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

004569

7/22/85

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 35977-L/-U Fenoxycarb: One-Year Interim Report, Chronic/Oncogenicity, Rat; Hazleton Europe No. 4342-161/123

Tox Chem No. 652C

FROM: David G. Van Ormer DVO 17 Jul 85
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Budd 7/19/85
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The subject Interim Study is adequate to satisfy the Toxicology Branch requirement for a rat 90-day feeding study, showing a NOEL. The only remaining unfilled data gap for use of fenoxycarb on nonagricultural turf is a 21-day dermal toxicity study on the technical material.

004569

Interim Report at 52 Weeks on a 104-Week Oral (Dietary Administration) Carcinogenicity and Toxicity Study in the Rat with Ro 13-5223/000 (Insect Growth Regulator). Hazleton Laboratories Europe. Report No. 4342-161/123. May 1985. Accession No. 258112

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The test material was Ro 13-5223/000 (fenoxycarb), Lot 2, a solid of purity 96.6 percent. The material was stored in the dark at room temperature. A vehicle was not used. Diet batches were prepared weekly and also stored at room temperature. Dose levels were selected by the sponsor (Hoffmann-La Roche) after examination of data from a 6-week dose-range study (HLE No. 161/122), in which stability and homogeneity of formulated diets also were determined. Test material concentration in the high- and low-dose diets was determined at 13-week intervals.

The test animals were 4-week old Sprague-Dawley rats of the Crl:CD(SD)Br strain, obtained from Charles River (UK) Ltd. The animals were examined during 2-week acclimatization. Ten animals of each sex were given histopathological prescreening of liver, lung, and kidney. Animal housing was in groups of five in stainless steel cages, all in the same room. Free access was provided to food and water. Ambient environmental conditions were adequately controlled. Assignment of animals to treatment groups was by a total randomization procedure, according to the report. Identification procedures appear adequate.

Sixty animals per sex per group were started on the study. The nominal dose levels were 0, 200, 600, and 1800 ppm. The dose ranges for the three treatment groups were 24.7 to 6.9, 75.1 to 20.7, and 217.2 to 62.9 mg/kg/day for the low, mid, and high doses, respectively. For the present, Toxicology Branch will base any calculations on the nominal values of the doses.

Effects Evaluated

Appearance and behavior were recorded twice daily, with lesions and palpable masses recorded weekly. Body weight and food consumption were recorded weekly to week 16, and at 4-week intervals to week 52.

All animals received ophthalmoscopic examination inititally. The eyes of ten animals per sex from the control and high dose were examined at week 51.

Urine and blood samples (orbital sinus puncture) were obtained from 10 animals per sex from the control and high dose after overnight deprivation of food (and of water before urine collection).

Samples of both blood and urine were taken initially and at weeks 25 and 51. The laboratory parameters measured included as follows:

1. Hematology - Hb, RBC, PCV, MCHC, MCH, MCV, platelet count, and WBC (total and differential).

2. Clinical chemistry - LDH, GOT, GPT, Alk.P, Na, K, Ca, total protein, albumin, A/G ratio, glucose, BUN, creatinine, cholesterol, and total bilirubin.

3. Urinalysis - volume, pH, specific gravity, color, glucose, ketones, protein, hemoglobin, urobilinogen, bilirubin, microscopy of spun deposits, and reducing substances.

At 52 weeks ten animals per sex per group were killed by intraperitoneal injection of pentobarbitone sodium. Each of the sacrificed animals (and any found dead or in extremis) received external examination and macroscopic examination of all tissues and organs in situ. Organ weights were obtained for all animals for the organs as follows: adrenals, brain, heart, kidneys, liver, ovaries, lungs, spleen, testes, and thyroids. Histological sections (stained with H & E) were obtained for approximately 48 tissues, depending on availability, and including any masses or gross lesions. Histology was performed on the control and high-dose groups. Samples of gross lesions and masses for the low- and mid-dose groups were embedded in paraffin wax. Microscopic examination of high-dose animal tissue later revealed treatment-related changes in the liver. As a result of discussions with the sponsor, sections were prepared for microscopic examination of the liver (only) from the low- and mid-dose animals (p. C2-164).

