10-3-82

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

MEMORANDUM

002214

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Henry Jacoby (21)
Registration Division (TS-769)

SUBJECT: Ronilan; EPA Reg.#7969-53; Miscellaneous Data; 6-Month Dog Study. CASWELL#323C; Acc. Nos.: 248123, 248124

Recommendation:

The study is acceptable as Core-Minimum Data and therefore satisfies the requirement for the requested dog study.

Review:

1. Report on the study of the toxicity of Vinclozolin in Beagle Dogs after 6-month administration in the Diet (BASF Gewerbehygiene und Toxikologie; he-ru/ro; 8/16/82).

Test Material: Vinclozolin; ≥ 98.1% purity

Groups of 6 male and 6 female purebred beagle dogs were administered the test material in the diet at dosages of 0 (controls), 100, 300, 600 and 2000 ppm for 6-months. From the period of adapatation (the 7th day before the beginning of administration of test material) and during the study, the body weight of each individual animal was determined weekly and food consumption daily. The dogs were given clinical examinations when they were weighed. The animals were also observed daily for toxic signs and mortality.

Ophthalomological examinations for all animals were done during the period of adaptation, at 3-months and at termination.

Clinical chemistries and hematologies were done at 12 days before the administration of the test material and at 30, 58, 113, 141 and 179 days during the study.

Clinical chemistry and determinations included: total bilirubin, creatinine, urea, sodium, potassium, total protein, glucose, inorganic phosphate, calcium, chloride, triglyceride, cholesterol, albumin, globulins, lactic dehydrogenase, glutamic pyruvic transaminase (SGPT), alkaline phosphatase (SAP), and glutamic oxalacetic transaminase (SGOT).

Hematological determinations included: hemoglobin, erythrocytes, hematocrit, mean hemoglobin content per erythrocyte, mean cell volume, mean corpuscular hemoglobin concentration, platelets, leukocytes, differential leukocytes, clotting analysis and reticulocytes.

Urine was collected overnight from all of the animals 17 days before administration of the test material and at 56, 116, and 176 days during the study. Urine determinations included: pH, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, specific gravity, and sediment.

At the end of the study, the dogs were anesthesized, exsanguinated, weighed and examined grossly.

Relative and absolute organ weight of the following organs were made: heart, liver, spleen, kidneys, testes/ovaries, thyroids, adrenal, pituitary, and brain.

The following organs were microscopically examined for all animals in all groups: heart, aorta, trachea, lung, esophagus, small intestine, large intestine, parotid, liver, gall bladder, pancreas, spleen, mesenteric lymph node, axillary lymph node, thymus, sternum with bone marrow, kidneys, urinary bladder, testes/ovaries, prostate/uterus, pituitary, adrenals, thyroids with parathyroids, brain, spinal cord, eye, sciatic nerve, skeletal muscle, skin, mammary gland and all gross lesions.

Statistical evaluation of the data was carried out by the "t" test at $p < .05$.

Results:

No deaths occurred during the study.

No treatment-related effect was noted with respect to toxic signs, food consumption or body weight during the study.

No ophthalmological treatment-related findings were noted.

Treatment-related findings in clinical chemistry were significant consistent increases in bilirubin and urea in males of the 600 and 2000 ppm group. Additionally, there were significant consistent increases in lactic dehydrogenase in males of the 2000 ppm group and decreases in SGPT in females of the 600 and 2000 ppm groups. Other sporadic changes were not considered treatment-related.

Hematological results showed consistent significant increases in mean hemoglobin content per erythrocyte, mean cell volume, platelets, jolly bodies, and reticulocytes in males of the 2000 ppm group. Females of the 2000 ppm group showed a decrease in mean corpuscular hemoglobin concentration, and increases in jolly bodies.

Urinalysis findings did not show any treatment-related findings.

Gross necropsy showed male dogs at 2000 ppm had smaller prostates.

The 100 ppm group did not show any significant changes in absolute or relative organ weight or histopathology.

In males at 300 ppm, there was a significant increase in absolute and relative adrenal weight and a decrease in absolute kidney weight.

In females at 300 ppm, there was a significant increase in absolute and relative adrenal weight and a decrease in relative pituitary weight. No histopathological findings were noted for males and females at 300 ppm.

In males at 600 ppm, there was a significant increase in the absolute and relative adrenal weight and a decrease in the absolute kidney weight. Histologically, the prostate showed atrophy and stromal proliferation and the kidneys showed fat droplets in the distal tubules.

In females at 600 ppm, there was vacuolation of the zona fasiculata and birefringene of the cortex in the adrenal. The bone marrow showed an increase in sideropexia, the spleen showed sinusoidal dialation and an accumulation of erythrocytes and the liver showed an increase in sideropexia.

In males at 2000 ppm, there was a significant increase in the absolute and relative adrenal weight, a decrease in absolute and relative kidney weight, an decrease in absolute brain weight and an increase in relative spleen weight. Histologically, the adrenal showed vacuolation of the zona fasiculata, the prostate showed atrophy and stromal proliferation, the kidneys had fat droplets in the distal tubules, the bone marrow had increased erythropoiesis and sideropexia, the spleen had sinusoidal dialation and an accumulation of erythrocytes and the liver displayed hepatocytes containing cytoplasmic hyaline inclusions.

For females at 2000 ppm, there was a significant increase in absolute and relative adrenal and spleen weight and an increase in the relative pituitarsy weight. Histologically, the adrenals had vacuolation of the zona fasiculata, an increase in lipoid - containing cells and birefringene of the cortex. The histological findings in the bone marrow, spleen and liver were comparable to the findings seen in the male dogs.

Conclusion:

The NOEL is 100 ppm for the study. The LEL is 300 ppm and the effect is increased absolute and relative adrenal weights. Although no histopathological findings were noted in the adrenal at 300 ppm, the absolute and relative increases in the adrenal at 600 and 2000 ppm were accompanied by histopathological findings.

Classification: Core-Minimum Data.

William Dykstra LDC 9/28/82

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