UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

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

FROM: Roland A. Gessert, D.V.M. Roland A. Gessert 8/17/84
Review Section I, Toxicology Branch (TS-769)

THROUGH: William Burnam, Chief
Toxicology Branch (TS-769)

DP# 8-2-R,
5/21/84

SUBJECT: Dimethoate Data Call-In. Rat Teratology Study. Submitted for Dimethoate Task Force. Acc. No. 253248. Caswell # 358.

Attached are Data Evaluation Reports on teratology studies conducted for the Dimethoate Task Force to partially satisfy the data call in for dimethoate. The preliminary study was conducted as a dose-finding study. The results of the preliminary study in which doses of 0, 3, 10, and 30 mg/kg/day were administered were used as a basis for the main rat teratology study.

Because the preliminary study used only six rats for each dose level, the data for the preliminary study are Core Supplementary.

In the main study, the NOEL for parenteral effects was 6 mg/kg/day, based on physical signs such as body tremors at 18 mg/kg/day. The NOEL for fetotoxicity and teratogenicity is 18 mg/kg/day (HDT). In this rat study dimethoate was not a teratogen. The data for the complete study meet Core Minimum requirements.

This study satisfies the data requirements for a rat teratology study. A rabbit teratology study is also required.

DATA EVALUATION REPORT

PRELIMINARY STUDY OF EFFECT OF DIMETHOATE ON PREGNANCY OF THE RAT. By James A. Edwards, Nicholas M. Leeming, and Ruth Clark. HRC Report No. DTF 1/84244. Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. April 13, 1984. Study conducted for Dimethoate Task Force participants: BASF Aktiengesellschaft, Celamerck GmbH Co. Kg, A/S Cheminova, Farmoplant S.P.A., I.PI.CI. S.P.A., and American Cyanamid Co.

This preliminary study was conducted to provide guidance in dose selection for a subsequent rat embryotoxicity study.

MATERIAL USED: Technical grade 97.3% pure dimethoate. Batch 611A, manufactured by I.PI.CI. S.P.A.; Novate Milanese, Italy.

ANIMALS: Sexually mature, time mated specific pathogen free rats (CrL:COBS CD (SD) BR strain) from Charles River U.K. Ltd., Margate, Kent, England.

Day of mating determined by vaginal plug or sperm in vaginal smear was considered day 0 of pregnancy.

Bred rats were delivered to HRC laboratory on Day 1, weighed, identified by ear marks, and divided into 4 groups.

Animal room was maintained at 22± 2°C and 50± 15% relative humidity with 13 air changes/hour. Room artificially lighted between 8 AM and 8 PM.

Animals were housed 3 per cage.

The rats were provided water and Spratts Laboratory Diet No. 1 ad libitum. Each batch of diet was analysed for nutrients and contaminants. The diet was analysed for vitamins and minerals at 6-month intervals. The water was analysed at 6-month intervals for nitrates, nitrites, minerals, and pesticide chemicals.

Dosing of dimethoate in 1% methylcellulose vehicle was by oral gavage, beginning on day 6 of pregnancy and continuing daily to and including day 15 of pregnancy. Dimethoate doses were 0, 3, 10, and 30 mg/kg/day. There were 6 rats for each dose level.

LIVE PARENT ANIMAL OBSERVATIONS:

1. All rats were handled and observed daily. Obvious changes or reactions were recorded.

2. Bodyweights: on days 1, 3, 6, 10, 14, 17, and 20 of pregnancy.

3. Food consumption: recorded for each cage on each weigh day.

4. Water consumption: measured daily for each cage of rats from day 9 of pregnancy.

NECROPSY OBSERVATIONS OF PARENTS (killed on day 20 of pregnancy by CO_2):

1. Congenital abnormalities and changes in maternal organs.
2. Ovaries and uteri examined for:

    a) number of corpora lutea
    b) number & distribution of live young
    c) number & distribution of embryonic (early & late) fetal deaths
    d) individual fetal weights (and litter weights)
    e) gross fetal abnormalities
    f) uterine horns without visible implantations were immersed in 10% ammonium sulfide to reveal evidence of early embryonic deaths.
    g) sex of fetuses following preservation.
    h) detailed visceral & skeletal examinations were not done in this preliminary study.

