MEMORANDUM

SUBJECT: PP#0F03852 (Head Lettuce) and PP#4F3003/FAP#4H5419 (Sorghum) - Submission of a 90-Day Study in Mice and Several Mutagenicity and Metabolism Studies on Esfenvalerate/Fenvalerate

TOX Chem No.: 268J
PC Code: 109303
DP Barcode: D224281
Submission No.: S482269

FROM: William B. Greear, M.P.H.
Toxicology Branch II
Health Evaluation Division (7509C)

TO: Karen Whitby
Risk Characterization and Analysis Branch
Hazard Evaluation Division (7509C)

CC: George LaRocca/John Hebert, PM #13
Insecticide-Rodenticide Branch
Registration Division (7505C)

THRU: Clark Swentzel, Acting Senior Scientist
Toxicology Branch II
Health Evaluation Division (7509C)

I. CONCLUSIONS:

The toxicological database does not support the establishment of tolerances for esfenvalerate in/on head lettuce or sorghum. The following studies are data gaps:

- 81-8SS Acute Neurotoxicity Screening Battery
- 82-2 21 Day Dermal
- 82-7 90-Day Neurotoxicity - mammalian
- 83-6 Developmental Neurotoxicity
- 84-4 Mutagenicity-Other Genotoxic Effects
- 85-1 General Metabolism

(See Section X. Toxicological Issues for additional information)

TABLE OF CONTENTS

II. REQUESTED ACTION:

The Registration Division has requested that TOX I review the following studies on fenvalerate and esfenvalerate. The studies have been submitted in support of PP#4F3003/FAP#4H5419-sorghum and PP#0F3852-head lettuce. (Comment:The studies submitted on fenvalerate are irrelevant since it was determined that the data can not be bridged, i.e. from fenvalerate to esfenvalerate. Thus, data on fenvalerate will not support tolerances for residues of esfenvalerate on RACs.)

1. Kogiso, S. (1985) *In vitro* chromosomal aberration test of S-1844 in chinese hamster ovary cells (CHO-K1). Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Takatsukasa, 4-2-1, Takarazuka, Hyogo 655, Japan. Laboratory Project ID LLT-50-0010, December 28, 1985. MRID 41215204. Unpublished.

2. Kogiso, S.(1985) Reverse mutation test of S-1844 in Salmonella typhimurium and Escherichia coli. Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Ltd. Takatsukasa, 4-2-1, Takarazuka, Hyogo 655, Japan. Laboratory Project ID LLT-50-0009, December 28, 1985. MRID 41316301. Unpublished.

3. Kogiso, S. (1985) *In vitro* gene mutation test of S-1844 in V79 Chinese hamster cells in culture. Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Takatsukasa, 4-2-1, Takarazuka, Hyogo 655, Japan. Laboratory Project ID LLT-50-0012, December 28, 1985. MRID 41316302. Unpublished.

4. Kogiso, S. (1985) Micronucleus test of S-1844 in mouse bone marrow cells. Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Takatsukasa, 4-2-1, Takarazuka, Hyogo 655, Japan. Laboratory Project ID LLT-50-0011, December 28, 1985. MRID 41316303. Unpublished.

5. Kogiso, S. (1986) Unscheduled DNA synthesis assay of S-1844 in HeLa cells. Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., 4-2-1 Takarazuka, Hyogo 655, Japan. Laboratory Project ID LLT-60-0022, February 24, 1986. MRID 41316304. Unpublished.

6. Suzuki, T., Kadota, T. and J. Miyamoto (1976) One year chronic toxicity study in mice (3 month interim report). Research

Department, Pesticide Division, Sumitomo Chemical Co., Ltd., Osaka, Japan. Study No. AT-60-0194, August 26, 1976. MRID 43546701. Unpublished.

7. Lee, P., Stearns, S. and W. Powell (1981) Metabolism of ^{14}C-chlorophenyl-SD 43775 in male and female rats after a single oral dose (8.4 mg/kg) administration. Shell Report RIR-22-021-80. MRID 00099109. Unpublished.

8. Lee, P., Stearns, S. and W. Powell (1981) Metabolism of ^{14}C-phenoxyphenyl-SD 43775 in male and female rats after a single oral dose (8.4 mg/kg) administration. Shell Report RIR-22-020-080. MRIDs 00085749, 00144164. Unpublished.

9. Lee, P., Stearns, S. and W. Powell (1981) Metabolism of ^{14}C-chlorophenyl-SD 92459 in male and female rats after a single oral dose (8.4 mg/kg) administration. Shell Report RIR-22-020-80. MRIDs 00085750, 000144165. Unpublished.

10. Lee, P., Stearns, S. and W. Powell (1981) Metabolism of ^{14}C-phenoxyphenyl-SD92459 in male and female rats after a single oral dose (8.4 mg/kg) administration. Shell Report RIR-22-023-80. MRIDs 00085751, 00144166. Unpublished.

11. Ohkawa, H., Kaneko, H., Tsuji, H. and J. Miyamoto (1979) Metabolism of fenvalerate (Sumicidin) in rats. J. of Pesticide Science 4:143-155. MRID 00141483.

12. Kaneko, H., Ohkawa, H. and J. Miyamoto (1981) Comparative metabolism of fenvalerate and the [2S, αS]-isomer in rats and mice. J. of Pesticide Science 6:317-326. MRID 00141484.

13. Lee, P., Stearns, S. and W. Powell (1985) Characterization of residues in the body fat of rats following a single oral dose of ^{14}C-SD 43775 and ^{14}C-SD 92459. Shell Report RIR-22-005-85. MRID N/A.

