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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

MAR 23 1989

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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Oxaryl: Review of a Teratology Study in the Rats

Caswell No. 561A
EPA ID No. 352-400

HED Project No. 9-560
Record No. 236693

TO: D. Ewards / R. Kumar, PM (12)
Registration Division (H7505C)

FROM: Whang Phang, Ph.D. 3/15/89
Pharmacologist
HFAS / Toxicology Branch II / HED (H7509C)

THROUGH: K. Clark Swentzel, Action Section Head
Section II
and
Marcia van Gemert, Ph.D.
Acting Branch Chief
HFAS / Toxicology Branch II / HED (H7509C)

In response to the data requirements identified in the Registration Standard of Oxaryl, the registrant submitted a teratology study in the rats. This study has been evaluated, and the Data Evaluation Report is attached. The conclusion is as follows:

Groups of pregnant rats (25/dose) received Oxaryl by gavage at doses of 0.2, 0.5, 0.8, and 1.5 mg/kg from gestation days 7 to 16. On day 22, the fetuses were retrived, and the dams were sacrificed. Under the conditions of the study, maternal toxicity was seen in 0.8 mg/kg and above as indicated by decreases in maternal body weight and food consumption and increased incidence of clinical signs which associated with cholinesterase inhibition. A decrease in fetal body weight was seen in 0.5 mg/kg group and above. No increases in the incidences of structural malformations or variations were seen in the treated groups relative to the controls. Based upon these findings, the test agent was not shown to be teratogenic. The LEL for maternal toxicity was 0.8 mg/kg; NOEL, 0.5 mg/kg. The LEL for developmental toxicity was 0.5 mg/kg; NOEL 0.2 mg/kg.

This study is classified as minimum.

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Reviewer: Whang Phang, Ph.D. 3/15/89
HFAS / Tox. Branch / HED (H7509C)
Secondary Reviewer: K. Clark Swentzel, Toxicologist
HFAS / Tox. Branch / HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Teratology (Rat)

CHEMICAL: Oxamyl: IN D1410-196; CAS No. 23135-22-0

TOX. CHEMICAL No.: 561 HED Project No.: 9-560

EPA MRID No.: 408592-01 EPA ID No.: 352-400

SPONSOR: E.I. du Pont de Nemours & Co., Inc.

TESTING LABORATORY: E.I. du Pont de Nemours & Co., Inc.
Haskell Laboratory for Toxicology and
Industrial Medicine
Newark, Delaware

CITATION: Rickard, L. B. (1988) Teratogenicity Study of IN D1410-196 in the Rats. Haskell Laboratory for Toxicology & Industrial Medicine: Medical Research No. 8424-001; Lab. Project No. 473-88. Oct 3, 1988.

Quality Assurance: A quality assurance statement was signed and included in the report.

CONCLUSION: Groups of pregnant rats (25/dose) received Oxamyl by gavage at doses of 0.2, 0.5, 0.8, and 1.5 mg/kg from gestation days 7 to 16. On day 22, the fetuses were removed, and the dams were sacrificed. Under the conditions of the study, maternal toxicity was seen in 0.8 mg/kg and above as indicated by decreases in maternal body weight and food consumption and increased incidence of clinical signs which associated with cholinesterase inhibition. A decrease in fetal body weight was seen in 0.5 mg/kg group and above. No increases in the incidences of structural malformations or variations were seen in the treated groups relative to the controls. Based upon these findings, the test agent was not shown to be teratogenic. The LEL for maternal toxicity was 0.8 mg/kg; NOEL, 0.5 mg/kg. The LEL for developmental toxicity was 0.5 mg/kg; NOEL 0.2 mg/kg.

This study is classified as minimum.

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METHODS AND MATERIALS

Test material: Ethanimidothioic acid, 2-(dimethylamino)-N-[[(methylamino)carbonyl]oxy]-2-oxo-methylester IN D1410-196 (toxicological sample); Oxamyl 97.2% pure; white crystalline solid

Test animals: 63 days old female Crl:CD BR nulliparous rats with mean body weight of 197 ± 0.81 gm and 84 days old male rats with mean body weight of 349.3 ± 1.41 gm were obtained from Charles River

Experimental design: Females were cohabitated with males (1:1) until mating was confirmed by the presence of a vagina plug. The females were then randomly assigned to the following dose groups:

Group	Dose* (mg/kg)	Mated Females
1	0.0**	25
2	0.20	25
3	0.50	25
4	0.80	25
5	1.50	25

* Administered by gavage, on Days 7-16 of gestation, at a dose volume of 10 ml/kg body weight.
* distilled water as the vehicle

The doses used in this study were based on the results of a pilot study in which groups of 7 pregnant rats/dose were administered (by gavage) Oxamyl at 0, 1.0, 1.5, 2.0, or 2.5 mg/kg/day. The dose volume was 10 ml/kg. The results indicated that dose-related adverse effects on body weight changes and food consumption were found. Also, a dose-related decrease in fetal weights was also seen. However, no adverse effects on reproductive parameters were reported.

Dosing solutions were prepared daily with distilled water based on a dosage volume of 10 ml/kg body weight. The doses were calculated based upon the current body weights. Duplicate samples of each test solution were taken for chemical analyses. The pregnant female rats were administered Oxamyl by gavage from gestation days 7 to 16.

The test animals were weighed on gestation days 1, 7 to 17, and 22. Feed was weighed on gestation days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 22. The animals were observed daily.

