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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JUL 17 1986

MEMORANDUM

SUBJECT: PROWL (Pendimethalin) Herbicide Technical
Submission of a 13-Week Feeding Study in Rats
(Accession No. 261305) - EPA Registration No. 241-245

Tox Chem No. 454BB

FROM: William B. Greear, M.P.H. William B. Greear 7/16/86
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THRU: Albin B. Kocialski, Ph.D., Supervisory Pharmacologist
Section VII, Toxicology Branch
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and

Theodore M. Farber, Ph.D., Chief
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Hazard Evaluation Division (TS-769C) 7/17/86

B.L. Gingher of the American Cyanamid Company has submitted, under a cover letter dated January 29, 1986, a study entitled "AC 92,553: A 13-Week Rat Feeding Study" for evaluation as required under the Registration Standard for pendimethalin. The study has been evaluated and has been classified as a "Guideline" study. The no-observed-effect level (NOEL) was determined to be 500 ppm.

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Reviewed by: William B. Greear, M.P.H.
Section VII: Toxicology Branch (TS-769C)
Secondary Reviewer: Albin B. Kocialski, Ph.D.
Section VII: Toxicology Branch (TS-769C)

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DATA EVALUATION RECORD

Study Type: Subchronic (13-Week) Feeding Study in Rats.

Tox. Chem. No. 454BB

Accession No: 261305

MRID No: Not available

Test Material: AC 92,553

Synonyms: Pendimethalin, PROWL

Study Number: Toxicology Report AX86-1

Sponsor: American Cyanamid Company
Princeton, NJ 08540

Testing Facility: American Cyanimid Company
Agricultural Research Division
Princeton, NJ 08540

Title of Report: AC 92,553: A 13-Week Rat Feeding Study

Author: J.E. Fischer

Report Issued: January 28, 1986

Conclusion: NOEL = 500 ppm (based on a decrease in hematocrit and hemoglobin in males, decreased body weight gain and food consumption, and hypertrophy of the liver accompanied by increased liver weights).

LEL = 5000 ppm.

Core Classification: Guideline.

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A. Materials

1. Test Compound - AC 92,553, Lot No. AC 3528-129-1, 92.1%, described as orange-yellow crystals.

2. Test animals - Species: rat; Strain: Charles River CD(SD)Br; Age: 4 weeks; Mean weight: 100 to 115 g (males), 87 to 103 g (females); Source: Charles River Breeding Laboratories, Wilmington, MA.

B. Study Design:

1. Animal assignment - At the end of a 10-day acclimatization period 120 male and 120 female rats were randomly distributed into 4 groups by a computerized randomization procedure, and identified by ear notches. The rats were assigned to the following groups.

Test Group	Dose in Diet (ppm)	Number of Animals Male	Female
1	0	30	30
2	100	30	30
3	500	30	30
4	5000	30	30

2. Animal maintenance - The animals were individually housed in suspended stainless steel wire mesh cages. The temperature was maintained at 73 ± 1 °F and relative humidity at 63 ± 9 percent. Twelve-hour per day lighting was provided by fluorescent lights.

3. Diet preparation - Test diets were prepared by adding the appropriate amount of the test material to a premix of 300 g of basal diet (Purina Certified Rodent Chow #5002) and blending in a Waring blender for 1 minute. The 300 g premix was added to 2 kg of basal diet and mixed in a small Hobart mixer for 2 minutes. This 2.3 kg premix was then blended with basal diet in a barrel mixer for 20 minutes. Test diets were prepared weekly and were retained in a freezer at -10 °F. For the 100 and 5000 ppm test diets, homogeneity was determined prior to initiation

of the study and stability was determined at 7 and 14 days. Also, the concentration of the test material in the diets was determined weekly.

Results - Homogeneity of test diets varied from 90.0 to 100.4 percent of the nominal concentration and stability varied from 87.1 to 101.4 percent. The concentration of the test material in the diets ranged from 92.6 to 110.0 percent of the target concentration throughout the 13-week study period.