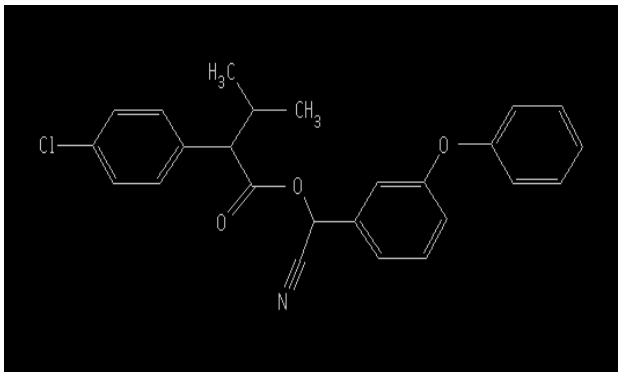
14. Lee, P., Stearns, S. and W. Powell (1985) Rat metabolism of fenvalerate (Pydrin Insecticide) Journal of Agricultural and Food Chemistry 33:988-993. MRID N/A.

15. Kaneko, H., Izumi, T., Matsuo, M. and J. Miyamoto (1984) Metabolism of fenvalerate in dogs. J. of Pesticide Science 9:269-274. MRID N/A.

III. PRODUCT INFORMATION (Updated June, 1997)

Esfenvalerate/fenvalerate are synthetic pyrethroid insecticides used to control a wide variety of insects infesting agricultural crops. The chemical name is cyano(3-phenyoxyphenyl)methyl-4-chloro-alpha-(1-methylethyl) benzeneacetate. The proprietary names for esfenvalerate and fenvalerate are ASANA and PYDRIN, respectively. The company codes are MO 70616 (esfenvalerate) and SD 43775 (fenvalerate).

The chemical structure is as follows:



Esfenvalerate/fenvalerate have a molecular weight of 419.9 and

the empirical formula is $C_{25}C_{22}ClNO_3$. Esfenvalerate contains 75 percent of the Aα isomer which is the insecticidally active isomer of fenvalerate. [Fenvalerate is composed of four isomers in equal proportions: the Aα or SS, Bα or RS, Aβ or SR, and the Bβ or RR.] The CAS and TOX Chem Numbers are 66230-04-4 and 268J for esfenvalerate and 51630-58-1 and 77A for fenvalerate.

IV. REQUIREMENTS (40 CFR 158.340) Esfenvalerate, # 109303
Updated: June, 1997

Technical (ASANA)	**Required**	**Satisfied**
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
81-7 Acute Delayed Neurotoxicity (Hen)	N	-
81-8 Acute Neurotoxicity Screening Battery	Y	N
82-1 Subchronic Oral (Rodent)	Y	Y
82-1 Subchronic Oral (Nonrodent)	Y	Y[1]
82-2 21-Day Dermal	Y	N
82-3 90-Day Dermal	N	-
82-4 90-Day Inhalation	N	-
82-5 90-Day Neurotoxicity (Hen)	N	-
82-5 90-Day Neurotoxicity (Mammal)	Y	N
83-1 Chronic Toxicity (Rodent)	N[2]	2
83-1 Chronic Toxicity (Nonrodent)	Y	Y
83-2 Carcinogenicity (2 Species)	Y	Y[3]
83-3 Developmental Toxicity (2 Species)	Y	Y
83-4 Reproduction	Y	Y
83-5 Chronic/Carcinogenicity	-	-
83-6 Developmental Neurotoxicity	Y	N
84-2 Mutagenicity - Gene Mutation	Y	Y
84-2 Mutagenicity - Structural Chromosomal Aberration	Y	Y
84-2 Mutagenicity - Other Genotoxic Effect	Y	N
85-1 General Metabolism	Y	N
85-2 Dermal Penetration	N	-
86-1 Domestic Animal	N[4]	-

Y = Yes; N = No; W = Waived.
[1] This requirement is satisfied by a 12-month dog study (#6160-103; August 21, 1986).
[2] Study not required (RfD doc. 7/1/96); discussion in TOXICOLOGICAL ISSUES below.

[3] Studies are conducted with fenvalerate but are acceptable for 83-2 (RfD doc 7/1/96).
[4] Study is only required for the end-use product (EP).

V: TOXICOLOGY PROFILE - ESFENVALERATE:

V. Toxicology Profile - Esfenvalerate

A. Acute Toxicity

Acute Toxicity of Esfenvalerate

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	N/A	LC_{50} = N/A	N/A
81-4	Primary Eye Irritation	00156509	Mild irritation	III
81-5	Primary Skin Irritation	00156510	Mild irritation	IV
81-6	Dermal Sensitization	41215203	Negative	
81-8	Acute Neurotoxicity	Data Gap	--	

(The following section contains executive summaries for fenvalerate and esfenvalerate studies used to support esfenvalerate)

Special Dermal Sensory Study in Guinea Pigs

In a special dermal sensory study (MRID 41116401) doses of Pydrin (2.4 EC - 0.053, 0.52, 1.05 and 2.1%), Asana (0.66 EC - 0.058, 0.58 and 1.15%) and Payoff 2.5 EC - 0.02, 0.2 and 0.8%) were applied to the skin of Duncan Hartley strain guinea pigs. Various changes were made in formulating mixtures for testing skin sensory stimulation. In general, Payoff 2.5 EC, 2 formulations of ASANA 1.9 EC and Asana 1.28 EC elicited more sensory stimulation than did Pydrin 2.4 EC. Varying the concentration of the isomer, active ingredient emulsifier and solvent altered skin sensory stimulation. Sensory stimulation was measured by biting, licking or scratching reactions. This study is supplementary due to its special protocol and does not satisfy any guideline requirement.

B. Subchronic Toxicity

Oral Studies in Rats

1) In a 90-day feeding study (MRID 40215601), 15 Sprague-Dawley rats/sex were administered 0, 75, 100, 125 or 300 ppm (corresponding to 0, 4.7, 6.2, 7.8 or 18.7 mg/kg/day) of Technical MO 70616 (esfenvalerate, 98.6%, Sample No. 730C). Additional groups of 15 rats/sex were administered the same doses in the 90- day study, but were sacrificed at 7 weeks. Neurological dysfunction was noted at 300 ppm. Kidney weights were increased in males and females at 300 ppm. **The LOEL is 300 ppm (18.7 mg/kg/day) based on neurological dysfunction. The NOEL is 125 ppm (7.8 mg/kg/day). The study is Acceptable** and **satisfies** the requirement for a guideline series 82-1 subchronic feeding study in rats.

