(24)

12-12-91 008967
Esfenvalerate 82-1c
and Fenvalerate 82-1c

Reviewed By: William B. Greear, M.P.H. William B. Greear 10/19/91
Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley 12/12/91
Section II, Toxicology Branch I - IRS (H7509C)

DATA EVALUATION REPORT

Study Type: Guideline Series 82-1 Subchronic Oral Toxicity (90-Day) Mouse

TOX Chem Nos.: 77A 268J

Test Material: S-1844; S-5602

MRID No.: 413597-01

Synonyms: S-5602 = Fenvalerate, SD 43775
S-1884 = Esfenvalerate, MO 70616

Study Number: Report No. GTS-8505/Laboratory Project ID LLT-50-00

Sponsor: E.I. du Pont de Nemours & Company, Inc.
Agricultural Products Department
Wilmington, DE 19880-0038

Testing Facility: Laboratory of Biochemistry and Toxicology
Takarazuka Research Center
Sumitomo Chemical Company, Ltd.
Takatsukasa, 4-2-1, Takarazuka,
Hyogo 655, Japan

Title of Report: Comparative Subacute Toxicity in B6C3F1 Mice Treated with S-1844 and S-5602 for 3 Months.

Author: Yuichiro Koyama

Report Issued: December 28, 1985

Conclusions:

S-1844 at the 500 ppm level compares similarly to S-5602 at the 2000 ppm level with respect to toxic manifestations except for certain parameters. The major difference is that microgranuomatous changes occur with exposure to S-5602 but not to S-1844.

NOEL (S-1844) = 150 ppm (F - 36.8 mg/kg/day; M 30.5 mg/kg/day)
LEL (S-1844) = 500 ppm (M 80.6 mg/kg/day; F 113 mg/kg/day) based on numerous clinical signs of toxicity, increased water intake, anemia, multiple clinical chemistry changes, enlargement of the inguinal lymph node, microscopic skin lesions, reactive responses in lymphatic tissue,

12
(1)

mucosal erosion and ulceration, gastritis, and dilation of the fundal gland of the stomach.

NOEL (S-5602) = < 2000 ppm (~462 mg/kg/day)
LEL (S-5602) ≤ 2000 ppm (~422 mg/kg/day) (based on numerous clinical signs of toxicity, increased water intake, anemia, multiple clinical chemistry changes, enlargement of the inguinal lymph node, microscopic skin lesions, reactive responses in lymphatic tissue, mucosal erosion and ulceration, gastritis and dilation of the fundal gland of the stomach, and microgranuloma and giant cell formation.

Classification:

Core-Minimum (S-1844)
Core-Supplementary (S-5602)

This study satisfies the requirement for a Guideline Series 82-1 subchronic oral study in rodents for compound S-1844 but not for S-5602.

A. Materials:

1. Test Compound #1 - S-1844; Description: A brownish liquid or solid; Purity: 94.5% with Aα:βα:Aβ:Bβ 87.2: 7.4: 4.8: 0.6: Contaminants: Not reported.

2. Test Compound #2 - S-5602; Description: A yellow-brownish viscous liquid; Purity: 95.5% with Aα:βα:Aβ:Bβ = 24.2: 25.4: 26.3: 24.1; Contaminants: Not reported.

B. Study Design:

1. Animal Assignments - Animals were randomly assigned to the following test groups:

Test Group	Dose in Diet (ppm)	Main Study 3 Months Male	Female
Control	0	12	12
S-1844	50	12	12
S-1844	150	12	12
S-1844	500	12	12
S-5602	2000	12	12

The animals were allowed to acclimate to laboratory conditions for a period of 1 week. The animals were housed individually in aluminum cages with wire mesh floors in a facility with temperatures of 23 ± 2 °C, relative humidity of 55 ± 10 percent, air exchange of 16X/hour and lighting of 8:00 to 20:00. Pulverized feed (CE-2 powdered feed, Clea Japan, Inc.) and water were available ad libitum.

