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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

August 23, 2004

MEMORANDUM

Subject: EPA Id # 109303. Esfenvalerate: Toxicology Chapter for the Registration Eligibility Document.

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Attached is the Toxicology Chapter for the Registration Eligibility Document for esfenvalerate.

Note: The original instructions for this project was to address the chemicals esfenvalerate (PC Code 109303), fenvalerate (PC Code 109301) and *beta* fenvalerate (PC Code 109304). It is ReRegistration Branch III's understanding that reregistration for fenvalerate is not longer being requested by the registrants. There were no toxicity studies submitted with *beta* fenvalerate as the test material. There were no supporting documents describing the similarity between esfenvalerate and *beta* fenvalerate provided to justify bridging studies to support registration of *beta* fenvalerate. Therefore, this Toxicology Chapter is not intended to address the registration issues for *beta* fenvalerate.

SEP 2 2 2004

Esfenvalerate

PC Code: 109303

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document

Date completed:

August 23, 2004

TXR # 0051089

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TABLE OF CONTENTS

1.0 HAZARD CHARACTERIZATION

Relationship between esfenvalerate and fenvalerate. Esfenvalerate is a pyrethroid insecticide and is an isomeric enriched technical grade of fenvalerate (PC Code 109301). There are more recent toxicity studies with esfenvalerate and there are also earlier studies with fenvalerate which have been used to characterize the toxicity of esfenvalerate. Fenvalerate use has been withdrawn.

Esfenvalerate and fenvalerate belong to the Type II subclass of pyrethroids that usually have a cyano group attached to the *alpha* carbon (refer to structure on page 2). The type II pyrethroids produce a characteristic toxicity response in both insects and mammals that is distinct from the type I pyrethroids. The Type I pyrethroids produce responses more closely resembling the fine tremors seen with DDT. The type II pyrethroids produce responses that include choreoathetosis writhing in mammals. It is generally recognized that the sodium conductance channel is the site of action of both type I and type II pyrethroids although the kinetics of the interaction between the type I and type II pyrethroids and the channel are different to produce the differences in responses.

Acute Toxicity. Esfenvalerate is considered moderately toxic via the oral route having an LD_{50} of 87.2 mg/kg (Toxicity Category II) but is less toxic by the dermal route (Toxicity Category III). Esfenvalerate is mildly irritating but not a sensitizer. No acute inhalation study with esfenvalerate was available.

Oral Subchronic and chronic toxicity. In the subchronic toxicity study with esfenvalerate in rats decreased body weight and signs of neurotoxicity (jerky leg movements) were evident. The indications of body weight decrease and signs of neurotoxicity (decreased motor activity and hindlimb grip strength) were also apparent in the two subchronic neurotoxicity studies with esfenvalerate. In a chronic feeding study, dogs demonstrated signs of neurotoxicity as indicated by emisis, head shaking, biting extremities as well as the systemic effects including normocytic anemia, increased serum cholesterol, and possible hepatic microgranulomatosis. Mice also show weight loss and anemia, reactive responses in the lymphatic tissue in multiple locations and hepatic microgranuloma and giant cell formation in the liver and spleen.

Esfenvalerate and other type II pyrethroids produce a dermal "pyrethroid reaction" that leads to a specific type of irritation in rats and mice probably resulting from contact with feed. This irritation results in scratching and skin lesions that can become infected and confounding the results of subchronic and chronic studies.

Dermal Subchronic toxicity. Subchronic dermal toxicity studies indicated that fenvalerate did not result in toxicity to rabbits at the limit dose. However, no NOAEL could be established for "abnormal gait" in the rat.

Neurotoxicity. Early in the development of pyrethroids there were concerns that higher doses resulted in a specific degeneration of the peripheral nervous system and extensive studies were conducted to attempt to determine the potential for fenvalerate or esfenvalerate to cause this type of neuropathy. The recently conducted acute and two independent studies subchronic studies with rats did not indicate neuropathy at the doses tested. The overall current conclusion is that

NOAELs have been established for induction of neuropathy (i.e. there was no neuropathy in the recent guideline subchronic neurotoxicity studies and only following higher near lethal doses will a sparse peripheral neuropathy possibly result.

Developmental and Reproductive Toxicity. The rat and rabbit developmental toxicity studies did not indicate that there was developmental toxicity (either quantitative or qualitative) at dose levels at or below maternal toxicity. There was no increased susceptibility in the rat or rabbit developmental toxicity studies at the highest doses tested.

The rat multi-generation reproduction study did not indicate any adverse effects on reproductive performance and parental toxicity consisted of dermal reactions and body weight effects and at higher doses there was abnormal gait in the P1 generation. At the highest dose, the F1 generation could not tolerate the same dose as the P generation and demonstrated in addition to abnormal gait, tremors, ataxia, hyperactivity, vocalization, hypersensitivity and eventual death even after lowering the dose.

Carcinogenicity. The existing data base consisting mainly of a rat study with fenvalerate and a mouse study with esfenvalerate did not indicate increased incidence of neoplasia. These studies are considered to have been studied at dose levels considered adequate for carcinogenicity evaluation. Fenvalerate/esfenvalerate is currently classified as a Group E chemical, no evidence of carcinogenicity in rats or mice.

Mutagenicity. There is no mutagenicity concern for fenvalerate/esfenvalerate based on the weight of evidence of the studies submitted thus far. There is, however, no study for the category "other mechanisms" and a study to meet this requirement is needed.

Immunotoxicity. There were no indications that indicate a specific concern for immunotoxicity.

Endocrine Effects. The studies submitted as guideline studies did not provide any obvious indications that fenvalerate/esfenvalerate have specific endocrine disruptive effects. Some studies appearing in the literature suggest that some pyrethroids and their metabolites may have endocrine disrupting effects. At least one publication (Maitri et al, Biochem. Biophys. Res. Commun. 214:905-909, 1995) reports that fenvalerate inhibits thyroid function and depresses 5'D-1 activity in mice. Another paper (Tyler et al, Environmental Toxicology and Chemistry, 2000, 19:80-809) raised the possibility that pyrethroids and their degradative metabolites as a class have endocrine activities. Fenvalerate/esfenvalerate may need further assessment for potential endocrine effects when guidelines for testing for endocrine effects are finalized.

Metabolism and Pharmacokinetics. The metabolism and pharmacokinetics data base for fenvalerate and esfenvalerate demonstrated the absorption, excretion and distribution and identification of the principle metabolites.

2.0 REQUIREMENTS

The requirements (CFR 158.340) food and other uses for esfenvalerate are listed in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1. Toxicity Data requirements for esfenvalerate.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	no
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
870.3150	Oral Subchronic (nonrodent)	yes	(a)
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	--
870.3465	90-Day Inhalation	yes	no
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)	refer to 870.4300b	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
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	no
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	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 (special protocol)	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	--
Special Studies for Ocular Effects		no	--
	Acute Oral (rat)	no	--
	Subchronic Oral (rat)	no	--
	Six-month Oral (dog)	no	--

(a) The dog chronic feeding study together with its preliminary dose range finding study meets this requirement

3.0 DATA GAP(S)

The following studies are to be conducted with **esfenvalerate.**

870.1300. Acute Inhalation Toxicity - required to satisfy the 870.1300 data gap.

870.3465. 90-day inhalation study - required because of the concern for repeated inhalation exposure from the greenhouse uses of formulated esfenvalerate/fenvalerate products. The protocol should include FOB measures and motor activity.

870.6300. Developmental neurotoxicity-with special protocol for pyrethroids. It is recommended that the registrant contact the Agency to discuss the test protocol (Draft OECD TG 426) with special emphasis on neonatal administration to pups by gavage as well as other possible modifications).

870.5xxx. Mutagenicity - other mechanism.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity for esfenvalerate is considered complete except for an acute inhalation toxicity study. No additional studies are required at this time.

The acute toxicity data on the esfenvalerate Technical is summarized below in Table 2.

Table 2. Acute Toxicity Data on esfenvalerate

Acute Toxicity of Esfenvalerate (PC Code 109303)

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral	00144973	LD_{50} = 87.2 mg/kg	II
81-2	Acute Dermal	00156508	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation	Not available	Not available	Not available
81-4	Primary Eye Irritation	00156509	Mild irritation	III
81-5	Primary Skin Irritation	00156510	Mild irritation*	IV
81-6	Dermal Sensitization	41215203	Negative*	N/A

*Esfenvalerate and other type II pyrethroids cause a special type of dermal irritation on contact that is indicated by tingling and other signs.

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete. No additional studies are required at this time.

870.3100 90-Day Oral Toxicity - Rat

First Study-Executive Summary. In a 90-day oral toxicity study (1984, Accession numbers 257018, 257019, 257020; no MRID No. 00151030) MO 70616 (esfenvalerate ; 98.7% parent isomers, 84% of which were the A-alpha isomer; batch/lot # not provided) was administered to 30 Sprague-Dawley rats/sex/dose in the diet at levels of 0, 50, 150, 300, or 500 ppm (mg/kg bw/day equivalents were not provided) for either 7 or 13 weeks. Fifteen animals/sex/group were killed at terminal sacrifice (13 weeks), 10 animals/sex/group were terminated at seven weeks, and an additional 5 animals/sex/group were selected for electron microscopy.