2) In a 90-day feeding study (MRID 00151030), 30 Sprague-Dawley rats/sex were administered 0, 50, 150, 300 or 500 ppm (corresponding to 0, 5, 15, 30 or 50 mg/kg/day (conversion of 0.1)) of Technical MO 70616 (esfenvalerate, 98.7%, Sample No. 730B). Body weight gain decreased at 300 ppm (females) and 500 ppm (females/males). Slight hypertrophy of the pituitary was observed in males at 500 ppm. Slight hypertrophy of parotid salivary gland was observed at 300 ppm (males/females) and 500 ppm (males/ females). Slight hypertrophy of submaxillary glands was observed at 500 ppm (males/ females). **The LOEL is 150 ppm (15 mg/kg/day) based on neurological dysfunction. The NOEL is 50 ppm (5 mg/kg/day). The study is Acceptable** and **satisfies** the requirement for a guideline series 82-1 subchronic feeding study in rats.

Oral Study in Mice

Esfenvalerate (94.5%) was administered to groups of 12 mice/sex at dose levels of 0, 50, 150 or 500 ppm (corresponding to M = 0, 10.5, 30.5 or 106 mg/kg/day, F = 0, 12.6, 36.8 or 113 mg/kg/day)(MRID 41359701) for 90 days. Fenvalerate was given to an additional group of mice at 2000 ppm (corresponding to M = 422 mg/kg/day; F = 462 mg/kg/day). Clinical signs of toxicity from esfenvalerate included fibrillation, tremors, convulsions, hypersensitivity, abnormal gait, salivation, scratching, licking, alopecia, scabs and sores, increased water intake, anemia, numerous changes in clinical chemistry, enlargement of the inguinal lymph node, a white substance in the urinary bladder, dark red spots in the stomach, dilation of the fundal gland, mucosal erosion and ulceration and gastritis of the stomach, hyperkeratosis, dermatitis, ulceration and formation of hair follicular cysts in the skin, and a reactive response in the lymphatic tissues (lymphadenitis). The toxic manifestations observed with fenvalerate were similar to those observed in the 500

ppm esfenvalerate group with the following major exception. Microgranulomatous changes and giant cell formation were present in several organs in the 2000 ppm group. **The LOEL for esfenvalerate is 500 ppm (106 mg/kg/day). The NOEL is 150 ppm (30.5 mg/kg/day). The LOEL for fenvalerate is 2000 (422 mg/kg/day) based on the effects noted above. The NOEL was not determined. The study is Core-Minimum** for esfenvalerate and it **satisfies** the requirement for a guideline series 82-1 subchronic feeding study in mice. The study is **Supplementary** for fenvalerate and it **does not satisfy** the requirement for a guideline series 82-1 subchronic feeding study in mice.

21 Day Dermal Study

No study available.

Subchronic Neurotoxicity

No study available.

C. Chronic Toxicity/Carcinogenicity:

Oral Studies in Rats

1) In a chronic/onco feeding study (MRID 00082244, 00111888), groups of 93 Sprague-Dawley rats/group were administered 1, 5, 25 or 250 ppm (representing approximately 0.050, 0.25, 1.25 or 12.5 mg/kg/day) of **fenvalerate** in the diet for 2 years. The control group consisted of 183 rats/sex. Two other groups were tested for 6 months, 22 rats/sex at 0 or 500 ppm (representing 0 and 25.0 mg/kg/day). Rats in the 500 ppm group exhibited a slight but insignificant weight depression. **The LOEL was ≥ 250 ppm (12.5 mg/kg/day). No increase in tumors at 250 ppm. The NOEL was determined to be 250 ppm (the HDT in the 2 year study.) The study is Supplementary** and **does not satisfy** the requirement for a guideline series 83-5 combined chronic/carcinogenicity study in rats since toxicity was not manifested at the highest dosage.

2) In a lifetime feeding study (2 years) (MRID 00079877), groups of 50 Crl: COBS CD (SD)BR rats were administered 0 or 1000 ppm (corresponding to 0 or 50.0 mg/kg/day) of **fenvalerate** in the diet. Spindle cell sarcomas were produced in male rats only. Treated males and females showed consistent weight loss. Reversible hind limb weakness was evident in only a few treated males within the final 12 weeks of administration. **The LOEL was 1000 ppm (50.0 mg/kg/day) based on loss of weight and neurological effects. The NOEL was 250 ppm (12.5 mg/kg/day) for the combined studies (MRID 00079877; 00082244 & 00111888).** NOTE: In Tox Document No. 009004 the

conclusion that fenvalerate is associated with the production of spindle cell sarcomas was retracted. The study is **Supplementary** and **does not satisfy** the requirement for a guideline series 83-5 combined chronic/ carcinogenicity study in rats. **When taken together** with chronic/carcinogenicity feeding study (MRID 00082244, 00111888) **the guideline requirement for a 83-2a, cancer study in the rat is satisfied**.

Oral Studies in Mice

1) In a 2-year feeding study (MRID 00079876), 50 male and 50 female B6C3F1 mice/group were administered 0 (vehicle), 0 (vehicle), 10, 50, 250 or 1250 ppm of **fenvalerate** (98%) (representing approximately 0, 0, 1.5, 7.5, 38.0 or 187.5 mg/kg/day) in the diet. At 1250 ppm there was decreased body weight, increased SGOT and decreased albumin. Female body weight was also decreased at 250 ppm. Multifocal granulomata[1] were observed in the lymph nodes, liver and spleen at 250 and 1250 ppm. **The LOEL was 50 ppm (7.5 mg/kg/day) based on granulomatous changes.. The NOEL was 10 ppm (1.5 mg/kg/day). The study is Acceptable** and **satisfies** the requirement for guideline series 83-5 combined chronic feeding/carcinogenicity study in mice.

