determinations. There was no presentation of gross pathology data. There was a lack of continuity in the histopathologic evaluations performed at the early and final sacrifices. Specifically, the tissue lists for each sacrifice and the number of tissues evaluated per group varied; no explanation was offered for these deficiencies. There was not sufficient opportunity for tumor expression because of the low number of rats surviving to the final sacrifice, and the insufficient histopathologic evaluation of tissues at the low and mid-dose levels. Furthermore, animals that died during the study or were sacrificed in moribund condition were not adequately examined.

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83-1 CHRONIC FEEDING STUDY OF PROMETRYN IN DOGS

Woodard Research Corporation; Project No. [unknown]; January 25, 1965; Accession No. 231965; MRID No. 42794

PROTOCOL: Groups of 3 male (5.8-8.6 kg) and 3 female (4.0-8.2 kg) beagles (4-8 months old) were dosed for 106 weeks with prometryn 80W (80% wettable powder - not otherwise specified) in their diet at "pure chemical" (active ingredient) concentrations of 0 (negative controls), 15, 150, and 1500 ppm (0.0, 0.375, 3.75, and 37.5 mg a.i./kg/day, respectively). The test article was formulated with a baked dog meal. Diet concentrations were grossly adjusted to compensate for variability in animal weight. Water was available ad libitum, and food was limited to 200 g of formulated feed/day and 45 g of reconstituted canned beef. Food consumption was measured daily. All dogs were observed daily, weighed weekly, given physical examinations daily for the first week, and weekly thereafter, and given neurologic and ophthalmic examinations monthly. The following clinical pathology parameters were measured at 0, 4, 8, 13, 19, 27, 40, 52, 68, 80, 91, and 104 weeks:

Hematology:

| | |
|---|---|
| Hematocrit | Sedimentation rate |
| Hemoglobin | Leukocytes (total and differential) |

Clinical Chemistry:

| | |
|---|---|
| Blood urea nitrogen | Alkaline phosphatase |
| Glucose | SGOT |

The following urinalysis parameters were measured at 0, 4, 8, 13, 19, 26, 39, 52, 67, 78, 91, 104 weeks:

Urinalysis:

| | |
|---|---|
| Specific gravity, | Sugar |
| pH | Appearance |
| Albumin | Microscopic sediment |

Surviving dogs were sacrificed at 106 weeks and examined grossly. The following tissues were examined histopathologically for control and high-dose dogs:

| | | |
|---|---|---|
| †*Heart | Trachea | Muscle (skeletal) |
| *Spleen | †*Thyroid | Pancreas |
| †*Liver | Thymus | Esophagus |
| †*Kidneys | *Adrenals | Stomach |
| *Testes | †Eye | Small intestine |
| *Prostate | *Brain | Large intestine |
| *Uterus | *Pituitary | Salivary glands (parotid) |
| *Ovaries | Spinal cord | Urinary bladder |
| †Bone marrow | Peripheral nerve | Mesenteric lymph nodes |
| †*Lungs | Skin | Gall bladder |

* These organs were weighed.
† These organs were evaluated histopathologically for all dogs.

RESULTS: There were reportedly no significant clinical signs in any dogs. No compound-related effects on weight gain were seen. Reportedly, there were no differences in food consumption in any group (no data were reported). In addition, there were no compound-related changes in any clinical pathology or urinalysis parameters. There were decreases in alkaline phosphatase and glucose levels in some dogs, however, as a consequence of the starvation diets (245 g of feed/dog/day).

One high-dose male had swollen kidneys and a congested liver which could have been compound-related. Organ weights were comparable for all groups. Two of 3 high-dose males, and 1 of 3 mid-dose males had slight to moderate degenerative hepatic changes, such as glycogen depletion, an increase in Kupffer cells, hepatocyte vacuolation and pigmentation, pyknotic nuclei, irregular hepatocyte size, and small parenchymal foci of macrophages. Three of 3 high-dose males had slight to moderate renal tubular degeneration, including degeneration of the loops of Henle, cortical congestion, thickening of capsular basement membranes, and hypercellularity of the glomeruli. Slight bone marrow atrophy was observed in 2 of 3 high-dose males. The hepatic and renal lesions were not reflected in the clinical pathology studies, probably because of the minor severity of the lesions. The defined doses are:

NOEL = 3.75 mg a.i./kg/day (150 ppm a.i.)
LEL = 37.5 mg a.i./kg/day (1500 ppm a.i.) - degenerative hepatic changes, renal tubule degeneration, and bone marrow atrophy.

STUDY CLASSIFICATION: This study is Core MINIMUM. Only 3 dogs/sex/group were used instead of the currently recommended 4 dogs/sex/group. All data were for individuals only; there were no group data. No food consumption data were reported. The quantity of feed available to the dogs was minimal. The use of such a restrictive diet would mask changes in food consumption in some dogs. There were very few clinical pathology parameters evaluated, which

could have been a problem if there had been extensive tissue damage. Since the doses used in this study elicited only minor toxicity, the scant clinical pathology studies cannot be perceived as an insufficiency. This study had all of the characteristics of an old, but well performed experiment. The duration of this study was double that required by current guidelines.

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83-4 THREE-GENERATION REPRODUCTION STUDY OF PROMETRYN IN RATS

Woodard Research Corporation; Project No. [unknown]; August 15, 1966; Accession No. 231966; MRID No. 24472

PROTOCOL: Groups of 10 male (39-56 g) and 20 female (38-55 g) 27 day old albino rats ($F_0$ generation) were dosed for 79 days with prometryn 50W (50% wettable powder - not otherwise specified) in their diet. The test article (active ingredient) concentrations were 0 (negative control), 50, and 100 ppm (0.0, 2.5, and 5.0 mg a.i./kg/day, respectively). The test article was formulated into the laboratory chow. The dose concentrations for all generations were reduced by half during the first 3 weeks to compensate for the high rate of food consumption of the young animals.

Food and water were available ad libitum. At the conclusion of the 79-day dosing period, the rats were mated for 10 days. Non-pregnant females were housed for an additional 10 days with a different male. The males were weighed biweekly except during mating. All rats were observed daily for clinical signs. The females were weighed biweekly except during mating, gestation, and lactation.

The $F_1a$ litters were weighed and examined for viability and abnormalities. The pups were sacrificed after being weaned. The $F_0$ dams were once again mated (with different males) 10 days after the $F_1a$ sacrifice. The $F_1b$ litters were weighed and examined for viability and abnormalities. After the $F_1b$ pups were weaned, the $F_0$ rats were sacrificed. Ten male and 20 female $F_1b$ weanlings were selected from each group for mating. They were fed the same dosing diets as the $F_0$ rats over a period of 79 days, then mated. The uteri of the $F_1b$ dams which did not bear two litters ($F_2a$ and $F_2b$) were removed and examined for implantation sites.

The $F_2a$ and $F_2b$ pups were weighed and examined for viability and abnormalities. The $F_2a$ pups were sacrificed after being weaned. As with the $F_1b$ generation, ten male and 20 female $F_2b$ weanlings were selected from each group for mating. The other $F_2b$ pups were examined for external abnormalities and problems in locomotion. They were then sacrificed and grossly examined for visceral anomalies. The $F_2b$ pups selected for mating were fed the dosing diets over a period of 75 days, then mated.