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

SEP 20 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Esfenvalerate - Updating data base (Esfenvalerate and Fenvalerate), transmitting several previously unrecorded Data Evaluation Records (DERs). **This memorandum does not address any tolerance or registration requests.**

TOX Chem No.	268J
PC Code:	~~109303~~
DP Barcode:	D229677
Submission No.:	S482269

FROM: Marion P. Copley, D.V.M., Section Head
Review Section IV, Toxicology Branch I
Health Effects Division (7509C)
Marion Copley 9/11/96

TO: Griffen/McCall
Registration Section
Health Effects Division (7509C)

THRU: William B. Greear, M.P.H.
Review Section IV, Toxicology Branch I
Health Effects Division (7509C)
KB
9/16/96

cc: Hebert/LaRocca, PM 13
Registration Division (7505C)

I. CONCLUSIONS:

Toxicology Branch I (Tox I) is not addressing the petition for tolerances on lettuce (PP 0F03852) in this subordinate bean. These will be addressed in the parent bean (D212386). The petitioner should be informed of the following toxicological data gaps for esfenvalerate (identified in the TB1 memorandum of April 2, 1991 and/or the HED RfD Committee document dated July 1, 1996) which should be submitted as soon as possible.

- 81-8SS Acute Neurotoxicity Screening Battery
- 82-2 21 Day Dermal
- 82-7 90-Day Neurotoxicity - mammalian
- 83-6 Developmental Neurotoxicity
- 85-1 General Metabolism

The newly submitted skin sensitization study (MRID 41215203) is acceptable (DER in ATTACHMENT 1).

ATTACHMENT 2 contains the following old Toxicology memoranda/DERs which have not been stored on microfiche:

- 2-Year Feeding Study in Rats (memorandum dated July 27, 1978)
- 3-Generation Reproduction in Rats (memorandum dated May 4, 1978)
- Oncogenicity Study in the Mice (memorandum dated July 21, 1978)

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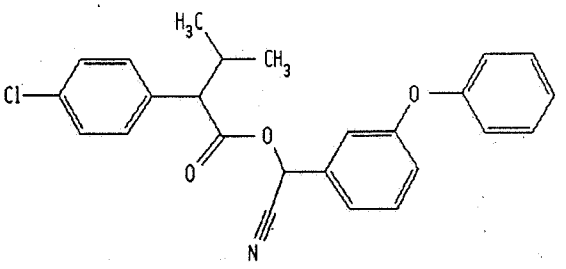
II. REQUESTED ACTION:

Under a cover letter dated September 23, 1994, Linda Mullin of DuPont Agricultural Products requested the establishment of tolerances for the residue of S-alpha-cyano-(3-phenoxyphenyl)-methyl S-4 chloro-alpha-(1-methylethyl)-benzeneacetate (esfenvalerate) in or on the raw agricultural commodity, head lettuce. Included in the parent package (D212386) was a list of studies for esfenvalerate/-fenvalerate that the Registrant is using to support the registration of esfenvalerate. There were also several studies (metabolism and an interim report mouse) included in this package. These studies and the tolerance request will be addressed in the parent bean. **This memorandum (subordinate bean (D229677) will only address the esfenvalerate data base.**

III. PRODUCT INFORMATION (Updated November 1990)

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.

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IV. REQUIREMENTS (40 CFR 158.340) Esfenvalerate, # 109303
Updated: September, 1996

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	4
84-2 Mutagenicity - Structural Chromosomal Aberration	Y	4
84-2 Mutagenicity - Other Genotoxic Effect	Y	4
85-1 General Metabolism	Y	N
85-2 Dermal Penetration	N	-
86-1 Domestic Animal	N[5]	-

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] Studies currently under review.
[5] Study is only required for the end-use product (EP).

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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). 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 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 tumor 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.

2) In a lifetime feeding study (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).** 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 oncogenicity 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 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) 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

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

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

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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

Studies under review.

G. Metabolism

No study available.

VI. DATA GAPS:

- o 81-8SS Acute Neurotoxicity Screening Battery
- o 82-2 21-Day Dermal
- o 82-7 90-Day Neurotoxicity (Mammalian)
- o 83-6 Developmental Neurotoxicity
- o 85-1 General Metabolism

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

The sponsor was informed in TOX I's memorandum of April 2, 1991 of the certain data gaps. The sponsor is again informed herein as to the data gaps.

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 appropriated 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]

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)

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

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. However, the database on esfenvalerate is adequate for this type of regulatory action. 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.

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[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. New Study for Review

The sponsor submitted the following study for review (The DER is in attachment #1):

- Maedgen, J.L. (10/24/86) Guinea pig skin sensitization of MO 70616 Technical. Stillmeadow, Inc., Houston, Texas 77036. Lab. Proj. No. 4274-86, 8/6/86-9/5/86. MRID 41215203. Unpublished.

E. Executive Summaries

"New" Executive Summaries (in current format) for several existing esfenvalerate and fenvalerate studies are either in the **TOXICOLOGY PROFILE:**

81-2a - Subchronic feeding - rat (MRID 40215601)
81-2a - Subchronic feeding - rat (MRID 00151030)
Study not evaluated by RfD Committee. The conversion to mg/kg/day was incorrect in the original DER.
81-2a - Subchronic feeding - mouse (MRID 41359701)
Study not evaluated by RfD Committee.
83-1b - 21-day probe for a 1 year dog feeding study (MRID 40376501)
83-1b - 1-year feeding study - dog (MRID 00163855)
83-2b - Carcinogenicity - mouse (MRID 00079876)
The RfD Committee noted the increased mortality observed at the high dose was about the same as the low dose and therefore should not be considered an effect of treatment. ATTACHMENT 5 contains a table of body weight.
83-2b - Carcinogenicity - mouse (MRID 00093662)
83-2b - Carcinogenicity - mouse (MRID 00071949)
83-4 - 2 Generation Reproduction - rat (MRID 43489001)
83-5 - Chronic/carcinogenicity - rat (MRID 00082244, 00111888)
83-5 - Chronic/carcinogenicity feeding - rat (MRID 00079877)
Select body weight tables are in ATTACHMENT 4 at the request of the RfD Committee.

or **ATTACHMENT #3**

83-1b - 6 Month feeding study - dog (MRID 00093652, 00128999)

This study was not evaluated by the RfD Committee.