2) In an 18 month feeding study (MRID 00071949), groups of about 30 ddy mice/sex were administered 0, 100, 300, 1000 or 3000 ppm (representing approximately 0, 15.0, 45.0, 150.0 or 450.0 mg/kg/day) of fenvalerate in the diet. At 1000 and 3000 ppm clinical signs of hypersensitivity were seen as well as mortality. Hematology, blood chemistry, body weight and organ weights were affected at 1000 and 3000 ppm and to a lesser extent at 300 ppm. Dose related granulomatous changes in the liver and spleen were observed at all levels. The 100 ppm group showed some of these changes, however, the changes were barely significant. **The LOEL is 300 ppm (45.0 mg/kg/day) based on granulomatous changes in the liver and spleen. The NOEL is 100 ppm (15.0 mg/kg/day). No carcinogenicity was observed.** The study is **Supplementary** and **does not satisfy** the requirement for a guideline series 83-2b carcinogenicity study in mice.

3) In a life span (20 month) feeding study (MRID 00093662), 50 male and 50 female ddy strain mice/group were administered 0, 10, 30, 100 or 300 ppm (representing approximately 0, 1.5, 4.5, 15.0 or 45.0 mg/kg/day) of Technical fenvalerate (91.4%, Lot No. 71739)

[1] Granulomata are only observed with fenvalerate. They are not related to treatment with esfenvalerate.

in the diet. Slight reductions in RBC and/or HGB were observed at 100 and 300 ppm. SGPT was increased in females at 300 ppm. Granulomatous changes were observed in the liver, spleen and lymph nodes (mandibular and mesenteric) at 100 and 300 ppm. **The LOEL was determined to be 100 ppm (equivalent to 15 mg/kg/day) based on the granulomatous lesions observed and on the change in hematological parameters. Fenvalerate was determined not to be carcinogenic in the ddy strain of the mouse. The NOEL was determined to be 30 ppm (equivalent to 3.48 mg/kg/day). The study is Supplementary** and **does not satisfy** the requirement for a guideline series 83-2b carcinogenicity study in mice.

Oral Studies in Dogs

1) In a 21-day probe for a 1 year feeding study (MRID 40376501) 2 male and 2 female beagles/group were administered 0, 100, 300 or 500 ppm (representing 0, 2.80, 6.40 or 9.38 mg/kg/day in males and 0, 2.25, 7.37 or 8.50 mg/kg/day in females of Technical MO 70616 (esfenvalerate, 98.7%, Lot No. 2-3-0-0). Ataxia, tremors, fasciculations, decreased body weight and food consumption were observed in the 300 and 500 ppm groups. **The LOEL was determined to be 300 ppm (6.40 mg/kg/day) based on nervous system involvement and decreases in body weight and food consumption. The NOEL is 100 ppm (2.25 mg/kg/day).** The study, together with MRID 00163855, is **acceptable** and **satisfies** the requirement for a guideline series 83-1b chronic feeding study in dogs.

2) In a 1-year feeding study (MRID 00163855), 6 male and 6 female beagles/group were administered 0, 25, 50, 100 or 200 ppm (representing approximately 0, 0.68, 1.36 or 5.29 mg/kg/day) of Technical MO 70616 (esfenvalerate, 98.7%, Lot No. 2-3-0-0). There were no effects on mortality, body weight, food consumption, hematology, clinical chemistry, gross and microscopic pathology and organ weights. **From the probe study, the LOEL was determined to be 300 ppm (6.40 mg/kg/day) based on nervous system involvement and decreases in body weight and food consumption. The NOEL was determined to be 200 ppm (5.29 mg/kg/day).** The study, together with MRID 40376501, is **Acceptable** and **satisfies** the requirement for a guideline series 83-1b chronic feeding study in dogs.

D. Developmental Toxicity

Oral Study in Rats

Esfenvalerate (97.1%, Lot # 71219) 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 (pilot study doses were 1.0, 2.0, 3.0, 4.0, 5.0 and 20 mg/kg/day)(MRID 43211504, 43211502). Maternal toxicity was observed at all doses in the main study. 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 hind limb 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 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 LOEL is 2.5 mg/kg/day based on behavioral/CNS clinical signs. The NOEL for maternal toxicity is 2.0 mg/kg/day (from the pilot study).** There was no evidence of developmental toxicity at any dose. **The NOEL is 20 mg/kg/day, the highest dose tested. The study is Acceptable** and **satisfies** the requirement for a guideline series 83-3a developmental toxicity study in rats.

Oral Study in Rabbits

Esfenvalerate was administered to groups of 20 New Zealand White female rabbits by gavage at doses of 0, 3.0, 10.0 or 20.0 mg/kg/day from gestation days 7 through 19 (pilot study doses were 0, 2.0, 3.0, 4.0, 4.5, 5.0 or 20.0 mg/kg/day)(MRID 43211503, 43211501). Maternal toxicity was observed at all doses in the main study. At 3.0 mg/kg/day there were 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 rabbit). At 10.0 mg/kg/day there was also hind limb 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 nd 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 LOEL is 3.0 mg/kg/day based on behavioral/CNS clinical signs. The NOEL is 2.0 mg/kg/day (from the pilot study).** There was no evidence of developmental toxicity at any dose. **The LOEL is greater than 20.0 mg/kg/day. The NOEL is equal to or greater than 20.0 mg/kg/day, the highest dose tested.** The study is **Acceptable** and **satisfies** the requirement

for a guideline series 83-3b developmental toxicity study in rabbits.

Developmental Neurotoxicity in Rats

No study available.

