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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Petition No. 3F2941. Fenoxycarb: Review of Teratogenicity Study, Rabbits; Hoffmann-LaRoche Report No. B-104 700.

Tox Chem. No. 652C

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Budd 3/14/85

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The subject teratogenicity study is acceptable.

The six-month dog study (Hoffmann-LaRoche No. B-104 927) is also acceptable, and the results are as follows:

NOEL = 150 mg/kg/day

LEL = 500 mg/kg/day (reduced weight gain in females)

Teratogenicity Study, Rabbits; Hoffmann-LaRoche (Basle) Report No. B-104 700. February 13, 1984. Accession No. 073304. Tox Chem. No. 652C.

The test material was fenoxycarb (Code No. $R_O$13-5223/000), Batch No. 18, stated to be stable under conditions of the study. Treatment was by daily oral gavage on gestation days 7 thru 19 at levels of 0, 30, 100 and 300 mg/kg in a volume of 5 ml/kg to dosage groups of 20 pregnant randomized rabbits. A supplementary study (Study B) utilized dosages of 0 and 200 mg/kg administered to 35 rabbits per dosage group. The test material was formulated in the vehicle fresh each week.

The test animals were Swiss hare rabbits (Inst. for Biological and Medical Research, Fullinsdorf), with initial body weight range 2440 to 3530 g. The Swiss hare strain was selected on the basis of available background data at the laboratory. Housing was one animal per cage under controlled ambient conditions, with water and diet (Nafag 814 cubes) ad libitum. Body weights were obtained on days 1, 7, 20 and 30. Observation was daily.

1 of 13

After sacrifice on day 30 the uteri were removed and examined for implantations and resorptions. The corpora lutea in each ovary were counted. Fetuses were weighed, examined macroscopically and submitted to crown-rump measurement. A 24-hour viability test was performed in an incubator at 34°C, following which the sacrificed fetuses received gross examination of the viscera. Fetuses for which skeletal examination by x-ray was inadequate were stained (Alizarin Red S) and preserved for subsequent inspection. Fetal heads were fixed in formalin/acetic acid for examination by a modified Julsingha and Bennett method.

Results:

Dose levels in the main study were based on results of a preliminary range-finding study, in which dosages of 100 and 300 mg/kg/day were generally well tolerated with a moderately reduced bodyweight at the top dose. The report states there was no evidence of either embryotoxic or teratogenic effects in the preliminary study.

Contrary to results of the range-finding study the main study produced incidences (at the mid and high dose groups) of malformations such as missing tail, open eye, and spina bifida. The study states that since the same malformations appear frequently in historical controls, a supplementary study using a dose level of 200 mg/kg (and a larger number of treated and control animals) was conducted in order to attempt to reproduce these malformations of "questionable significance." The results from both the main and supplementary study (Study B) were presented in figures and tables separately.

Maternal weight gain was reduced 20% at top dose (300 mg/kg/day, main study) and reduced 24% at 200 mg/kg/day in Study B.

Tabulated data show no treatment-related effects on the reproductive, fetal, or litter parameters (live and dead fetuses, sex ratio, percent resorptions, litter weight, bodyweight of live fetuses, crown-rump length, and 24-hour survival).

Malformations in the main study appear to show a dose-related effect, which the Report states to be an artifact for the reasons as follows:

2

1. The incidence and type of malformations presented by the control group of Study B are similar ("analogous") to those found in the high dose group of the main study.

2. There was no pattern of association (in malformations) between the 200 mg/kg group of Study B and the 300 mg/kg group (top dose) of the main study.

3. The malformations at the top dose (main study) are the same type as often observed in historical controls, and are particularly similar to those observed among controls in Study B.

4. Malformations were not presented by fetuses at either 100 or 300 mg/kg in the range-finding study.

Toxicology Branch accepts the above discussion to support a lack of significant treatment-related terata in the data of the studies.

Tabulation of Wilson screening (examination of fetal heads) reveals similar incidences and variations in soft tissue structure among all groups (including controls) of both the principle and supplementary study. The main study presented no variations which do not occur in historical controls, according to the Report.