2. Diet Preparation - Diets were prepared every 2 weeks. An appropriate amount of the basal diet was mixed in an appropriate amount of corn oil with the test material. The mixture was blended with the remaining basal diet in a Dalton All Purpose Mixer (25 AML-QR). The concentration of corn oil in the diet was adjusted to 2 percent. Stability analysis of S-1844 and homogeneity analysis of S-1844 and S-5602 in the diet were conducted. The concentration of S-1844 and S-5602 at each dietary level was determined from every two preparations.

Results - Data on homogeneity of the 50 and 500 ppm S-1844 diets and the 2000 ppm S-5602 diet were reported to range from 44 to 46 ppm, 445 to 463 ppm, and 1940 to

2000 ppm, respectively. The stability of S-1844 in the diet is shown in Table 1 below:

Table 1. Stability of S-1844 in the Diet[1]

Theoretical Level (ppm)	Analyzed Value (ppm) and Standard Deviation			
	After Formulation	After 1 Week	After 2 Weeks	After 4 Weeks
50	43 ± 1.00	43 ± 1.15 44.1 ± 1.00	37 ± 1.00 38 ± 1.00	43 ± 1.00
150	128 ± 2.08	129 ± 1.15 135 ± 2.52	119 ± 2.08 117 ± 3.21	121 ± 1.53
500	436 ± 7.02	432 ± 8.74 440 ± 11.2	412 ± 1.15 420 ± 3.61	419 ± 3.61

[1]Taken from P.000105 of the report.

The concentration of S-1844 in the diet marginally decreased after 2 weeks by 4 to 14 percent.

The concentration of S-1844 and S-5602 in the test diets ranged from 86 to 100 percent of the theoretical levels when measured on April 15, May 11, June 6, and July 5, 1985.

3. Statistics - An F test was used to analyze the variance between the control and test groups with respect to body weight, food consumption, water intake, organ weight, hematological and blood biochemical data. If differences were not significant, Student's t-test was used. Fisher-Behrens test was employed when the differences were significant. The U-test was used for analysis of the urinalysis data. Fisher's Exact test was used to analyze the gross pathological and histopathological findings.

4. Quality Assurance - The data in the study were "validated" at six intervals. The QAU statement was signed by Masanori Takalsuka on December 20, 1985.

C. Methods and Results:

1. Observations - The animals were observed daily for clinical signs, mortality, and moribundity. After 27 days, mice in the 500 ppm S-1844 and 2000 ppm S-5602 groups were additionally observed three times a week in the afternoon.

Results - No deaths occurred. The following signs were seen in mice in the 500 ppm S-1844 and 2000 ppm S-5602 groups: fibrillation, tremors, convulsions, hypersensitivity, abnormal gait, salivation (week 1 only), scratching, licking (after week 3), alopecia, scabs and sores (after week 4). Hypersensitivity tended to decrease in occurrence, especially after week 4.

2. Body Weight - Animals were weighed initially, on day 3 and once a week thereafter.

Results - Body weight gain of mice in the 500 ppm S-1844 and 2000 ppm S-5602 groups was decreased when compared to controls. Males were affected to a greater extent than females (see Table 2 below - values are reviewer calculated):

Table 2. Body Weight Gain (g) and (% Loss Relative to Controls)

Group (ppm)	Interval (Days)			
Male	0-28	28-63	63-90	0-90
Control (0)	4.44	3.90	0.97	9.31
S-1844 (50)	4.47 (0.7)	3.53 (-9.5)	0.86 (-11.3)	8.87 (-4.7)
S-1844 (150)	4.36 (-1.8)	3.18 (-18.5)	0.83 (-14.4)	8.37 (-10.1)
S-1844 (500)	2.51 (-43.5)	1.71 (-56.2)	0.35 (-63.9)	4.58 (-50.8)
S-5602 (2000)	3.37 (-24.1)	2.62 (-32.8)	0.96 (-1.0)	6.95 (-25.3)
Female				
Control (0)	4.97	3.37	0.83	8.83
S-1844 (50)	5.11 (2.8)	3.41 (1.2)	0.79 (-4.8)	9.31 (5.4)
S-1844 (150)	4.68 (-5.8)	3.58 (6.2)	0.39 (-53.0)	8.65 (-2.0)
S-1844 (500)	2.35 (-52.8)	2.54 (-24.6)	0.86 (3.6)	5.75 (-34.9)
S-5602 (2000)	3.60 (-27.6)	3.13 (-7.1)	0.95 (14.5)	7.68 (-13.0)

3. Food/Water Consumption and Compound Intake - Food and water intake were measured over a 48-hour period during each week for each cage.