"Jerky leg movements" (described as shaking of the forepaws in a fanning motion as the limb was raised, prolonged or exaggerated flexion of the hind limb, and momentary suspension of the hind limb in a posterior position during ambulation) and/or unsteady gait were noted by 18 males and 24 females from the 300 ppm group at some point during the study, and by one male from the 150 ppm group during week 11. Body weight gains were decreased in males treated at the 300 and 500 ppm dose levels during weeks 1-6 and in females treated at the 500 ppm dose level during weeks 1-5. At 500 ppm, five females, three of these deaths were from "self-inflicted trauma" and two were suspected as occurring as the eventual sequella of neurological clinical signs. At some point during the study, all animals in the 500 ppm group exhibited an unsteady gait and/or "jerky leg movements", with the earliest observations occurring by the end of week 1. In addition, four females were hypersensitive to sound during a portion of the study, and one female was hyperactive during weeks 11-14. The most severely affected were hypersensitive to sound and had body tremors and/or convulsions eventually leading to death. The females that died from self-inflicted trauma exhibited rough hair coat and/or scabs on the tail prior to death. There was a corresponding decrease in food consumption by females in the 500-ppm group during weeks 1-5, while relative food consumption (g/kg bw) by both sexes was increased during weeks 6-13. At terminal necropsy, 3 males and 1 female from the 500 ppm group and 1 female in the 300 ppm group had a scab-covered area at the base of the tail, with corresponding microscopic observations of slight to moderate dermatitis. No treatment-related effects were found on absolute or relative organ weights. At the 500 ppm treatment level, 2/10 interim sacrifice males and 3/15 terminal sacrifice males exhibited slight hypertrophy of the parenchyma cells of the pars intermedia in the pituitary gland. Slight hypertrophy of the parenchyma cells of the parotid salivary gland was noted at interim sacrifice in 4/10 males and 4/10 females from the 500 ppm group, and at terminal sacrifice in 6/15 males and 4/10 females from the 500 ppm group. Two of the rats also had concurrent hypertrophy of the submaxillary salivary glands. At terminal sacrifice 1/14 males and 3/15 females from the 300-ppm group had slight hypertrophy of the parenchyma cells of the parotid salivary gland. There were no significant treatment-related effects on hematology, clinical chemistry, or urinalysis parameters. **The LOAEL is 150 ppm based on clinical signs of neurologic dysfunction ("jerky leg movements"). The NOAEL is 50 ppm.**

This 90-day oral toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study in the rat (OPPTS 870.3100; OECD 408).

ORNL REVIEWER'S COMMENTS: This updated Executive Summary does not alter the conclusions of the original DER. The decreased body weight gains, and differences in food consumption were not quantified in the original DER. The original DER stated that electron microscopy was conducted on nervous tissues from one animal; however, these results were not reported in the DER. Although the DER stated that the test material (MO 70616) was Fenvalerate/Pydrin, according to two different DERs

(MRID 41359701 and 41359701), MO 70616 is a synonym for esfenvalerate.* The original reviewer requested that information describing the "self-inflicted trauma"that caused the deaths of 3 females from the 500 ppm group be forwarded to the agency; it is not known if this information was submitted. *Since the composition of the test material is described as being 84% A-isomer, the test material is esfenvalerate and not fenvalerate.

Second Study-Executive Summary. In a 90-day oral toxicity study (1987, MRID 40215601) MO 70616 [esfenvalerate; purity 98.6% (82.9% A-alpha isomer); batch/lot # not provided] was administered to 15 Sprague-Dawley rats/sex in the diet at levels of 0, 75, 100, 125, or 300 ppm (mg/kg bw/day equivalents were not provided) for 13 weeks. An additional 10 animals/sex/ group were maintained at the same doses and then killed at an interim sacrifice at 7 weeks. Selected organs were weighed, including liver, lungs, heart, kidneys, testes, ovaries, uterus, and brain; however, histopathology was not done on any tissues.

At the 300 ppm dose level, 5 females exhibited hyperactivity during weeks 11-13, and 5 to12 rats (both sexes) exhibited "jerky leg movements,"described as prolonged posterior extension, flexion, and/or elevation of one or both hind limbs. Decreased body weight gains were noted for 300 ppm males throughout the study and for 300 ppm females during weeks 3-7 and 12. There were no treatment-related effects on organ weights noted at interim sacrifice. At terminal sacrifice, females from the 300 ppm group had increased absolute and relative kidney weights, and males from the 300 ppm group had increased relative kidney weights. In an earlier 13-week study with MO 70616 in the rat (1984, Accession numbers 257018, 257019, 257020; no MRID provided), sections of kidney tissue from all animals from groups treated at dose levels of 0, 50, 150, 300, or 500 ppm were examined microscopically at both interim and terminal necropsies, and no treatment-related findings were reported; therefore the increased kidney weights observed in the current study were not considered adverse effects of treatment.

The LOAEL is 300 ppm based on decreased body weight gains and clinical signs of neurologic dysfunction (hyperactivity and "jerky leg movements") in both sexes. The NOAEL is 125 ppm.

This study is classified **Acceptable/Non-Guideline** and does not satisfy the guideline requirement for a 90-day oral toxicity study in the rat (82-1, OPPTS 870.3100; OECD 408) because no histopathology was done.

COMMENTS: This updated Executive Summary does not alter the conclusions of the original DER with regard to assigning the LOAEL and NOAEL, except the ORNL reviewer added decreased body weight gains to the basis for the LOAEL. The ORNL reviewer questions whether this study should be classified Acceptable/Guideline since no histopathology was done. The decreased body weight gains were not quantified in the original DER. In an earlier (1984) 13-week study with MO 70616 in the rat (Accession numbers 257018, 257019, 257020; no MRID provided), females treated with 150, 300, and 500 ppm had increased relative kidney weights at the 7-week interim sacrifice but not at the terminal sacrifice, and males treated at 300 and 500 ppm dose levels had increased relative kidney weights at terminal sacrifice; however, these observations were not considered treatment-related due to the small magnitude of the differences, the lack of dose-response relationships, and/or the likelihood that these differences reflected differences in body weights among the control and treated animals. In the same study (Accession numbers 257018, 257019, 257020), sections of kidney tissue from all animals from all groups were examined microscopically at both interim and terminal necropsies, and no treatment-related findings were reported.

870.3100 90-Day Oral Toxicity - Mouse (MRID 41359701 , HED Doc 08967).

Executive Summary. In a special 90-day oral toxicity study (1985, MRID 41359701) esfenvalerate (S-

1844, purity: 94.5%, Aα:Bα:Aβ:Bβ=87.2: 7.4: 4.8: 0.6; batch/lot # not provided) was administered to 12 B6C3F1 mice/sex/dose in the diet at levels of 0, 50, 150, or 500 ppm (equivalent to 0, 10.5, 30.5, or 106 mg/kg bw/day for males and 0, 12.6, 36.8, or 113 mg/kg bw/day for females). An additional group of 12 animals/sex received fenvalerate (S-5602, purity: 95.5%, Aα:Bα:Aβ:Bβ = 24.2: 25.4: 26.3: 24.1; batch/ lot # not provided) in the diet at a dose of 2000 ppm (equivalent to 422 and 462 mg/kg bw/day for males and females, respectively).

Esfenvalerate. Decreased body weight *gains* were observed in the 150 ppm mid- (up to 18.% for the 28-63 day interval) and 500 ppm high- (44 to 64%) dose male and high-dose female (25 to 53%). The decrease in males at 150 ppm is considered minimal. Effects noted in the 500 ppm high dose included, significantly decreased water consumption during the first week of treatment but became significantly increased by week 7 through the remainder of the study. The following clinical signs were evident: fibrillation; tremors; convulsions; hypersensitivity (decreasing occurrence after week 4); abnormal gait; salivation (week 1 only); scratching; licking (after week 3); alopecia; and scabs and sores (after week 4). There were also statistically decreased RBCs and HGB males had decreased HCT and females had decreased MCH and MCHCs. Clinical chemistry revealed significantly decreased ($p \leq 0.05$) glucose, cholesterol, triglyceride, total protein and phospholipid concentrations in both sexes and decreased albumin in males. There were significantly increased activities of lactate dehydrogenase (LDH, $p<0.01$ females only), leucine aminopeptidase (LAP, $p<0.01$) and alanine aminotransferase (ALT, $p<0.05$, females only). The urine was significantly more concentrated and had a lower pH than control mice. At necropsy, increased incidences of alopecia, scabs, and sores as well as hyperkeratosis, dermatitis, ulceration, and/or hair follicular cysts were noted. There were increased absolute liver weights, increased absolute and relative salivary gland weights, and decreased absolute spleen weight (females only). Four/12 high-dose males had dark red spots in the stomach and 2/12 high-dose males were found to have fundic gland dilation, erosion and ulceration of the gastric mucosa, and gastritis. A white substance was found in the urinary bladder of 4/12 high-dose males. Inguinal lymph node enlargement was observed in 3/12 and 7/12 high-dose males and females, respectively. Additional histopathology findings included increased incidences of "starry sky formation" in the spleen, mesenteric lymph nodes, and thymus of both sexes, and mandibular and inguinal lymph node hyperplasia in male mice. **The LOAEL for esfenvalerate is 500 ppm (106 mg/kg bw/day for males; 113 mg/kg bw/day for females), based on clinical signs consistent with neuro- and hepatic toxicity, effects on water intake, anemia, gross and microscopic skin lesions, reactive responses in lymphatic tissue in multiple locations, and gastric mucosal erosion and ulceration, gastritis, and fundic gland dilatation. The NOAEL for S esfenvalerate is 150 ppm (30.5 mg/kg bw/day for males; 36.8 mg/kg bw/day for females).** A slight decrease in weigh gain in males was not included in the LOAEL.