4. Statistics - Food consumption, body weight, weight gain, hematology, clinical chemistry, and organ weight were analyzed by analysis of variance using Dunnett's procedure for comparing several treatments to a single control.

5. Quality assurance - Conducted on July 12, 1985, August 26, 1985, and October 17, 1985. The Quality Assurance Statement was signed by C.A. Lennon.

C. Methods and Results:

1. Observations - All rats were observed for appearance, behavior, gait, and changes in excreta 7 days a week.

Results - Males and females in the 5000 ppm group displayed a dark yellow discoloration of the urine. This was attributed to metabolites or unmetabolized test material which are both yellow in appearance. One female in the 100 ppm group died on day 13. Death was not attributed to exposure to the test material by the attending pathologist.

2. Body weight - All rats were weighed initially and weekly thereafter.

Results - Body weight gain was decreased in males and females in the 5000 ppm group. The decrease in body weight gain in females was slight.

3. Food consumption and compound intake - Individual weekly food intake was recorded.

Results - Food consumption was decreased in males and females in the 5000 ppm group when compared to controls. The average intake of the test material

was 7.6, 39.2, and 381.5 mg/kg/day for males in the control to high-dose groups, respectively. The average intake of test mixture was 8.7, 43.4, and 410.8 mg/kg/day for females in the control to high-dose groups, respectively.

4. Blood was collected from 10 rats/sex/group by heart puncture under ether anesthesia at 45 and 46 days and at termination. (This required that the rats be sacrificed.) The CHECKED (X) parameters were examined.

a. Hematology

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

Results - There was a decrease in the hematocrit and hemoglobin levels in males in the 5000 ppm group at termination. The platelet count was slightly increased (not statistically significant).

b. Clinical Chemistry

X	Electrolytes	X	Other
	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
	Phosphorous		Cholesterol
X	Potassium		Globulin
X	Sodium	X	Glucose
	Enzymes	X	Total bilirubin
X	Alkaline phosphatase	X	Total protein
	Cholinesterase		Triglycerides
	Creatinine phosphokinase		
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (SGPT)		
X	Serum aspartate aminotransferase (SGOT)		
X	Gamma glutamyl transpeptidase		

Results - There appeared to be a dose-related decrease in SGOT in all male treatment groups at 45 days and at termination. The decrease was not statistically significant at any dose level. There was a slight increase in total protein in males in the 5000 ppm group at 45 days. There appeared to be a dose-related increase in potassium levels in all male treatment groups at 45 days and at termination. Statistical significance was achieved in the male 500 and 5000 ppm groups at 45 days and in the male 5000 ppm group at termination. However, the increases were minimal. There appeared to be a dose-releated increase in albumin in all female treatment groups at termination. Statistical significance was achieved only in the 500 and 5000 ppm dose groups.

5. Urinalysis - Urine was collected from 10 fasted rats/sex/group at 45 days and at termination. The CHECKED (X) parameters were examined.

X		X	
X	Appearance	X	Glucose
	Volume	X	Ketones
	Specific gravity		Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)		Nitrate
X	Protein		Urobilinogen
X	Color	X	Yeast

Results - Unremarkable.

6. Sacrifice and pathology - At termination the animals were sacrificed with an overdose of ether and exsanguinated. The rats were examined externally, then the organs were examined in situ. The tissues were then removed and examined. The tissues were fixed in 10% phosphate buffered neutral formalin, cut, mounted in paraffin blocks, sectioned at 4 to 6 microns, mounted on slides, stained with hematoxylin and eosin, and examined microscopically. The CHECKED (X) tissues were examined microscopically. The (XX) organs in addition were weighed.