83-4 - 3 Generation reproduction study - rat (MRID 00085501)
The RfD Committee considered this study to be unacceptable and not upgradable due, in part, to the great disparity between the desired dose levels and actual concentrations, particularly in the highest dose.

83-5 - Chronic/onco feeding - rat (MRID 00093664, 00093665)
The RfD Committee considered this study to be unacceptable for both chronic toxicity and cancer due to major study problems.

F. <u>Old DERs for Microfiche</u>

The following memoranda/study DERs for fenvalerate should be microfiched in order to receive document numbers, therefore, the documents are attached (ATTACHMENT #2). The Reproduction and Chronic rat documents have been retyped and the original signature pages attached.

- 2-Year Feeding Study in Rats (memorandum dated July 27, 1978)
- 3-Generation Reproduction in Rats (memorandum dated May 4, 1978)
- Oncogenicity Study in the Mice (memorandum dated July 21, 1978)

ATTACHMENT 1

EPA Reviewer: William B. Greear, MPH, Date
Review Section 4, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion P. Copley, D.V.M., Date 9/5/96
Review Section 4, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea pig
OPPTS 870.2600 [§81-6]

DP BARCODE: D212386
P.C. CODE: 109303
SUBMISSION CODE: S482269
TOX. CHEM. NO.: 268J

TEST MATERIAL (PURITY): MO 70616 Technical (100% Esfenvalerate)

SYNONYMS: Fenvalerate A-alpha, S-Fenvalerate, Asana, SS-Pydrin, S-1844, DPX-YB656-84, Sumicidin A-alpha, Benzeneacetic acid, 4-chloro-alpha-(1-methylethyl)-,cyano(3-phenoxyphenyl)methyl ester, (S-(R*,R*))

CITATION: Maedgen, Joseph L. (10/24/86) Guinea Pig Skin Sensitization of MO 70616 Technical. Stillmeadow Inc., Houston, TX 77036. Lab. Proj. No. 4274-86, 8/6/86-9/5/86. MRID 41215203. Unpublished.

SPONSOR: Shell Development Company
Houston, TX 77001

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 41215203) with MO 70616 Technical (100%; WRC Tox #730C) in ethanol, young adult Duncan-Hartley guinea pigs, 5 male and 5 female animals/group were tested using the method of Buehler. The 4 groups consisted of a vehicle control (ethanol), a positive control (0.1% w/v 2,4-dinitrochlorobenzene in dimethyl ether), the irritation control and test groups, both using undiluted MO70616 Technical.

The average skin reaction score was 0.08 after the initial treatment and 0.00 after challenge (day 29). **In this study, MO 70616 Technical is not a dermal sensitizer.**

This study is classified as acceptable. The study satisfies the guideline requirement for a dermal sensitization study (81-6) in the guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality statements were provided. No Flagging statement was provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: MO 70616 Technical
   Description: Viscous amber liquid
   Lot/Batch #: WRC Tox #730C
   Purity: 100% ai.
   CAS #: 66230-04-4
   Verification of concentration/homogeneity: not provided

2. Vehicle and positive control: ethanol
   Positive control: 0.1% dinitrochlorobenzene in dimethyl ether

3. Test animals: Species: Guinea pig
   Strain: Duncan-Hartley
   Age and weight at start of treatment: young adult, 385-455 g
   Source: Camm Research Lab Animals Wayne, NJ
   Acclimation period: 21 days
   Diet: Purina Guinea Pig Chow ad libitum
   Water: tap ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - start: 8/6/86 end: 9/5/86

2. Animal assignment and treatment - Forty guinea pigs were divided into groups of 5 animals/sex and were assigned to a vehicle control group (ethanol), a positive control group (0.1% dinitrochlorobenzene in dimethyl ether) a skin irritation group (undiluted MO 70616 Technical) and a treatment group (undiluted MO 70616 Technical). Approximately 48 hours prior to treatment, the back of the trunks were clipped free of hair to expose an area at least 8 X 10 cm^2. Then a depilatory agent (Neet) was used. Three of the groups were treated with the appropriate test material, positive control or vehicle on Day 1, 8 and 15 by placing 0.5 ml of the appropriate material beneath a 1.5 inch by 2 inch (patch and piece of adhesive) Beiersdorf Coverlet dressing. The patches were placed laterally from the midline of the back on the left front quadrant. Then the entire trunks were wrapped with 4 ml clear polyethylene film. The patches were held in place for 6 hours. The same test site was used for all treatments. On Day 29 (challenge) the animals were treated identically as on the previous 3 treatment days with the addition of a second treatment site receiving 0.5 ml placed laterally on the right rear quadrant. The skin irritation group was treated once after depilating the back of the trunk on the right rear

quadrant. Observation for skin irritation were made 24 and 48 hours after each treatment and challenge dose. A marked increase in positive skin reactions after the Day 29 challenge was indicative of a sensitizing reaction. Body weights were determined on Days 0 and 28. (Note: A range-finding study was used to select a non-irritating dose for treatment.)