Results - Food consumption was not affected by treatment. Mean compound intake was 10.5, 30.5, and 106 mg/kg/day for males in the 50, 150, and 500 ppm S-1844 groups, respectively. Mean compound intake was 12.6, 36.8, and 113 mg/kg/day for females in the 50, 150, and 500 ppm groups, respectively. Mean compound intake was 422 and 462 mg/kg/day for males and females in the 2000 ppm S-5602 group. Water intake was decreased during the first few weeks and then increased after 5 weeks in animals in the 500 ppm S-1844 and 2000 ppm S-5602 groups (See Table 3 below).

Table 3. Water Intake (g/kg/day) and (% of Increase/Decrease Controls)

Group (ppm)	Week				
Male	1	4	7	10	13
Control (0)	331.3	245.5	209.1	172.0	161.2
S-1844 (50)	310.6 (-6.2)	287.6 (17.1)	225.15 (7.8)	187.9 (9.2)	174.1 (8.0)
S-1844 (150)	308.5 (-6.9)	239.89 (-2.3)	205.0 (-2.0)	175.7 (2.2)	175.3 (8.7)
S-1844 (500)	248.2** (-25.1)	236.1 (-3.8)	246.4 (17.8)	224.7* (17.4)	257.3** (59.6)
S-5602 (2000)	261.9** (-20.9)	249.4 (-1.6)	232.9 (11.4)	210.1** (22.2)	208.0** (29.0)
Female					
Control (0)	439.2	332.8	275.3	222.4	235.9
S-1844 (50)	414.1 (-5.7)	327.7 (-1.5)	276.4 (0.3)	223.9 (0.7)	210.9 (-10.9)
S-1844 (150)	398.3 (-9.3)	309.3 (-7.1)	253.7 (-7.8)	218.8 (-1.6)	206.6 (-12.4)
S-1844 (500)	313.4** (-28.6)	293.2* (-11.9)	316.7* (15.0)	277.0** (24.6)	263.6 (11.7)
S-5602 (2000)	336.4* (-23.4)	286.7** (-13.9)	283.0 (2.8)	278.1** (25.0)	258.6 (9.6)

*Statistically significant at $p < 0.05$.
**Statistically significant at $p < 0.01$.

176

4. Ophthalmological Examination - Once a week prior to termination, the eyes of mice in the control, 500 ppm S-1844, and 2000 ppm S-5602 groups were examined.

Results - Unremarkable.

5. Blood Samples were taken from all mice sacrificed at termination. The CHECKED (X) parameters were determined.

a. Hematology

X		X	
X	Hematocrit (HCT)		Total plasma protein (TP)
X	Hemoglobin (HCB)	X	Leucocyte differential count
X	Leucocyte count (WBC)	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)	X	Mean corpuscular HGB concentration (MCHC)
X	Platelet count	X	Mean corpuscular volume (MCV)
	Erythrocyte morphology		Clotting time
			Reticulocyte count

Results - In the 500 ppm S-1844 group, RBC, HGB, and HCT were decreased and there was an increase in the neutrophil count and a decrease in the lymphocyte count. Females in the 500 ppm S-1844 group also exhibited decreases in the MCH, MCHC, and leucocyte count (see Table 4 below). In the 2000 ppm S-5602 group, HGB, HCT, MCH, MCV, and the lymphocyte count were decreased and there was an increase in the neutrophil count. Females in the 2000 ppm S-5602 group also exhibited a decrease in the MCHC.

Table 4. Selected Hematological Values

Group (ppm)

Males	RBC (10^5)	WBC (10^2)	HGB (g/dl)	HCT (%)	MCV (U^3)	MCH (pg)	MCHC (%)	NTP[1] (%)	LYC[2] (%)
Control (0)	103	17.6	16.4	47.3	45.8	15.9	34.7	6.75	92.8
S-1844 (50)	102	16.8	16.4	47.2	46.0	16.0	34.7	9.17	90.2
S-1844 (150)	103	13.8	16.4	47.4	46.3	15.9	34.5	6.00	91.6

[1]Neutrophil count.
[2]Leucocyte count.

