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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

TO: Portia Jenkins, PM Team # 12
Insecticide/Rodenticide Branch
Registration Division TS-767C

THRU: R. Bruce Jaeger, Section Head
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

THRU: Dr. T. M. Farber, Chief
Toxicology Branch
Hazard Evaluation Division TS-769C

FROM: D. Ritter, Adjuvants Toxicologist
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

Subject: 3125-108 - Azinphos-Methyl Registration Standard: Submission of Rat Teratology Study.

Caswell #: 374.

TOX Project #: 8-0438.

Sponsor: Mobay Corporation, Kansas City, MO.

Mobay is submitting a rat teratology study in response to the Azinphos-Methyl (Guthion) Registration Standard issued in December, 1986.

Title: "A Teratology Study with azinphos-Methyl (GUTHION Technical) in the Rat.", Report # 96987, R. L. Kowalski, et al.
MRID40464801.

The study is rated CORE Minimum Data because:

1. The identity of the vehicle used to administer the test material, EL-719, is needed.

The DER is attached.

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Reviewer: D. Ritter, Toxicologist 11/16/88 Caswell #: 374
Rev. Sec. # I/Toxicology Branch
Secondary Reviewer: R. Bruce Jaeger, Section Head
Rev. Sec. # I/Toxicology Branch

DATA EVALUATION RECORD

Study: Developmental Toxicity, Rat.

MRID: 40464801.

Performing Laboratory: Toxicology Department, Miles Inc., Elkhart, IN.

Author(s): R. L. Kowalski, G. R. Clemens, J. J. Bare and R. E. Hartnagel, Jr.

Study ID Number: 94987.

Date of Study: 12/22/87.

Title: A Teratology Study with Azinphos-Methyl (GUTHION Technical) in the Rat.

CORE Rating: Minimum Data: The identity of the vehicle, EL-719, used to administer the test material is needed.

QA Statement: Statisfactory.

CONCLUSIONS: The Maternal NOEL for reproductive effects is 2.0 mg/kg bw/day, the highest level tested.

The Fetotoxic/Teratogenic NOEL is 2.0 mg/kg bw/day, the highest level tested, based on the lack of decreased fetal weights, intrauterine mortality, lack of early or late resorptions and no adverse effects on fetal development.

The ChE NOEL is 0.5 mg/kg bw/day based on brain ChE inhibition in the Group II dams sacrificed at 20 days. Brain ChE was not inhibited in the fetuses of dams sacrificed at 20 days of gestation at any level tested, and the fetal Brain ChE NOEL is therefore 2.0 mg/kg bw/day.

METHODS:

Test Article Administration -

The dose levels were selected based on a range-finding assay performed earlier. In this study the administration by gavage to mated rats of levels of 3.0 mg/kg bw/day and greater produced overt signs of toxicity, including fasciculation, weight loss and death, with tremors and salivation also occuring at doses of 4.5, 6.0 and 7.0 mg/kg bw/day. No fetotoxic or developmental effects were reported, however. The doses selected for this study were calculated to produce slight maternal toxicity but no developmental effects.

Azinphos-methyl (87.7 % AI) was mixed in a 6% solution of Emulphor 719 (probably an ethoxylated fatty acid of vegetable origin). The concentrations were 0, 0.005%, 0.01 %, and 0.02 %, equivalent to 0.5, 1.0 and 2.0 mg/kg bw/day. The mixture was administered by oral gavage once daily on days six through fifteen of gestation.

Test Animals -

Male and female Charles River Crl:CDBR rats were mated, two females per male, and the day of sperm in the vaginal smear was considered to be day 0 of gestation. There were 33 mated dams per dose group. Dams were then caged separately and given feed and water ad libitum. Five dams at each treatment level were assigned to "Group I", which would be sacrificed after 16 days of gestation; the remainder to "Group II", which would be sacrificed after 20 days of gestation.

Husbandry - Standard GLP.

Feed and Water - available ad libitum.

Body Weights - on days 0, 6, 8, 10, 12, 15 and 20 of gestation.

Cageside Observations - made daily for morbidity and toxic signs.

Feed consumption was recorded on days 0, 5, 6, 11, 15 and 19 of gestation.