II. **RESULTS AND DISCUSSION:**

A. Induction reactions and duration - On Day 1, the average skin reaction scores were 0.00 and 0.08 for the vehicle control and test group. On Day 29, the irritation control group had a score of 0.00 after a single application. Minimal to slight irritation was occasionally seen during the induction period for both groups. (see Table 1)

B. Challenge reactions and duration - On Day 29, the average skin reaction scores were 0.05 and 0.08 for the vehicle control and test groups, respectively. (See Table 1)

C. Positive control - On Days 1 and 29, the average skin reaction scores were 0.05 and 1.90, respectively. Moderate erythema and mild edema were observed n the 3rd induction application and at challenge. (See Table 1)

D. Body weights and mortality were not affected by treatment. Additional tests are not required.

E. Deficiencies - One minor deficiency is inadequate verification of the concentration of the active ingredient (a.i.) in the test material. It is not considered essential in a short term study. Identification of the purity is adequate.

PYDRIN

Page_____ is not included in this copy.

Pages 24 through 25 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

ATTACHMENT 2

(Document has been retyped 9/5/96MPC. Handwritten notes in italics)
(Fenvalerate - MRID Nos. 00082244, 00111888)

DATE: July 14, 1978

SUBJECT: Pydrin™ Insecticide 2.4 Emulsifiable Concentrate SD43775
Technical - Lifetime Feeding Study in Rats
P.P. No. FF2013 E.P.A. File Symbol 201-401 Caswell No. 77A

FROM: Toxicology Branch
Registration Division

TO: Charles Mitchell and Chemistry Branch
Product Manager #17

Recommendations

A two-year chronic feeding study of SD-43775 Technical in rats is reviewed herein and has been found adequate to support a systemic N.E.L. of 250 PPM. No remarkable compound-related toxicological or pathological effects are evident. Gross and histopathological examinations of all animals used in the study have been reported except as indicated in part A.6.

Review

Lifetime Feeding Study in Rats with SD-43775 Technical *(code 6-1-0-0,98%)* (Litton Bionetics, Inc., LBI Project No. 2541, 4178, submitted by the Shell Chemical Co., ?/9/78, Acc. Nos. 097075-097082).

A. Procedure

1. Organization of the Study

Twelve hundred rats /Sprague-Dawley / 145 g (males) and 118 g (females) average wts., were randomly assigned to treatment groups after a 9-day acclimatization period as follows:

Dietary Level (PPM)	Number of Rats Males	Females
0 (control)	183	183
1	93	93
5	93	93
25	93	93
250	93	93
0 (control)*	22	22
500*	22	22

* Sacrificed at 25 weeks.

The rats were housed in groups of 3 except for 1 group of 4 in each of the 500 PPM and associated control groups; however, each animal was identified by an ear tag.

2. Preparation of Test Compound - Diet Mixtures

Test compound was blended into the diet as a pre-mix of diet and test compound-hexane solution. Hexane was added to diet for the control groups, Volumes of hexane and test compound-hexane solutions added to diet were equal.

Levels of test material in the diet were periodically estimated by chemical analysis throughout the study. Results of the analysis are as follows:

Nominal level (PPM)	Range (PPM)	Average (PPM)
0	0.1-0.2	0.1
1	0.67-2.6	1.2
5	4.2-8.5	5.1
25	14-49	25
250	210-310	360
500	450-640	590

3. Observations

Observations of toxic signs and deaths were made daily. Body weights of all animals and food consumption of 20 % of all animals/sex/dosage level were recorded weekly during the initial 13 weeks and monthly thereafter. Animals were palpated weekly.

4. Hematology, Clinical Chemistry, Urinalysis

At intervals of 13, 26, 52 and 78 weeks, 10 rats/sex/dosage level (20 rats/sex from controls) were evaluated for hematology, clinical chemistry, and urinalysis. All terminally sacrificed animals were similarly evaluated. Urine was collected while animals were individually housed and fasted overnight. Investigated parameters include the following:

a). Hematology: Hemoglobin, hematocrit (packed cell volume), erythrocyte count, leukocyte count, differential leukocyte count, platelet count, sedimentation rate (excluding animals sacrificed at 2 years), prothrombin time, clotting time.

b). Clinical Chemistry: Calcium, phosphate, creatinine, CPK, uric acid, cholesterol, bilirubin, alkaline phosphatase, LDH, SGOT, glucose, BUN, chloride, potassium, sodium, protein, protein fractions.

c). Urinalysis: Color, specific gravity, pH, sugar, albumin, ketones (acetone), bilirubin, occult blood, microscopic examination of sediment.

5. Gross Pathology

All animals were subjected to necropsy. Weighed organs include brain, heart, liver, kidneys, testes, adrenal glands, and spleen.

6. Histopathology

Groups of animals examined histopathologically include the following:

	Group (PPM)					
	0	1	5	25	250	0	500
Month	No. Of animals/sex/dosage level						
3	20			10	10	10	10
6	20			12	12	12	12
12	20			10	10		
18	20			10	10		
24	(61M,46F)		(33M,22F)	(32M,28F)	(32M,27F)	(34M,17F)	
Moribund or found dead	(42M,57F)		(18M,29F)	(19M,23F)	(19M,24F)	(17M,31F)	

One hundred sixty eight animals in the 1 and 5 PPM groups which were killed at 13, 25, 52 and 78 weeks were not histopathologically examined. Three rats in the 250 PPM female group were killed and not histopathologically examined due to a sexing error.

The following tissues and organs were examined microscopically:

Brain
Spinal cord
Sciatic nerve
Pituitary
Thyroid
Parathyroid
Salivary glands
Heart
Lungs
Spleen
Liver
Pancreas
Adrenal glands
Mesenteric lymph nodes
Bone with marrow
Kidneys
Bladder
Prostate
Testes
Ovaries
Uterus
Fallopian tubes
Stomach
Small intestine (3 levels)
Large intestine (3 levels)
Skeletal muscle (thigh)
Skin (flank)
Mammary gland
All gross lesions

B. Results

1. Mortality

The test material did not significantly affect survival of the animals during the study. Survival patterns can be realized by comparing the table showing division of animals into treatment groups (part A.1.) with the table describing groups of animals examined histopathologically (part A.6.).