RESULTS:

APPENDIX 1. PRINCIPAL SIGNS:

At all dose levels (except controls), fecal pellets were abnormal in size and shape, the incidence increasing with dose. At the 3 mg/kg/day dose level, this was the only sign seen.

At 10 mg/kg/day, some rats showed body tremors and hyperpnea.

At the high dose (30 mg/kg/day), all the rats showed body tremors, hypersensitivity to sound and touch stimuli, cold extremeties, and hyperpnea. Some of the rats at this level also showed a hunched posture, unsteady abnormal gait, lethargy, and pilo-erection.

APPENDIX 2. CAGE FOOD CONSUMPTION: Decreased food consumption was noted in the high dose group only.

APPENDIX 3. WATER CONSUMPTION: Water consumption was not consistently related to treatment level. Water consumption of the low and mid dose rats was sligtly less than controls while consumption of high dose rats was greater than controls.

APPENDIX 4. MATERNAL BODY WEIGHTS (with live young): Body weight gains were markedly lower at termination in the high dose rats and were slightly lower at the mid dose level. No body weight effect was seen at the low dose level.

APPENDIX 5.

MEAN FETAL WEIGHT may have been slightly lower than controls at the high dose. However, mean fetal weights of the low and mid doses were slightly higher than controls.

Other litter parameters appeared to be unaffected by treatment. Gross necropsy showed no fetal abnormalities or malformations.

The NOEL for parental effects was 3 mg/kg/day. (Body tremors and hyperpnea were observed at 10 mg/kg/day.)

The NOEL for fetal effects was 10 mg/kg/day. Fetal weight was slightly lower than controls at 30 mg/kg/day.

The NOEL for teratogenic effects was 30 mg/kg/day (HDT).

Because this was merely a dose range-finding study involving only 6 rats per dose group, the data are classified as Core Supplemental.

DATA EVALUATION REPORT

EFFECT OF DIMETHOATE ON PREGNANCY OF THE RAT. By James A. Edwards, Nicholas M. Leeming, and Ruth Clark. HRC Report No. DTF 3/84245. Huntingdon Research Centre; Huntingdon, Cambridgeshire, England. April 13, 1984. Study conducted for Dimethoate Task Force participants: BASF Aktiengesellschaft, Celamerck GmbH Co.Kg, A/S Cheminova, Farmoplant S.P.A., I.PI.CI. S.P.A., and American Cyanamid Co.

TEST CHEMICAL: Dimethoate. Technical grade of 97.3% purity. Batch 611A, manufactured by I.PI.CI. S.P.A.; Novate Milanese, Italy.

DOSES: 0, 3, 6, and 18 mg/kg/day from day 6 through day 15 of pregnancy by oral gavage in 1% methylcellulose vehicle. Dosing suspensions were prepared freshly each day.

ANIMALS: Sexually mature, time mated specific pathogen free rats (CrL: COBS CD (SD) BR strain) from Charles River U.K. Ltd.; Margate, Kent, England. Day of mating, determined by vaginal plug or sperm in vaginal smear, was considered day 0 of pregnancy.

Delivered to laboratory on day 1, temporarily identified by tail mark, weighed, divided into 4 groups of 25 rats each, given ear mark identification, and placed into cages (5 rats per cage).

Animal room maintained at 22± 2° C and 50± 15% relative humidity with 13 air changes/hour. Room artificially lighted between 8 AM and 8 PM.

The rats were provided with water and Spratt's Laboratory Diet No. 1 ad libitum. Each batch of diet was analysed for nutrients and chemical and microbial contaminants. The water was analysed at 6 month intervals for nitrates, nitrites, minerals, and pesticide chemicals.