Skeletal examination of neonates with the aid of either x-rays or staining showed no treatment-related effects in any group (including controls) from either the principle or the supplementary study.

Conclusion: Minimum Data

Terata not observed up to 300 mg/kg/day (HDT)

Embryotoxicity not observed up to 300 mg/kg/day (HDT).

NOEL, maternal toxicity = 100 mg/kg/day

LEL, maternal toxicity = 200 mg/kg/day (supplementary study; weight gain 24% less than controls).

OPP:HED:TOX:VAN ORMER:sb 2/14/85 X73713 #12-D11

MRID: Not assigned

DVD 5 Feb 85

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Study Type: Six-month Dog Feeding

Accession Number: Not assigned

MRID Number: Not assigned

Sponsor: Hoffman - La Roche and Company Ltd.

Contracting Lab: Hoffman - La Roche

Date: April 30, 1983

Test Material: Fenoxycarb (Ro 13-5223) Technical; Ethyl [2-p-(p-phenoxyphencxy) ethyl] carbamate

Protocol:

The following description of the materials and methods used for this study was abstracted and paraphrased from the original report.

1. Test Material: The test substance was described as Ro 13-5223/no, a whitish powder, lots 16 and 18. The purity was 95% (lot 16) or 98% (lot 18).

2. Species Tested: The test species was Beagle dogs. At the initiation of the study the males were 36.1 ± 1.2 weeks of age and weighed 10.5 ± 1.3 kg. The females were 36.4 ± 1.2 weeks of age and weighed 9.4 ± 0.9 kg. They were housed 3 dogs/cage in a conventional air conditioned room maintained at 18 ± 2°C with a relative humidity of 55 ± 10%. They were fed on a defined maintenance diet, certified for acceptable contaminant levels, (Nafag standard dog cubes, No. 939/930 and tap water ad libitum).

3. Dosing Schedule: Six male and 6 female dogs were used per dose group. The animals were randomly allocated to the different groups. The test material was administered at concentrations of 50, 150, or 500 mg/kg/day for a period of 26 consecutive weeks by means of gelatin capsules. Six dogs of each sex received empty gelatin capsules and served as controls.

4. Parameters examined: a) body weights were measured 5 times during week 1, 3 times during weeks 2-6, and once weekly for the remainder of the study; b) general state of health was checked daily; c) eyes (the cornea, chambers, lens, and retina) were examined prior to the start of the study and during week 26; d) hematology and clinical chemistry analyses were performed prior to the start of the study and at weeks 3, 7, 13, 19, 27, and 29/30; e) urine analyses were performed during weeks 11 and 26 and on specific animals or groups during weeks 13, 17, 27 and 30; f) mortality was recorded continuously as necessary; g) organ weights were measured following sacrifice for: brain, heart, lungs, liver, kidneys, spleen, testicles, prostate, ovaries, uterus, thyroid glands, adrenal gland, and pituitary gland; and h) histogical examinations were conducted on a variety of tissues or organs collected

at sacrifice.

5. Statistics used: The Dunn test was used for comparisons of control and treated groups.

Results:

Body Weights and Body Weights Gains

A summary of mean body weights and percent gains at selected weeks during the study is shown in Table 1. There were no statistically significant differences in the body weight gain of control male dogs and those treated with test material at 50, 150 or 500 mg/kg/day. Similarly, there were no statistically significant differences in the body weight gain of female control dogs treated with 50 or 150 mg/kg/day of the test material. However, the body weight gain of females dogs treated with 500 mg/kg/day of test material were significantly depressed throughout the study. A spot-check analysis of variance (ANOVA) of values at 13 and 26 weeks by MITRE showed a significant difference ($p \leq 0.05$). Based on this, the NOEL for body weight gain in female dogs is 150 mg/kg/day and the LEL is 500 mg/kg/day.

Feed Intake

Feed intake was not measured, therefore feed efficiency could not be calculated.

