prior to dosing and for three days postdose were analyzed for radioactivity and metabolites.

These experiments provided an initial and cursory effort at identification and quantitation of major metabolites in the urine and feces of rats following single oral doses (2 or 20 mg/rat) of [^{14}C-cyclopropane]permethrin. Approximately 78.5% of the administered radioactivity was recovered over the 3-day experimental period (dose group not specified). A conjugated metabolite, 3-(2,2-dichlorovinyl)-1-methylcyclopropane-1,2-dicarboxylic acid, was identified in both the urine and feces that reportedly accounted for approximately 2.2% of the administered dose. No additional data were provided regarding characterization of the remaining recovered radioactivity.

This metabolism study in the rat is classified **Unacceptable/Guideline** and does not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. The unacceptability is the result of deficiencies in level of detail provided which prevent verification/validation of findings (e.g., insufficient data regarding characterization of recovered radioactivity, no dose confirmation, no lot/batch numbers for the test article).

(3) In a metabolism study (MRID 00065903), groups of rats were given oral doses (1.6-4.8 mg/kg) of radiolabeled isomers ([^{14}C-acid] or [^{14}C-alcohol] labeled) of permethrin (radiochemical purity >99%; no lot/batch nos.) in dimethylsulfoxide vehicle. Metabolism and disposition was assessed over a 4 to12-day period

Recovery of administered radioactivity was 97-100% at 12 days after administration of the test article. The test material appeared to be rapidly absorbed and excreted in the urine and feces. Quantitative differences in excretion profile were characterized by greater amounts of *trans*-permethrin in the urine suggesting greater metabolism of the *trans* isomer than the *cis* isomer. Most of the urinary metabolites and some fecal metabolites appeared to be hydroxylation products, and glucuronide and sulfate conjugates of these products. Qualitative differences in metabolite profiles were also noted for the two isomers. Excretion of radioactivity via expired air was negligible. Fat tissue, liver, and kidney contained the highest levels of radioactivity, although there did not appear to be potential for sequestration at the dose regimens studied. The study authors concluded that the metabolism in rats of the *cis* and *trans* isomers of permethrin was characterized by ester cleavage, oxidation at the *cis* or *trans* methyl group of the dimethyl moiety, and oxidation at the 2' or 4' position of the phenoxy group.

This review is conducted on a best available copy of the report. However, most data tables and some text were not legible and, therefore, verification of the study authors' interpretations and conclusions was not possible. This metabolism study in the rat (MRID 00065903), apparently a draft manuscript for submission to the J. of Agricultural and Food Chemistry, is classified **Unacceptable/Guideline** and does not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. *Although the study appeared to be an in-depth examination of the metabolism of the *cis* and *trans* isomers of permethrin in the rat and could potentially achieve guideline requirements, the resulting study report was generally unreadable and exhibited notable deficiencies.

2.4 Metabolism - Dog (870.7485)

Two metabolism studies were conducted using adult Beagle dogs. In MRID 0054721, groups of four male and four female beagle dogs were given [^{14}C-alcohol]permethrin (PP557; no lot/batch nos.; 59.7 mCi/mM; purity not reported) or [^{14}C-acid]permethrin (PP557; no lot/batch nos.; 1.87 mCi/mM; purity 99%) as a single oral dose (6.5 mg/kg and 6.2 mg/kg, respectively) in a gelatin capsule. Excreta were collected over a 7-day period and tissues collected and analyzed at termination. In MRID 00042160, two beagle dogs (gender not specified) were given 10 daily doses (1.0 mg/kg via gelatin capsules) of [^{14}C-alcohol]permethrin (PP557; no lot/batch nos.; 59.7 mCi/mM; purity not reported). Excreta were collected after seven days and adipose tissues analyzed at termination.

These experiments provided preliminary information regarding the metabolism and disposition of permethrin in dogs. Data were insufficient for determination of definitive mass balance for administered radioactivity. Following oral administration of a single dose of [^{14}C-alcohol]permethrin (6.5 mg/kg) or [^{14}C-acid]permethrin (6.2 mg/kg), approximately 84-87% of administered radioactivity was eliminated via the feces and urine in 24-48 hours (MRID 000054721). Fecal excretion (~45-56% of dose) was somewhat greater than urinary excretion (~30-38% of dose) and the rate of excretion was slightly less for the [^{14}C-alcohol]permethrin. At seven days postdose, radioactivity was detected in the tissues selected for analysis (peri-renal and subcutaneous fat, liver, kidney, lung, heart, blood, and brain). The highest tissue levels (0.5-0.7 µg eq./g) were found in the fat tissues. Although radioactivity was detected in all tissues seven days following the single oral dose, levels were minimal and there was no evidence for significant sequestration. Following a single oral dose, TLC analysis of organic solvent extracts revealed up to four metabolites in the urine and six in the feces, none of which were characterized. The excretory pattern for dogs given multiple doses of [^{14}C-alcohol]permethrin (1.0 mg/kg/day for 10 days) (MRID 00042160) was similar to that observed for the single dose study. The repeat-dose study also provided preliminary data showing a shift in the cis:trans ratio (an increase in the cis isomer) of residues in peri-renal and subcutaneous fat, and noted that this shift was indicative of a preferential metabolism of the trans isomer.

These metabolism/disposition studies in the dog are classified **Unacceptable/Non-Guideline** and do not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in dogs. The unacceptability is the result of deficiencies in level of detail provided which prevent verification/validation of findings (e.g., insufficient data regarding characterization of recovered radioactivity, no dose confirmation, no lot/batch numbers for the test article, mass balance data lacking in MRID 00042160). Furthermore, the studies were conducted prior to GLP Guidelines and lacked quality assurance statements.

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MRID	Citation
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00054719	Mills, I.H.; Mullane, M. (1976) PP557: Absorption and Excretion in the Rat: Report No. CTL/P/228. (Unpublished study received Aug 22, 1977 under 10182-EX-3; submitted by ICI Americas, Inc., Wil- mington, Del.; CDL:096334-D)
00054721	Mills, I.H.; Slade, M. (1977) PP557: Absorption, Distribution and Excretion in the Dog: Report No. CTL/P/285. Includes undated methods entitled: Measurement of radioactivity and Extraction, clean-up and chromatography. (Unpublished study received Dec 5, 1977 under 10182-EX-3; prepared by Imperial Chemical Industries, Ltd., submitted by ICI Americas, Inc., Wilmington, Del.; CDL: 096334-F)
00062806	FMC Corporation (1980) Analysis of Physical Observations: Bio/dy- namics Project 76-1695; FMC Study No. ACT 115.35. (Compilation; unpublished study received Dec 5, 1980 under unknown admin. no.; CDL:243863-A)
00065903	Gaughan, L.C.; Unai, T.; Casida, J.E. (1976) Permethrin Metabolism in Rats. (Unpublished study, including submitter summary, re- ceived Jan 3, 1978 under 279-3013; prepared by Univ. of Cali- fornia--Berkeley, Div. of Entomology & Parasitology, submitted by FMC Corp., Philadelphia, Pa.; CDL:096692-B)
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