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

MEMORANDUM

DATE: OCT 14 [redacted]

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. No. 241-243; Two Year Toxicity Study in Dogs; AC-92,553 - Final Report.

TOX Chem. No. 454BB

FROM: John Doherty 9/22/81
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TO: Robert Taylor, PM #25
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Background:

The American Cyanamid Company has submitted a two year chronic toxicity study with the herbicide AC-92,553 (pendimethalin, PROWL) to fulfill the requirement for a six month or longer non-rodent feeding study.

Conclusions:

1. The study was reviewed and assigned a Core Minimum classification and can be used to support registration actions for the herbicide pendimethalin (AC-92,553).

2. The Core Minimum classification is based on there being only four dogs per sex per dose level and only three female control dogs.

3. A NOEL of 12.5 mg/kg/day is assigned; at higher levels (50 and 200 mg/kg/day) there were noted increases in alkaline phosphatase activity in the blood. In the mid and high dose test groups, the liver was affected with microscopic lesions including inflammation and hemosiderosis and also showed increased weight.

REVIEW

Two Year Toxicity Study in Dogs AC 92,553 - Final Report

Litton Bionetics, Inc., Project No. 20755, December, 1979.
EPA Accession Nos. 244444 and 244445.

Thirty-two purebred beagle dogs were selected from 10 different litters and randomly placed into four groups of four female and four males. The dogs were all 4 1/2 to 5 1/2 months of age when they were started on the experiment. The dogs were dosed daily, seven days a week by gelatin capsule, with 0, 12.5, 50 or 200 mg/kg/day of AC 92,553 (batch # 77-02, 91.4% purity). The animals were dosed by gelatin capsule prior to feeding for the first three weeks of the study and after feeding for the remainder

of the study. The daily dosage was determined based on the current weight of the dog which was determined weekly. After the two year dosing period (106 weeks), the dogs were sacrificed by administration of Somlethol containing sodium pentobarbital.

NOTE: One female control dog was found to be missing from its cage during the 29th week of the study and was presumed to be stolen. Thus, the experiment continued with only three female control dogs.

Results:

1. Survival: One high dose male dog died in the 95th week. This dog began to show a consistent decreased food intake during the 91st week. Histology of this dog's lungs indicated that pneumonia may have caused the premature death.

2. Body Weight (measured weekly): All male dogs dosed with AC 92,553 were lower in weight than the control dogs. However, there was no clear dose relationship between weight gain and test chemical administered. The low dose male group was as much as 13% or less lower than the control with the usual difference being 10%. This is not considered biologically significant, and was not statistically different (only 4 dogs/group were used).

3. Clinical Signs: Yellow coloration of the dogs hair was observed in all dogs and the duration was associated with the level of AC 92,553 in the test diet. For example, the color was noted beginning at week 8 and lasted through week 26 in all dogs. Thereafter the incidence was reduced and the effect was confined to the 50 and 200 mg/kg/day dose groups. After 36 weeks the effect was noted only in the high dose group animals. The NOEL was considered to be 12.5 mg/kg, but the toxicological significance (if any) of this coloration is questionable.

4. Haematology, clinical chemistry, and urinalysis were conducted at pretest, and on weeks 12, 26, 52, 79, and 104. The dogs were fasted for 18 hours prior to blood and urine sampling.

   [Haematology included erythrocyte count, hemoglobin concentration, hematocrit, total and differential leukocyte count, platelet count, reticulocyte count, and erythrocyte morphology.

   Clinical chemistry included blood urea nitrogen, glucose, serum alkaline phosphatase, glutamic - oxalacetic transaminase, glutamic - pyruvic transaminase, and bromosulphalein retention. No electrolytes were measured.

   Urinalysis included color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood, and microscopic examination of sediment.]

No consistent dose related changes were noted in haematology. Urinalysis indicated a possible test chemical effect in the last week of the study (the presence of occult blood and albumin in the high dose group males).

Clinical chemistry findings were considered within normal limits for all dosed groups except for alkaline phosphatase which showed increases for the mid and high dose group males at 26 weeks and thereafter.

Serum Alkaline Phosphatase of Males

Group	Week 26	52	79	104
Control	100	100	100	100
Low	112	127	109	90
Mid	142	203*	203*	187*
High	169*	209*	188*	208*

Data are as % control.
* $p < 0.05$ as compared to controls: Dunnett's t-test.

In dogs, increases in alkaline phosphatase may reflect bone injury, hepatocellular disease, and adrenal hyperfunction.

A NOEL for this effect on alkaline phosphatase is the low dose of 12.5 mg/kg/day.

5. Organ weights and organ weight as a percentage of body weights, (brain, heart, liver, kidneys, pituitary, thyroids, and testes or ovaries were analysed).

The liver weight was considered to be adversely affected by the test chemical in the mid dose group (males) and high dose group (males and females).

Group	Males	Females
Control	352.55/2.502[1]	312.40/2.782
Low	339.68/2.568	327.08/2.465
Mid	406.13/3.530*	313.68/3.099
High	359.70/3.214	374.58/3.534

* $p < 0.05$ as compared to controls: Dunnett's t test.

[1]Absolute weight/relative weight.

The kidneys also showed some evidence of increased weight in the mid and high dose groups (in males only). The small number of dogs in each dose group precluded a definite conclusion of a test chemical effect on the kidney weight.

6. Gross Pathology - Mild degenerative lesions were noted in several tissues and organs in all dogs. A single dog (number 9A, high dose group female) had an irregular patch of parenchyma (1.0 cm x 0.7 cm) in the left liver lobe. All other gross aberrations were considered as being typical for dogs of this age.

7. Histopathology - Thirty-nine tissues/organs types were evaluated histologically. The liver was associated with several lesions in a dose related manner as follows:

Number of Dogs With Liver Lesions

Liver Lesion	Male				Female			
	Control	Low	Mid	High	Control	Low	Mid	High
Number Examined	4	4	4	4	3	4	4	4
Inflammation, multifocal		1	2	1		2	3	2
Biliary hyperplasia				2		1	3	2
Bile Stasis			1	2		1	2	1
Hemosiderosis	1		2	2	1		4	2

The intensity of the lesions were also noted to be more severe in the mid and high dose groups (see page 409 of report).

A NOEL for microscopic lesions in the liver is 12.5 mg/kg/day.

An unusual finding of chronic inflammation of the choroid plexus of the third and fourth ventricles was found only in the mid and high dose group animals. The testing laboratory concluded that this lesion was incidential and not related to ingestion of the test chemical. Toxicology Branch notes the presence of the inflammation in the choroid plexus but does not consider this lesion to be conclusively linked to the presence of the test chemical.

No true neoplastic tissues were reported.

This study is Core Minimum. Only four dogs per sex per dose group were used and one dog from the female control group was lost during the study. The limited number of dogs per sex per dose group did not allow firm conclusions of possible pathological changes noted in the high dose groups (for example, the condition described as "inflammation of the choroid plexus"). These changes if indeed related to ingestion of AC 92,553 occur above the assigned NOEL of 12.5 mg/kg/day.

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