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Esfenvalerate

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DATA EVALUATION REPORT

Study Type: 13-Week Feeding in Rats

Tox Chem No.: ~~77A~~ 268J

MRID No.: 402156-01

Test Material: Benzeneacetic acid, 4-chloro-a-(1-methylethyl)-cyano-(3-phenoxyphenyl)methyl ester [S-(R*,R*)]

Synonyms: MO 70616
ES-Fenvalerate
ASANA

Study Number: T.P.S. - 227-102-634-86
WTP 374
DuPont SRO-150-87

Sponsor: E.I. du Pont de Nemours & Company
Newark, DE

Testing Facility: Toxicology, Pathology Services
Mount Vernon, IN 47620

Title of Report: 13-Week Dietary Admix Study of MO 70616 Technical in Rats

Author: D.M. Larson

Report Issued: April 14, 1987

Conclusions:

NOEL = 125 ppm
LEL = 300 ppm (HDT) based on neurological effects (i.e., hyperactivity and "jerky leg movements")

Classification: Core-Minimum

A. Materials:

1. Test Compound - ASANA; Description: white semisolid at room temperature; Sample No. 730C; Purity: 98.6% (82.9% A-alpha); Contaminants: not stated.

2. Test Animals - Species: rat; Strain: Sprague-Dawley; Age: 49 to 50 days old; Weight: 216.9 to 281.6 g (males), 145.4 to 200.5 g (females); Source: Camm Research, Wayne, NJ.

B. Study Design:

1. Animal Assignment - Animals were acclimated to laboratory conditions for 14 to 15 days. There was a 12-hour light on/light off period. The temperature ranged from 71 to 80 °F, humidity was 50%, and there were 10 to 15 changes of air per hour. The rats were individually housed in one room in stainless steel cages with wire mesh bottoms. Cages were cleaned biweekly and the racks were rotated. Flush pans were rinsed once each day. The rats were segregated by sex and randomly assigned to treatment groups as follows:

Test Group	Dose in Diet (ppm)	Main Study 13 Weeks Male	Main Study 13 Weeks Female	Interim Sacrifice 7 Weeks Male	Interim Sacrifice 7 Weeks Female
Control	0	15	15	10	10
Dose #1 (Low)	75	15	15	10	10
Dose #2	100	15	15	10	10
Dose #3	125	15	15	10	10
Dose #4 (High)	300	15	15	10	10

In addition, a "calibration" group of 10 male and female rats was employed to provide clinical chemistry calibration values at the interim (5/sex) and terminal (5/sex) sacrifice.

2. Diet Preparation - The test material was heated to 50 to 55 °C and mixed with acetone. The solutions were then mixed with 3 kg of diet in a Univex mixer until the acetone had evaporated off. The contents of the mixer were added to the stock diet (Purina Certified Rodent Chow Meal #5002) in order to prepare a premix. The premixes were then added to 80 kg of the stock diet in order to prepare test diets. Test diets were stored at room temperature for less than 10 weeks which the author implies

is the "stability period." The stability of ASANA was previously determined in the chronic dog study. Samples of the test diets were sent to the sponsor for analysis of homogeneity and stability in the diet for 10 weeks.

Results - ASANA is stable at room temperature for over 2 years. The total amount of the enantiomers was 98.6%. Analyses of ASANA in test diets were 97 to 105% of nominal values. The stability of ASANA in test diets over a period of 10 weeks was unchanged.

3. Animals received food and water ad libitum.

4. Statistics - Differences between control and the treated group values for weekly body weights, estimated food consumption, hematologic and serum chemistry values, and organ weight data were analyzed for statistical significance by the method of Dunnett.

5. Quality assurance inspections were made at 15 intervals during the study. The statement was signed by M.J. Bandoll.

C. Methods and Results:

1. Observations - Rats were observed for clinical signs of toxicity, mortality, and general physical appearance at least twice daily. The animals were visually examined for neurological signs, especially abnormal limb movements. This was performed by W.A. Kelly who was study director for the previous 13-week study. (A general examination was done prior to initiation of the study. This included an ophthalmoscopic examination.)

Results - With the exception of neurological signs, clinical observations were limited to incidental findings. No distinct neurological signs were noted prior to week 10. Beginning after week 10, one female in the 300 ppm group became hyperactive. By the time the study was concluded five females in the 300 ppm group were observed to be hyperactive. Male rats did not exhibit hyperactivity. During weeks 11, 12, and 13 of the study 6, 5, and 12 rats in the 300 ppm group exhibited "jerky" leg movements. The jerky leg movements were characterized by prolonged posterior extension, flexion and/or elevation of one or both hindlimbs.

2. Body Weight - The rats were weighed upon receipt, once during pretest, at study initiation, and weekly thereafter for the remainder of the study.

Results - Males in the 300 ppm group had a statistically significant decrease in total body weight gain during weeks 1 and 2. Over the 13-week period males in the 300 ppm group had lower total body weight gain when compared to other groups. Females in the 300 ppm group exhibited a statistically significant decrease in body weight gain during weeks 3, 4, 5, 7, and 12. Females in the 125 ppm group had a statistically significant decrease in body weight gain during weeks 4, 7, and 12. Total body weight gain was decreased in all test groups when compared to controls. However, a dose-response relationship was not present. Total body weight gain for males and females could not be correlated with administration of the test material.