Table 4. Selected Hematological Values (cont'd)

Group (ppm) Males (cont'd)	RBC (10^5)	WBC (10^2)	HGB (g/dl)	HCT (%)	MCV (U^3)	MCH (pg)	MCHC (%)	NTP[1] (%)	LYC[2] (%)
S-1844 (500)	91.4*	17.0	14.6*	42.5*	46.5	15.9	34.4	15.2	64.7
S-5602 (2000)	101	15.9	15.7*	45.7	45.0	15.5*	34.4	16.5*	83.0*
Females									
Control (0)	101	19.1	16.2	48.6	46.2	16.1	33.4	6.83	92.9
S-1844 (50)	98.9	17.5	16.0	47.5	48.2	16.2	33.7	6.75	92.7
S-1844 (150)	99.1	17.0	26.0	47.6	48.1	16.1	33.5	4.92	94.5
S-1844 (500)	95.1*	10.5	14.9*	45.3	47.6	15.6*	32.8*	12.1	87.7
S-5602 (2000)	96.9	19.3	14.8*	45.2*	46.8*	15.3*	32.7*	12.5*	87.2*

[1]Neutrophil count.
[2]Leucocyte count.
*Statistically significant at $p < 0.05$.

b. Clinical Chemistry

X	
	Electrolytes:
X	Calcium
	Chloride
	Magnesium
	Phosphorus
	Potassium
	Sodium
	Enzymes
X	Alkaline phosphatase
	Cholinesterase
	Creatinine phosphokinase
X	Lactic acid dehydrogenase (LDH)
X	Serum alanine aminotransferase (SGPT)
X	Serum aspartate aminotransferase (SGOT)
	Gamma glutamyltransferase
X	Leucine aminopeptidase

X	
	Other:
X	Albumin
X	Blood creatinine
X	Blood urea nitrogen
X	Cholesterol
	Globulins
X	Glucose
X	Total bilirubin
X	Total protein
X	Triglycerides
	Thyronine (T^4)
	Triiodothyronine (T^3)
X	Albumin/Globulin ratio
X	Phospholipids

Results - Glucose was decreased in animals in the 500 ppm S-1844 and 2000 ppm S-5602 groups. Cholesterol, phospholipids, and triglycerides were decreased in animals in the 500 ppm S-1844 group and in males in the 2000 ppm S-5602 group. In addition, glucose and triglycerides were decreased in males in the 150 ppm S-1844 group (see Table 5 below). BUN was increased in females in the 500 ppm S-1844 and 2000 ppm S-5602 groups. Total protein was decreased in animals in the 500 ppm S-1844 group. Bilirubin and albumin were decreased in males in the 500 ppm S-1844 group. SGPT was increased in animals in the 500 ppm S-1844 group, and SGOT and LDH in the 2000 ppm S-5602 groups. Alkaline phosphatase was increased in males in the 2000 ppm S-5602 group.

These changes in the 150ppm group males were of low magnitude and only occurred in 1 sex. There were no other changes in this group. Therefore they are not used to establish the LEL.

Table 5. Selected Clinical Chemistry Values

Group (ppm)	Glu (mg/dl)	Chol (mg/dl)	ALB (g/dl)	TPR (g/dl)	BIL (mg/dl)	BUN (mg/dl)	ALP (U/l)
Males							
Control (0)	181	111	3.32	5.41	.117	22.8	114
S-1844 (50)	167	110	3.28	5.36	.108	21.9	114
S-1844 (150)	156**	113	3.34	5.47	.108	23.5	115
S-1844 (500)	125**	67**	2.78**	4.61**	.075*	28.6	102
S-5602 (2000)	153*	101*	3.20	5.29	.092	25.2	122*
Females							
Control (0)	169	94.8	3.37	5.33	.092	19.2	156
S-1844 (50)	164	95.2	3.38	5.33	.063	21.3	145
S-1844 (150)	170	100	3.41	5.36	.083	20.2	156
S-1844 (500)	141**	75.2**	3.24	5.13**	.083	25.5**	175
S-5602 (2000)	139**	99.4	3.28	5.38	.067	25.0**	143

*Statistically significant at $p < 0.05$.
**Statistically singificant at $p < 0.01$.