X	Digestive	X	Cardiovasc., Hemat.	X	Neurologic
X	Tongue	X	Aorta	XX	Brain (3 levels)
X	Salivary glands	XX	Heart	X	Periph. nerve (sciatic)
X	Esophagus	X	Bone marrow		
X	Stomach	X	Lymph nodes	X	Spinal Cord
X	Duodenum		(mesenteric,	X	Pituitary
X	Jejunum		mandibular)	X	Eyes (optic nerve)
X	Ileum	XX	Spleen		Glandular
X	Cecum	X	Thymus	XX	Adrenals
X	Colon		Urogenital		Lacrimal gland
	Rectum	XX	Kidneys	X	Mammary gland
XX	Liver	X	Urinary bladder	X	Parathyroids
	Gallbladder	XX	Testes	XX	Thyroids
X	Pancreas	X	Epididymides		Other
	Respiratory	X	Prostate	X	Bone
X	Trachea	X	Seminal	X	Skeletal muscle
X	Lung		vesicles	X	Skin
		XX	Ovaries	X	All gross lesions
		XX	Uterus	X	Sternum
		X	Vagina		

Results

a. Organ weight - the absolute and relative weights of the liver and kidneys were significantly increased in males in the 5000 ppm group. In females, there appeared to be a dose-related increase in the absolute and relative weight of the liver in all female treatment groups. Statistical significance was only achieved in the 5000 ppm group. There appeared to be a dose-related decrease in the absolute and relative

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weight of the uterus and ovary in all female treatment groups. Statistical significance was achieved in the 500 and 5000 ppm groups for relative weight and in the 5000 ppm group for absolute weight.

b. Gross pathology - Males and females in the 5000 ppm group exhibited a yellow discoloration of abdominal fat and several rats had dark red thyroids. Four males in the 5000 ppm group had pale or mottled livers. None of the above-mentioned gross lesions were observed in rats in the control, 100, and 500 ppm groups.

c. Microscopic pathology - There was an increase in liver alterations in males and females in the 5000 ppm group. Hepatic (parenchymatous) cells were enlarged (diffuse hypertrophy) due to increased cytoplasmic volume. The cytoplasm was finely vesiculated (a hydropic change), and on occasion, revealed the presence of "myelin figures" (representing localization of closely packed concentric rings of smooth endoplasmic reticulum). These changes were stated to be characteristic of enzyme induction.

Discussion

d. Summary - Males and females in the 5000 ppm group displayed a dark yellow discoloration of the urine. Body weight gain and food consumption were decreased in males and females in the 5000 ppm group. However, the decreased body weight gain in females was minimal. The hematocrit and hemoglobin levels were decreased and the number of platelets slightly increased in males in the 5000 ppm group at termination. There appeared to be a dose-related decrease in SGOT in male treatment groups at 45 days and at termination. The decreases were not statistically significant. There was a slight increase in total protein in males in the 5000 ppm group at 45 days. There appeared to be a dose-related increase in potassium levels in male treatment groups at 45 days and at termination. Statistical significance was achieved in the male

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500 and 5000 ppm groups at 45 days and in the male 5000 ppm group at termination. However the increases were minimal. There appeared to be a dose-related increase in albumin in female treatment groups at termination. Statistical significance was achieved only in the 500 and 5000 ppm groups. The majority of the changes in clinical chemistries were slight and not considered to be of biological significance. At necropsy, males and females in the 5000 ppm group displayed a yellow discoloration of abdominal fat. There was an increased incidence of pale or mottled livers in males in the 5000 ppm group and of dark red thyroids in males and females in the 5000 ppm group. The absolute and relative weight of the liver and kidney were increased in males in the 5000 ppm group. In females, there appeared to be an increase in the absolute and relative weight of the liver at all dose levels. However, statistical significance was achieved only at the 5000 ppm dose level. There also appeared to be a dose-related decrease in the absolute and relative weight of the uterus and ovary in all female treatment groups. However, statistical significance was achieved only in the 500 and 5000 ppm groups for relative weight and in the 5000 ppm group for absolute weight. Microscopic examination of the tissues revealed diffuse hypertrophy of the liver which was indicative of enzyme induction.

The no-observable-effect level (NOEL) is as follows:

NOEL = 500 ppm (based on a decrease in hematocrit and hemoglobin in males, decreased body weight gain and food consumption, and hypertrophy of the liver accompanied by increased liver weights).

LEL = 5000 ppm.

Core Classification: Guideline.

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R:94394:Greear:CBI-15:KENCO:7/14/86:9/20/86:DAA:LMF