This is classified **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study in the mouse (OPPTS 870.3100; OECD 408) for esfenvalerate.

Fenvalerate. Effects noted at 2000 ppm fenvalerate were generally similar to those found in mice treated with 500 ppm esfenvalerate. The same clinical signs were observed; both sexes had decreased body weight gains; and initially decreased followed by significantly increased water intakes. Both sexes had decreased HGB, MCH, and WBCs, and increased percentages of neutrophils. In addition, female mice had decreased HCTs, MCV, and MCHC. Both sexes had decreased glucose concentrations, males had decreased cholesterol and triglyceride concentrations, and females had increased BUNs. Both sexes had significantly increased AST, LDH, LAP, and ALT activities. The urine of treated mice was more acidic and concentrated. At necropsy, increased incidences of alopecia, scabs, and/or sores were noted from both sexes along with microscopic skin lesions that included hyperkeratosis, dermatitis, ulceration, and/or hair follicular cysts. Treatment also increased the absolute and relative liver weights, absolute salivary gland weights (females only), relative salivary gland weights, and absolute and relative spleen weights. Additional histopathology included increased incidences of "starry sky formation" in the spleen, mesenteric lymph nodes, and thymus of females, and lymphoid

hyperplasia in the mandibular and inguinal lymph nodes of both sexes and the ancillary lymph nodes of males. The primary difference between esfenvalerate and fenvalerate was the presence of hepatic microgranulomas and giant cell infiltration in the liver, spleen, and/or mandibular and mesenteric lymph nodes of mice treated with fenvalerate. **The LOAEL for fenvalerate is ≤2000 ppm (422 and 462 mg/kg bw/day for males and females, respectively) based on clinical signs consistent with neuro- and hepatic toxicity, effects on water intake, anemia, gross and microscopic skin lesions, reactive responses in lymphatic tissue in multiple locations, gastric mucosal erosion and ulceration, gastritis, and fundic gland dilatation, and hepatic microgranulomas and giant cell formation in the liver and spleen. A NOAEL was not identified.**

This study is classified **Acceptable/Nonguideline** and does not satisfy all of the guideline requirements for a 90-day oral toxicity study in the mouse (OPPTS 870.3100; OECD 408) for fenvalerate. It does, however, provide useful supplementary information.

ORNL REVIEWER'S COMMENTS: This Executive Summary does not alter the conclusions from the original DER. The times of the first occurrences of most of the clinical signs were not reported in the original DER and therefore could not be included. On p. 14 of the DER (microscopic pathology; non-neoplastic lesions), there is a reference to "Table 9" for details of organs with giant cell infiltration and "Table 10" for details regarding observations of lymphadenitis simplex in several different locations. However, Table 9 of the DER contained urinalysis results, Table 8 contained selected histopathology findings. Although the report stated that MO 70616 was a synonym for Esfenvalerate, according to a different DER (Accession numbers 257018, 257019, 257020; no MRID provided) MO 70616 is Fenvalerate.

870.3150 90-Day Oral Toxicity - Dog

There is no series 870.3150 subchronic toxicity study with *esfenvalerate* in dogs available but there is a chronic feeding study with a supporting range finding study (see below).

870.3200 21/28-Day Dermal Toxicity –

A. First Study - 1992 (rabbits).

Executive Summary. In a 21-day dermal toxicity study (1992, MRID 42325101), Fenvalerate (technical) (95.4% a.i.) was applied to the shaved skin of 5 New Zealand white rabbits/sex/dose at dose levels of 0, 100, 300, or 1000 mg/kg bw/day, 6 hours/day during a 21-day period for an unspecified number of days/week . There were no compound related effects on mortality, clinical signs, body weight, food consumption, feed efficiency, hematology, clinical chemistry, organ weights, or gross and histologic pathology. **The systemic NOAEL is greater than or equal to 1000 mg/kg bw/day, and the systemic LOAEL is not identified.**

There were treatment-related increased incidences of dermal irritation which included the following: moderate erythema in 2/8, 2/10, 4/8, and 4/10 animals; mild edema in 0/8, 1/10, 3/8, and 3/10 animals; superficial necrosis in 0/8, 0/10, 3/8, and 4/10 animals; and scar tissue in 0/8, 0/10, 3/8, and 2/10 animals in the control, low-, mid-, and high-dose groups, respectively. **The dermal LOAEL is 300 mg/kg/day, based on increased incidence of dermal irritation (moderate erythema, mild edema, superficial necrosis, and/or scar tissue). The dermal NOAEL is 100 mg/kg/day.**

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a 21-day dermal toxicity study in the rabbit (OPPTS 870.3200; OECD 410).

ORNL REVIEWER'S COMMENTS: This Executive Summary does not alter the conclusions of the

previous DER with regard to systemic toxicity. The original reviewer set different NOELs for dermal irritation in the discussion section and the section entitled "Results of the Review" (100 and 300 mg/kg bw/day, respectively). The ORNL reviewer used a NOAEL of 100 mg/kg bw/day as it was consistent with both the discussion section and the rationale provided for the NOEL/LOEL in the "Results of the Review" section; however, it must be noted that none of the incidences of dermal findings exhibited a dose-response pattern, even when the sexes were combined. The batch/lot # was not reported in the original DER; it is unknown whether this information was included in the study report. The original DER also failed to report the number of days/week the animals were treated or the total number of treatments the animals received.

B. Second study - 2000 (rats).

In a 21-day dermal toxicity study (2000, MRID 45275401) esfenvalerate (98.6% a.i., batch/lot # DPX-YB656) was applied to the shaved skin of 10 rats/sex (Crl:CD®(SD)IGS BR) at dose levels of 0, 25, 125, 500 or 1000 mg/kg bw/day, 6 hours/day everyday during a 21-day period. The rats were assessed for clinical signs, dermal effects and FOB and motor activity were assessed at pretest and just prior to sacrifice.

Abnormal hindlimb gait was noted during the daily assessment for clinical signs and was noted in 0, 1, 10, 10 and 10 females and 1, 0, 5, 10 and 10 males for the control, 25, 125, 500 and 1000 mg/kg/day dose groups, respectively. Abnormal gait was seen usually on days 0 to about day 6 or 7 with only occasional occurrences on later days and was not noted in the FOB assessment prior to sacrifice. The single incident at 25 mg/kg/day in females was noted on Day 2 when the rats treated at higher doses also displayed this condition. However, the single incident in the control male group was noted on Day 10 after most of the males stopped showing the condition. Since abnormal gait is consistent with esfenvalerate toxicity and all of the females at the next higher dose develop this condition, the single incident at 25 mg/kg/day is considered related to treatment. **Motor activity** data were confounded by the pretest baseline data being elevated in the higher dose groups but even after accounting for the higher baseline there was an increased mean number of movements and duration of movements in the female 500 and 1000 mg/kg/day dose groups. However, it could not be determined whether the property of esfenvalerate to produce a dermal sensory stimulation may have been related to certain reactions in females such as hyperactivity and reactivity, corneal opacity and increased motor activity at doses of 500 mg/kg/day and above or if these were the result of systemic esfenvalerate following dermal absorption. **The NOAEL is 25 mg/kg/day. The LOAEL is 125 mg/kg/day based on abnormal hindlimb gait. Note:** It should be noted that 25 mg/kg/day is regarded as a LOEL since one female was affected. Since there was no commutative effect, this incident of abnormal gait in a single animal was not considered an *adverse* effect.

The LOAEL for local site of application for dermal *irritation* is > 1000 mg/kg/day. However, no NOAEL and LOAEL is being assigned for sensory stimulation following dermal application since HED does not have established criteria for evaluating this endpoint.

Classification: This 21-day dermal toxicity study in the rat is ACCEPTABLE/Guideline and satisfies the guideline requirement for a 21-day dermal toxicity study (OPPTS 870.3200 ; OECD 410) in the rat.

870.3465 90-Day Inhalation – Rat

There is no subchronic inhalation toxicity study available. Refer to the chronic toxicity study with dogs below.

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time.

870.3700a Prenatal Developmental Toxicity Study - Rat

Executive Summary *(Revised from the original DER).* Esfenvalerate (97.1% purity) was administered to groups of 25 Sprague Dawley Crl:CD®BR female rats by gavage at doses of 0, 2.5, 5.0, 10.0 or 20.0 mg/kg/day from gestation days 6 through 15 in the main study (1991, MRID No.: 43211504) and in the pilot study (1991, MRID No.: 43211502) the doses were 1.0, 2.0, 3.0, 4.0, 5.0 and 20 mg/kg/day.