2. Toxic Signs

No remarkable test compound-related toxic signs were evident. The predominant lesion was on the ear, presumably due to attachment of the ear tag. Other clinical signs appear to be due to aging or injury, e.g., alopecia, swellings, emaciation, labored breathing, body sores, crusts around nose and eyes.

3. Body Weight Data

The test material changed body weight according to the data presented below:

Dosage level(PPM)	Initial	13wks	25 wks	53wks	77 wks	101 wks
0 (male)	147.4	446.1	540.2	596.6	712.0	727.8
1	139.3*	453.1	560.0*	609.5	714.2*	767.0
5	146.0	441.7	526.0*	565.6*	704.8	715.4
25	145.6	430.0*	519.9*	582.4	674.4*	684.1*
250	147.6	434.1*	510.6*	581.1	703.1	682.4*
0	136.5	439.0	561.3	-----	-----	-----
500	136.3	422.9	563.0	-----	-----	-----
0 (female)	116.3	357.0	291.5	346.3	429.5	457.5
1	110.3*	259.4	293.7	393.3	401.3*	449.5
5	119.2	254.1	290.5	345.1	425.9	489.0
25	123.4	250.9	295.9	352.0	419.3	453.3
250	118.0	252.3	290.1	347.8	422.3	443.0
0	116.9	260.4	293.0	-----	-----	-----
500	121.2	235.4*	290.5	-----	-----	-----

*Significantly different from control ($p<0.05$)

Significant differences are sporadic and appear to be marginal. A definite dose-related compound effect is not apparent.

4. Food Consumption Unremarkable.

5. Urinalysis: Unremarkable

6. Hematology: Unremarkable

7. Clinical Chemistry: Unremarkable. However, decreased levels of α-2 serum proteins were found at 26 weeks in males and females fed 500 PPM.

8. Organ Weights, Organs/Body/Weight Ratios: Generally unremarkable. Sporadic significant differences were calculated, but a dose-related compound effect was not observed.

9. Histopathology

a). Results at 3 Months

Changes attributable to the test compound were not evident. Pathological manifestations were confined mainly to the lungs and mesenteric lymph nodes. Examination of mammary glands was not indicated.

b). Results at 25 Weeks

No test material-related effects were indicated. Outstanding pathological changes include chronic respiratory disease, focal myocarditis or myocardial fibrosis, nematodiasis, and malignant lymphomas. Microscopic examination of mammary glands was not indicated for all animals in each dosage group.

c). Results at 52 Weeks

No test-compound related effects were found. Parenchymal changes in liver did not usually reflect a fatty change. Lymphoid hyperplasia present in several organs did not elicit functional impairment. Splenic hemosiderosis was present in many animals.

d). Results at 18 Months

No effects attributable to the test-compound were observed. Neoplastic, hyperplastic, and inflammatory lesions were found in all dosage groups. The most common neoplasms were pituitary chromophobes. Adrenal cortical changes and mammary gland secretory activity were associated with the chromophobes. Splenic hemosiderosis was common in all dosage groups, especially females.

e). Results at Terminal Sacrifice

i). Lesions of the nervous system were primarily radiculoneuropathy and degenerative myelopathy and were found in all dosage groups. Degenerative neurological changes were attributed to aging and were not considered to be due to an effect of the test material.

ii). Proliferative and neoplastic lesions generally occurred with either similar incidences or a random distribution throughout all groups of animals examined as terminal sacrifices and intercurrent deaths. Pituitary tumors were frequently observed in all groups. The incidence of mammary tumors in female rats is shown in the following table:

~~(table not in report)~~

iii). Non-neoplastic lesions were either similarly or randomly distributed throughout all dosage groups. Most

MAMMARY TUMORS

	GROUP 1			GROUP 2			GROUP 3			GROUP 4			GROUP 5		
TUMORS	CONTROL			1 ppm			5 ppm			25 ppm			250 ppm		
	Term Kill	Int. Death	TOTAL	Term Kill	Int. Death	TOTAL	Term Kill	Int. Death	TOTAL	Term Kill	Int. Death	TOTAL	Term Kill	Int. Death	TOTAL
BENIGN	15/46	10/56	25/102	7/21	9/28	16/49	8/28	10/23*	18/51	13/27	8/24	21/51	8/17	12/31*	20/48*
%	33%	18%	25%	33%	32%	33%	29%	43%	35%	48%	33%	41%	47%	39%	42%
MALIGNANT	5/46	13/56	18/102	5/21	4/28	9/49	8/28	3/23	11/51	6/27	3/24	9/51	3/17	8/31	11/48
%	11%	23%	18%	24%	14%	18%	29%	13%	22%	22%	13%	18%	18%	26%	23%
TOTAL	20/46	23/56	43/102	12/21	13/28	25/49	16/28	13/23	29/51	19/27*	11/24	30/51	11/17	20/31	31/48*
%	43%	41%	42%	57%	46%	51%	57%	57%	57%	70%	46%	59%	65%	65%	65%

* Statistically significant from controls ($p<0.05$)

iii). Non-neoplastic lesions were either similarly or randomly distributed throughout all dosage groups. Most commonly observed lesions include chronic kidney disease, myocardial degeneration, adrenal cortical degeneration in females, splenic hemosiderosis and/or hematopoiesis, and minimal to mild pulmonary disease. No lesion was attributed to the test material.

C. Conclusions

a). Classification: Core Guidelines

b). No outstanding toxicity due to administration of the test compound was reported; therefore, the systemic N.E.L is concluded to be 250 PPM. In a concurrent 26 week study, a 500 PPM level of the test material did not induce remarkable toxicological signs. Formation of mammary gland tumors appears to be spontaneous as a result of aging and not as a result of a test compound effect.

