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DATA EVALUATION REPORT

STUDY TYPE: Two Generation Reproduction Study - Rats
OPPTS 870.3800 (83-4)

Tox Chem No.	268J
MRID No.	43489001
PC No.	109303

TEST MATERIAL (PURITY): DPX-YB757-84 (Esfenvalerate, (98.8% a.i.)

SYNONYMS: [S-(R*,R*)]-4-Chloro-alpha-(methylethyl) benzeneacetic acid; cyano(3-phenoxyphenyl) methyl ester; S-Fenvalerate: Asana; Sumicidin A-alpha; SS-Pydrin; S-1844; CAS # 66230-04-4

CITATION: Biegel, L.B. (1994) Reproductive and fertility effects with DPX-YB656-84 multigeneration reproduction study in rats. Dupont, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, Dupont HLR 331-94; Med. Res. Proj. No. 9657-001, December 1, 1994. (MRID 4348901)

SPONSOR: Dupont

EXECUTIVE SUMMARY: 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). (The dietary concentrations approximate 0, 3.75, 5.0, 17.5 and 35.0/17.5 mg/kg/day). One litter per generation.

Mean compound intake for males was 0, 5.10, 6.70 and 18.87 for male in the 0, 75, 100 and 350/150 ppm groups, respectively. Mean compound intake for females was 0, 5.47, 7.27 and 25.1 for the 0, 75, 100 and 350/150 ppm groups respectively. The authors indicated the following effects in the study (reviewer agrees):

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.

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.

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 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 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.

This study is **Acceptable** and **satisfies** the guideline requirement for a Series 83-4 Multigeneration Reproduction study in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

A. MATERIALS AND METHODS

1. Test Material: PDX-YB757-84 (Esfenvalerate)
   Description: gold viscous liquid
   Lot/Batch #: 20253
   Purity: 98.8%
   CAS No.: 66230-04-4

2. Vehicle: Acetone
   Description: N/A

Lot/Batch #: N/A
Purity: N/A

3. Test animals: Species: rat
Strain: Crl:CD BR
Age at start of dosing: male-68 days, female 65 days
Weight: males 323.3-328.4g, females 209.9-213.3g
Source: Charles River Laboratories, Inc. Kingston, NY
Housing: individually in stainless steel wire-mesh cages during the pretest, premating and testing period; during the mating period the animals were housed as breeding pairs
Environmental Conditions:
Temperature: 23±2°C
Humidity: 50±10%
Air changes: not provided
Photoperiod: 12-hour on/12-hour off light cycle
Acclimation period: 6 days

3. Diet preparation The test material was warmed to a uniform liquid state and dissolved in acetone. the mixture was then added to Purina Certified Rodent Chow #5002 meal and thoroughly mixed. All diets were prepared weekly. Stability was determined on 3 samples per diet at 7 and 14 days at room temperature, and at 14 days when refrigerated. Homogeneity was determined on 3 samples of the 150 percent at the top, middle and bottoms of mixer. A sample of esfenvalerate (98.8%) was analyzed for stability once at the beginning of the study and at termination. Samples from various diets were analyzed for concentrations on test day 55 of the P_1 generation and test days 15 and 147 of the F_1 generation.

Results - The stability of esfenvalerate (98.8%) was determined to be 98.2±1% on 6/23/93 (prior to the start of the study) and 92.4±2.2% on 3/21/94 (near the end of the study). The stability of the test materials in the diet was measured on 6/29/93 and found to range from 90.2% to 106% of nominal concentrations for diets stored frozen refrigerated or at room temperature for 14 days. Tests for homogeneity revealed the following ranges of concentration: 76.0 to 85.5 ppm for the 75 ppm diet, 85.9 to 98.2 ppm for the 100 ppm diet and 351 5o 363 ppm for the 350 ppm diet. Diets prepared near the beginning, middle and end of the study had concentrations ranging from 93.1 to 117% of nominal concentrations.

4. The animals received food and water ad libitum.

5. Statistics - See Attachment #1 for methods of analysis used.

B. PROCEDURES AND STUDY DESIGN

1. Mating: Seventy-three days after initiation of the study, each P_1 female was mated with a randomly selected male in the same dose group until a copulatory plug was observed or until 3 weeks had passed. F_1 rats were mated after they had been administered their diets for 105 days. Siblings were not mated.