Table 5. Selected Clinical Chemistry Values (cont'd)

Group (ppm)	SGOT (U/l)	LDH (U/l)	LAP (U/l)	TRG (mg/dl)	PL (mg/dl)	SPGT (U/l)
Males						
Control (0)	100	318	41.2	32.5	194	52.9
S-1844 (50)	91.3	310	42.5	27.8	191	72.8
S-1844 (150)	85.2	302	42.2	19.2**	193	71.0
S-1844 (500)	154	546	37.2**	5.17**	130**	123
S-5602 (2000)	179**	587**	53.3**	6.00**	161**	163**
Females						
Control (0)	88.2	291	39.8	13.3	170	40.7
S-1844 (50)	89.2	327	38.1	15.3	172	45.4
S-1844 (150)	87.3	333	36.3	22.6	177	48.9
S-1844 (500)	112	409**	35.6**	4.56**	116**	68.6*
S-5602 (2000)	158**	460**	53.8**	11.4	164	81.3**

*Statistically significant at $p < 0.05$.
**Statistically significant at $p < 0.01$.

6. Urinalysis - One week prior to termination individual urine samples were obtained from all animals. The CHECKED (X) parameters were determined.

X		X	
| |	Appearance	|X|	Glucose
| |	Volume	|X|	Ketones
|X|	Specific gravity	|X|	Bilirubin
|X|	pH	|X|	Blood
| |	Sediment (microscopic)	| |	Nitrite
|X|	Protein	|X|	Urobilinogen
		| |	Reducing substances

Results - Upon examination of Table9 (see attached), the following tendencies were observed:

a. Decreased pH of males in the 500 ppm S-1844 group and animals in the 2000 ppm S-5602 group.

b. Slight increase in protein in males in the 500 ppm S-1844 group.

c. Increase in ketones in animals in the 500 ppm S-1844 group and females in the 2000 ppm S-5602 group.

d. Increase in bilirubin, urobilinogen, and specific gravity in females in the 500 ppm S-1844 and 2000 ppm S-5602 groups.

7. Sacrifice and Pathology - All animals that died or were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were histologically examined in animals in the control, 500 ppm S-1844, and 2000 ppm S-5602 groups. The (XX) organs, in addition were weighed from all test groups. (The tissues of animals in the 50 and 150 ppm S-1844 groups that were histologically examined were: "liver, kidneys, spleen, lungs, pituitary, adrenal, mesenteric lymph node, mandibular lymph node, thymus, salivary glands, stomach and skin.")

X	Digestive system
X	Tongue
XX	Salivary glands
X	Esophagus
X	Stomach
X	Duodenum
X	Jejunum
X	Ileum
X	Cecum
X	Colon
	Rectum
XX	Liver
X	Gall bladder
X	Pancreas
	Respiratory
X	Trachea
X	Lung
	Nose
	Pharynx
	Larynx

X	Cardiovasc./Hemat.
X	Aorta
XX	Heart[1]
X	Bone marrow
X	Lymph nodes
XX	Spleen
X	Thymus
	Urogenital
XX	Kidneys
X	Urinary bladder
XX	Testes
X	Epididymides
X	Prostate
X	Seminal vesicles
XX	Ovaries
	Uterus

X	Neurologic
XX	Brain
X	Periph. nerve
X	Spinal cord (3 levels)
XX	Pituitary
X	Eyes (optic nerve)
	Glandular
XX	Adrenal gland
X	Lacrimal gland
X	Mammary gland
X	Parathyroids
XX	Thyroid[1]
	Other
X	Bone
X	Skeletal muscle
X	Skin
X	All gross lesions and masses

[1]Examined histologically in the control, 500 ppm S-1844, and 2000 ppm S-5602 groups.

a. Organ Weight - The absolute and relative liver weights of animals in the 2000 ppm S-5602 group were increased (see Table 6 below). Animals in the 500 ppm S-1844 group exhibited decreased absolute liver weight. The absolute and relative weights of the spleen in animals in the 2000 ppm S-5602 group were increased. Although the increase in the absolute weight of the spleen in females was not statistically significant, it is believed to be related to administration of the test material. There was an increase in the absolute and relative weight of the salivary gland in animals in the 500 ppm S-1844 group. A similar trend was observed in animals in the 2000 ppm S-5602 group. Several other instances occurred in which statistically significant increases in absolute or relative weight occurred. These incidences were sporadic and not believed to be related to treatment.