Maternal toxicity. At 2.5 mg/kg/day there were behavioral/CNS clinical signs including erratic jerking and extension of forelimbs (22/25 rats), rapid side-to-side head movement (19/25 rats), and excessive grooming (22/25 rats). At 5 mg/kg/day there was also hindlimb jerking and soft or mucoid stools. At 10 mg/kg/day hypersensitivity to touch and tremors were also seen. At 20 mg/kg/day there were high carriage, goose stepping ataxia, ataxia and convulsions. Incidence and frequency increased with increasing dose. Most signs were observed at 4 hours post dosing but resolved by the next day. At 20 mg/kg/day some signs were observed as early as 1 hour post dosing. The pilot study had similar types of signs at 4 mg/kg/day and above but no signs at 3 mg/kg/day and below. **The NOAEL is 2.0 mg/kg/day (from the pilot study) and the LOAEL is 2.5 mg/kg/day based on behavioral/CNS clinical signs.**

Developmental Toxicity. There was no evidence of developmental toxicity at any dose. **The NOAEL is 20 mg/kg/day, the highest dose tested.**

This study is classified ACCEPTABLE/Guideline. This study satisfies the guideline requirement for a developmental study (83-3a) in rats.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

Executive Summary. *(Revised from the original DER).* Esfenvalerate was administered to groups of 20 New Zealand White female rabbits by gavage at doses of 0, 3, 10 or 20 mg/kg/day from gestation days 7 through 19 in a developmental toxicity study (1990, MRID No.:43211503). In a pilot study (1990, MRID No.: 43211501) the doses were 0, 2.0, 3.0, 4.0, 4.5, 5 or 20 mg/kg/day.

Maternal toxicity. At 3.0 mg/kg/day there behavioral/CNS clinical signs including erratic jerking and extension of forelimbs (11/20 rabbits), rapid side-to-side head movement (2/20 rabbits), excessive grooming (11/20 rabbits) and sneezing (3/20 rabbits). At 10.0 mg/kg/day there was also hindlimb jerking and hypersensitivity to touch. At 20.0 mg/kg/day there were tremors, ataxia, diarrhea, decreased defecation and urination. Incidence and frequency increased with increasing dose. Most signs were observed at 1 to 4 hours post dosing and lasting to the next day for rabbits in the 10.0 and 20.0 mg/kg/day groups. The pilot study had similar types of signs at 3.0 mg/kg/day and above but no signs at 2.0 mg/kg/day. Body weight, body weight gain and food consumption were also decreased in the 10 and 20 mg/kg/day group in the main study. Body weight and food consumption changes were not observed in the pilot study. **The NOAEL is 2.0 mg/kg/day (from the pilot study) and the LOAEL is 3.0 mg/kg/day based on behavioral/CNS clinical signs.**

Developmental Toxicity. There was no evidence of developmental toxicity at any dose. **The NOEL is equal to or greater than 20.0 mg/kg/day, the highest dose tested. The LOAEL is greater than 20.0 mg/kg/day.**

This study is classified **ACCEPTABLE/Guideline.** This study satisfies the guideline requirement for a developmental study (83-3b) in rabbits.

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time.

870.3800 Reproduction and Fertility Effects - Rat

Executive Summary *(Revised from the Original DER).* In a two generation reproduction study in rats (1994, MRID No.: 43489001), esfenvalerate (98.8%, Lot # 20253) was administered to groups of 30 male and 30 female Crl:CD BR rats at dose levels of 0, 75, 100 or 350 ppm to the P generation. The 350 ppm dose group was reduced to 150 ppm during weaning of the F1 generation. However, the 150 ppm dose was still too toxic to the F1 parental group and an F2 generation was produced for the controls, 75 and 100 ppm dose levels only. Mean compound intake in mg/kg/day during the premating periods was approximately 4.21, 5.55 and 18.8 for males and 5.56, 7.18 and 25.1 for females for the 75, 100 and 350 ppm dose groups P1 groups. For the F1 groups, mean compound intake in mg/kg/day was 5.98 and 7.84 for males and 7.31 and 10.4 for females for the 75 and 100 ppm dose groups. The males and females in the group dosed with 150 ppm received a mean dose of 18.93 (for 28 days) and 19.25 (for 42 days) mg/kg/day prior to sacrifice.

Parental systemic toxicity and reproductive effects. Parental toxicity consisted of dermal reactions manifested by sores and scars with nearly all females in the high dose group affected and at least one male in the 75 ppm dose P group was affected. These dermal reactions as well as other indications of neurotoxicity were so severe that F1 adults dosed at 150 ppm had to be sacrificed and no progeny for an F2 generation were produced. Body weight was decreased slightly at 75 ppm during premating (4.9% ♂ and 4.7% ♀)) and gestation (7.1% for days 7-14) for the F1 group with slightly greater decreases at 100 ppm but not for the P1 group. Clinical signs indicative of type II pyrethroid toxicity were evident in the P1 generation (350 ppm) by abnormal gait/mobility (29 ♂ and 27 ♀ affected, none affected at lower doses). Abnormal gait was also seen in the F1 group and there were additional signs of neurotoxicity including: tremors (28 ♂ and 29 ♀), vocalization (8 ♂ and 4 ♀), ataxia (17 ♀), hyperactive (5 ♀) and hypersensitive (10 ♀). Since there were additional signs of neurotoxicity at 150 ppm in the F1 males and females, it is concluded that there is a qualitative increase in susceptibility in the F1 generation relative to the P1 generation. Exposure to esfenvalerate during gestation and lactation may be the cause of this increase in susceptibility. There were no adverse effects on the reproductive parameters such as fertility indexes, mating performance or gestation length. **The systemic LOAEL is 75 ppm (4.21 mg/kg/day) based on skin condition and decreased body weight.**

Offspring toxicity. At 100 ppm there were statistically significant decreases in the mean number of pups born alive (↓13%). Pup weight at day 14 and 21 was decreased for both the F1 and F2 generations (↓~6%). There were also 5 incidents of subcutaneous hemorrhage in the F2 pups in the 100 ppm dose group (none at lower doses). The F1 pups born to dams receiving 350 ppm esfenvalerate were noted to have abnormal gait, tremors, eyes not open and "small bodies". **The LOAEL for offspring toxicity (as pups to day 21) is 100 ppm (7.18 mg/kg/day in females) based on decreases in pup weight, decreases in litter size and increases in subcutaneous hemorrhage. The NOAEL is 75 ppm (5.56 mg/kg/day in females).**

This study is classified as **Acceptable/Guideline** and satisfies the requirement for a Series 83-

1 multigeneration reproduction study in rats.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time.

870.4100a (870.4300) Chronic Toxicity – Rat

Refer to 870.4300 below.

870.4100b Chronic Toxicity - Dog

Executive Summary. In a chronic toxicity study (1986, MRID No.: 00163855 and supplement 1985, MRID No.: 40376501) MO 70616 (esfenvalerate, purity 98.7%; lot #2-3-0-0) was administered to 6 beagle dogs/sex in feed at doses of 0, 25, 50, 100, or 200 ppm (estimated 0.625, 1.25 or 5 mg/kg bw/day) for one year. Doses were selected based on the results of a range-finding study (refer to MRID 40376501), in which 2 beagle dogs/sex/dose were administered the test material (purity = 98.7%, lot number WRC 730C) in feed at doses of 0, 100, 300, or 500 ppm.

In the chronic toxicity study, no treatment-related effects were found on mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, or gross and microscopic pathology. Based on these results, as well as lack of diet stability data, the study was originally considered Unacceptable(Ungradable)/Guideline.

Later, supplementary information including the results of the range finding study were submitted. The length of the study was not reported in the DER but is assumed to be 21-days. In this dose range study 3/4 dogs dosed at 500 ppm vomited on day 1 and ataxia, tremors and fasciculations were observed during week 3. One dog in the 300 ppm group was also ataxic during week 3. 500 ppm group dogs lost weight 6-25% and 300 ppm dogs lost 3-10% of their body weight during the study. Food consumption was also decreased in these groups. No other treatment-related effects were reported. **Based on the combined results of the range-finding and definitive studies the LOAEL is 300 ppm (estimated 7.5 mg/kg/day) based primarily on decreased body weights in both sexes and ataxia in one male during week 3. The NOAEL is 200 ppm (estimated 5 mg/kg/day).**

The combined information in the range finding and definitive studies are sufficient to upgrade the classification to **Acceptable/Guideline** and the two studies combined satisfy the guideline requirement for a chronic oral study in the dog [83-1, OPPTS 870.4100; OECD 452].

ORNL REVIEWER'S COMMENTS: This updated Executive Summary does not alter the conclusions of the original DER. The DER stated that the test material (MO 70616) was Fenvalerate; however, other DERs (MRID 41359701, 40215601) have stated that MO 70616 was Esfenvalerate. MO 70696 is the code for esfenvalerate. There were several deficiencies noted in the original DER for the main study, but all were resolved with the later submission of the range-finding study.

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time.

