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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 Reg. #: 2724-314; Safrotin EC Insecticide;
Rat teratology study with propetamphos; miscellaneous data
Caswell #: 706A
Accession #: 254426

TO: William Miller
Product Manager (16)
Registration Division (TS-767)

THRU: Robert P Zendzian
~~Christine P. Chaisson~~, Ph.D.
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)
2/15/85

FROM: William Dykstra, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)
William Dykstra 1/24/85
2/25/85

1. Chemical: Propetamphos; Safrotin EC Insecticide; Caswell Number: 706A.

2. Test material:

| | | |
|---|---|---|
| Name | : | Propetamphos, techn. grade |
| Batch | : | P.10/82 |
| Concentration | : | purity about 89% |
| Manufacturer | : | SANDOZ LTD., CH-4002 Basle |
| Storage | : | room temperature |
| Solubility | : | 110 ± 5 ppm (23°) water |
| Description | : | brownish colored oily liquid |
| Density | : | $d^{20} = 1.13$ |
| Storage | : | room temperature |
| Expiration date | : | Oct. 1985 |

3. Study/Action type: Pilot teratology and main study teratology in rats;

4. Study Indentification: Teratogenicity study in rats with propetamphos; pilot and full studies were conducted by the Agrotoxicology Dept. of Sandoz Ltd., in Basle, Switzerland. Sandoz report 6058/84: May 30, 1984; Dr. C. Klotzsche, MD.; Head, Agrotoxicology.

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5. Reviewed By:

William Dykstra, Ph.D. WHD 1/24/85
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6. Approved by:

Robert P Zendzian
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7. Conclusions

a. Propetamphos was negative for terata and fetotoxicity at 6.0 mg/kg/day (HDT) when given by gavage during days 6-15 of gestation. The maternal NOEL is 1.5 mg/kg/day (LDT). The maternal LEL of 3.0 mg/kg/day produced toxic signs of cholinergic poisoning. At 6.0 mg/kg/day, toxic signs and decreased body weight gain were observed.

b. The pilot study is acceptable as supplementary data since it was conducted to establish dosages for the main study.

c. The main study is acceptable as core-minimum data. The teratogenic potential of propetamphos in this study was adequately evaluated and was negative.

8. Recommendations:

a. The submitted studies are acceptable. No additional data are needed. The teratogenic potential of propetamphos is in the rat has been adequately evaluated.

9. Background:

The previously submitted rat teratology study with propetamphos was part of a reproduction study. The high-dose of 20 ppm for reproduction did not produce any maternal toxicity from which to evaluate the teratogenic potential.

The reproduction study was acceptable as core-minimum data but the teratology segment was classified as supplmentary data since no maternal toxicity, other than cholinesterase depression, was produced.

The present study in rats has been submitted to further address the teratogenic potential of propetamphos. A rabbit teratology study with propetamphos was previously submitted and was acceptable.

10. Discussion of Individual Tests or Studies: The pilot teratology study was performed to choose dosages for main teratology study.

11. Materials and methods (Protocls): Details of the materials and methods are avilable in Appendix A (Confidential Business Infomation).

12. Reported Results (by study author).

a. Pilot Study

Analytical evaluation of dosing solutions of the test material at pre-test, start of the study and end of the study showed good correlation of expected and acutal concentrations for propetamphos.

In the pilot study, body weight gain in the treated groups was decreased in comparison to controls.

Decreased food consumption did not correlate with decreased weight gain.

There were no toxic signs or mortality in controls and low-dose animals. At 5 mg/kg, "five of ten animals showed weakness and were flacid during the treatment period." At 10 mg/kg, "severe signs of poisoning occurred".

One animal died on day four of treatment.

At 20 mg/kg, two animals died on day 7 and 8. "Because of these severe symptoms the treatment was dicontinued after 9 days".

b. Main Study

In the main study, toxic signs occurred in 24/25 animals in the high-dose group and 15 of 23 in the mid-dose group. The toxic signs consisted of drowsiness, exophthalmus and muscle tremors.

No mortallity ocurred in the study. "Decreased body weight occurred in all groups and was 10% decreased in the high-dose group". No compound-related findings occurred in maternal animals at gross necropsy.

There were no effects on maternal fertility or gestation indices, numbers of fetuses or litters, early resorption, fetal sex ratio, live fetuses or fetal weight. There were no dead term fetuses. At the low,- mid- and high-doses, fetal resorptions occurred as 1, 3, 2, respectively in comparison to 1 in the controls.

No major or minor anomolies were found at visceral or external examination.

"One delayed ossification of the skull occurred in one fetus of the control group (0.36%), six fetuses in the low-dose (1.9%) five fetuses of the mid-dose (1.9%), and five fetuses of the high-dose (1.8%). In historical control, delayed ossification was observed in 2.16% fetuses with the highest incidence of 7.5%."