2. Animal Assignment - Animals were assigned by computer-generated, stratified randomization to the following test groups.

Table 1: Animal Assignment

Test Group		Dose in Diet (ppm)a
No. of Animals/sex		
30	30	
P_1	F_1	
I-0	I-1	0
II-0	II-1	75
III-0	III-1	100
IV-0	IV-1	350/150b

a Dietary concentration adjusted for 98.8% purity
b Dietary concentration reduced on 10/28/93 to 150 ppm approximately 4 months after start of dosing (6/30/93)

C. OBSERVATION SCHEDULE

1. Parental animals: Observations for mortality and clinical signs of toxicity were made at least once daily. In addition, each rat was handled and examined for abnormal behavior and/or appearance.

Results: [Note: When F_1 pups were weaned, and early in their adulthood, rats in the treated groups were observed to scratch and they developed sores. Therefore, canola oil (containing vitamin E) or vitamin E oil was applied topically.] At 350 ppm, P_1 male rats exhibited abnormal gait/mobility, alopecia, scabs and sores. Two males in the 350 ppm group died. One death was due to

genitourinary tract inflammation. However, the second death was believed to be compound-related ulcerative dermatitis. Female P_1 rats exhibited abnormal gait at 350 ppm. One P_1 female in the 100 ppm group was sacrificed in extremis. Its death was attributed to dystocia. F_1 males in the 350/150 ppm group exhibited signs indicative of neurotoxicity (abnormal gait/mobility, ataxia, barrel rolls, general spasms, hypersensitivity, popcorn seizures, tremors and vocalization) and signs involving the skin (alopecia, swollen face, scabs and sores). the signs were observed in all males in the 350 ppm group that died or were sacrificed in extremis at Day 34. Death was attributed to compound administration. Clinical signs involving the skin were observed in males at 75 and 100 ppm. Female F_1 rats in the 350/150 ppm groups exhibited neurotoxic signs (abnormal gait/mobility, ataxia, hyperactivity, hypersensitivity, tremors and vacuolization) and signs affecting the skin (alopecia, scabs and sores). These signs were so severe that all but 9 female rats in the 350/150 ppm group had been found dead or were sacrificed in extremis by Day 33 (Table 2).

Table 2: Summary of Clinical Signs of Toxicity[1]

P1				
Dose Level (ppm)	0	75	100	350/150
Male				
Abnormal gait/mobility	0	0	0	29*
Alopecia	1	1	3	8*
Scab	0	0	0	2*
Sore	1	1	1	8*
Female				
Abnormal gait/mobility	0	0	0	27*
F1				
Dose Level (ppm)	0	75	100	150
Male				
Swollen face	0	0	2	4*
Tremors	0	0	0	28*
Vocalization	0	0	0	8*
Female				

Table 2: Summary of Clinical Signs of Toxicity[1]				
Abnormal gait/mobility	0	0	0	28*
Alopecia	10	9	10	28*
Ataxia	0	0	0	17*
Hyperactive	0	0	0	5*
Hypersensitive	0	0	0	10*
Total scabs	6	7	11	28*
Total sores	5	6	6	30*
Stained fur	0	0	0	7*
Tremors	0	0	0	29*
Vocalization	0	0	0	4*

1 No. of rats with clinical sign. Data extracted from Tables 7, 23, 34 and 50, pp. 78, 95, 108-109 and 127-128, MRID 43489001

* Statistically significant trend at $p \leq 0.05$

2. Body weight - All P_1 and F_1 rats were weighed once each week during the premating feeding period. Females were also weighed on Days 0, 7, 14 and 21 of gestation and lactation. Females without known litters and all males were weighed weekly.