TABLE 1

SUMMARY OF MEAN BODY WEIGHTS (Kg) AND PERCENT WEIGHT GAINS

| Sex | Dose (mg/kg/day) | MEAN BODY WEIGHTS (KILOGRAMS) AND PERCENT GAINS AT WEEK: 0 | 1 | 2 | 3 | 6 | 13 | 26 |
|---|---|---|---|---|---|---|---|---|
| M | 0 | 10.9 | 11.1 (102)[a] | 11.4 (105) | 11.3 (104) | 11.9 (109) | 11.8 (108) | 12.7 (117) |
| M | 50 | 10.2 | 10.5 (103) | 10.7 (105) | 10.7 (105) | 11.2 (110) | 11.0 (108) | 12.2 (120) |
| M | 150 | 10.9 | 11.0 (101) | 11.1 (102) | 11.0 (101) | 11.3 (104) | 11.1 (102) | 12.3 (113) |
| M | 500 | 10.2 | 9.9 (97) | 10.3 (101) | 10.3 (101) | 10.6 (104) | 10.5 (103) | 11.6 (114) |
| F | 0 | 9.5 | 9.4 (99) | 9.8 (103) | 9.8 (103) | 10.1 (106) | 10.2 (107) | 11.1 (117) |
| F | 50 | 9.6 | 9.6 (100) | 9.6 (100) | 9.7 (101) | 10.0 (104) | 10.2 (106) | 10.9 (114) |
| F | 150 | 9.8 | 9.5 (97) | 9.6 (98) | 9.8 (100) | 9.9 (101) | 10.2 (104) | 10.8 (110) |
| F | 500 | 8.7 | 8.3 (95)* | 8.2 (94)* | 8.4 (97)* | 8.5 (98)* | 8.7 (100)* | 9.1 (105)* |

[a]Numbers in parentheses indicate percent of the body weight gains from week 0.
*Significantly different from controls ($p \leq 0.05$). Weeks 13 and 26 confirmed by MITRE.

Mortality

There were no deaths attributed to treatment. The NOEL for mortality in dogs is 500 mg/kg/day (highest dose tested) based on this study and the LEL was not determined. One accidental death of a male dog in the 150 mg/kg/day group reported during the 19th week was due to a necrotizing infection of the urinary tract and was probably a result of injury from catheterization for urine collection.

Clinical Symptoms

No treatment related symptoms were observed. Those observed were limited to individual cases. Symptoms in the control group were limited to: an eye lesion in a male dog; hematuria in a male dog; unusual body position and slight weight loss in a female dog during week one only; and an ear inflammation in a female dog during week 20.

In the 50 mg/kg/day group, symptoms were limited to a fight-related swollen jaw in a male dog during week 1.

In the 150 mg/kg/day groups, a female dog exhibited slight lacrimation during week 5.

In the 500 mg/kg/day groups, some individual male dogs had slight diarrhea during weeks 1, 11, 12, 13, and 14, while sporadic diarrhea was observed in female dogs during the first week.

Hematology

Essentially all hematology values were within normal

TABLE 2

SUMMARY OF INCIDENCES OF ELEVATED ENZYME LEVELS

| Treatment Group (mg/kg/day) | Animal Number | Week | Enzyme | Level (IU/L) | Group Mean (IU/L) | Control Mean (IU/L) |
|---|---|---|---|---|---|---|
| 0 | 33 M | 3 | SGPT | 276.0 | 44.9 ± 73.3 | 44.9 ± 73.3 |
| | 31 M | 7 | SGPT | 54.0 | 24.43 ± 10.98 | 24.43 ± 10.98 |
| | 31 M | 7 | GLDH | 6.77 | 3.3 ± 1.35 | 3.31 ± 1.35 |
| | 31 M | 13 | SGPT | 54.8 | 25.7 ± 12.4 | 25.7 ± 12.4 |
| 0 | 38 F | 27 | SGPT | 92.9 | 28.5 ± 20.8 | 28.5 ± 20.8 |
| 50 | 23 M | 3 | SGPT | 172.0 | 35.5 ± 43.5 | 44.9 ± 73.3 |
| | 23 M | 3 | GLDH | 10.50 | 3.45 ± 2.36 | 3.63 ± 1.74 |
| 150 | 21 M | 13 | SGPT | 59.7 | 27.9 ± 14.3 | 25.7 ± 12.4 |
| | 21 M | 27 | SGPT | 65.7 | 28.3 ± 16.5 | 28.5 ± 20.8 |
| 150 | 52 F | 19 | SGPT | 53.7 | 26.6 ± 13.3 | 23.9 ± 6.1 |
| 150 | 50 F | 7 | CHE | 6053 | 3381 ± 984 | 3433 ± 60 |
| 500 | 11 M | 7 | SGPT | 53.6 | 28.1± 12.0 | 24.43 ± 10.98 |
| 500 | 60 F | 19 | SGPT | 52.3 | 27.9 ± 10.1 | 23.9 ± 6.1 |

