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

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SEP 24 1992

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Fenvalerate - Submission of a 21-Day Dermal Study in Compliance with the Reregistration Toxicology Data Requirements (Reregistration Case # 2280)

TOX Chem No.:	77A
PC No.:	109301
DP Barcode No.:	D178935
Submission no.:	S418880

FROM: William B. Greear, M.P.H. William B. Greear 9/11/92
Review Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Linda Deluise/Ernestine Dobbins, PM Team # 52
Reregistration Branch
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THRU: Marion P. Copley, D.V.M., Section Head Marion Copley 9/15/92
Review Section IV, Toxicology Branch I
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I. CONCLUSIONS:

The 21-Day Dermal Study (DuPont HLR 127-92; 5/14/92) has been classified Core-Guideline and it satisfies the requirement for a Guideline Series 82-2 21-Day Dermal Study.

II. REQUESTED ACTION:

Under a cover letter dated May 20, 1992, Marie M. Chubb of Du Pont has submitted a 21-Day Dermal Study on DPX-Y4306-90 (fenvalerate) for review in compliance with the reregistration toxicology data requirements.

III. RESULTS OF THE REVIEW:

NOEL (systemic) >1000 mg/kg/day (HDT)

NOEL (dermal irritation) = 300 mg/kg/day
LEL (dermal irritation) = 1000 mg/kg/day (based on increases in the incidence of moderate erythema, mild edema, superficial necrosis and scar tissue.

Classification: Core-Guideline

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Reviewed by: William B. Greear, M.P.H. William B. Greear 9/11/92
Review Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M.
Review Section IV, Toxicology Branch I (H7509C) Marion P. Copley
9/10/92

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 82-2
21-Day Dermal - Rabbit

TOX. CHEM No.: 77A
PC NO.: 109301
MRID NO.: 423251-01

TEST MATERIAL: Fenvalerate

SYNONYMS: DPX-Y4306-90; IN Y4306-90; Pydrin (technical); cyano(3-phenoxyphenyl) methyl-4-chloro-alpha-(1-methylethyl)-benzeneacetate

STUDY NUMBER: Du Pont HLR 127-92; Med. Research No. 9084-001

SPONSOR: Du Pont

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Del 19714

TITLE OF REPORT: Repeated Dose Dermal Toxicity: 21-Day Study With DPX-Y4306-90 (Fenvalerate) in Rabbits

AUTHOR(S): Susan A. MacKenzie

REPORT ISSUED: May 14, 1992

CONCLUSION: NOEL (systemic) >1000 mg/kg/day (HDT)

NOEL (dermal irritation) = 300 mg/kg/day
LEL = 100 mg/kg/day (based on increases in incidence of moderate erythema, and mild edema and superficial necrosis of scar tissue.

Classification: Core-Guideline

Study Acceptability: The study satisfies the requirement for a Guideline Series 82-2 21-Day Dermal Study.

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A. MATERIALS:

1. Test compound: Fenvalerate (technical); Description: amber brown viscous liquid or crystalline mush; purity 95.4%

2. Test animals: Rabbit, Strain: NZW, Age: 17 week old adult; Weight: Day 1 M=2212-2281 g; F=2208-2305 g, Source: Hazleton Research Products, Denver, PA.

B. STUDY DESIGN:

1. Animal Assignment: Animals were randomly assigned to the following groups:

21-Day Dermal

Test Group	Dose (mg/kg/day)	Number of Animals male	female	Treated Area (cm^2)
I-CONTROL	0	5	5	
II-LOW	100	5	5	16
III-MID	300	5	5	16
IV-HIGH	1000	5	5	154

The animals were quarantined for approximately 2 weeks and were observed for general health. The animals were housed individually in suspended, stainless steel, wire-mesh cages. The envirnmental conditions were set for a temperature of 18-22°C, relative humidity of 40-60%, and a 12-hour on 12-hour off light cycle. Food (Purina Certified High Fiber Rabbit Chow #5325) was provided to the animals at a rate of 125 g/day and water was available ad libitum.

2. Dose Selection: In a previous study, animals were administered 100 or 400 mg/kg/day dermally over a 22-day period. Exposure was for 6 hrs/day with a total of 14 applications. Four of seven animals died in the 400 mg/kg/day group. The author speculated that due to skin irritation the animals may have damaged the skin barrier by scratching, thus increasing absorption of the test material. Therefore a range-finding study was conducted at dosages of 50, 100, 200 or 300, mg/kg/day for 13-18 days and at 400, 500, 750 or 1000 mg/kg/day for 4 to 9 days. Precautions were taken to prevent the animals from damaging their skin. No clinical signs of toxicity were observed; however, erythema of the skin was present.

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Therefore, the dosages selected for testing were 100, 300 and 1000 mg/kg/day. The 1000 mg/kg/day was noted to be the dosage needed for the "Limit Test" for repeated dose dermal studies.

3. Treatment: On the day prior to dosing, the hair of each rabbit was removed from the scapular to lumbar region by shaving. The test material was applied to the test site and allowed to stay in contact with the skin for a period of 6 hours. The test site was covered with a gauze pad and the rabbits were wrapped with layers of plastic film, stretch gauze bandage and elastic adhesive bandage. The rabbits were fitted with plastic collars and both hind feet were bandaged in order to prevent scratching the skin. The controls were similarly treated with deionized water. The bandages were removed after 6 hours and the test sites were washed with 50-70% acetone, followed by Ivory soap and water to remove the excess test material. The area was rinsed with water and the test sites were patted dry. Dermal irritation was scored using the method of Draize and the animals were observed for clinical signs of toxicity.