RD initial R.E.:7/14/78:lf

(Initial 7/27/78)

(12)

DATE: July -- 1978 attached for signatures (14)

SUBJECT: Pydrin TM Insecticide. 2.4 Emulsifiable Concentrate SD43775 Technical - Lifetime Feeding Study in Rats.
P.P. No. FF2013 E.P.A. File Symbol 201-401 Caswell No. 77A
no Doc.#

FROM: Toxicology Branch
Registration Division

TO: Charles Mitchell and Chemistry Branch
Product Manager #17

Recommendations

A two-year chronic feeding study of SD-43775 Technical in rats is reviewed herein and has been found adequate to support a systemic N.E.L. of 250 PPM. No remarkable compound-related toxicological or pathological effects are evident. Gross and histo-pathological examinations of all animals used in the study have been reported except as indicated in part A.6.

Review

Lifetime Feeding Study in Rats with SD-43775 Technical (Code 6-1-0-0,787) (Litton Bionetics, Inc., LBI Project No. 2541, 1/78, submitted by the Shell Chemical Co., /9/78, Acc. Nos. 097375-097382).

A. Procedure

1. Organization of the Study

Twelve hundred rats /Sprague-Dawley 145 g (males) and 118 g (females) average wts., were randomly assigned to treatment groups after a 9-day acclimatization period as follows;

Dietary Level (PPM)	Number of Rats Males	Females
0 (control)	183	183
1	93	93
5	93	93
25	93	93
250	93	93
0 (Control) *	22	22
500 *	22	22

* Sacrificed at 25 weeks.

The rats were housed in groups of 3 except for 1 group of 4 in each of the 500 PPM and associated control groups; however, each animal was identified by an ear tag.

2. Preparation of Test Compound - Diet Mixtures

Attached for signatures

iii) Non-neoplastic lesions were either similarly or randomly distributed throughout all dosage groups. Most commonly observed lesions include chronic kidney disease, myocardial degeneration, acrenal cortical degeneration in females, splenic hemosiderosis and/or hematopoiesis, and minimal to mild pulmonary disease. No lesion was attributed to the test material.

C. Conclusions

a). Classification: Core Guidelines

b). No outstanding toxicity due to administration of the test compound was reported; therefore, the systemic M.E.L. is concluded to be 250 PPM. In a concurrent 26 week study, a 500 PPM level of the test material did not induce remarkable toxicological signs. Formation of mammary gland tumors appears to be spontaneous as a result of aging and not as a result of a test compound effect.

RD inital R.E.:7/14/78:lf

7/27/78

(Document has been retyped 9/5/96MPC. Handwritten notes in italics)
(Fenvalerate - MRID No. 00085501)

DATE: May 4, 1978

SUBJECT: Three-generation Reproduction Study with Pydrin (SD-43775) Caswell No. 77A

FROM: William Dykstra, Ph.D.
Toxicology Branch

TO: Charles Mitchell
Product Manager #17

Registrant: Shell Oil Company
One Shell Plaza
P.O. Box 2463
Houston, Texas 77001

Recommendations

1. The three-generation reproduction study in rats with pydrin (SD-43775) is acceptable as core-minimum data. The NOEL for reproductive parameters is considered to be 250 ppm. The NOEL for systemic toxicity in the parents is considered to be 25 ppm based on the reduced mean body weight of the F_2b parents at the high dose level.

2. The determination of SD-43775 in the hamster diet shows that diet preparation was prepared according to specifications.

Review

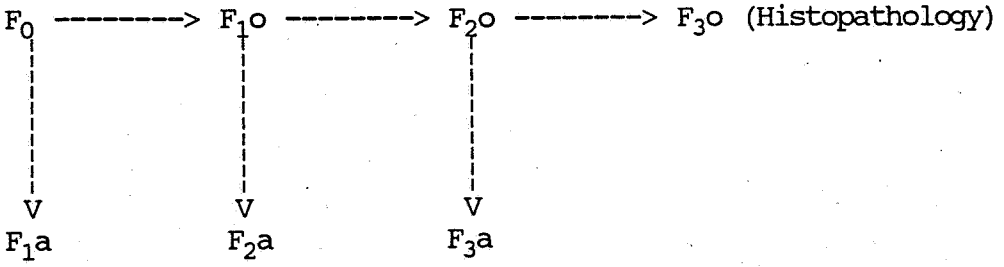
Three-generation Reproduction Study in Rats (LBI Project No. 2540, final report submitted Oct. 24, 1977, revised Feb. 1978)

Test Material: SD-43775 Technical, Code 6-1-0-1; golden brown, highly viscous liquid, *(98%)*

The test material was incorporated into the diet of weanling rats (Sprague-Dawley origin) for nine weeks prior to selection of the (F_0) parent generation. The experimental design and dose levels are outlined below for the F_0 generation:

Group No.	Number of Rats Male	Female	Dietary level ppm
1 (Vehicle control)	11	22	0
2	11	22	1
3	11	22	5
4	11	22	25
5	11	22	250

Two females and one male from the same treatment group were housed together for mating and a similar arrangement was implemented for succeeding generation as follows:



The following information was collected on each litter: Date of delivery, abnormalities at birth, live and dead pups - Days 1, 5 and 22, Sex ratio- Day 1, 5 and 21, Body Weights by litter - Day 1 and 21, general appearance throughout nursing. At least 10 males and 10 female F_3o weanlings from each treatment group were necropsies. All parent generations were necropsied. From the F_3o weanlings, the brain, heart, liver, and kidneys were weighed. These plus the following tissues were preserved in 10% buffered formalin:

thyroid	prostate
spleen	pancreas
adrenal gland	mesenteric lymph nodes
testes	ovaries
uterus	oviduct
small intestine	stomach
lung	