Results - Male P_1 rats in the 350 ppm group had significantly decreased body weights from test day 7 through day 105 (92% of controls). Body weight gain was also significantly decreased to 85% of control values. Female P_1 rats in the 350 ppm group had significant decreases in body weights from day 7 through day 70 (92% of controls). Body weight gain was also significantly decreased to 68% of control values. During gestation day 0-21, female P_1 rats in the 350 ppm group had significantly decreased body weights. This was attributed to "pre-existing conditions". Body weight was statistically significantly lower at the start of the gestation period. Also, body weight gain was not affected by treatment. Body weight gain was significantly decreased for females in the 350 ppm group from Day 0 to Day 21 (93% of controls) of lactation. F_1 males in the 350/150 groups had significantly decreased body weights during the premating phase and were subsequently sacrificed on Day 34. Body weight gain was also significantly

decreased in the 100 ppm group (93% of controls). F_1 female rats in the 350/150 and 100 ppm groups had significantly decreased body weight (94% of controls @ 100 ppm) and body weight gain (350/150 ppm) during the premating phase. In addition, F_1 females in the 75 ppm group had significantly decreased body weight (94% of controls) from days 70 to 98 of the premating phase. Body weights of F_1 females in the 100 ppm group were decreased on gestation Days 0 and 14 to 93.3% and 94.7% of control values, respectively. Body weights of F_1 females in the 75 ppm group were significantly decreased on gestation Days 0, 7 and 14 to 92.9%, 93.3% and 93.3% of control values, respectively (Table 3).

Table 3: Body Weight Gain (g) and -Percent(%) Change of P_1 and F_1 Rats

	Dose Level (ppm)			
P_1 Male	**0**	**75**	**100**	**350**
Day				
0-7	45.3	46.3	41.5 (8.4)	9.8* (78.4)
7-14	34.5	33.4 (3.2)	36.9	34.4
14-21	31.1	33.7	27.6 (11.3)	23.8* (23.5)
29-35	27.1	25.5 (5.9)	20.8* (23.2)	19.1* (29.5)
0-70	228.2	231.8	220.2 (3.5)	185.4* (18.8)
P_1 Female	**0**	**75**	**100**	**350**
Day				
0-7	18.1	16.0 (11.6)	17.4 (3.9)	5.7* (68.5)
7-14	18.4	17.5 (4.9)	15.6 (15.2)	8.3* (54.9)
28-35	9.2	5.8 (37.0)	7.6 (22.4)	4.9 (46.7)
0-70	86.3	88.2	80.3 97.0)	58.3 (32.4) *
P_1 Female	**0**	**75**	**100**	**350**
Lactation Day				

Table 3: Body Weight Gain (g) and -Percent(%) Change of P_1 and F_1 Rats				
	Dose Level (ppm)			
0-7	12.6	10.5 (16.7)	11.6 (7.9)	-0.7* (105.6)
7-14	5.3	11.1	5.1 (3.8)	1.6 (69.8)
0-21	1.5	5.5	6.4	-4.2 (179.0)
F_1 Male	**0**	**75**	**100**	**150**
Day				
0-7	45.1	44.4 (1.6)	41.1* (8.9)	34.0* (24.6)
7-14	58.3	58.2	53.8* (7.7)	48.4* (17.0)
0-105	546.6	520.8 (4.7)	508.1 (7.0)	a
F_1 Female	**0**	**75**	**100**	**150**
Day				
0-7	39.7	38.3 (3.5)	36.6* (7.8)	28.9* (27.2)
7-14	43.0	44.3	40.7 (5.3)	39.1* (9.1)
28-35	18.9	17.6 (6.9)	20.6	20.3
0-105	261.5	249.5 (4.9)	247.1 (5.5)	a
F_1 Female	**0**	**75**	**100**	**150**
Gestation Day				
0-7	31.8	31.1 (2.2)	36.9	a
7-14	26.7	24.8 (7.1)	23.1 (13.5)	a
0-21	138.2	137.3 (0.1)	140.5	a
F_1 Female	**0**	**75**	**100**	**150**
Lactation Day				
0-7	15.4	16.4	13.9 (9.7)	a

Table 3: Body Weight Gain (g) and -Percent(%) Change of P_1 and F_1 Rats				
	Dose Level (ppm)			
7-14	5.3	4.7 (11.3)	9.3	a
0-21	-5.5	1.7	1.9	a

1 Data extracted from Table 3, 12, 14, 16, 30, 39, 41 and 43, pp. 74, 84, 86, 88, 104, 116, 118 and 120, MRID 43489001
a Data not available due to mortality
* Statistically significant difference from control at $p \leq 0.05$

3. Food consumption, food efficiency and compound intake - Individual food consumption was determined weekly throughout the premating period for the P_1 and F_1 rats. Food consumption was also recorded for pregnant females on Days 0, 7 and 14 of gestation.