On day 22 of gestation, females were sacrificed and examined for gross pathologic changes. The liver and gravid uterus were removed and weighed. Each uterus was examined for resorptions and live and dead fetuses. Early resorptions were detected with ammonium

sulfide. Corpora lutea were counted and recorded.

Live fetuses were weighed, sexed, and examined for external alterations. "The maximum stunted weight (MSW) was calculated by substracting the lightest weight from the total weight, dividing by the remaining number of fetuses and multiplying by 0.666. A fetuses weighing the same or less than the MSW was considered stunted; its weight was omitted when the mean litter weight was calculated". For visceral examination, the first fetus and thereafter every other fetuses in a litter were examined. The head was fixed in Bouin's fluid and examined.

For fetal skeletal examinaiton, the remaining fetuses were sacrificed with pentobarbital, fixed in 70% ethanol, eviscerated, macerated in 1% aqueous KOH, and stained with alizarin red S.

The details of the statistical analyses are presented in the Attachment.

RESULTS:

The analyses of the test solutions indicated that samples which were held for 5 hrs at room temperature yielded values between 94 and 105% of the nominal concentrations, and fresh solutions showed concentrations between 92 and 116% of the nominal concentrations.

Maternal Findings

1). Mortality: No death was reported in all dams on the test.

2). Observation: The data on clinical observations were excerpted from the report and presented in Table 1. During the treatment period (gestation days 7-16), increased number of dams in 1.5 mg/kg group showed signs of diarrhea, eye discharge, salivation, tremors, and wet legs, perinea and underbodies. These increases were statistically significant. The increased incidence of tremors was also seen in 0.8 mg/kg dams, and it was dose-related.

3). Body weight change: During the treatment period (gestation days 7-17), the body weight gain was decreased in dams which received Oxamyl at doses of 0.5 mg/kg or more (Table 2). This decrease showed a dose-related response, and that in 0.8 and 1.5 dams was also statistically significant ($p \leq 0.05$). However, the body weight decrease in 0.5 mg/kg dams was equivocal.

4). Food consumption: The data on food consumption were excerpted from the report and presented in Table 3. Like the body weight changes, the food consumption in the dams of 0.5 mg/kg or greater dose groups showed a dose-related decrease during the treatment phase. In addition, the decrease in food consumption seen in 0.8 and 1.5 mg/kg dams was statistically significant (Table 3).

5). Postmortem observations: Gross examination did not reveal any increase in the compound-related effects in all treated dams relative to the control.

The absolute liver weight data did not indicate any marked difference between treated and control groups although the ratios of liver weight to body weight showed a significant trend (Table 4).

6). Reproductive effects: The data of reproductive effects were excerpted from the report and present in Table 5. The reproductive parameters such as pregnancy rate, incidence of total resorptions, incidence of early deliveries, death rate, sex ratio, number of corpora lutea, or number of stunted fetuses did not indicate any difference between treated and control groups (Table 5).

Fetal Findings:

1). Body weight: There was a significant decrease in mean fetal weights of males and females or combined weights of both sexes at or above 0.5 mg/kg dose groups (Table 5).

2). Malformations: The incidence of fetal malformation is excerpted from the report and presented in Table 6. Although isolated incidence of hydrocephaly, gastroschisis, and fused ribs and vertebra were seen, no marked or dose-related increase in external, visceral, head, and skeletal malformation was seen in treated groups relative to the controls.

3). Variations: There were no dose-related or statistically significant increases in the incidences of fetal variations in the treated groups relative to those of the controls (Table 7).

DISCUSSION

Groups of pregnant rats (25/dose) received Oxaryl by gavage at doses of 0.2, 0.5, 0.8, and 1.5 mg/kg from gestation days 7 to 16. On day 22, the fetuses were removed, and the dams were sacrificed. At doses of 0.8 mg/kg and above, maternal toxicity was indicated by significant dose-related decreases in body weight gains and food consumption. The adjusted maternal body weight which excluded the products of the conception was also decreased in dams at dose levels of 0.5 mg/kg or above (Table 4). However, the decrease was not statistically significant, and that in 0.5 mg/kg was equivocal.

In addition, there were increases in the incidences of tremor, salivation, diarrhea, eye discharge, and wet fur in various areas of the body in 1.5 mg/kg dams. An increase in the incidence of

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tremor was also seen in 0.8 mg/kg animals. The clinical signs seen in 0.8 and 1.5 mg/kg dams were related to cholinesterase inhibition which was the mode of action for Oxamyl. Based upon the above results, the LEL for maternal toxicity is 0.8 mg/kg; NOEL, 0.5 mg/kg.

The reproductive parameters such as pregnancy rate, resorption, early delivery, sex ratio, corpora lutea, and the number of stunted fetuses were not affected by the administration of Oxamyl.

Statistically significant decrease in fetal weight was seen in the males and females of 0.5, 0.8, and 1.5 mg/kg groups. Since Oxamyl also caused decreases in the maternal food consumption and body weight changes at doses of 0.5, 0.8, and 1.5 mg/kg, the decrease in fetal body weight could be influenced by the maternal effect. No compound-related increases in the incidence of structural malformations or variations were seen in the fetuses of the treated groups relative to the controls. Based upon these findings, LEL for the developmental toxicity was 0.5 mg/kg; NOEL, 0.2 mg/kg. However, the test agent was not shown to be teratogenic.

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OXAMYL

Page _____ is not included in this copy.

Pages 7 through 20 are not included in this copy.

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