870.4200a Carcinogenicity Study - rat

Executive Summary: In a combined chronic/carcinogenicity study (1979, MRID 00079877 with a supplemental report in 1981, Accession no. 241208) technical SD-43775 (**fenvalerate**; purity 98%, batch/lot # not provided) was administered to 49 to 51 CRL:COBS CD (SD) Br albino rats/sex/dose in the diet at dose levels of 0 or 1000 ppm (50 mg/kg bw/day based on a food conversion factor of 0.05 for the rat) for two years. Females receiving the test material began dying approximately 16 weeks earlier than female controls and approximately 10 weeks earlier than treated males; however, the cumulative mortalities of all groups were similar (46, 42, 41, and 49% for male, female controls, treated males, and treated females, respectively). The only treatment-related clinical sign was hind limb weakness characterized as an abnormal gait in which the hind limbs would "falter," and the rat would use its front legs to pull itself along the floor of the cage. Six of 51 treated males exhibited transient hind limb weakness during the first 8 weeks, compared to none of the controls or treated females. Treated males had statistically significantly decreased body weights during weeks 16-104, and treated females had statistically significantly decreased body weights during weeks 44-104. The magnitude of the body weight differences between treated and control rats was not reported. There were no corresponding decreases in food consumption noted. Treated females had statistically increased gamma-globulin values (12.24% vs. 8.69% for controls); however, the toxicologic significance is unknown. **The LOAEL is 1000 ppm (50 mg/kg/day), based on body weight decreases in both sexes and transient hind limb weakness in males. Since there was one treatment dose, the NOAEL was not established.**

There was no treatment-related increase in tumor incidence for any anatomical site. Dosing was considered adequate based on clinical signs and decreased body weights at the one dose tested

This chronic/carcinogenicity study in the rat is **Acceptable/Non-Guideline**. Although alone it does not satisfy the guideline requirements for a chronic/carcinogenicity study in the rat [OPPTS 870.4300; OECD 453], it may be used to provide supplemental information when considered in conjunction with other, similar studies.

870.4200b Carcinogenicity (feeding) - Mouse

Executive Summary: In a mouse oncogenicity study (1997, MRID 44260601), 80 CD-1 mice/sex/dose were fed diets containing **esfenvalerate** (98.8% total isomers, 84.8% S,S isomer) at levels of 0, 35, or 150 ppm [equivalent to 0, 4.29/5.74, or 18.3/24.7 mg/kg/day (M/F)] for 18 months. In addition, a 350 ppm group was started concurrently, but was terminated after 57-58 days due to excessive morbidity and mortality.

Food consumption, overall food efficiency, hematology, and clinical chemistry parameters were unchanged or not of toxicological concern. Ophthalmoscopic examination revealed no changes. Changes and lesions observed in treated mice were attributable to self-mutilation or secondary effects of self-mutilation. Self-mutilation occurred due to the induction by the test substance of dermal sensations that stimulate scratching by the mice (a well-known toxicological effect of pyrethroids). Thus, these lesions are not considered to be a direct effect of esfenvalerate on the mice; however, the skin sensations which preceded these, and stimulated the scratching and self-mutilation are a direct systemic effect associated with administration of esfenvalerate.

All treated mice exhibited significantly ($p<0.05$) increased alopecia, serosanguinous fluid from sores, skin sores, and swollen ears. There was a significant ($p<0.05$) increase in mortality in the 350 and 150 ppm treatment groups due to skin inflammation/necrosis caused by self-trauma. Despite treatment to ameliorate the effects of self-trauma, excessive morbidity and mortality in the 350 ppm group continued and this group was removed from the study on test days 57-58. The animals were examined at necropsy and tissues were collected. Data from these animals were not used in the evaluation of the oncogenicity

or chronic toxicity of esfenvalerate. At 358 days, survival in the 150 ppm group was 70-71% versus 95% in the 35 ppm treatment group and controls. At termination (547 days), survival in the 150 ppm group was 41-46% versus 66-75% ($p<0.05$) in the other groups. The survival rates exceeded the guideline requirement (not less than 25%) for this interval. In the 350 ppm group, significantly lower mean body weight was recorded from the first or second week of the study until the last weigh period on day 56 (↓15% and 11%, males and females, respectively). No data on body weight gains were submitted for this group. In the 150 ppm group, body weights were sporadically lower, but only significantly lower ($p<0.05$) in females at termination (9%). Body weight gains from 0-547 days were significantly reduced in females (↓22%, $p<0.05$). No toxicologically significant decreases in body weights were observed in the 35 ppm treatment group; however, body weight gains were reduced (↓7-19%), but were not statistically significant. The reductions in body weight (cachexia) can be attributed to the chronic inflammation the mice experienced over the course of the study. At termination, increased absolute (↑25%, $p<0.05$) and relative (↑52%, $p<0.01$) spleen weights were detected in the 150 ppm females. The increased spleen weights are believed to be due to the increased extramedullary hematopoiesis in females afflicted with skin erosion and/or ulcers. Grossly, the 150 ppm male and female mice exhibited enlarged spleens (27-31/80 treated vs 11-17/80 controls), increased skin ulceration/erosion (24-29/80 treated vs 4-7/80 controls), and alopecia (30-31/80 treated vs 7-17/80 controls). The 150 ppm females also exhibited enlarged mandibular lymph nodes (11/80 treated vs 4/80 controls). Microscopically, the 150 ppm groups had increased skin erosions/ulcers (39-44/80 treated vs 6-14/80 controls) and eye lesions (erosions/ulcers/keratopathy - 5-8/80 treated vs 0-2/80 controls). These lesions are considered secondary physiologic responses to the chronic inflammation due to self mutilation. Also increased in the 150 ppm group were spleen extramedullary hematopoiesis (48-56/80 treated vs 22-26/80 controls), bone marrow granulocytic hyperplasia (42-44/79 treated vs 10-18/79), and mandibular lymph node lymphocytic/plasmacytic hyperplasia (29-32/79 treated vs 9-17/79 controls). In conclusion, the dose levels employed in this study were the highest possible because of self-mutilation. Self-mutilation occurred due to induction by the test substance of dermal sensations (typical of pyrethroids); these sensations stimulate scratching which then progresses to self-mutilation. **Based on the observations of skin lesions due to scratching in all treated mice, as a response to the dermal sensations induced by esfenvalerate, the systemic LOAEL in this study is 35 ppm (4.29/5.74 mg/kg/day [♂/♀]). A NOAEL is not established.**

No treatment-related increase in neoplasia was observed at the highest dose which could be achieved with esfenvalerate in CD-1BR mice (see discussion).

The submitted study is classified as **ACCEPTABLE/Guideline** and satisfies the guideline requirements for an oncogenicity study (§83-2(b)) in mice.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data base for Mutagenicity is considered incomplete. A study from the "other mechanisms" category is required.

Study	Results
Gene mutation	

Study	Results
Salmonella/mammalian activation gene mutation assay. Takarazuka Research Center, Study No.: LLT-50-0009, December 28, 1985. MRID No.: 41316301.	No evidence of induced mutant colonies up to and including 5000 µg/plate in *Salmonella typhimurium* strains TA98, TA1537, TA1538 and in *Escherichia coli* strain WP2 (evrA).
HGPRT locus mammalian cells in culture: gene mutation assay. Takarazuka Research Center, Study LLT-50-0012, December 28, 1985. MRID No.: 41316302.	No evidence of induced mutant colonies in the HGPRT mammalian gene locus in Chinese Hamster V70 cultured cells.
Chromosome aberration	
In vitro mammalian cytogenetic chromosomal aberration study in Chinese Hamster ovary cells. Takarazuka Research Center, Study No.: LLT-50-0010, December 28, 1985. MRID No.: 41215204.	No evidence of induction of chromosomal aberrations or polyploid cells induced by esfenvalerate.
Other mechanism	
No study.	

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity:

870.6100 Delayed Neurotoxicity Study - Hen

Study is not applicable for a pyrethroid.

870.6200 Acute Neurotoxicity Screening Battery

Executive Summary. In an acute oral neurotoxicity study (2000, MRID 45228301), a single dose of technical grade Esfenvalerate (Batch # DPX-YB656-84, 95.58% purity) was administered by gavage (in corn oil, 10 mL/kg) to groups of 10 male and 10 female Crl:CD®(IGS)BR rats at doses of 0, 1.75, 1.90, 20, or 80 mg/kg. Functional observational battery (FOB) and motor activity tests were preformed pretreatment, on the day of test material administration (day 1, 7-8 hours postdosing), and on days 8 and 15 post-treatment. At the completion of the study (day 15), 6 rats/sex in the control and high-dose groups were subjected to perfusion fixation, and brain and nervous system tissues were examined

microscopically.

During the FOB assessment on the day of treatment, *tremors* were observed in 0/10, 0/10, 1/10, 2/10, and 6/10 females in the control, 1.75, 1.90, 20, and 80 mg/kg groups, respectively. Since a dose response was evident, the single incident of tremors at 1.90 mg/kg is considered treatment related. In males, tremors were noted in the 20 (1/10) and 80 (2/10) mg/kg dose groups only. *Abnormal gait* was observed in 1/10, 0/10, and 4/10 males in the 1.90, 20, and 80 mg/kg groups but only in the 80 mg/kg females (7/10). In the absence of a dose-response relationship, the single incidence of abnormal gait in male rats in the 1.90 mg/kg group was not considered treatment related. Incidences of abnormal gait remained significantly increased ($p<0.05$) in both males (8/10) and females (3/10) in the 80 mg/kg groups on day 2 (as indicated by cage side observation, not FOB). In the *motor activity* test, the mean number of movements for females was 21% lower than the control number on the day of treatment. Duration of movement was non-significantly decreased by 17% for males and 19% for females in the 80 mg/kg group. Effects on the FOB and motor activity were no longer evident at the day 8 observation. Effects on *body weight* were minimal as losses occurred only during the 1-2 day interval being 17.1 gm for males and only 2.1 gm for females. For females, total weight gains but not final body weights were significantly ($p < 0.05$) reduced in the 1.90 (↓28%), 20 (↓32%), and 80 (23%) mg/kg groups but there was no dose response. There were no histopathological findings in the brain or tissues of the nervous system that could be attributed to treatment. **The LOAEL is 1.90 mg/kg in females and 20 mg/kg in males based on tremors. The NOAELs for females and males are 1.75 and 1.90 mg/kg, respectively.**

This study is classified **Acceptable/Guideline** as an acute oral neurotoxicity study and does fulfill FIFRA guideline requirements for an acute oral neurotoxicity study in rats **[OPPTS 870.6200 (§81-8)]**.