Results - Food consumption was decreased in P_1 males in the 350 ppm group at most intervals during the premating period. P_1 females in the 100 and 350 ppm groups had significant decreases in the daily mean food consumption, 19.0 and 18.0 g food/rat/day, respectively, compared to controls with 20.5 g food/rat/day. The mean food efficiency of P_1 females in the 350 ppm group was significantly decreased when compared to controls, 0.047 compared to 0.060 g weight gain/g food consumed. During the initial 14 days of the premating phase, the mean daily food consumption of P_1 male rats in the 350 ppm group was significantly decreased when compared to controls. This group was terminated after 34 days due to mortality. Mean daily food consumption of F_1 female rats in the 350/150 ppm group was significantly decreased during the initial 21 days of the premating phase. Compound intake during the premating phase is given in Table 4.

TABLE 4 Test Substance Intake (mean mg/kg body weight/day)[a]
During Premating

Male			Female		
75 ppm	100 ppm	300/150 ppm	75 ppm	100 ppm	350/150 ppm
P Generation					
4.21	5.55	18.8	5.56	7.18	25.1

TABLE 4 Test Substance Intake (mean mg/kg body weight/day)[a]
During Premating

Male			Female		
F_1 Generation					
5.98	7.84	18.93	5.37	7.36	N/A

a Data extracted from *(study Dupont HLR 331-94, tables 6, 21, 33 and 48, pages 77, 93, 107 and 125.*

4. Reproductive performance - Parental reproductive performance was assessed from breeding and parturition records of animals in the study. The following indices were calculated:

$$\text{Mating Index (\%)} = \frac{\text{Number copulating}^a}{\text{Number cohoused}} \times 100$$

$$\text{Fertility index (\%)} = \frac{\text{Number bearing litters}^b}{\text{Number copulating}^a} \times 100$$

$$\text{Gestation Index (\%)} = \frac{\text{Number of litters with at least one live pup}}{\text{Number of litters}} \times 100$$

[a] Evidence of copulation = copulatory plug, found dead pregnant, or delivery of litter.
[b] Including those found dead pregnant during gestation

Results - There were no biologically or statistically significant differences in the mating indices, fertility indices or gestation length of the P_1 or F_1 groups (see Table 5).

Table 5: Summary of Reproductive Indices[1]

	P_1 Generation			
Group	I-0	II-0	III-0	IV-0
Dose Level (ppm)	0	75	100	350
Mating Index (%)	96.7	96.7	96.7	100.00
(#copulated/cohoused)	(29/30)	(29/30)	(20/30)	(30/30)
Fertility Index (%)	86.2	75.9	96.6	80.0
(#delivered/copulated)	(25/29)	(22/29)	(28/29)	(24/30)
Gestation Length (days)	22.7	22.5	22.3	22.3

Table 5: Summary of Reproductive Indices[1]

	F_1 Generation			
Group	I-1	II-1	III-1	IV-1
Dose Level (ppm)	0	75	100	150
Mating Index (%)	86.7	96.7	93.1	[a]
(#copulated/cohoused)	(26/30)	(29/30)	(27/29)	
Fertility Index (%)	73.1	79.3	63.0	[a]
(#delivered/copulated)	(19/26)	(23/29)	(17/27)	
Gestation Length (days)	22.7	22.6	22.6	[a]

[1] Data extracted from Table 56, p. 135, MRID 43489001
[a] Data not available due to mortality

5. Litter observations - According to the report, the following litter observations were made: Litter size and pup survival, pup weights, clinical observation of pups and gross pathology. The following indices were calculated:

$$\text{Pups Born Alive (\%)}^{a} = \frac{\text{Number of pups born alive}}{\text{Number of pups born}} \times 100$$

$$\text{Viability Index (\%)}^{a,b} = \frac{\text{Number of pups alive Days 4 Preculling}}{\text{Number of pups born alive}} \times 100$$

$$\text{Lactation Index (\%)}^{a,b} = \frac{\text{Number of pups alive at weaning (21 postpartum)}}{\text{Number of pups alive Day 4 Post culling}} \times 100$$

$$\text{Litter Survival (\%)} = \frac{\text{Number of litter weaned}}{\text{Number of viable litters delivered}} \times 100$$

[a] Determined for each litter. Mean and standard deviation for each dose level were calculated.
[b] Excluding litters sacrificed due to death of dam during lactation.