Post-Mortem Examinations -

Cholinesterase Determination -

On gestation day 16, following the final dosing, all Group I dams were weighed and then killed by CO_2 asphyxiation. The maternal brain, plasma and

red cell cholinesterase (ChE) activities were measured on brains frozen over dry ice, and on blood taken by cardiac puncture. ChE inhibition was measured using Ellman's reagent with dithiobisnitrobenzoic acid.

On day 20 of gestation, 20 Group II dams (19 for the low dose group) were killed and their body weights, feed consumption, maternal plasma, brain and erythrocyte ChE activity were determined as for the Group I dams.

Brains were taken whole, examined grossly and frozen over dry ice.

One randomly selected Group II fetus from the first 20 litters per dose group was used for brain ChE analysis.

Effects on Gestation -

In both Groups I and II, the pregnancy rates, number of dams with live fetuses, corpora lutea, implantations, resorptions, litter size, fetal weights, fetal sexes, viability, pre and post-implantation losses, clinical signs and gross post-mortem changes were determined. Fetuses were weighed and examined for gross external, visceral and skeletal effects, and the fetal brain ChE activity were determined for the Group II dams.

1/2 of the fetuses from each dam were killed by intracranial barbiturate injection and the visceral and external architecture was examined grossly. These animals were then placed in Bouin's solution and sectioned using a free hand razor through the eyes and cranium. The other half were cleared and stained using the KOH alizarin Red S method for skeletal examination.

Statistical Evaluation -

Student's "t" test, Dunnett's test, Kruskall-Wallace and Dunn's statistics were used to evaluate the data. In addition, this reviewer evaluated the Cholinesterase data independently using Student's "t" test to construct TABLE V.

RESULTS:

Maternal Toxicity -

General Effects -

There were no adverse effects reported for signs of toxicity, maternal body weights (see Table I) or feed consumption (see Table II).

Gestational Effects - (See TABLE III)

The fertility index (no. gravid/no. mated) was reduced in the low-dose group but not in the mid- or high-dose group.

There was no mortality.

No dams suffered abortion.

The numbers of corpora lutea were not affected by treatment.

Numbers of implantation sites and numbers of fetuses were reduced in the low dose group but not in the mid- or high-dose group when compared to the controls. This is not considered to be related to compound exposure.

There was no effect on fetal mortality.

Average litter size was comparable for all groups.

Sex ratios were within normal limits as were fetal body weights.

Pre- and post-implantation losses were comparable between historical controls and treatment groups (e.g., see the NOTE appended below).

Developmental Toxicity - (See TABLE IV)

No malformations of either the viscera (soft tissue) or of the skeletal architecture were reported for the fetuses of any group at any level tested. There were numerous incidences of "variations", e.g., extra ribs, incomplete ossifications, etc.; however, there was no dose-dependent occurence of these.

Cholinesterase Effects - (See TABLE V)

Group I dams (16 days) had significantly reduced red cell and Brain ChE inhibition at 2.0 mg/kg bw/day. The Plasma ChE at this level was reduced also, but not significantly so.

Group II dams (20 days) Plasma and Red Cell ChE activity was comparable for all groups. Maternal Brain ChE activity was significantly reduced ($P < 0.01$) in the mid- and high-dose groups. Fetal brain ChE activity in this Group was reduced in the low-dose group but this was not considered to be dose-related since there was no corresponding reduction in the mid- and high-dose groups when compared to control values.

DISCUSSION:

The NOEL for maternal toxicity in this study is 2.0 mg/ kg bw/day based on reproductive parameters.

For the pups, the NOEL for fetotoxicity and teratological effects is 2.0 mg/kg bw/day, the highest level tested.

The ChE NOEL in dams was 0.5 mg/kg bw/day based on brain ChE inhibition at the 20 day sacrifice period (Group II dams). There was no brain ChE inhibition in the 20 day fetuses.

The data presented here suggest that, although there is some effect of orally administered Guthion on maternal ChE activity at 16 and 20 days of gestation, the chemical either does not reach the fetus or the fetus is not as sensitive as the maternal organism to ChE depression, at the levels tested here.

Note: The authors provided historical control data from twenty-two teratology studies performed at this laboratory. In general, these data support the authors conclusions that variations from the concurrent control values fall within the limits of the historical data provided.

Azinphos-methyl RIN: 7365-92

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