E. Reproductive Toxicity

Oral Study in Rats

In a 2-generation reproduction in rats (MRID 43489001), DPX-YB656-84 (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, 350 or 350/150 ppm (dietary concentration reduced to 150 ppm after approximately 4 months of dosing). Mean compound intake for males was 0, 5.10, 6.70 and 18.87 for males (low to high dose, respectively). Mean compound intake for females was 0, 5.47, 7.27 and 25.1 (low to high dose, respectively). One litter per generation. The authors indicated the following effects in the study (reviewer agrees): At 350 ppm there were statistically significant decreases in mean body weights, body weight gains and food consumption of P_1 and F_1 females during premating; decreases in food efficiency of P1 females during premating; decrease in mean body weight of P_1 females during gestation and lactation; decrease in body weight gain on lactation days 0-7; increases in dermal ulcerations and corresponding microscopic skin ulcerations, inflammation and acanthosis/hyperkeratosis of the skin of P_1 males and F_1 males and females; increases in signs of neurotoxicity in P_1 and F_1 rats; increased parental mortality; decreases in pup survival and pup weights of F_1 generation pups; increase in toxic signs including neurotoxicity; and increased mortality in F_1 generation pups. At 100 ppm there were statistically significant decreases in food consumption of P_1 females; decreases in mean body weights, body weight gain and food consumption of F_1 males; decrease in mean body weight of F_1 females during premating and gestation; increases in grossly and microscopically observed skin ulcerations, inflammation and acanthosis/hyperkeratosis of the skin of F_1 rats; decreases in day 21 pup weights of F_1 generation pups; decreases in litter size and pup weights of the F_2 generation pups and an increased incidence of subcutaneous hemorrhage in pups. At 75 ppm there were statistically significant decreases in mean body weights of F_1 females during premating and gestation; and increased incidences of skin ulcerations and corresponding microscopically observed skin ulcerations, inflammation or hyperkeratosis/hyperkeratosis of the skin of 1 P_1 male, 1 P_1 female, and 3 F_1 males. **The LOEL for parental toxicity is 75 ppm (5.10 mg/kg/day) based on decreases in mean body weights of F_1 females and an increased incidence of skin lesions. The NOEL could not be determined. The LOEL for reproductive**

toxicity is 100 ppm (6.70 mg/kg/day) based on decreases in F_1 pup weights on day 21 of lactation; decreases in litter size and F_2 pup weights and an increased incidence of subcutaneous hemorrhage. The NOEL is 75 ppm (5.10 mg/kg/day). This study is **Acceptable** and **satisfies** the guideline requirement for a Series 83-4 Multigeneration Reproduction study in rats.

F. Mutagenicity

Gene Mutation

1) In a reverse gene mutation assay in bacteria (MRID 41316301), *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* strain WP2(uvrA) were exposed to S-1844 (95.5%) in DMSO at concentrations of 15, 50, 150, 500, 1500, or 5000 μg/plate in the presence and absence of mammalian metabolic activation (S9-mix). The S9 was prepared from Kanechlor-400 induced male Sprague-Dawley rat liver. S-1844 was tested to a limit concentration of 5000 μg/plate (a precipitate was also seen on the plates at 5000 μg/plate both with and without S9-mix and at 1500 μg/plate without S9-mix). S-1844 did not significantly increase the number of revertant colonies over solvent control values in any of the six bacterial strains at any dose tested, either with or without S9-mix. The positive and solvent control values were appropriate. **There was no evidence of induced mutant colonies over background. This study is classified as acceptable.** It **satisfies** the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

2) In a mammalian cell gene mutation assay at the HGPRT locus (MRID 41316302), Chinese hamster V79 cells cultured in vitro were exposed to S-1844 (95.5% a.i.) in DMSO at concentrations of 3×10^{-5}, 1×10^{-4}, 3×10^{-4}, and 1×10^{-3} M (12.6, 42, 126, 420 μg/mL, respectively) in the presence of mammalian metabolic activation (S9-mix) and at concentrations of 1×10^{-5}, 3×10^{-5}, 1×10^{-4}, and 3×10^{-4} M (4.2, 12.6, 42, 126 μg/mL, respectively) in the absence of S9-mix. S-1844 was tested up to cytotoxic concentrations as determined in a preliminary cytotoxicity assay (22% cell survival at the top concentration tested with S9-mix and 20% cell survival at the top concentration tested without S9-mix). The positive and solvent controls induced the appropriate responses. **There was no evidence of induced mutant colonies over background. This study is classified as acceptable.** It **satisfies** the requirement for FIFRA Test Guideline 84-2 for in vitro mutagenicity (mammalian forward gene mutation) data.

Structural Chromosomal Aberration

1) In a mammalian cell cytogenetics chromosomal aberration assay (MRID 41215204), CHO-K1 cell cultures were exposed to S-1844 (95.5% a.i.) in DMSO at concentrations of 1 x 10^{-5}, 2 x 10^{-5}, 5 x 10^{-5}, or 1 x 10^{-4} M (4.2 μg/mL, 8.4 μg/mL, 21 μg/mL, 42 μg/mL respectively) without exogenous metabolic activation (S9-mix) and at concentrations of 5 x 10^{-5}, 1 x 10^{-4}, 2 x 10^{-4}, or 5 x 10^{-4} M (21 μg/mL, 42 μg/mL, 84 μg/mL, 210 μg/mL respectively) with S9-mix. S9-mix was obtained from Kanechlor-400 induced male Sprague-Dawley rat liver. S-1844 was tested up to cytotoxic concentrations with growth inhibition seen at concentrations of 5 x 10^{-5} M (35.3% of control value) without S9-mix and at 5 x 10^{-4} M (40.8% of control value) with S9-mix. Positive and solvent controls induced the appropriate response. **There was no evidence of a significant induction of chromosomal aberrations or polyploid cells over background**. **This study is classified as acceptable.** It **satisfies** the requirement for FIFRA Test Guideline 84-2 for in vitro cytogenetic mutagenicity data.

Other Genotoxic Effects

An acceptable study is not available.

G. Metabolism

An acceptable study is not available.