Tissues from 10 male and 10 female weanlings of each dose group were submitted to A.A. Stein, M.D., Microscopy for biological Research, LTD, Albany, N.Y., for histopathologic evaluation:

Results: Samples of prepared experimental diets were periodically sent to the Sponsor for chemical analysis of the test compound. Results are summarized below:

Desired Dose Level (ppm)	Actual (ppm)	Range (ppm)	Sample size
1	1.2	0.67-2.6	26
5	5.1	4.2-8.5	18
25	25.0	14.0-49.0	19
50	120.0	10-310	19

First generation (Parents F_0 - Offspring F_1a and F_1b)

No remarkable effects noted in F_0 parents at treatment of necropsy. No effect on reproductive parameters in F_1a and F_1b litters, except an apparent decreased fertility in females at 1 ppm dose level. However, this effect showed no dose response relationship in the higher treatment groups during the F_1 generation.

Second generation (Parents F_1o - Offspring F_2a - F_2b)

The general appearance and behavior of the parent rats of the second generation were judged to reflect no compound - related effect. The necropsy of the F_1b parents demonstrated a frequency of kidney changes (mottled, pale appearance) suggestive of a compound - related response; no effect on reproductive parameters in F_2a and F_2b litters except an apparent decrease in female fertility of the low level (1 ppm) test group. Since a dose - response relationship was not involved, this reduced reproductive capacity was not judged to be compound induced.

Third generation (Parents F_2b - Offspring F_3a and F_3b)

The mean body weights of the parents of the third generation F_2b adults revealed a significant reduction at the high level (250 ppm) when control and treated groups were compared. The necropsy of F_2b parents revealed gross kidney changes similar to changes noted in the F_1b parents. However the distribution with regard to dose was not judged to be consistent with a compound - related change. No effect on reproductive parameters in the F_3a and F_3b litters except an apparent decrease in female fertility of the low level (1 ppm) test group. Since a dose-response relationship was not involved, this reduced reproductive capacity was not judged to be compound induced. Histopathological examination of the F_3b weanling was unremarkable. ~~(see attached table).~~

Conclusion: The NOEL for reproductive parameters is considered to be the high-dose level (250 ppm). The NOEL for systemic toxicity of the parents is considered, from the evidence of body weight loss of the F_2b parents, to be 25 ppm. The systemic toxicity effect observed in the F_2b parents is evidence that the highest dose level produced a toxic effect.

Classification: Core-Minimum Data

Typists:TH
RD initial G.E.Whitmore 4/26/78
(initial for G.E.W.5/8/78)

(13) UNITED STA[illegible] ENVIRONMENTAL PROTECTION A[illegible]NCY (18)

DATE: May 4, 1978

SUBJECT: Three-generation Reproduction Study with Pydrin (SD-43775) Caswell # 774

no doc. number not 9002 as in liners

FROM: William Dykstra, Ph.D 12410 5/4/78
Toxicology Branch

TO: Charles Mitchell
Product Manager #17

Registrant: Shell Oil Company
One Shell Plaza
P.O. Box 2463
Houston, Texas 77001

Recommendations

1. The three-generation reproduction study in rats with pydrin (SD-43775) is acceptable as core-minimum data. The NOEL for reproductive parameters is considered to be 250 ppm. The NOEL for systemic toxicity in the parents is considered to be 25 ppm based on the reduced mean body weight of the F2b parents at the high dose level.

2. The Determination of SD-43775 in the hamster diet shows that diet preparation was prepared according to specifications.

Review

Three-generation Reproduction Study in Rats (LBI Project No. 2540, final report submitted Oct. 24, 1977, revised Feb. 1978)

Test Material: SD-43775 Technical, Code 6-1-0-1; golden brown, highly viscous liquid, 98%

The test material was incorporated into the diet of weanling rats (Sprague-Dawley origin) for nine weeks prior to selection of the (F_0) parent generation. The experimental design and dose levels are outlined below for the F_0 generation:

Group No.	Number of Rats Male	Female	Dietary level ppm
1 (Vehicle control)	11	22	0
2	11	22	1
3	11	22	5
4	11	22	25
5	11	22	250

Two females and one male from the same treatment group were housed together for mating and a similar arrangement was implemented for succeeding generations as follows: (continue on next page)

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Second generation (Parents F_1b - Offspring F_2a - F_2b)

The general appearance and behavior of the parent rats of the second generation were judged to reflect no compound - related effect. The necropsy of the F_1b parents demonstrated a frequency of kidney changes (mottled, pale appearance) suggestive of a compound - related response, no effect on reproductive parameters in F_2a and F_2b litters except an apparent decrease in female fertility of the low level (1 ppm) test group. Since a dose - response relationship was not involved, this reduced reproductive capacity was not judged to be compound induced.

Third generation (Parents F_2b - Offspring F_3a and F_3b)

The mean body weights of the parents of the third generation (F_2b adults) revealed a significant reduction at the high level (250 ppm) when control and treated groups were compared. The necropsy of F_2b parents revealed gross kidney changes similar to changes noted in the F_1b parents. However the distribution with regard to dose was not judged to be consistent with a compound - related change. No effect on reproductive parameters in the F_3a and F_3b litters except an apparent decrease in female fertility of the low level (1 ppm) test group. Since a dose-response relationship was not involved, this reduced reproductive capacity was not judged to be compound induced. Histopathological examination of the F_3b weanling was unremarkable.

Conclusion: The NOEL for reproductive parameters is considered to be the high-dose level (250 ppm). The NOEL for systemic toxicity of the parents is considered, from the evidence of body weight loss of the F_2b parents, to be 25 ppm. The systemic toxicity effect observed in the F_2b parents is evidence that the highest dose level produced a toxic effect.