A minor anomaly in the sternebrae was seen in one control fetus and two middose fetuses, but did not occur in fetuses of the control and high-dose groups.

A major skeletal anomaly was seen in one control fetus and one mid-dose fetus, but none were found in the low-dose or high-dose groups.

"In the control group, the major anomaly occurred as multiple defects of the whole skeletion. The whole sternum was bipartite, the fore-limbs shortened, and irregulary shaped. Thoracic vertebal bodies number 10-12 were dumbbell shaped, one additional digit unilateralis and one additional toe bilateralis. Also a hydrocephalis internus was observed."

"In the mid-dose, one fetus had an additional ossified arch in the lumbar vertebae near number 1."

13. Study Author's Conclusions/Quality Assurance Measures.

Quality Assurance and G. L. P. of the study were carried out by Dr. A. Riggenbach on 1/23/84, 2/10/84, 2/13/84, 2/21/84, 2/28/84 and 3/7/84 and findings were reported to the study director.

The study author concluded that the test material produced "severe toxic signs and mortality in the pilot study at 10 and 20 mg/kg. These dosages were considered too toxic for the main study. Less severe toxic signs were observed at 5 mg/kg. Although the 2.5 mg/kg level showed no toxic signs, all treated groups showed weight gains markedly less than controls during the 10 day dosing period. The body weight difference between treated and control animals was reduced in the week following the end of the dosing period," end of quote.

In the main study, the study author concluded that "Treatment related maternal signs, typical of organophosphate intoxication, were exhibited by majority of mid and high dose females. Predominate signs were depression, tremor and exophthalmus. During the 10 day dosing interval, the high dose mean body weight was less than controls, suggesting a compound related effect. After treatment ended, the high dose weight gain exceeded that of controls, indicating a tranisent effect from which recovery occurred. No treatment related gross pathology was observed.

There were no effects on maternal fertility or gestation indices, numbers of conceptuses or litters, early resorption, fetal sex ratio, live term fetuses or fetal weight. There were no dead term fetuses. Slightly increased fetal resorption incidences at mid and high dose levels were not statistically significant.

"No major or minor anomalies were found upon external and visceral examination. Retarded crainal ossification, higher in treated groups than in controls, showed no dose relationship and was in all cases below the level expected based on historical control data. Skeletal examination revealed no dose related retardation. Minor and major anomalies were limited to control and mid dose groups, were few in number and showed no pattern". end of quote.

"In this test, propetamphos produced maternal toxicity at 6 mg/kg/day; 1.5 mg/kg was a No Effect Level. There were no sighs of embroytoxicity or teratogenic effects." end of quote.

14. Reviewer's Discussion and Interpretation of Study Results:

No individual animal data were provided for results in the pilot teratology study. The mean values of 10 animals showed dose-related decreases in body weight at days 6, 15, and 21 of the study. Food consumption was unaffected by treatment.

In the main study, the following number of females were mated; 28, 26, 25 and 25 in the control, 1.5, 3.0 and 6.0 mg/kg dosage levels, respectively. The number of pregnant dams which produced litters were 25, 24, 23 and 24 in these same groups. No dams died or aborted in the study. The precent of body weight gains were 13.8, 13.5, 13.2, and 12.5 for these same groups. The percent decreased body weight gain in the 6.0 mg/kg group (high-dose) is compound-related. The percent decrease is less than the range (12.9-16.4%) of body weight gain in the historical controls during the period of 1981-82.

Toxic signs of poisoning such as drowsiness, muscle tremors and exophthalmus occurred in 15 of 25 mid-dose dams, and 24 of 25 high-dose dams during the study. No low dose dams were affected in this manner. These toxic signs are considered compound-related.

No necropsy findings considered to be related to treatment were observed in any groups.

Food consumption of treated dams during the study showed no effects which were considered treatment-related.

Pregnancy data for litters showed no effects in mean values of corpora lutea, implantations, litter size, pre-implantation loss and post-implantation loss. All mean values were within the range of historical control data for these parameters.

Fetal data showed no effects in body weight, placenta weight and sex ratio although the value for sex ratio (.80) in the high-dose group was slightly below the range of historical controls (0.82-1.18). The sex ratio value of the high-dose group was not dose-related and was not considered treatment-related.

No external anomalies were present in any of the fetuses.

Visceral examination showed unilateral or bilateral enlarged renal pelvis in 2, 4, 3, and 3 fetuses of the control, low-, mid, and high-dose groups, respectively.

These anomalies were not considered compound-related.

Delayed ossification of fetal skeletal structures occurred in all groups and had no relationship to dose.

One fetus in the control group and one fetus in the mid-dose group displayed terata. The low and high-dose group showed no major anomalies.

The control fetus with terata showed multiple defects in the whole skeleton and had hydrocephalus internus.

The mid-dose fetus with terata had an additional ossified arch of the lumbar vertebrae.

The fetal findings were not considered treatment-related.