VI. DATA GAPS:

- o 81-8SS Acute Neurotoxicity Screening Battery
- o 82-2 21-Day Dermal
- o 82-7 90-Day Neurotoxicity (Mammalian)
- ❍ 83-6 Developmental Neurotoxicity
- ❍ 84-4 Mutagenicity-Other Genotoxic Effects
- o 85-1 General Metabolism

VII. ACTION TAKEN TO REMOVE DATA GAPS AND OBTAIN ADDITIONAL INFORMATION:

The sponsor is again informed herein as to the data gaps that exist for esfenvalerate.

VIII. ENDPOINTS USED FOR RISK ASSESSMENT:

A. Dermal Absorption

There is evidence of dermal absorption characterized by skin sensory stimulation (scratching, biting and licking activity) with esfenvalerate in guinea pigs at dose levels of 5-100 mg placed on the back of guinea pigs (MRID 41116401). In the absence of data on dermal absorption, a 100% absorption factor is assumed.

B. Acute Dietary Endpoint (One Day)

Study Selected - Guideline No.: Developmental Toxicity 1) 83-3a and 2) 83-3b

Based on developmental toxicity studies in rats (MRID 43211502, 43211504) and rabbits (MRID 43211501, 43211503) the **Endpoint and dose used in risk assessment**: 2 mg/kg/day; NOELs established in the pilot rat and rabbit developmental toxicity studies. Behavioral/CNS clinical signs were seen at 2.5 mg/kg/day in rats and at 3.0 mg/kg/day in rabbits. A MOE of 100 should serve as a reference for dietary exposure. **Comments about studies and/or endpoint:** The NOELs and LOELS were determined by combining the pilot and main studies. **This risk assessment is required.**

C. Short Term Occupational or Residential Exposure (1 to 7 Days):

Based on developmental toxicity studies in rats (MRID 43211502, 43211504) and rabbits (MRID 43211501, 43211503) the **Endpoint and dose used in risk assessment**: 2 mg/kg/day; NOELs established in the pilot rat and rabbit developmental toxicity studies. Behavioral/CNS clinical signs were seen at 2.5 mg/kg/day in rats and at 3.0 mg/kg/day in rabbits. A MOE of 100 should serve as a reference for occupational/residential exposure. **Comments about studies and/or endpoint:** The NOELs and LOELs were determined by combining the pilot and main studies. Although, there was a 21-day dermal study (MRID 42325101) available on fenvalerate, it was decided not to use it for risk assessment purposes because it was conducted on fenvalerate in which esfenvalerate constitutes only one-quarter of the substance. In addition, this study did not evaluate local dermal absorption (skin sensory stimulation) that was observed in the Guinea pig study discussed in the Dermal Absorption section of this document. **This risk assessment is required.**

D. Intermediate Term Occupational or Residential (1 Week to 21 Days):

Based on developmental toxicity studies in rats (MRID 43211502, 43211504) and rabbits (MRID 43211501, 43211503) the **Endpoint and dose used in risk assessment**: 2 mg/kg/day; NOELs established in the pilot rat and rabbit developmental toxicity studies. Behavioral/CNS clinical signs were seen at 2.5 mg/kg/day in rats and at 3.0 mg/kg/day in rabbits. A MOE of 100 should serve as a reference for intermediate term occupational/ residential exposure. **Comments about studies and/or endpoint:** The NOELs

and LOELs were determined by combining the pilot and main studies. Although, there was a 21-day dermal study (MRID 42325101) available on fenvalerate, it was decided not to use it for risk assessment purposes because it was conducted on fenvalerate in which esfenvalerate constitutes only one-quarter of the substance. In addition, this study did not evaluate local dermal absorption (skin sensory stimulation) that was observed in the Guinea pig study discussed in the Dermal Absorption section of this document. **This risk assessment is required.**

E. Chronic Occupational or Residential Exposure (Greater than 21 Days)

Based on developmental toxicity studies in rats (MRID 43211502, 43211504) and rabbits (MRID 43211501, 43211503) the **Endpoint and dose used in risk assessment**: 2 mg/kg/day; NOELs established in the pilot rat and rabbit developmental toxicity studies. Behavioral/CNS clinical signs were seen at 2.5 mg/kg/day in rats and at 3.0 mg/kg/day in rabbits. A MOE of 100 should serve as a reference for chronic occupational/residential exposure. **Comments about studies and/or endpoint:** The NOELs and LOELs were determined by combining the pilot and main studies. Although, there was a 21-day dermal study (MRID 42325101) available on fenvalerate, it was decided not to use it for risk assessment purposes because it was conducted on fenvalerate in which esfenvalerate constitutes only one-quarter of the substance. In addition, this study did not evaluate local dermal absorption (skin sensory stimulation) that was observed in the Guinea pig study discussed in the Dermal Absorption section of this document. **This risk assessment is required.**

F. Inhalation Occupational or Residential Exposure:

Comments about studies and/or endpoint: No appropriate inhalation toxicity studies are available. Risk assessments should be inclusive of the inhalation (100%) and dermal (100%) exposure and should be based on the 2 mg/kg dose used for the dermal risk assessments.

G. Carcinogenic Classification and Basis:

The RfD/Peer Review Committee met on April 11, 1996 and decided that esfenvalerate should be classified as "Group E"--Evidence of Non-Carcinogenicity for Humans.

H. RfD and Basis:

The RfD Peer Review Committee met on April 11,1996 and determined that the RfD is 0.02 mg/kg/day based on the results of the developmental toxicity studies in rats and rabbits (NOEL = 2 mg/kg/day) with an uncertainty factor of 100.