Results - The mean number of F_1 pups/litter on Days 4 (preculling), 7, 14 and 21 was decreased at 350 ppm. In addition, the viability (77.3%), lactation (53.7%) and litter survival indices (75.0%) were significantly decreased from corresponding control values of 99.2%, 95.3% and 95.8%, respectively. F_1 pup weights were

significantly decreased at 350 ppm at all time points, Days 0, 4 (preculling), 4 (postculling) 7, 14 and 21 by approximately 29% on Day 21. F_1 pup weights were also significantly decreased in the 100 ppm group on Day 14 and 21 by approximately 6%. The mean number of F_2 pups/litter born alive and on day 4 preculling was significantly decreased at 100 ppm. (Data at 350 ppm could not be assessed due to mortality). F_2 pup weights were significantly decreased in the 100 ppm group at Days 4 (postculling), 7, 14 and 21, by approximately 5% on Day 21. See Tables 6,7 and 8.

Table 6: Mean Pup Numbers and Survival F_1 Generation[1]

Group	I-0	II-0	III-0	IV-0
Dose level (ppm)	0	75	100	350
Mean Number of Pups/Litter				
Born	12.8	14.0	13.8	13.3
Born Alive	12.5	14.0	13.3	12.8
Day 4 Preculling	12.4	13.7	13.6	9.4*
Day 4 Postculling	7.3	7.8	8.0	7.3
Day 7	7.3	7.8	7.9	5.3*
Day 14	7.3	7.8	7.9	3.8*
Day 21	7.2	7.8	7.9	3.8*
Survival (%)				
Sex ratio (males)	0.48	0.56	0.49	0.59
Gestation index[a]	96.0	100.0	96.4	100.0
Mean% Born alive	95.0	100.0	95.8	97.2
0-4 Day Viability	99.2	98.0	98.8	77.3*
Lactation index[b]	95.3	100.0	99.5	53.7*
Litter survival[c]	95.8	100.0	100.0	75.0*

1 Data extracted from Table 57, p. 136, MRID 43489001
a Percent litters delivered having at least 1 live pup
b Mean percent survival from Day 4 Postculling to Day 21
c Percent litters born with at least 1 pup alive on Day 21
d Value improperly given in data extracted from Table 57
* Significantly different from controls at $p \leq 0.05$

Table 7: Mean Pup Numbers and Survival F_2 Generation[1]				
Group	I-1	II-1	III-1	IV-1
Dose level (ppm)	0	75	100	150
Mean Number of Pups/Litter				
Born	14.4	13.6	12.6*	a
Born Alive	14.3	13.6	12.6*	a
Day 4 Preculling	14.1	13.6	12.3*	a
Day 4 Postulling	7.6	7.7	7.5	a
Day 7	7.6	7.7	7.5	a
Day 14	7.5	7.7	7.5	a
Day 21	7.5	7.7	7.4	a
Survival (%)				
Sex ratio (males)	0.45	0.45	0.51	a
Gestation index[b]	100.0	100.0	100.0	a
Mean% Born alive	99.2	100.0	99.5	a
0-4 Day Viability	93.7	99.7	97.2	a
Lactation index[c]	99.3	100.0	99.3	a
Litter survival[d]	94.7	100.0	100.0	a

1 Data extracted from Table 65, p. 144, MRID 43489001
a Data not available due to mortality
b Percent litters delivered having at least 1 live pup
c Mean percent survival from Day 4 Postculling to Day 21
d Percent litters born with at least 1 pup alive on Day 21
* Significantly different from controls at $p \leq 0.05$

Table 8: Mean Pup Weights (g) of the F_1 and F_2 Generation[1]				
	F_1 Generation			
Group	I-0	II-0	III-0	IV-0
Dose level (ppm)	0	75	100	150
Day 0	6.8	6.5	6.5	5.8*
Day 4 Preculling	11.1	10.7	10.6	8.5*
Day 4 Postculling	11.1	10.7	10.6	8.5*
Day 7	17.4	16.9	16.8	12.5*
Day 14	35.6	34.0	33.4*	24.9*
Day 21	58.2	55.6	54.5*	41.3*