Statistical analyses were performed only on the alterations which were interpreted by the authors as treatment related. These changes were relative liver weights and alkaline phosphatase activity. The report states that all primary data (or copies thereof) and specimens from the first 52 weeks are retained in the files of Hazleton Laboratories, Europe.

Results:

Test material concentration in treatment diets (low and high dose) is tabulated as 87 to 104 percent of nominal values. During the first 52 weeks of the study five animals died: one male at low dose, two males at mid dose, and one female each at mid and high dose. All other animals were stated to be in good clinical condition.

Body weights (means) of both sexes at high dose were somewhat lower than controls. Food consumption of males at high dose was slightly lower than control value.

Platelet counts in males at high dose are somewhat lower than controls at both 25 and 51 weeks. Total WBC and lymphocyte counts for high-dose females appear somewhat depressed at 51 weeks, relative to concurrent controls. Predose mean values for several hematology parameters in control animals are not easily related to control values tabulated for weeks 25 and 51.

Clinical chemistry data show statistically elevated values for alkaline phosphatase at high dose in both sexes at 51 weeks, and in males (high dose) at 25 weeks.

Individual urinalysis data (group means not presented) show elevations in protein in both sexes at both the concurrent control and high dose (both weeks 25 and 51) relative to predose values. The same relation exists for the ketone values in males at 25 weeks. Indeed, for numerous parameters in the study the mean values for concurrent controls appear to "track" treatment values rather than predose values.

Absolute organ weight tabulation shows elevated liver weights in both sexes at all doses and without apparent dose relation. Organ-body weight ratios show no apparent meaningful trends or significant alterations from control values, with exception of the group means for the liver ratio in the mid-dose males and high-dose females. Values of the mean liver ratio for these two groups are statistically elevated from control mean values.

Histopathology tabulation shows five cases of myocarditis at top dose in males vs. one in control. There is a dose response in focal necrosis of the liver in males (2/10 at low dose). Pigmented histiocytes are elevated in males at the top two doses, accompanied by centrilobular liver hypertrophy, which shows a dose-related response at the top two doses. The focal necrosis and hypertrophy show a dose-response relationship in severity, as well as incidence. Liver fibrosis is elevated in males at top dose (3/10 vs. zero in control). Spleen pigment is elevated at high dose in both sexes.

Pituitary adenomas appear in females in a dose-related incidence, but not significantly elevated above control values. Other neoplasias reported were a fibrosarcoma in a control male, a hemolymphoreticular leukemia (undifferentiated) in one mid-dose male, and an odontoma in one high-dose female.

The Report states there were no treatment-related effects seen in ophthalmoscopy in the high dose animals.

Summary and Conclusion

High dose: Body weight depression (both sexes); reduced platelet count (males); depressed WBC and lymphocyte counts (females); statistically elevated alk. phos. (both sexes); significantly elevated liver-body weight ratio (females); myocarditis (males); focal necrosis, pigmented histiocytes, centrilobular hypertrophy, and fibrosis in liver of males; elevated spleen pigment (both sexes).

Mid dose: significantly elevated liver-body weight ratio (males); focal necrosis, pigmented histiocytes, and centrilobular hypertrophy of the liver (males).

Low dose: focal necrosis of the liver in males (2/10).

The observations of focal liver necrosis and centrilobular hypertrophy (males) show dose-response in both incidence and severity. This dose-response is supported by the observations of pigmented histiocytes and liver fibrosis in high-dose males.

Toxicology Branch will accept low dose (200 ppm) as a NOEL for this 51-week Interim Report. The incidence and dose-response observed for liver pathology at 104 weeks will be evaluated after data are received.