I. Risk Characterization

Based on a review of the literature, the following is evident concerning the type II pyrethroid, fenvalerate (and most likely

S-fenvalerate) related neurotoxicity. "It is possible to identify two distinct types of neurologic pyrethroid-related effects: A reversible muscular weakness (pharmacologic effects) due to altered sodium conductance and repetitive firing of nerves and a more chronic neuropathologic effect at high doses manifested as sparse axonal damage." Although large (near lethal) oral doses (in the rodent) result in the peripheral nerve lesions, resembling axonal degeneration, there is no evidence that smaller dietary doses of fenvalerate for longer periods of time produce these changes.[2]

[2] "Neuropharmacologic and Neuropathologic Effect of Fenvalerate in Mice and Rats": Parker, Albert, VanGelder, Patterson, Taylor: Fundamental and applied toxicology: 5, 278-286 (1985)

Pyrethroids are known to produce repetitive firing primarily of sensory neurons and to a lesser extent, motor neurons. This is due to increased sodium conductance of the membrane during excitation and is considered reversible and transient. Although it is reported to occur in both type I and type II pyrethroids it is reported to be more pronounced in cyano-pyrethroids (type II) such as fenvalerate.[3]

In humans, dermal exposures to pyrethroids have been associated with a transient tingling and itching. A study developed to evaluate this skin sensory stimulation response in animals determined that low doses can cause this response. It is speculated that the repetitive firing is responsible for the skin sensations.[2]

IX. PENDING REGULATORY ACTIONS:

There are no pending regulatory actions against this pesticide at this time that TOX I is aware of.

X. TOXICOLOGICAL ISSUES:

A. Bridging from Fenvalerate to Esfenvalerate

Several data gaps exist for esfenvalerate. The RfD Committee concluded (RfD Doc dated July 1, 1996) that "except for carcinogenicity, fenvalerate data should not be used in support of esfenvalerate registration." In addition, "Although the chronic rat studies were conducted only with fenvalerate, the Committee concluded that a new esfenvalerate study in the rat would not be required since dog studies indicated that this species is more sensitive to the toxic effects of fenvalerate and esfenvalerate than the rat."

B. 21 Day Dermal Study

The Toxicology Endpoint Selection (TES) Committee determined that, although there was a 21-day dermal study (MRID 42325101) available for fenvalerate, it was decided not to use it for risk assessment purposes because it was conducted on fenvalerate in which esfenvalerate constitutes only one-quarter of the substance. In addition, this study did not evaluate local dermal absorption (skin sensory stimulation) that was observed in the Guinea pig study discussed in the Dermal Absorption section of this document. Therefore a new 21-day dermal study with esfenvalerate (evaluating skin sensory stimulation) should be conducted.

[3] "Pyrethroid-Mediated Skin Sensory Stimulation Characterized by a New Behavioral Paradigm": Cagen, Malley, Parker, Gardiner, VanGelder, Jud: Toxicology and Applied Pharmacology: 76, 276-279 (1983)

C. Developmental Neurotoxicity

The RfD Committee concluded that, based upon the findings of 1) neurotoxicity in the developmental toxicity studies in rats and rabbits at all dose levels, 2) increased parental and pup mortality and neurotoxicity observed in the 2-generation study, and 3) neuropathology in the comparative mammalian toxicity study with fenvalerate and esfenvalerate (MRID No. 41637801, HED Doc. No. 009081) at higher dose levels, a developmental neurotoxicity study (83-6) is recommended.

D. Mutagenicity

The following newly submitted mutagenicity studies are acceptable:

- 84-2 Bacterial Gene Mutation
- 84-2 Chinese Hamster V79 Gene Mutation
- 84-2 CHO: In Vitro Chromosomal Aberration

The following mutagenicity studies are unacceptable:

- 84-4 UDS in Hela Cells
- 84-2 Mouse Micronucleus

The requirement for guideline series 84-2 Gene Mutation and 84-2 Structural Chromosomal Aberration studies are satisfied. The requirement for a guideline series 84-4 Other Genotoxic Effects study on esfenvalerate has not been satisfied by the UDS study. The results of the mutagenicity studies (Executive Summaries) are attached in the form of one-liners. Also, attached are their respective DERs. The unscheduled DNA synthesis study (MRID 41316304) was not reviewed in depth because the protocol was found to be deficient. Hence, the study is not acceptable and does not satisfy the requirement for a guideline series 84-4 Other Genotoxic Effects study. (On April 11, 1996, The RfD/Peer Review committee met and decided that there is no concern for mutagenicity at this time.)

E. Metabolism

The metabolism studies are not on esfenvalerate and are unacceptable because bridging studies are not allowed at this time.
This position is based on the results of the RfD/Peer Review Report of Esfenvalerate of July 1, 1996 in which it was concluded "...that, except for carcinogenicity, Fenvalerate data should not be used in support of Esfenvalerate registration." It should be noted that studies #'s 7, 8, 9 and 10 have already been reviewed in connection with a previous action on fenvalerate (HED Doc# 004681). The remaining study (#13) and literature articles (#'s 11, 12, 14 and 15) are being returned unreviewed at this time.

F. 90-Day Feeding Study in Mice

The 3-month feeding study in mice on fenvalerate is not needed since the pesticide of concern is esfenvalerate. Therefore, it is being returned unreviewed at this time.

CITATION	MATERIAL	MRID NUMBER	RESULTS	TOXCAT	CORE GRADE DOC.#
(84-2)In Vitro Cytogenetics **Species:**Chinese hamster **Lab. Name:Sumitomo Study No:**LLT-50-0010 **Date:12/28/85**	Esfenvalerate (95.5%)	41215204	In a mammalian cell cytogenetics chromosomal aberration assay (MRID 41215204), CHO-K1 cell cultures were exposed to S-1844 (95.5% a.i.) in DMSO at concentrations of 1 x 10^{-5}, 2 x 10^{-5}, 5 x 10^{-5}, or 1 x 10^{-4} M (4.2 μg/mL, 8.4 μg/mL, 21 μg/mL, 42 μg/mL respectively) without exogenous metabolic activation (S9-mix) and at concentrations of 5 x 10^{-5}, 1 x 10^{-4}, 2 x 10^{-4}, or 5 x 10^{-4} M (21 μg/mL, 42 μg/mL, 84 μg/mL, 210 μg/mL respectively) with S9-mix. S9-mix was obtained from Kanechlor-400 induced male Sprague-Dawley rat liver. S-1844 was tested up to cytotoxic concentrations with growth inhibition seen at concentrations of 5 x 10^{-5} M (35.3% of control value) without S9-mix and at 5 x 10^{-4} M (40.8% of control value) with S9-mix. Positive and solvent controls induced the appropriate response. **There was no evidence of a significant induction of chromosomal aberrations or polyploid cells over background**. This study is classified as acceptable. It does satisfies the requirement for FIFRA Test Guideline 84-2 for in vitro cytogenetic mutagenicity data.		Acceptable

