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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

This report supercedes the October 8, 2003 HIARC report (TXR No. 0052151). *Note to Reader*: Revisions to Section I.7. *Recommendation for a Developmental Neurotoxicity Study.* Last paragraph of Section I.7 contains a revised dose analysis for determining the size of the UF_{DB}.

TXR NO.: 0052543

DATE: **May 12, 2004**

MEMORANDUM

SUBJECT: **PERMETHRIN** -Third Report of the Hazard Identification Assessment Review Committee.

FROM: Jessica Kidwell, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Karen Whitby, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Carol Christensen, Risk Assessor
Reregistration Branch 2
Health Effects Division (7509C)

PC Code: 109701

On **April 18, 2002**, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for permethrin with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to permethrin was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document. On **September 9, 2003**, the HIARC re-evaluated the database uncertainty factors for acute and chronic dietary risk assessments and residential (non-dietary) exposure scenarios. **This report supercedes the previous HIARC reports for permethrin (TXR Nos. 0052151 and 0050731).**

Committee Members in Attendance on April 18, 2002

Members present were:	Elizabeth Doyle (Co-Chair), Pamela Hurley, Elizabeth Mendez, David Nixon, John Liccione, Jess Rowland (Co-Chair), Paula Deschamp, Virginia Fornillo, and Brenda Tarplee (Executive Secretary).
Member(s) in absentia:	William Burnam, Ayaad Assaad, and Jonathan Chen.
Data evaluation prepared by:	Yung G. Yang, Toxicology Branch
Also in attendance were:	Kenneth Dockter, Shanna Recore, Renee Sandvig, Pauline Wagner, and Stacey Milan (CRM, SRRD).

Committee Members in Attendance on September 9, 2003

Members present were:	Ayaad Assaad, William Burnam, Paula Deschamp (RARC Representative), William Dykstra, Jessica Kidwell (Executive Secretary), John Liccione, Susan Makris, Jess Rowland (Co-Chair), P.V. Shah, Brenda Tarplee, Karen Whitby (Co-Chair).
Member(s) in absentia:	Jonathan Chen, Pamela Hurley, Elizabeth Mendez.
Also in attendance were:	Carol Christensen (HED/RRB2), Rita Kumar (RD), Anna Lowit (HED/RRB2), Pauline Wagner (HED/RRB2), Yung Yang (HED/Tox).
Report Concurrence:	Brenda Tarplee, B.S.S., Science Info. Management Branch.

INTRODUCTION

On **April 18, 2002,** the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for permethrin with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to permethrin was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document. On **September 9, 2003**, the HIARC re-evaluated the database uncertainty factors for acute and chronic dietary risk assessments and residential (non-dietary) exposure scenarios. This report supercedes the previous HIARC reports for permethrin (TXR Nos. 0052151 and 0050731).

I. FQPA HAZARD CONSIDERATIONS

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).

2. Evidence of Neurotoxicity

The HIARC concluded that there is a concern for neurotoxicity resulting from exposure to permethrin. Executive summaries are as follows.

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 less 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).

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.

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 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.

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.

3. <u>Developmental Toxicity Study Conclusions</u>

<u>Developmental Toxicity Study in Rats</u>

<u>Executive Summary:</u> 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.

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. Reproductive Toxicity Study Conclusions

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.

5. <u>Additional Information from Literature Sources</u>

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).

6. Pre-and/or Postnatal Toxicity

The HIARC concluded that there is no concern for pre- and/or postnatal toxicity resulting from exposure to permethrin.

A. 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.

B. Degree of Concern Analysis and Residual Uncertainties

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.

C. Proposed Hazard-based Special FQPA Safety Factor(s):
The HIARC concluded that there are no concerns or residual uncertainties for pre- and/or post-natal toxicity with permethrin for any of the available studies. Therefore, the hazard based default special FQPA safety factor can be removed (1X) when assessing dietary and residential (non-dietary) risks resulting from the uses of permethrin.

7. Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that there is a concern for developmental neurotoxicity resulting from exposure to permethrin. Based on the weight of evidence presented, the HIARC concluded that a developmental neurotoxicity study (DNT) is required for permethrin.

A. Evidence that suggest 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.

B. Evidence that do not support a need for a developmental neurotoxicity study:
- 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.

On 04/18/02, the HIARC determined that the requirement of a DNT study was considered to be "for cause" and that a 3X database uncertainty factor (UF_{DB}) was needed until the data are received and evaluated (HIARC Report, TXR No. 0050731).

Subsequently, the HIARC met on 9/9/03 to re-evaluate the need for and size of the UF_{DB} for lack of the DNT based on a dose analysis that included an evaluation of the acute and subchronic neurotoxicity studies in addition to the 3-generation reproduction study. They determined that a **10X UF_{DB}** was required for **acute and chronic dietary risk assessments** as well as for **residential (non-dietary) exposure scenarios.** This decision was based on the following considerations:

The current regulatory dose level for both the acute and chronic dietary risk assessments is the NOAEL of 25 mg/kg/day selected from the acute neurotoxicity study in adult rats (MRID No. 45657401).