DOSING: of dimethoate in 1% methylcellulose vehicle was by oral gavage, beginning on day 6 of pregnancy and continuing daily to and including day 15 of pregnancy. Dimethoate doses were 0, 3, 6, and 18 mg/kg/day. These doses were based on a preliminary dose range-finding study conducted at doses of 3, 10, and 30 mg/kg/day. (See preceding report.) Dosage volumes were adjusted for individual animals according to body weight on days 6, 10, and 14 of pregnancy.

LIVE PARENT OBSERVATIONS:

1. All rats were handled and observed daily. Obvious changes or reactions were recorded.

2. Bodyweights: were taken on days 1, 3, 6, 10, 14, 17, and 20 of pregnancy.

3. Food consumption: recorded for each cage on each weigh day.

NECROPSY: on pregnancy day 20. Examined for gross congenital abnormalities and changes in maternal organs. Also, ovaries and uteri were examined for:

a) number of corpora lutea
b) number and distribution of live young
c) number and distribution of embryonic/fetal deaths
d) individual fetal weights (and litter weights)
e) gross fetal abnormalities

FETAL EXAMINATIONS:

Half the pups in each litter were preserved in Bouin's solution for free-hand sectioning (Wilson technique) for visceral abnormalities. The remaining pups were preserved in methyl alcohol for subsequent macroscopic examination and evisceration, clearing, and alizarin staining (modified Dawson technique) for skeletal examination.

Following preservation, sex of fetuses was determined by internal examination. Anogenital distance was also recorded.

RESULTS:

PARENT ANIMALS: There was no mortality in the study.

At the high dose (18 mg/kg/day), 13/25 rats showed immediate post-dosing salivation, as compared with 5/25 and 6/25 for the low and mid dose rats. 12/25 of the high dose rats also showed brown facial staining.

All the high dose rats and all the mid dose rats (6 mg/kg/day) voided small rounded fecal pellets.

All the high dose rats also demonstrated hypersensitivity to sound and touch stimuli, body tremors, and unsteady gait. These signs were not seen at the low and mid dose levels.

FOOD CONSUMPTION: At the high dose level, mean food consumption was lower than controls and low and mid dose groups. Food consumption in the low and mid dose groups was not affected by treatment.

BODY WEIGHT: Body weight gains during treatment and gestation were noticeably less than controls in the high dose treatment group; they were similar to or slightly greater than controls in the low and mid dose groups.

PREGNANCY RATE was 100% for the controls and 88%, 92%, and 92% for the low, mid, and high dose groups, respectively.

LITTER DATA:

There were no differences between controls and treatment groups in mean live young, early or late embryonic deaths, corpora lutea, pre- or post- implantion loss, litter weights, or fetal weights.

There was no increase in visceral anomalies in fetuses from treated groups that could be related to treatment.

There appeared to be a slightly increased incidence over controls of skeletal anomalies in fetuses from treated groups; particularly in reduced ossification at various sites in the high dose group. For skeletal anomalies, the laboratory's summaries show a mean fetal incidence of 8.3% in controls, and 13.1%, 12.2%, and 17.1% in the low, mid, and high dose groups respectively. The group mean control incidences of skeletal anomalies for the six studies immediately preceding this study were 13.4%, 21.3%, 12.5%, 15.3%, 19.4%, and 15.1%. The laboratory considers the 8.3% control incidence in this study to be unusually low, and does not consider the incidence of skeletal anomalies to be related to treatment.

The NOEL for maternal toxicity is 6 mg/kg/day, based on increased reaction to sound and touch stimuli, body tremors, and unsteady gait in the high dose rats (18 mg/kg/day). Rats receiving 18 mg/kg/day also had lower food consumption and lower body weight gains compared with controls.

The NOEL for fetotoxicity and teratogenicity in this study is 18 mg/kg/day (HDT).

This reviewer's conclusion from this study is that dimethoate is not a teratogen in the rat at dose levels up to and including 18 mg/kg/day when given by gavage on days 6 through 15 of gestation.

The data meet the Core Minimum requirements.