870.6200 Subchronic Neurotoxicity Screening Battery

Executive Summary. In a subchronic neurotoxicity study (1999, MRID 45202301), esfenvalerate (97.3% a.i., batch/lot # 60610G, 86% S,S-isomer) was administered to 12 Sprague-Dawley (CrlCD®(SD)BR rats/sex/group at dose levels of 0, 40, 120, or 360 ppm (equivalent to 0, 3, 8.9, or 28.8 mg/kg bw/day for males and 0, 3.7, 10.7, or 35 mg/kg bw/day for females) for 13 weeks. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in 12 animals/sex/group prior to treatment initiation and at weeks 2, 5, 9, and 13 of treatment. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, the control and high-dose groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues and their brains were weighted and measured.

At 120 ppm, *absolute mean body weights* were statistically decreased occasionally ($p<0.05$) in mid-dose males (5 to 7%) and in high-dose (9 to 14%) males and females (generally $p<0.01$) starting at day 8. Overall mean *body weight gains* were also decreased in mid-dose males (about 13%, $p<0.05$) and in high-dose males (22%) and females (28%), respectively. The decreases in body weight were not directly related to decreased *food consumption* as food consumption was decreased ($p<0.01$) only in high-dose males (18%) and females (22%) during the first week of treatment. *Motor activity* was statistically decreased ($p<0.05$ or 0.01) at week 2 in mid (↓29%)- and high-dose (↓32%), respectively) females, with the decreases occurring at each of the six intervals measuring activity.

At 300 ppm, males had an increased incidence of scabbing (5/12) and lesions (4/12) of the inguinal/sacral/ urogenital/scrotal regions, with the earliest onset occurring at day 30. Three of these five males exhibited ulcerations in these areas during gross pathology. Two of these had "ataxic gait" and one had "slight tremors" at week 13. Statistically significant FOB findings ($p<0.05$) observed at week 2 only were noted and included decreased *forelimb grip strength* in males (↓19%) and females (↓16%), respectively) and increased incidence in the *ease of removal* from the home cage in females (9/12 vs.

3/12 controls). Although not statistically significant, other findings observed during the week 2 FOB assessments included: decreased hindlimb grip strength in males (↓12%) and females (↓16%), respectively), decreased hindlimb foot splay in males (↓14%) and females (↓13%), respectively), increased grooming in males (4/12 vs. 0/12 controls), and decreased rearing in females (↓40% of controls). No significant effects were observed at any other time point for any measurements. High-dose There were no treatment-related effects on mortality, ophthalmology, brain weight, or neuropathology. **The LOAEL is 120 ppm (8.9 mg/kg/day for males and 10.7 mg/kg/day for females) based on decreased body weight and body weight gain in males and decreased motor activity in females. The NOAEL is 40 ppm (3.0 mg/kg/day for males and 3.7 mg/kg/day for females).**

This study is considered **ACCEPTABLE/Guideline** and fulfills FIFRA guideline requirements for a subchronic oral neurotoxicity study in rats (OPPTS 870.6200b).

(Second study-2000).

Executive Summary. In a subchronic neurotoxicity study (2000, MRID 45157501) Esfenvalerate (98.58% a.i., batch # 84) was administered to 12 Crl:CD rats/sex/group at dietary concentrations of 0, 50, 100, or 300 ppm (equivalent to 0, 3.22, 6.39, or 20.08 mg/kg bw/day for males and 0, 3.73, 7.26, or 22.78 mg/kg/day for females) for 91 days. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in 12 animals/sex/group pretest and during weeks 4, 8, and 13. At study termination, 6 animals/sex/group were perfused for neuropathological examination and the control and 300 ppm groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

Males in the 100 ppm dose group displayed reduced forelimb grip strength (Week 8, ↓26%, $p < 0.05$) and this parameter was reduced to 33 to 38% at next higher dose. Skin wounds, a symptom of type II pyrethroid exposure occurred later in the treatment period and 3 of 12 at 100 ppm and 6 of 12 at 300 ppm males were affected. Only one high dose female was affected. Two males were sacrificed due to the severity of the lesions.

At 300 ppm, clinical signs consisted of abnormal gait in all males and females starting by day 2 of treatment. Final body weight was decreased by 12% in male rats ($p<0.05$), which was consistent with reduced food intake and lowered food efficiency, and reduced final body weight gains of 18-21% in both sexes ($p<0.05$). FOB testing revealed abnormal gait and decreased forelimb and hindlimb grip strength. Abnormal gait was observed in some rats of both sexes at all three observation periods ($p<0.05$), but grip strength was reduced primarily during week 4 ($p<0.05$). Males also displayed decreased hindlimb foot splay (Weeks 4 and 8). Motor activity was increased in males (26%) during Week 8 only. This increase is of questionable significance. There were no treatment related gross or microscopic lesions of the central or peripheral nervous tissue. Brains were not weighed. **The LOAEL is 100 ppm (6.39 mg/kg/day) based reduced forelimb grip strength and superficial skin wounds in male rats. The NOAEL is 50 ppm (3.22 mg/kg/day).**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (870.6200b).

870.6300 Developmental Neurotoxicity Study

No study is currently available at this time. A developmental neurotoxicity study that follows a special protocol is required.

4.9 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered to be complete. The following two studies provide the basis for the metabolism data in rats and mice for esfenvalerate and fenvalerate. No additional studies are required at this time.

870.7485 Metabolism - Rat

a. First Study. EXECUTIVE SUMMARY: In a non-guideline metabolism and disposition study (1985, MRID 45351601), groups of five male and five female rats (Sprague-Dawley strain) and mice (ddY strain) were given single or 10-day repeated oral doses of ^{14}C-esfenvalerate (sp. act. 33.5-35.5 mCi/mmol, >99% purity, no lot number, phenoxy phenyl or chlorophenyl ring label position), ^{14}C-fenvalerate (sp. act. 34.0-35.5 mCi/mmol, >99% purity, no lot number, phenoxy phenyl or chlorophenyl ring label position), or ^{14}C-esfenvalerate containing three isomers at doses of 2.5 or 10 mg/kg in corn oil by gavage. Nonlabeled fenvalerate (Lot no. LUG-50205) or esfenvalerate (Lot no. KS-5210) were given concurrent with the radiolabeled test article. Absorption, excretion, distribution, and metabolite characterization were performed.

Overall recovery of administered radioactivity was an acceptable 94.2-102.7% among the experimental groups and was independent of label position.

Absorption of the test material indicated that systemic absorption over the time periods and doses tested ranged from approximately 20-60%. For both label positions, absorption was greater for mice than for rats (49-53% vs 24-35% for the alcohol label and 38-51% vs 20-39% for the acid label position).

Fecal elimination was more prominent than urinary excretion. Since biliary elimination was not assessed, what proportion, if any, of the fecal radioactivity represented absorbed dose. Over a 7-day post-dose period, urinary excretion was greater in mice (~35-60% of the dose) than in rats (~20-39%) when considering all dose and label positions. Urinary excretion was essentially complete 24-48 hours after dosing. Fecal excretion was also essentially complete 48 hours after dosing. There were no significant gender- or dose-related differences in excretion patterns.

The time-course data based upon 24 to 48 hour sampling intervals was insufficient for estimating elimination half-times and no plasma time-course data were available to determine C_{max}, t_{cmax}, and AUC values.

Although the test article and/or its metabolites were distributed to most of the examined tissues and organs, concentrations were minimal and generally accounted for <50 ng eq/g tissue in the 2.5 mg/kg dose groups and <100-200 ng eq/g tissue for the 10 mg/kg fenvalerate group. There did not appear to be gender-related differences and individual variability did not seem out of the ordinary for this type of study.

For rats given ^{14}C-acid esfenvalerate, ^{14}C-acid esfenvalerate isomer mix, or fenvalerate, six biotransformation products were characterized from the feces. Four fecal biotransformation products were characterized. Substantial amounts of parent compound (44.5-59.9% of the administered dose) were detected in the fecal samples at 0-2 days following a single dose. The major fecal metabolite was a 4'-hydroxylation product (2 to 5.5%). There were no significant differences in metabolism processes relative to the acid or alcohol moieties. Unchanged parent compound was also detected in the feces of mice (25.6 to 48.1% of the dose for both label positions). Four biotransformation products were detected but only the 4'-hydroxylation product consistently represented >2% of the administered radioactivity. There did not appear to be biologically relevant gender-related differences in the fecal metabolite profiles of mice.