00431



TABLE 3

INCIDENCE OF ABERRANT LEVELS OF PLASMA CONSTITUENTS

| Treatment Group (mg/kg/day) | Animal Number | Week | Constituent | Level (mg/DL) | Group Mean | Control Mean |
|---|---|---|---|---|---|---|
| 0 | 33 M | 3 | Triglyceride | 0.88 | 30.97 ±10.87 | 30.97 ±10.87 |
| 150 | 51 M | 13 | Cholesterol | 48.4 | 140.1 ± 43.5 | 138.4 ± 23.8 |
| 150 | 20 F | 19 | Blood Urea | 52.9 | 35.4 ± 7.3 | 30.8 ± 4.7 |
| 500 | 59 M | 7 | Blood Urea | 70.2 | 41.7 ± 12.1 | 29.3 ± 6.0 |



10

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physiological ranges. The few exceptions, which appeared in both the treated and control groups, were limited to isolated incidences of elevated white blood counts and slightly elevated eosinophil and monocyte counts.

Clinical Chemistry

No treatment related changes were observed. Values of plasma enzymes, with several exceptions, were normal. The exceptions were limited to isolated sporadic cases of elevated SGPT, CHE and GLDH. These are summarized in Table 2. Although occassional statistical differences between controls and the 150 and 500 mg/kg/day were reported for GLDH levels, these were not biologically significant since all group mean values were within normal limits and the value for the treated animals were lower than the values for the control group.

Values for levels of other plasma constituents were within normal physiological ranges except for isolated incidences of decreased triglyceride and cholesterol levels in one animal each and elevated blood urea levels in two other animals (See Table 3). Generally, no dose related changes of any biological significance related to treatment were observed for total protein and electrophoretic components.

Urinalysis

Urinalyses revealed no relevant treatment related differences between treated and control animals.

11

Ophthalmoscopy

No treatment related toxiocological effects to the cornea, chambers, lens, or retina were observed.

Organ Weights And Organ To Body Weight Ratios

Absolute adrenal weights of females in the 500 mg/kg/day group were lower than those of the controls. This was not considered to be of toxiocological importance since the organ weights relative to body weights of the animals in the 500 mg/kg/day group and the controls were not significantly different. The NOEL for organ weight data is 500 mg/kg/day (highest dose tested). LEL was not established.

Gross Necropsy and Histopathology

Macroscopic examination of organs revealed no treatment related toxicologic effects. Similarly, histopathologic examination of tissues revealed no treatment related pathology. The NOEL for pathology is 500 mg/kg/day (highest dose tested). LEL was not established.

Conclusion

Groups of 6 male and 6 female dogs received Ro 13-5223 in the diet at levels of 0, 50, 150, or 500 mg/kg/day for 26 weeks.

Treatment of male dogs with test material at concentrations of 50, 150 and 500 mg/kg/day for 26 weeks resulted in no treatment related adverse effects. No adverse effects were observed in female

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dogs similarly treated with 50 or 150 mg/kg/day dosages. Females dogs treated with test material of 500 mg/kg/day for 26 weeks exhibited a stagnation of body weight gains throughout the study. Based on this the LEL for body weight gain in female dogs is 500 mg/kg/day and the NOEL is 150 mg/kg/day.

Core Classification: Core Minimum.

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5 Feb 85