Table 8: Mean Pup Weights (g) of the F_1 and F_2 Generation[1]				
	F_1 Generation			
Group	I-0	II-0	III-0	IV-0
Dose level (ppm)	0	75	100	150
	F_2 Generation			
Group	II-1	IV-1	VI-1	VIII-1
Dose Level (ppm)	0	75	100	150
Day 0	6.7	6.6	6.7	a
Day 4 Preculling[b]	11.0	10.9	11.0	a
Day 4 Postculling	10.9	10.9	10.9*	a
Day 7	17.7	17.7	17.5*	a
Day 14	36.7	35.8	35.8*	a
Day 21	62.4	60.5	59.2*	a
1 Data extracted from Table 58 and 66, pp. 137 and 145, MRID 43489001 a Data not available due to mortality * Significantly different from controls at $p \leq 0.05$				

Clinical Observations: At 350 ppm F_1 pups exhibited abnormal gait/mobility, lip not open. no fur, small whole body, sores, tremors and weakness. F_2 pups at 100 ppm had an increase in the incidence of subcutaneous hemorrhages.

4. Necropsy

a. Parental animals - All surviving P_1 and F_1 parental rats were subjected to gross pathological examinations, including animals that died or were sacrificed in extremis and for animals for which mating did not produce offspring. All F_1 males and females were sacrificed or found dead after 34 or 43 days of feeding. F_1 males and females in the 0, 75 and 100 ppm groups were sacrificed after approximately 164 or 174 days of feeding. Lactating females were sacrificed on lactation day 21. the following CHECKED (X) tissues were collected from all parental animals.

Males	Females	Both Sexes
Testes (weighed)	Ovaries	Pituitary
Epididymides	Uterus	Select gross lesions
Seminal vesicles	Vagina	
Coagulating gland		

[Histopathological examination was conducted only for the control and high-dose group of the P_1 generation and the control and mid-dose group for the F_1 generation. Gross lesions from the low- and mid-dose groups were also examined.]

Results

(1) Gross pathology - Skin ulcerations were noted in 1 P_1 male and 1 female at 75 ppm and in 5 P_1 males at 350 ppm. Skin ulcerations (incidence per group) were also observed in F_1 male rats in the 75 (3), 100 (7) and 350/150 ppm (27) groups. Skin ulcers/erosions around the head, neck and/or face were observed in F_1 females in the 100 (1) and 350/150 ppm (24) groups.

(2) Microscopic pathology - Skin ulceration, inflammation and acanthosis/hyperkeratosis of the skin were observed in 1 male in the 75 ppm group and 5, 6 and 3 males (for each of the individual findings, respectively) fed 350 ppm. Acanthosis/hyperkeratosis of the skin was observed in 1 female at 75 ppm. A few F_1 females in the 100 ppm group had skin inflammation and acanthosis/hyperkeratosis around the head, neck and/or face.

(b) Offspring

(1) Gross necropsy - No differences among control and treated groups.

D. Discussion

The study was well conducted and the conclusions reached by the study investigators more or less agreed with this reviewer's assessment of the study. There was no NOEL determined for parental toxicity because there were significant decreases in mean body weight of F_1 females during premating and gestation, grossly observed skin lesions with

corresponding histopathology. Nevertheless, it is not a requirement that a parental NOEL be determined. The purpose of a reproduction study is to characterize the reproductive toxicity of the chemical in question and determine a NOEL. This was achieved. At this point in time several, TOX I is aware of several toxicity studies including reproductive, subchronic and chronic studies which have demonstrated the neurotoxicity of esfenvalerate in multiple species. Additional studies may be needed to further characterize and/or quantify the neurotoxic potential of esfenvalerate Currently, the acute neurotoxicity screening battery (guideline series 81-8SS) and 90-day subchronic neurotoxicity study (guideline series 82-5) are outstounding data gaps. [The sponsor was informed of these data gaps in a TOX I memorandum of April 2, 1991.]

E. Deficiencies

The study has one deficiency in that the animals, starting with weaned F_1 pups developed skin lesions caused by esfenvalerate which appeared to be getting progressively worse, so all the animals were treated with canola oil, which contains vitamin E. The irritation was fairly well controlled, but use of the treatment regimen introduced a confounding factor into the study.