Classification: Core-Minimum Data

Typists:TH
RD Initial G.E.Whitmore 4/26/78

E for GEW 5/8/78

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(Document has been retyped 9/10/96MPC. Handwritten notes in italics)
(Fenvalerate - MRID No. 00071949)

(From: pp# 71-2013, 7/21/78; R. Engler)

Review

1. 18-Month chronic toxicity study of S5602 in mice. Sumitomo AT-70-0176, Dec. 29, 1977 (tab 125, 127 and 128)

Pydrin was administered in the diet to ddy mice for 18 months. The dose levels and number of animals assigned were as follows:

Dose (PPM)	Males	Females
0	29	35
100	37	25
300	30	30
1,000	30	30
3,000	29	31

Mice were observed daily, after 78 weeks they were sacrificed (3000 PPM males and sacrificed after 72 weeks). Hematology, Blood Chemistry, gross pathology (including organ weights and ratio), and histopathology was performed. All animals were examined histologically, the number of apparently autolyzed animals is small.

Results:

Clinical signs of hypersensitivity were seen at 1000 and 3000 PPM, these subsided gradually. Mortality was increased for both sexes at 3000 PPM and the males only at 1000 PPM; increase in early deaths occurred at about 40 weeks of the study. The body weights (and gains) were affected at 3000 PPM and for males at 1000 PPM. Females at 100, 300, and 1000 PPM had somewhat lower body weights than controls but the effect was not significant. Hematology and blood chemistry were affected at 1000 and mostly 3000 PPM in such parameters as decreased Hbg and RBC, increased leukocytes and monocytes, increased GPT, GOT, LAP and LDH. Organ weights and ratios were also affected at 1000 and more so at 3000 PPM. Histopathologically granulomatous changes were observed in liver and lymph nodes. The incidence and severity were dose related. The histopathological findings were reviewed by a second pathologist (Dr. Ito) who also reported giant cell infiltration of the spleen. 100 PPM was a NEL for these changes, or very conservatively the lowest effect level. The incidence of parasites (nematodes) was determined by Ito as well but no correlation was found between parasitic nematodes and granulomata and it was thus concluded that the effect was compound related. The effect is further discussed by Okuno and Myamoto. Their conclusion corroborate the LEL of 100 PPM and they also suggest that the granulomatas are a reversible organ reaction. This conclusion is also corroborated by Dr. Long, EPA pathologist. Increases in tumor frequency was not observed in this study.

Conclusion:

The mouse study (ddy strain), shows a NEL of about 100 PPM or possibly less for granulomatous changes in liver and spleen, but no oncogenic potential. Granulomatas are usually the result of microbial infection or irritation by metals. The outcome of the second mouse study initiated by Shell and a demonstration that the effect seen in ddy mice is in fact reversible should clarify the situation.

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ATTACHMENT 3

ATTACHMENT 3

	ESFENVALERATE
81-1 Acute Oral LD50 Species: Rat West Hollow Research Center 6155M; 3/19/84 MRID 00144973 Tox Cat: II Minimum 001504	In an acute oral toxicity study (MRID 00144973), Fischer 344 (5 males and 5 females/dose level) were administered 38, 92, 180 or 380 mg/kg/day of Technical MO 70616 (esfenvalerate, 97%, Tox Sample No. 730A) and were observed for 14 days. Additional groups of rats were administered fenvalerate (92%, Tox Sample No. 77D) at dose levels of 150, 370, 850 or 1500 mg/kg. Most deaths occurred within 24 hours of dosing. Clinical signs observed were ataxia and/or incoordination, tremors, convulsions, hypersensitivity to touch and sound, hyperactivity, lacrimation, depressed myotactic reflex, polyuria, hunched posture and prostration, **The oral LD50 for Technical MO 70616 (esfenvalerate) is 87.2 mg/kg but could not be calculated for Technical fenvalerate.** The study is **Core-Minimum** and **satisfies** the requirement for a guideline series 81-1 acute oral toxicity study.
81-2 Acute Dermal LD50 Species: Rabbit Stillmeadow, Inc. 3881-85; 12/13/85 MRID 00156508 Tox. Cat: III Minimum 005291	In an acute dermal toxicity study (MRID 00156508), New Zealand White albino rabbits (5 males and 5 females/dose level) were dermally administered 0 or 2.0 g/kg of Technical MO 70616 (esfenvalerate, 98.7%, Lot No. 2-3-0-0) and were observed for 14 days. One treated animal died on day 2. Clinical signs included ataxia, body tremors, constricted pupils, muscle tremors, poor hind limb coordination, small feces and erythema and edema of the skin. **The dermal LD50 for Technical MO 70616 is greater than 2000 mg/kg.** The study is **Core-Minimum** and **satisfies** the requirement for a guideline series 81-2 acute dermal toxicity study.
81-3 Acute Inhalation LC50 (waived)	
81-4 Primary Eye Irritation Species: Rabbit Stillmeadow, Inc., 3882-85; 12/10/85 MRID 00156509 Tox. Cat.: III Guideline 005291	In a primary eye irritation study, (MRID 00156509), 9 New Zealand White albino rabbits received 0.1 ml of Technical MO 70616 (esfenvalerate, 98.7%, Lot No. 2-3-0-0) in the right eye of each rabbit. Three of the 9 rabbits received an eye wash. Ocular examinations were made at 1, 24, 48 and 72 hours and at 7 days. **Mild conjunctivitis was observed in all rabbits but cleared by day 7.** The study is **Core-Guideline** and **satisfies** the requirement for a guideline series 81-4 primary eye irritation study.
81-5 Primary Dermal Irritation Species: Rabbit Stillmeadow, Inc. 3883-85; 12/19/85 MRID 00156510 Tox. Cat.: IV Guideline 005291	In a dermal irritation study (MRID 00156510), New Zealand White albino rabbits (3 males and 3 females) received a dermal application of 0.5 ml of Technical MO 70616 (esfenvalerate, 98.7%, Lot No. 2-3-0-0). Four hours after treatment the test material was removed and the test sites were graded at 1, 24, 48 and 72 hours. **Mild erythema and edema were observed in 1 animal 1 hour after treatment. The study is Core-Guideline** and **satisfies** the requirement for a guideline series 81-5 primary dermal irritation study.