Table 6. Selected Mean Organ Weights

Group (ppm)	Absolute Weight (g)			Relative Weight (%)		
	Liver	Spleen	Saliv. Gland	Liver	Spleen	Saliv. Gland
Males						
Control (0)	1.01	.0598	.256	3.32	.198	.846
S-1844 (50)	.992	.0602	.236**	3.35	.203	.797
S-1844 (150)	1.01	.0620	.245	3.42	.210	.831
S-1844 (500)	.883**	.0605	.295**	3.43	.236	1.16**
S-5602 (2000)	1.10**	.0671*	.262	3.94**	.240**	.938*
Females						
Control (0)	1.01	.0797	.181	3.85	.305	.693
S-1844 (50)	1.02	.0789	.171	3.86	.298	.647
S-1844 (150)	1.02	.0815	.182	3.92	.313	.700
S-1844 (500)	.921**	.0678**	.282**	4.00	.295	1.23**
S-5602 (2000)	1.14**	.1120	.217**	4.57**	.454*	.874**

*Statistically significant at $p < 0.05$.
**Statistically significant at $p < 0.01$.

b. Gross Pathology - There was an increased incidence of alopecia, scabs and sores in males and/or females in the 500 ppm S-1844 and 2000 ppm S-5602 groups. In the 500 ppm S-1844 group, there was also an increased incidence of a white substance in the urinary bladder of males, dark red spots in the stomach of males, and enlargement of the inguinal lymph node in females.

Table 7. Selected Gross Lesions

	Dose Level (ppm)									
	Males (N = 12)					Females (N = 12)				
	S-1844				S-5602	S-1844				S-5602
Observation	0	50	150	500	2000	0	50	150	500	2000
Alopecia	3	3	4	9*	8*	4	5	3	12**	12**
Scabs	0	0	0	6**	1	0	0	0	5*	2
Sores	0	0	0	4*	0	0	0	0	3	2
Urinary bladder - white substance	1	1	0	4	0	0	0	0	0	0
Stomach - dark red spots	0	0	0	4*	0	0	0	0	0	0
Inguinal lymph node - enlargement	0	0	0	3	1	0	0	0	7*	3

* $p < 0.05$.
** $p < 0.01$.

c. Microscopic Pathology

1) Non-neoplastic Lesions - There was an increased incidence of skin lesions in animals in the 500 ppm S-1844 and 2000 ppm S-5602 groups that included hyperkeratosis, dermatitis, ulceration, and the formation of hair follicular cysts. The incidences are reported in Table 8 below. There was also an increase in the incidences of stomach lesions including dilation of fundal glands, mucosal erosion, mucosal ulceration and gastritis in the glandular portion of the stomach of males

in the 500 ppm S-1844 group. There were several organs with giant cell infiltration, e.g., spleen, liver, and the mandibular and mesenteric lymph nodes of animals in the 2000 ppm S-5602 ppm group (see Table 9). Microgranulomas of the liver only occurred in the 2000 ppm S-5602 group. There were increases of "starry sky" formation in the spleen, mesenteric lymph node and thymus of males and females in the 500 ppm S-1844 group and in females in the 2000 ppm S-5602 group. Lymphadenitis simplex (lymphoid hyperplasia) was observed in several lymph nodes, e.g., mandibular, and inguinal in 500 ppm S-1844 males and 2000 S-5602 females; mandibula, ancillary and inguinal in 2000 ppm S-5602 males (see Table 10).