Five biotransformation products were characterized in the urine of rats given ^{14}C-acid esfenvalerate, ^{14}C-acid esfenvalerate isomer mix, or fenvalerate. CPIA-glucuronide was the most prevalent metabolite. For rats given ^{14}C-alcohol esfenvalerate, ^{14}C-alcohol esfenvalerate isomer mix, or fenvalerate, three biotransformation products were characterized. A sulfate conjugate of OH-PB acid was the primary urinary metabolite (16.4-23.9% of the dose). For mice, three urinary metabolites were

characterized. Little parent compound was detected in the urine and most radioactivity (7.9-17.3% of the administered dose) was associated with a taurine conjugate of PB acid.

This metabolism study is **Acceptable/Non-Guideline** and does not satisfy the requirements for a Metabolism and Pharmacokinetics Study [OPPTS 870.7485 (§85-1)] in rats and mice. This study provides useful data that described the absorption, excretion, tissue distribution, and metabolite characterization of esfenvalerate and fenvalerate in male and female mice and rats following single and repeated oral dosing. There were, however, key deficiencies (no data on dose confirmation, stability or homogeneity, no Quality Assurance statement, no confirmation of GLP compliance) that precluded its acceptance as an 85-1 Guideline study.

b. Second Study. EXECUTIVE SUMMARY: In a metabolism study (1985, MRID 45351602) groups of 54 male and 54 female ddY mice were given ^{14}C-esfenvalerate (Lot number not provided; radiochemical purity >98%) or ^{14}C-fenvalerate (Lot number not provided; radiochemical purity >98%) in the diet for 28 days. Nonlabeled esfenvalerate (Lot No. LUG-50205, analytical grade, no purity stated) and fenvalerate (Lot. No. KS-5210, analytical grade, no purity stated) were incorporated into the respective diets to achieve concentrations of 25 ppm and 100 ppm (fenvalerate only). Groups of six mice were sacrificed at various time points during the 28-day treatment period.

Based upon body weight data and feed consumption, the study reported doses of 115-119 µg esfenvalerate/mouse/day (25-ppm dose group), and 112-118 and 424-477 µg/mouse/day, respectively, for the 25-ppm and 100-ppm fenvalerate groups.

Tissue analysis indicated that the test articles and/or biotransformation products were widely distributed in mice. Radioactivity in individual tissues, however, were quiet low. During the treatment period, radioactivity in tissues tended to increase up to Day 10, after which the concentrations fluctuated slightly or tended to decrease. Absorption, excretion, and overall mass balance data were *not* reported.

Parent compound and two metabolites, 2-chlorophenyl-isovaleric acid (CPIA) and hydroxylated CPIA, were characterized from the liver and kidneys of mice treated with esfenvalerate. For mice fed fenvalerate, these metabolites and an additional metabolite, CPIA-cholesterol ester were detected. Although CPIA and hydroxyl CPIA levels decreased to below detection limits rapidly after cessation of treatment with fenvalerate or esfenvalerate, the CPIA-cholesterol ester formed from fenvalerate was more persistent and was still detectable in the liver and kidney four days after cessation of treatment. The levels of metabolites in the liver and kidney of fenvalerate-treated mice reflected the 4-fold dose difference for this test compound, suggesting that absorption of parent compound and metabolism were not saturated at the 100 ppm dietary exposure.

This metabolism study (MRID 45351602) is **Acceptable/Non-Guideline** and does not satisfy the complete requirements for a Metabolism and Pharmacokinetics Study [OPPTS 870.7485 (§85-1)] in mice. Although the study adequately described the metabolite burdens in tissues of mice following 28-day dietary exposure to esfenvalerate (25 ppm) and fenvalerate (25 ppm and 100 ppm), the study protocol was not consistent with 85-1 requirements. This study is an appropriate and important ancillary study to an 85-1 Guideline report (MRID 45351601) in rats and mice that addressed absorption and excretion of the test articles.

870.7600 Dermal Absorption - Rat

There is no guideline dermal absorption study available at this time with esfenvalerate.

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 9.2 for Endpoint Selection Table.

Comments. Although the dose and endpoint selected for the chronic RfD and for all other risk assessments (short, intermediate and long term occupational and residential and for incidental oral exposure) is from an acute neurotoxicity (gavage) study, its use is supported by two long-term dietary studies conducted with esfenvalerate: the 2-generation reproduction study in rats (LOAEL = 4.21 mg/kg/day; a NOAEL was not established); and the mouse oncogenicity study (LOAEL = 4.29 mg/kg/day for systemic effects; a NOAEL was not established). An estimate of the NOAEL can be made by dividing the LOAEL from each of these studies by a 3 X uncertainty factor. This results in an estimated NOAEL of about 1.4 mg/kg/day and is comparable to 1.75 mg/kg selected from the acute neurotoxicity study. Neither the rat reproduction study or the mouse oncogenicity study indicated cumulative systemic effects. Therefore, this dose and endpoint is appropriate for this route and duration of exposure and an additional uncertainty factor for using a short-term study for a long-term risk assessment is not required. The NOAEL of 1.75 mg/kg from the acute neurotoxicity study is also close to the NOAEL for the rat developmental toxicity study that demonstrated a NOAEL of 2 mg/kg/day that was based on data from the pilot study since the definitive study did not demonstrate a NOAEL at 2.5 mg/kg/day.

5.2 Dermal Absorption

There is no series 85-2 dermal penetration/absorption study available. In 1997, the HIARC estimated a dermal absorption rate of 25% based on the 6-45% dermal absorption observed with the structurally related pyrethroids permethrin (22-45%), deltamethrin (15%) and tralomethrin (6-25%) (HED Doc. No. 014444 ; 0051481).

Dermal Absorption Factor: 25%

The dermal absorption factor is required for risk assessment since oral doses were selected for these exposure periods.

5.3 Classification of Carcinogenic Potential

The HED RfD Peer Review Committee, in accordance with the 1996 Draft Carcinogen Risk Assessment Guidelines, classified esfenvalerate /fenvalerate as a Group E chemical based on the lack of evidence of carcinogenicity in mice and rats. The 1997 mouse carcinogenicity with esfenvalerate (see above for executive summary) was submitted subsequent to the 1996 meeting but did not indicate a new concern for carcinogenicity.

5.3.1 Quantification of Carcinogenic Potential

Not applicable.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

A. Determination of Susceptibility

The HIARC concluded that there is no indication of increased pre- or postnatal qualitative or quantitative susceptibility in either the rat or rabbit developmental toxicity studies or in the 2-generation reproduction study. No developmental toxicity was observed in rats and rabbits in the presence of maternal toxicity (clinical signs of neurotoxicity). In the 2-generation reproduction study, a decrease in mean body weight and skin lesions were observed in the parents at the lowest dose tested (4.21 mg/kg/day); a NOAEL was established. For offspring toxicity, the NOAEL was 5.56 mg/kg/day and the LOAEL was 7.18 mg/kg/day, based on decreases in pup mean body weight and litter size and increases in subcutaneous hemorrhages.

In the 2-generation reproduction study, the HIARC noted a *qualitative* difference in response between the P1 animals (exposed as adults only at 350 ppm or 18.8/25.1 mg/kg/day (M/F)) and the F1 animals (exposed both *in utero* at 350 ppm and perinatally at 150 ppm for an approximate overall mean dose of 19 mg/kg/day). The F1 animals could not tolerate the 350 ppm dose level and it was reduced to 150 ppm. Abnormal gait/mobility was observed in the P1 animals. In the F1 animals, not only was abnormal gait observed, but additional clinical signs of neurotoxicity were noted (tremors, vocalization, ataxia, hyperactivity and hypersensitivity). However, the HIARC concluded that the observed difference between the P and F1 generations with regard to the additional clinical signs of neurotoxicity is not a concern for qualitative susceptibility *per se* since these findings has no impact on the regulatory dose selected for risk assessment since it occurs at a higher dose and a similar difference in the response was not seen at lower doses.

B. Degree of Concern Analysis and Residual Uncertainties.

There are no concerns or residual uncertainties for pre and/or post natal toxicity following exposure to esfenvalerate/fenvalerate.

C. Special FQPA Safety Factor(s):

The HIARC determined that the special FQPA Safety Factor can be removed (1x) because: 1) there is no evidence of quantitative or qualitative susceptibility following *in utero* exposure to rats or rabbits or pre/postnatal exposure to rats and 2) there are no residual uncertainties for pre/postnatal toxicity.

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.

6.2 Recommendation for a Developmental Neurotoxicity Study

A special developmental neurotoxicity study in rats is required for esfenvalerate.

Summary and basis for recommendation. The HIARC recommended that the DNT study for esfenvalerate be modified to assess potential latent behavioral effects that have been attributed to exposure of rodents to pyrethroids during development (Eriksson and Fredriksson, 1991). This would entail retaining the offspring on study for approximately 4-6 months past cessation of treatment (that is, until at least 90 days of age, instead of 60-70 days of age), and conducting behavioral testing (i.e., motor activity, auditory startle, and cognitive function) and neuropathology assessments at that time. Other assessments that could be considered for addition to the protocol include: a) receptor density of muscarinic and nicotinic cholinergic receptors (mAChR and nAChR) coupled to biochemical measurements of the activity and b) effects on axonal/dendritic growth. For further information that may be useful in designing this modified DNT protocol, it is recommended that the registrant consult the draft Proposal for a Test Protocol on Neurobehavioral Impact Following Direct Exposure of Pyrethroids During Critical Window of Exposure for Brain Development, National Chemicals Inspectorate Sweden (2 May 2002), and comments on this proposal from a Special Meeting of the European Commission to discuss questions related to developmental neurotoxicity (19 June 2002). The registrant should consult with the Agency prior to conducting this study.