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TOX
ONELINERS

P. C. No:109303 TOXCHEM NO.:268J Chemical Name:Esfenvalerate

CITATION	MATERIAL	MRID NUMBER	RESULTS	TOX CAT	CORE GRADE DOC.#
(84-2)Ames test **Species:** Salmonella **Lab. Name:** Sumitomo **Study No:** LLT-50-009 **Date:** 12/28/85	Esfenvalerate (95.5%)	41316301	In a reverse gene mutation assay in bacteria (MRID 41316301), *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* strain WP2(uvrA) were exposed to S-1844 (95.5%) in DMSO at concentrations of 15, 50, 150, 500, 1500, or 5000 μg/plate in the presence and absence of mammalian metabolic activation (S9-mix). The S9 was prepared from Kanechlor-400 induced male Sprague-Dawley rat liver. S-1844 was tested to a limit concentration of 5000 μg/plate (a precipitate was also seen on the plates at 5000 μg/plate both with and without S9-mix and at 1500 μg/plate without S9-mix). S-1844 did not significantly increase the number of revertant colonies over solvent control values in any of the six bacterial strains at any dose tested, either with or without S9-mix. The positive and solvent control values were appropriate. **There was no evidence of induced mutant colonies over background.** This study is classified as acceptable. It satisfies the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.		Acceptable

ESFENVALERATE SALMONELLA/MAMMALIAN ACTIVATION; GENE MUTATION (84-2)

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TOX
ONELINERS

P. C. No:109303 TOXCHEM NO.:268J Chemical Name:Esfenvalerate

CITATION	MATERIAL	MRID NUMBER	RESULTS	TOXCAT	CORE GRADE DOC.#
(84-2)In Vitro Gene Mutation **Species:** Chinese Hamster V79 **Lab. Name:** Sumitomo **Study No:** LLT-50-0012 **Date:** 12/28/85	Esfenvalerate (95.5%)	41316302	In a mammalian cell gene mutation assay at the HGPRT locus (MRID 41316302), Chinese hamster V79 cells cultured in vitro were exposed to S-1844 (95.5% a.i.) in DMSO at concentrations of 3×10^{-5}, 1×10^{-4}, 3×10^{-4}, and 1×10^{-3} M (12.6, 42, 126, 420 μg/mL, respectively) in the presence of mammalian metabolic activation (S9-mix) and at concentrations of 1×10^{-5}, 3×10^{-5}, 1×10^{-4}, and 3×10^{-4} M (4.2, 12.6, 42, 126 μg/mL, respectively) in the absence of S9-mix. S-1844 was tested up to cytotoxic concentrations as determined in a preliminary cytotoxicity assay (22% cell survival at the top concentration tested with S9-mix and 20% cell survival at the top concentration tested without S9-mix). The positive and solvent controls induced the appropriate responses. **There was no evidence of induced mutant colonies over background.** This study is classified as acceptable. It satisfies the requirement for FIFRA Test Guideline 84-2 for in vitro mutagenicity (mammalian forward gene mutation) data.		Acceptable

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TOX
ONELINERS

P. C. No:109303 TOXCHEM NO.:268J Chemical Name:Esfenvalerate

CITATION	MATERIAL	MRID NUMBER	RESULTS	TOX CAT	CORE GRADE DOC.#
(84-2)Micronucleus **Species:** Mouse **Lab. Name:** Sumitomo **Study No:** LLT-50-0011 **Date:** 12/28/85	Esfenvalerate (95.5%)	41316303	In an ICR mouse bone marrow micronucleus assay (MRID 41316303), 6 males per dose were treated once intraperitoneally with S-1844 (95.5% a.i.) at doses of 40, 80 or 150 mg/kg. Bone marrow cells were harvested at 24 hours post-treatment. In a second assay the mice were treated once intraperitoneally with the test material at 150 mg/kg and bone marrow cells harvested at 24, 48 and 72 hours post-treatment. The vehicle was corn oil. A preliminary acute toxicity study showed toxic effects (deaths) at concentrations of 200 mg/kg and above (2, 3 and 6 of 6 mice died at 200, 500 and 1000 mg/kg respectively and no deaths occurred at 100 mg/kg). There were (presumably) no signs of acute toxicity in the main micronucleus assays at any dose tested as none were mentioned; however, bone marrow depression was seen 48 hours after treatment at 150 mg/kg with recovery by 72 hours. It is not certain that S-1844 was tested to a sufficiently high dose. The positive and solvent controls induced the appropriate response. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any dose or cell harvest time.** This study is classified as unacceptable because the information presented in the study does not provide justification for the use of a single sex (male) or provide assurance that the highest dose tested was sufficient. The study could be upgraded to acceptable if data were presented showing no sex bias in the toxicity of S-1844 or related compounds to mice and if 150 mg/kg could be shown, from any data generated in this study and not presented or from other studies, to be an acceptable upper (MTD) dose in ICR mice. As presented, the study does not satisfy the requirement for FIFRA Test Guideline 84-2 for *in vivo* cytogenetic mutagenicity data.		Unacceptable

Sign-off date: 07/17/97
DP Barcode: d224281
HED DOC Number: 012275
Toxicology Branch: tb1