Table 8. Selected Histopathology

Dose Level (ppm)

Males

Organ	Lesion	S-1844 0	S-1844 50	S-1844 150	S-1844 500	S-5604 2000
Stomach -	Dilation of fundal gland	0/12	0/12	0/11	2/12	0/12
	Mucosal erosion	0/12	0/12	0/11	2/12	0/12
	Mucosal ulceration	0/12	0/12	0/11	2/12	0/12
	Gastritis	0/12	0/12	0/11	2/12	0/12
Skin -	Hyperkeratosis	0/12	0/12	0/12	0/12	1/10
	Dermatitis	0/12	0/12	0/12	6/12	1/10
	Ulceration	0/12	0/12	0/12	6/12	1/10
	Hair follicular cyst	0/12	0/12	0/12	3/12	1/10

2) Neoplastic Lesions - None.

D. Discussion

No deaths occurred. Fibrillation, tremors, convulsions, hypersensitivity, abnormal gait, salivation, scratching, licking, alopecia, scabs, and sores were observed in the 500 ppm S-1844 and 2000 ppm S-5602 groups. Mean body weight gains were decreased in the 500 ppm S-1844 and 2000 ppm S-5602 groups. Initially, water intake was decreased (> 20%) and then increased (> 20%) in the 500 ppm S-1844 and 2000 ppm S-5602 groups. RBC, HGB, HCT, and lymphocyte counts were decreased and the neutrophil count increased in the 500 ppm S-1844 group. In addition, females in the 500 ppm S-1844 group exhibited decreases in the MCH, MCHC, and leucocyte count. In the 2000 ppm S-5602 group, HGB, HCT, MCH, MCV, and lymphocyte count were decreased and the neutrophil count

increased. In addition, females had a decrease in MCHC. Both groups were similar in that slight anemia was present. Both groups were similar with respect to clinical chemistry. One or more of the sexes in the 500 ppm S-1844 and 2000 ppm S-5602 ppm groups exhibited increases in BUN, SGPT, SGOT, and LDH and decreases in glucose, triglycerides, cholesterol, and phospholipids. Glucose and triglycerides were also decreased in males in the 150 ppm S-1844 group. They differed in that total protein, bilirubin, and albumin were decreased in males in the 500 ppm S-1844 group but not in the 2000 ppm S-5602 group. The pH of the urine was decreased in the 500 ppm S-1844 and 2000 ppm S-5602 groups. There was an increase in ketones, bilirubin, urobilinogen, and specific gravity in the 500 ppm S-1844 and 2000 ppm S-5602 groups. The absolute and relative weight of the liver was increased in the 2000 ppm S-5602 group. The absolute and relative weight of the spleen was increased in the 2000 ppm S-5602 group. Both the 500 ppm S-1844 and 2000 ppm S-5602 groups were similar in that the absolute and relative salivary gland weights were increased. Both the 500 ppm S-1844 and 2000 ppm S-5602 groups exhibited increases in alopecia, scabs, sores, and enlargement of the inguinal lymph node. Males in the 500 ppm S-1844 group had a white substance in the urinary bladder and dark red spots in the stomach. These gross lesions only occurred in the male 500 ppm S-1844 group. Upon histological examination of the skin, hyperkeratosis, dermatitis, ulceration, and the formation of hair follicular cysts were observed in both the 500 ppm S-1844 and 2000 ppm S-5602 groups. Both groups exhibited dilation of the fundal gland, mucosal erosion and ulceration and gastritis of the stomach. Reactive responses in the lymphatic tissues characterized by "starry sky formation," lymphoid hyperplasia, and lymphadenitis simplex were present in both groups, but appeared to be more prevalent in the 500 ppm S-1844 group. The groups differed in that microgranulomas of the liver and giant cell infiltration of several organs were present only in the 2000 ppm S-5602 group. Changes observed at 150 ppm were not considered treatment related (see Clin. Chem. Results section).

Comment

In several studies, including 2-year studies, microgranuloma formation has been found to be associated with the Bβ-isomer of fenvalerate. The microgranulomatous changes observed in the 2000 ppm S-5602 ppm group (< 26% Bβ-isomer in fenvalerate) and not in the 500 ppm S-1844 group (2% Bβ-isomer) confirm this general observation.

Attachments

PYDRIN

Page_____ is not included in this copy.

Pages 16 through 18 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.