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 dose levels in the subchronic neurotoxicity study are 0, 15, 92, or 150 mg/kg/day. It is considered possible that the results of the DNT study could impact the endpoint selection for risk assessments because the lowest

dose that may be tested in the DNT (15 mg/kg/day), based on the HIARC's dose analysis, could become an effect level which would necessitate an additional factor resulting in doses which would then be lower than the current doses used for oral (25 mg/kg/day), dermal (25 mg/kg/day), and inhalation (11 mg/kg/day) risk assessments. Given these circumstances, the HIARC does not have sufficient reliable data justifying selection of an additional safety factor for the protection of infants and children lower than the default value of 10X. Therefore, an UF_{DB} of 10X will be applied to all dietary and non-dietary exposure risk assessments to account for the lack of the DNT study with permethrin.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - General Population Including Infants and Children

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): 1000 (10x for interspecies extrapolation, 10x for intraspecies variations, and 10x for lack of developmental neurotoxicity study).

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) = $\frac{25 \text{ mg/kg/day}}{1000}$ = **0.025 mg/kg/day**

2. Acute Reference Dose (aRfD) - Females (13-50 years old)

Study Selected: None

MRID No.: None.

Executive Summary: None

Dose and Endpoint for Establishing aRfD: None

Uncertainty Factor (UF): None

Comments about Study/Endpoint/Uncertainty Factor: Since there is no developmental or reproductive toxicity of concern for permethrin, no appropriate endpoint or study is selected for the female (13-50) group. The selected dose/endpoint for general population would provide adequate protection for females 13-50 years old.

Acute RfD (Females 13-50 years old) = Not Applicable.

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): 1000 (10x for interspecies extrapolation, 10x for intraspecies variations, and 10x for lack of developmental neurotoxicity study).

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 = $\frac{25 \text{ mg/kg/day}}{1000}$ = **0.025 mg/kg/day**

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.

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.

6. Dermal Absorption

Dermal Absorption Factor: 30%

An acceptable dermal penetration study in rats (MRID 43169001) is available. The reviewer noted that there was a general progression of increased permethrin absorption 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 from corneum. The dermal absorption factor of 30% is based on a 24-hour measure and 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.

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.

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.

9. Margins of Exposure

Summary of target Margins of Exposure (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	1000	1000	N/A
Dermal	1000	1000	1000
Inhalation	1000	1000	1000

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.

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.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

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 fattyvacuoles 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.

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.

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 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 9.567×10^{-3} based on female mouse lung adenoma and/or carcinoma combined tumor rates (Memo, L. Brunsman, 9/25/02, TXR No. 0051166).

IV. MUTAGENICITY

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

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).

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.

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).

V. HAZARD CHARACTERIZATION

Permethrin (3-phenoxybenzyl-methyl-3-(2,2-dichloroethenyl)-2,2 dimethyl-cyclopropanecarboxylate) is a synthetic pyrethroid insecticide registered for use on many food/feed crops and for applications to livestock and their housing. Permethrin is a racemic mixture of the cis and trans isomers. It has been indicated that increased content of cis isomer would increase its severity of clinical signs and toxicity. The current registered technical active product has a content of cis isomer ranging from 35% to 55%. The toxicology database of permethrin showed that studies of the test material has a content of cis isomer ranging from 25% to 50%. The HIARC determined that the toxicology database, with the exception of the developmental neurotoxicity study, is adequate to support the re-registration of permethrin.

Permethrin has a low acute toxicity (toxicity category 3 or 4) via the oral, dermal, or inhalation route of exposure. Permethrin is not an eye or skin irritant and not a skin sensitizer. Following oral administration, permethrin is rapidly absorbed, metabolized, and excreted in urine and feces. Permethrin is a type I pyrethroid with the primary target organ of 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.

Results from developmental and reproductive toxicity studies demonstrated that there is no evidence of increased quantitative or qualitative sensitivity following *in utero* and/or postnatal exposure to permethrin. There is no evidence that permethrin induces any endocrine disruption.

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, with a Q_1^*(mg/kg/day)$^{-1}$ for Permethrin of 9.567×10^{-3}. 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.

VI. DATA GAPS / REQUIREMENTS

Developmental neurotoxicity study in rats (OPPTS 870.6300)

VII. ACUTE TOXICITY

Acute Toxicity of permethrin

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral in Rats	242899	LD_{50} = 3580 mg/kg(M) 2280 mg/kg (F)	III
81-2	Acute Dermal in Rabbits in Rats	242899 099258	LD_{50} >2000 mg/kg	III
81-3	Acute Inhalation in Rats	096692	LC_{50} >23.5 mg/L	IV
81-4	Primary Eye Irritation in Rabbits	242899 099258	No corneal opacity or conjunctival irritation.	IV
81-5	Primary Skin Irritation in Rabbits	242899 096692	All irritation cleared by 48 hours.	IV
81-6	Dermal Sensitization in Guinea Pigs	099258 099263	Non-sensitizer	N/A

Data extracted from HED Doc. No. 008216.

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for Permethrin

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 = **1000** **Acute RfD** = 0.025 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.025 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 = **1000** **Chronic RfD** = 0.025 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.025 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 = 1000	**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 = 1000	**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

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 = 1000 **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 = 1000 **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 = 1000 **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 = 1000 **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 = 1000 **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 = 1000 **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.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Cancer (Oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" with 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.