3. Food Consumption - Food consumption was recorded upon receipt of the rats, once during pretest, at initiation of the study, and weekly thereafter for the remainder of the study.

   Results - Males in the 300 ppm group exhibited a slight decrease in food consumption during weeks 1 and 8 of the study. Females in the 300 ppm group exhibited a slight decrease in food consumption during weeks 1 and 7 of the study. The decreases in food consumption were negligible.

4. Blood was collected from fasted rats via vein puncture of the right atrium at pretest when ten male and female rats were sacrificed in order to determine hemocellular normalcy. In addition to the 10 rats/sex/group scheduled for interim sacrifice and 15 rats/sex/group scheduled for terminal sacrifice, groups of 5 rats/sex were sacrificed at both the interim time period and terminally for calibration of clinical instrumentation. The CHECKED(X) parameters were measured.

   a. Hematology

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

Results - No treatment-related changes were observed.

b. Clinical Chemistry

X	Electrolytes
X	Calcium
X	Chloride
	Magnesium
X	Phosphorous
X	Potassium
X	Sodium
	Enzymes
X	Alkaline phosphatase
	Cholinesterase
	Creatinine phosphokinase
	Lactic acid dehydrogenase
X	Serum alanine aminotransferase (SGPT)
X	Serum aspartate aminotransferase (SGOT)

X	Other
X	Albumin
	Blood creatinine
X	Blood urea nitrogen
	Cholesterol
X	Globulins
X	Glucose
	Total bilirubin
X	Total protein
	Triglycerides
X	Albumin/globulin ratio

Results - No treatment-related changes were observed.

5. Urinalysis - Rats scheduled for interim or terminal sacrifice were administered 40 mL/kg of water and placed in metabolism cages overnight (approximately 16 hours). The CHECKED (X) parameters were examined.

X	
X	Appearance
X	Volume
X	Specific gravity
X	pH
	Sediment (microscopic)
X	Protein

X	
X	Glucose
X	Ketones
X	Bilirubin
X	Blood
	Nitrate
X	Urobilinogen

Results - No treatment-related changes were observed.

6. Sacrifice and Pathology - After 7 weeks, a total of 100 male and female rats were sacrificed for the interim necropsy. One hundred forty-nine male and female rats were sacrificed for the terminal necropsy. The external surfaces, all orifices, the cranial cavity, carcass, the external and cut surfaces of the brain and spinal cord, the nasal cavity and paranasal sinuses, the thoracic, abdominal, and pelvic cavities with their associated organs and tissues, and the neck with its associated organs and tissues were examined grossly. Only the following CHECKED (X) tissues were collected. The (XX) organs in addition were weighed.

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

Results

a. Organ Weights - At 8 weeks no differences in absolute or relative organ weights could be attributed to administration of the test material. At 14 weeks, there was a dose-related increase in the relative weight of the liver in males in the mid- and high-dose groups. Although the increases in relative liver weights in males in the mid- and high-dose groups were significant they were small increases. In addition, the absolute weights of the liver showed no difference between animals in control and test groups. Therefore, the increased relative liver weights were not attributed to administration of the test material. The relative and absolute weight of the kidney was increased in females in the high-dose group. Males in the high-dose group exhibited a relative increase in kidney weights. The increase in kidney weights was attributed to the administration of the test material. In addition to these changes, occasional increases in other organ weights were present, but could not be related to treatment.

b. Gross Pathology - Unremarkable.

c. Microscopic Pathology - Not performed.

D. Discussion:

Beginning after week 10, one or more females in the 300 ppm group were observed to be hyperactive. By the time the study was concluded, five females in the 300 ppm group were observed to be hyperactive. During weeks 11, 12, and 13 of the study, 6, 5, and 12 male and female rats in the 300 ppm group exhibited "jerky leg" movements. Instances of decreases in weekly body weight gain occurred during the course of the study. However, the decreases in body weight gain were not dose-related and are, therefore, not considered to be related to treatment. Food consumption was comparable among treated and control rats. There were no treatment-related changes in hematology, clinical chemistry, and urinalysis. At the interim sacrifice, there were sporadic differences in absolute and relative organ weights among the control and test groups. However, these differences could not be related to administration of the test material. At terminal sacrifice, there was an increase in the absolute and relative weight of the kidneys in females in the high-dose group and an increase in the relative weight of the kidneys in males in the high-dose group. The increase in kidney weight is considered to be treatment related. The gross necropsy examination was unremarkable. Microscopic examination of tissues was not performed in this study. However, a microscopic examination was performed on numerous tissues in a previously conducted study at the same lab with the same strain of rat receiving equivalent and higher dose levels (i.e., 50, 150, 300, and 500 ppm). Increased kidney weights were also observed in this previously conducted study (Accession Nos. 257018-257020). Kidney histopathology was however negative in that study. Therefore, it is reasonable to assume that histopathalogy was not conducted in this study due to the findings of the previous study.