   After assessing dermal irritation, the mid section was wrapped with a conforming bandage and left in place until the next exposure period. The animals were sacrificed on test day 22 or 23.

4. Statistics: One-way analysis of various (ANOVA) was used to analyzed body weights, body weight gains and organ weights. When differences among group means (F-statistic) were significant for body weights and body weight gains, Dunnett's and least significant differences (LSD) tests were used to make pairwise comparisons between the control and test groups. The results of clinical observations were analyzed by Fisher's Exact test with Bonferroni correction. Clinical laboratory data were analyzed by ANOVA and Bartlett's test, followed by Dunnett's test. When the results of the Bartlett's test were significant, the Kruskal-Wallis test was used with the Mann-Whitney U test to compare group means. Test for comparisons of group means used a significance level of =0.05.

5. Quality assurance examinations were conducted from 11/6/92 to 4/23/92. The stated was signed by James Mackay II on 5/11/92.

C. METHODS AND RESULTS:

1. Observations: An abbreviated clinical observation battery (see Table 1 attached for CNS involvement was conducted daily at the time clinical signs of toxicity and dermal irritation was assessed).

Results - One male and one female each in the control and 300 mg/kg/day groups died. The male control animal was found dead on day 4 and death was attributed to luxation of the cervical vertebrae. The three other rabbits died on day 7. Both female rabbits had not been eating and one animal had diarrhea, mucus in the feces and an absence of feces 2-4 days prior to death. These signs were not dose-related and were attributed to mild mucoid enteritis. Moderate erythema was observed in all treated groups except for males in the 100 mg/kg/day group and the control group. A dose-response was not present. Slight to mild edema was observed in animals in all the treated groups but was not present in the controls. This observation occurred with the greatest frequency in the female 300 and 1000 mg/kg/day groups (see Table 1). Superficial necrosis was increased in males in the 1000 mg/kg/day group. Scar tissue was present in females in the 300 and 1000 mg/kg/day groups. The author attributed the lesions as resulting from mechanical irritation from daily washing and bandaging.

Table 1:Selected Clinical Signs of Toxicity in Rabbits

	Dose Level (mg/kg/day)							
Clinical Sign	Control		100		300		1000	
	M	F	M	F	M	F	M	F
Erythema Moderate	0	2	0	2	1	3	2	2
Edema Mild	0	0	1	0	0	3	0	3
Superficial Necrosis	0	0	0	0	0	3	1	3
Scar Tissue	0	0	0	0	0	3	0	2
Excessive attempts at licking	0	2	1	4	4	2	3	4

2. Body Weight: Determined twice weekly.

Results - Unremarkable.

3. Food Consumption and Feed Efficiency: Determined weekly.

Results - Unremarkable.

4. Blood samples were taken from all rabbits 8 days prior to the first treatment and just prior to termination. The CHECKED (X) parameters were determined

a. Hematology

X		X	
X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count		
	Total plasma protein (TP)		

Results - Unremarkable

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorous	X	Cholesterol
X	Potassium	X	Globulins
X	Sodium	X	Glucose
	Enzymes	X	Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total serum protein (TP)
	Cholinesterase (ChE)		Triglycerides
	Creatinine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase (also SGPT)		
X	Serum aspartate aminotransferase (also SGOT)		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

Results - Unremarkable.

5. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination for animals in the control and 1000 ppm groups. The (XX) organ of all animals sacrificed at termination were weighed.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
	Tongue	X	Aorta		Brain
X	Salivary glands	X	Heart		Periph. nerve
X	Esophagus	X	Bone marrow		Spinal cord (3 levels)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	X	Spleen		Eyes (optic n.)
X	Jejunum	X	Thymus	Glandular	
X	Ileum	Urogenital		XX	Adrenal gland
X	Cecum	XX	Kidneys		Lacrimal gland
X	Colon	X	Urinary bladder		Mammary gland
X	Rectum	XX	Testes	X	Parathyroids
XX	Liver	X	Epididymides	X	Thyroids
X	Gall bladder	X	Prostate	Other	
X	Pancreas	X	Seminal vesicle	X	Bone
Respiratory		X	Ovaries	X	Skeletal muscle
X	Trachea	X	Uterus	X	Skin
X	Lung			X	All gross lesions and masses*

In addition, treated and untreated skin, liver, kidneys and lesions from the rabbits in the 100 and 300 mg/kg/day groups were examined microscopically.

Results:

a. Organ weight - Unremarkable.

b. Gross pathology - Unremarkable.

c. Microscopic pathology - Unremarkable.

D. DISCUSSION:

Slight to moderate erythema of the skin was observed in all groups including the controls. Moderate erythema was noted in all female treated groups and in males in the 300 and 1000 mg/kg/day group. Slight to mild edema was observed in males in the 100 and 1000 mg/kg/day groups and in females in the 300 and 1000 mg/kg/day groups. Superficial necrosis was present in males and/or females in the 300 and 1000mg/kg/day groups. And scare tissue occurred in females in the 300 and 1000 mg/kg/day groups. The NOEL for skin irritation is considered to be 100 mg/kg/day taking into account the certain amount of variability of the results.