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	FENVALERATE
82-2 21-day Dermal Species: Rabbit Haskell Lab HLR 127-92; 5/14/92 MRID 42325101 Acceptable HED DOC 009756	In a 21-day dermal study (MRID 42325101), 5 male and 5 female New Zealand rabbits/ group were dermally administered Technical fenvalerate (95.4%) at 0, 100, 300 or 1000 mg/kg/day for an exposure period of 6 hours/day. Modest erythema was observed in all female treated groups and in males at 300 and 1000 mg/kg/day. Mild edema was observed in males in the 1000 mg/kg group and in females in the 300 and 1000 mg/kg group. Superficial necrosis was observed in males and/or females in the 300 and 1000 mg/kg/day group. **The LOEL is 300 mg/kg/day based on skin irritation. The NOEL is 100 mg/kg/day.** The study is **Core-Guideline** and **satisfies** the requirement for a guideline series 82-2 subchronic dermal study.
83-1(b) Feeding 6 months Species: Dog 208-B; 5/26/81 MRID 00093652, 00128999 HED DOC 004041 Guideline	In a 6-month feeding study (MRID 00093652, 00128999), 6 male and 6 female beagles/ group were administered 0, 250, 500 or 1000 ppm (representing approximately 0, 6.25, 12.5 or 26 mg/kg/day) of Technical fenvalerate (91%) in the diet. Body weight decreased in females and thinness was observed in both sexes at 1000 ppm. Emesis and head shaking were observed in males at all dose levels and ataxia and tremors were observed in males at 500 and 1000 ppm. Other neurological signs included intention tremors and dysmetria of the limbs. **The LOEL of 250 ppm (6.25 mg/kg/day) was based on emesis, head shaking, biting of extremities, normocytic anemia, increased serum cholesterol, nerve dysfunction and the occurrence of hepatic microgranuloma. The NOEL was determined to be less than 250 ppm.** The study is **Core-Guideline** and **satisfies** the requirement for a guideline series 83-1b chronic feeding study in dogs (for fenvalerate).
83-4 3-Generation Reproduction Species: Rat Litton 2540; 1978 MRID 00085501 Unacceptable	In a 3-generation reproduction study (MRID 00085501), groups of 22 female rats and 11 male rats were administered 0, 1, 5, 25 or 250 ppm (corresponding to 0, 0.005, 0.02, 0.5, 1.25 or 12.5 mg/kg/day of fenvalerate in the diet, however there are serious questions as to the actual dose received. Reduced weight gain of the F2b parent generation was observed. **The LOEL is greater than the highest dose tested (concentration uncertain due to concentration disparities). The reproductive NOEL is greater than the highest dose.** The study is **Unacceptable, not upgradable** and **does not satisfy** the requirement for a guideline series 83-4 reproduction study for fenvalerate in rats.
83-3(c) Developmental Toxicity Species: Mouse Sumitomo: 11/5/76 MRID 00109852 HED DOC 009002	In a teratology study (MRID 00109852), pregnant mice were exposed to 0, 5, 15 or 50 mg/kg of fenvalerate from Gestation Day 6-15. About 20 mice delivered by caesarian section and about 23 mice were allowed to deliver naturally. At 50 mg/kg, irregular respiration, hypersensitivity, tremors and salivation were observed. (No individual animal or litter data). **The LOEL is greater than or equal to 50 mg/kg. The NOEL for teratogenicity was not determined. teratogenicity was not determined.** No Core grade was assigned.
83-3(b) Developmental Toxicity Species: Rabbit Tunstall 887; 10/75 MRID 00109819 HED DOC 009002	In a teratology study (MRID 00109819), groups of 21 rabbits were administered 0, 12.5, 25.0 or 50 mg/kg of fenvalerate from Gestation Day 6-18. Dams in the 50 mg/kg group showed reduced body weight gain. (No individual animal data.) **The LOEL is greater than or equal to 50/kg. The NOEL for teratogenicity was not determined.** No Core grade was assigned.

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83-5 Feeding 2-year Species: Rat Nihon Dobutsu Co. AT-10-0278 4/20/81 MRID 00093664; 00093665 HED DOC 004041 Unacceptable	In a 2-year feeding study (MRID 00093664-00093665), group of 80 Wistar/SLC strain rats were administered 0, 50, 150, 500 and 1500 ppm (corresponding to 0, 2.5, 7.5, 25.0 or 75.0 mg/kg/day) of 93.4% fenvalerate in the diet. Body weight gain was decreased in males in the 1500 ppm group and in females in the 500 and 1500 ppm groups. Giant cell infiltration was observed in lymph nodes and adrenal glands at 500 and 1500 ppm and in the spleen at 1500 ppm. Dose related increases of reticuloendothelial cell proliferation were noted in the mesenteric lymph nodes at 500 and 1500 ppm. **The LOEL is 500 ppm (25.0 mg/kg/day) based on giant cell infiltrates and reticuloendothelial cell proliferation. The NOEL is 150 ppm (7.5 mg/kg/day).** The study is **Unacceptable** and **does not satisfy** the requirement for a guideline series 83-5 combined chronic/carcinogenicity study in rats.

ATTACHMENT 4

select body weight tables for
2-year feeding study in rats
MRID 00079877 (2 pages taken from study report pages 00014,00015)

PYORIN

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ATTACHMENT 5

body weight table for chronic mouse study
MRID 000079876 (taken from page 21 of the study report)

PYDRIN

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