In accordance with *the 2002, OPP Guidance Document on Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment*, since there are not sufficient reliable data to assign a different factor than the 10X default factor, the HIARC concluded that a Database Uncertainty Factor (UF_{DB}) of 10X is required until the data from the special DNT study are received and evaluated.

7.0 OTHER ISSUES

None.

8.0 REFERENCES

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9.0APPENDICES
Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table - See Section 4.1

9.1.2 Subchronic, Chronic and Other Toxicity Tables

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents	Accession numbers 257018, 257019 and 257020 - 1984. Acceptable/Guideline Doses 0, 50, 150, 300 or 500 ppm.	NOAEL = 50 ppm LOAEL = 150 ppm based on neurological signs manifested by "jerky leg movements.
870.3100 90-Day oral toxicity in rats	MRID # 40215601 Acceptable/Non-Guideline, Doses 0, 75, 100, 125 or 300 ppm	NOAEL = 125 ppm LOAEL = 300 based on decreased body weight and neurolotical signs (hyperactivity and jerky leg movements).
870.3100 90-Day oral toxicity in mice.	Special study comparing both fenvalerate and esfenvalerate.	
870.3150 90-Day oral toxicity in non-rodents.	No study available. There is a pilot dose range finding study associated with the chronid feeding study in dogs - see below.	
870.3200 21/28-Day dermal toxicity-rats	45275401 (2000)	Study has been requested and needs review.
870.3200 21/28-Day dermal toxicity-rabbit	MRID 43435101 (1992). Acceptable/Guideline Doses 0, 100, 300 or 1000 mg/kg/day.	NOAEL = > 1000 mg/kg/day (HDT) - no systemic effects.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3250 90-Day dermal toxicity	No study available.	
870.3465 90-Day inhalation toxicity	No study available.	
870.3700a Prenatal developmental in rodents	MRID 43211502 and 43211504. ACCEPTABLE/Guideline (when combined). 0, 1, 2, 2.5, 3, 4, 5, 10 or 20 mg/kg/day (in one or the other studies).	**Maternal** NOAEL = 2 mg/kg/day LOAEL = 2.5 mg/kg/day based on behavioral/CNS clinical signs. **Developmental** NOAEL = > 20 mg/kg/day. No effects at 20 mg/kg/day (HDT).
870.3700b Prenatal developmental in nonrodents	MRID 43211501 and 54311503. ACCEPTABLE/ GUIDELINE (when combined). 0, 2, 3, 4, 4.5, 5, 10 or 20 mg/kg/day.	**Maternal** NOAEL = 2 mg/kg/day LOAEL = 3 mg/kg/day based on behavioral/CNS clinical signs. . **Developmental** NOAEL > 20 mg/kg/day. No effects at 20 mg/kg/day (HDT).
870.3800 Reproduction and fertility effects	MRID 43489001. ACCEPTABLE/ GUIDELINE 0, 4.21, 5.55 or 18.8 mg/kg/day in males; 0, 5.56, 7.18 or 25.1 mg/kg/day in females.	**Parental/Systemic** LOAEL = 4.21 mg/kg/day based on skin condition and decerased body weight. NOAEL not established. **Reproductive** LOAEL > 25.1 mg/kg/day. No direct adverse effects on reproductive performance. **Offspring** NOAEL = 5.56 mg/kg/day LOAEL = 7.18 mg/kg/day based on decerased body weight. litter size and subcutaneous hemorhages.
870.4100a Chronic toxicity rodents	Refer to 870.4300 below.	

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b Chronic toxicity dogs	Range finding study: 00163855 (1986) and definitive study: 40376501 (1985) Acceptable/Guideline when combined. Doses 0, 0.625, 1.25, 5, 7.5 or 12.5 mg/kg/ day in either study.	NOAEL = 5 mg/kg/day LOAEL = 7.5 mg/kg/day based on decreased group body weight and ataxia in one male.
870.4200 Carcinogenicity -mice	MRID 444260607 ACCEPTABLE/ Guideline 0, 4.29 or 18.3 mg/kg/day in males, 0, 5.74 or 24.7 mg/kg/day in females. (A dose of 57 to 58 mg/kg/day was not tolerated.	Systemic toxicity: NOAEL = Not establised. LOAEL = 4.29 mg/kg/day in males and 5.74 mg/kg/day in females based on skin lesions. **No evidence of carcinogenicity**
870.4300. Combined Chronic Feeding/ Carcinogenicity -rats	MRID 00079877. ACCEPTABLE/Non-Guideline. 0 and 50 mg/kg/day.	NOAEL = Not established. LOAEL = 50 mg/kg/day based on decreased body weight and transient hind limb weakness in males. No evidence of carcinogenicity.
870.6200a Acute neurotoxicity screening battery	MRID 45228301 ACCEPTABLE/ Guideline 0, 1.75, 1.90, 20 or 80 mg/kg/day (in corn oil)	NOAEL = 1.75 mg/kg/day LOAEL = 1.90 mg/kg/day based on tremors in females.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.6200b Subchronic neurotoxicity screening battery	MRID 45202301 ACCEPTABLE/ Guideline 0, 3, 8.9 or 28.8 mg/kg/day in males; 0, 3.7, 10.7 or 35 mg/kg/day in females. ..... MRID 45157501 ACCEPTABLE/ Guideline 0, 3.22, 6.39 or 20.08 mg/kg/day in males; 0, 3.73, 7.26 or 22.78 mg/kg/day in females.	NOAEL = 3 in males or 3.7 in females mg/kg/day LOAEL = 8.9 in males or 10.7 in females mg/kg/day based on decreased body weight and motor activity in females. ..... NOAEL = 3.22 mg/kg/day in males. LOAEL = 6.39 mg/kg/day based on reduced forelimb grip strength and skin lesions.
870.6300 Developmental neurotoxicity	No study is available. A developmental neurotoxicity study with a special protocol is being requested.	
870.7485 Metabolism and pharmaco-kinetics		
870.7600 Dermal penetration	No Study.	
Special studies	No special studies were required for the registration of esfenvalerate. There were earlier studies which attempted to demonstrate special neuropathological responses at higher doses to fenvalerate. The subchronic neurotoxicity screen study did not demonstrate any histopathological effects thus establishing a NOAEL for possible neurohistopathological effects.	

9.2. Summary of Toxicology Endpoint Selection for Esfenvalerate/Fenvalerate.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary General Population including Infants and Children	NOAEL = 1.75 mg/kg UF = 1000[a] **Acute RfD** = 0.0018 mg/kg.	FQPA SF = 1 **aPAD** = Acute RfD / FQPA SF **= 0.0018 mg/kg**	**Acute neurotoxicity screen.** LOAEL = **1.90 mg/kg** based on **tremors.**
Chronic Dietary all populations	NOAEL = 1.75 mg/kg/day UF = 1000[a] **Chronic RfD** = 0.0018 mg/kg/day	FQPA SF = 1 X **cPAD** = Chronic RfD / FQPA SF **= 0.0018 mg/kg/day**	**Acute neurotoxicity screen.** LOAEL = **1.90 mg/kg** based on **tremors.**
Incidental Oral (All Durations)	NOAEL= 1.75 mg/kg/day	**Residential** LOC for MOE = 1000[a] **Occupational** = NA	**Acute neurotoxicity screen.** LOAEL = **1.90 mg/kg** based on **tremors.**
Dermal (All Durations)	Oral NOAEL= 1.75 mg/kg/day (dermal absorption rate = 25%)	**Residential** LOC for MOE = 1000[a] **Occupational** LOC for MOE = 100	**Acute neurotoxicity screen.** LOAEL = **1.90 mg/kg** based on **tremors.**
Inhalation (All Durations)	Oral NOAEL= 1.75 mg/kg/day (Inhalation absorption rate = 100%)	**Residential** LOC for MOE = 1000[a] **Occupational** LOC for MOE = 100	**Acute neurotoxicity screen.** LOAEL = **1.90 mg/kg** based on **tremors.**
Cancer	**Classification: Group "E" chemical.**		

[a] Additional 10x database uncertainty factor for lack of a special developmental neurotoxicity study.
UF = Uncertainty factor, FQPA SF = Food Quality Protection Act Safety Factor, NOAEL = No observed adverse effect level. LOAEL = lowest observed adverse effect level. PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable.

Note: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure

databases (dietary, 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.

Summary of Toxicological Dose and Endpoints for esfenvalerate for Use in Human Risk Assessment[11] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern, MOE = margin of exposure

13544

R102239

Chemical:	**Esfenvalerate**
PC Code:	**109303**
HED File Code	**13000 Tox Reviews**
Memo Date:	**08/23/2004**
File ID:	**TX0051089**
Accession Number:	**412-05-0037**

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