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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

PC 015801

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Mevinphos Developmental Toxicity - Rat (§ 83-4; OPPTS 870.3700]

Supplement to Document No. 007089 - DER for MRID No. 40201401 - A Teratology Study in Rats with Mevinphos. This amendment provides an Executive Summary to upgrade the original DER.

EPA Reviewer: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy Date: 3/18/99
Reregistration Review Branch I, Health Effects Division (7509C)

Branch Senior Scientist: Whang Phang, Ph.D. Whang Phang Date: 3/18/99
Reregistration Review Branch I, Health Effects Division (7509C)

AMENDED DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity - Rat

OPP Number: 83-4
DP BARCODE: D251794
PC CODE: 015801

OPPTS Number: 870.3700
SUBMISSION CODE: S547036
TOX CHEM NO: 160B

TEST MATERIAL (PURITY): Mevinphos (66.5% cis-isomer; 21.2% trans-isomer)

CHEMICAL NAME: 2-carbomethoxy-1-methylvinyl dimethyl phosphate

CITATION: Schroeder, R., Daly, I. (1987) A Teratology Study in Rats with Mevinphos. Bio/dynamics, Inc.: Study Number: 85-3009, March 2, 1987. MRID 40201401. Unpublished.

SPONSOR: AMVAC Chemical Corporation, Los Angeles, CA

EXECUTIVE SUMMARY: In a prenatal developmental study in rats (MRID 40201401), mevinphos (66.5% cis-isomer; 21.2% trans-isomer) was admininstered by gavage to 24 mated Sprague-Dawley CD rats/group from days 6 through 15 of gestation at doses of 0, 0.20, 0.75, 1.0 or 1.25 mg/kg/day. The dose volume was 10 ml/kg/day. The standard developmental study parameters were measured; cholinesterase measurements were not included.

Seven (7) dams in the 1.25 mg/kg/day group died during treatment, therefore this dose group was eliminated. Clinical signs prior to death were typical of organophospate toxicity. Dose-related clinical signs of toxicity in the 1.0 mg/kg/day group included tremors, lethargy, excessive salivation and lacrimation, chromodacryorrhea, anogenital staining and soft stools. Two females in the 0.75 mg/kg/day group had tremors on Day 15 of gestation. There were no treatment-related effects on body weights, body weight gain, gravid uterine weights or food consumption. There were no statistically significant differences between treated and control animals in

pregnancy rate, number of corpora lutea/dam, implantations/dam, number of abortions, male/female ratio, number of live litters, number of fetuses/dam, number of live fetuses/dam and fetal weight. There was no evidence of a treatment-related effect on external, visceral or skeletal malformations and variations.

Maternal NOAEL = 0.2 mg/kg/day; Maternal LOAEL = 0.75 mg/kg/day based on clinical signs of tremors

Developmental NOAEL is ≥ 1.0 mg/kg/day (Highest dose tested); Developmental LOAEL is > 1.0 mg/kg/day

This prenatal developmental study is classified **Acceptable/Guideline** and does satisfy the guideline requirements for a prenatal developmental study (OPPTS 870.3700; OPP 83-4) in rats.

83-3 STUDY TYPE: Teratology (in Rats) TOX. CHEM. NO.: 160B

ACCESSION NUMBER: N/R MRID NO.: 402014-01

TEST MATERIAL: Mevinphos (technical)

SYNONYMS: N/A

STUDY NUMBER(S): 85-3009

SPONSOR: Mevinphos Task Force

TESTING FACILITY: Bio/dynamics, Inc.

TITLE OF REPORT: Mevinphos - A Teratology Study in Rats with Mevinphos

AUTHOR(S): Raymond E. Schroeder M.S., D.A.B.T. and Ira W. Daly, Ph.D., D.A.B.T.

REPORT ISSUED: March 2, 1987

[NOTE: A range-finding study (Laboratory Project No. 85-3008, May 5, 1986) was performed by dosing mated female CD® rats by gastric intubation with 0 (vehicle control), 0.25, 0.50, 1.0, and 2.0 mg/kg/day of mevinphos on gestation days 6 through 15. No maternal or fetal effects were seen at the 0.25 and 0.50 mg/kg/day dose levels. The 1.0 mg/kg/day dose caused marked reduction in mean body weight gain. The 2.0 mg/kg/day dose was lethal to all dams. There were no fetal effects observed in the three lowest doses.]

PROTOCOL: Groups of 24 male (approximately 50 weeks old) and 24 female (207-285 g, 12 weeks old) Sprague-Dawley CD Rats were randomly assigned to five groups. Mating was accomplished by cohabitating individual males and females. Gestation day 0 was defined by the presence of a vaginal plug or the presence of sperm on a vaginal smear. Technical mevinphos (Lot No. 50826; 66.5% cis-isomer, 21.2% trans-isomer) was formulated in distilled water. The females were dosed by gastric intubation on gestation days 6 through 15 at levels of 0 (vehicle control), 0.20, 0.75, 1.00, and 1.25 mg/kg/day. The dose volume was 10 ml/kg/day. Dose formulations were prepared weekly. Mock-formulations of the 0.2 and 1.25 mg/kg/day doses were analyzed for homogeneity and stability, and each weekly dose formulation was analyzed for dose concentration. Formulations deviating from the nominal concentration by ± 15% were discarded.

The females were examined twice daily for clinical signs, and they were given detailed physical examinations on gestation days 0, 6, 10, 12, 15, and 20. Body weights were recorded on gestation days 0, 6, 10, 12, 15 and 20. Measurements of food consumption were made during gestation intervals 0-6 days, 6-10 days, 10-15 days, and 15-20 days.

Dams which aborted prior to gestation day 19 were sacrificed, and all surviving mated females were sacrificed on gestation day 20. They were examined grossly, and all abnormal tissues were fixed. The intact uteri with ovaries were removed from the dams and weighed. They were evaluated for live and dead fetuses, corpora luteae, implantations, and early and late resorptions. All

fetuses were weighed, sexed, and examined for external malformations. Half of the fetuses were examined for soft tissue malformations, and the other half were clarified and stained with Alizarin Red S for skeletal examination. Late resorptions were examined only for external malformations. The 1.25 mg/kg/day group was terminated early because of excessive mortality. Fetuses recovered from the dams in this group which survived to gestation day 20 were examined the same as those in the other groups.

RESULTS: Measurements of homogeneity, stability, and dose concentration were well within an acceptable range.

There were no mortalities except in the 1.25 mg/kg/day group. Seven of the dams (29.2%) had died when the group was terminated after 6-10 days of treatment (gestation days 11-15; pregnancy day 0 was staggered among the dams). Clinical signs in these dams included tremors, lethargy, excessive salivation, chromodacryorrhea, excess lacrimation, red nasal discharge, gasping, moist rales, and anogenital staining. Gross lesions included discolored and enlarged skin, discolored lungs and thymuses, enlarged and edematous salivary glands, and discolored pituitary glands.

For the balance of this review only the 0, 0.20, 0.75, and 1.00 mg/kg/day groups will be discussed. Dose-related clinical signs in the two highest groups included tremors, excess lacrimation, chromodacrhorrhea, excess salivation, anogenital staining, and soft stools. Many rats had nondose-related swollen cervical areas which were attributed to sialodacryoadenitis (SDA) virus infections. These infections reportedly had no effect on the study. There were no biologically significant differences between the dosed and control groups in body weight gain, gravid uterine weights, or food consumption. The following tables present the reproductive findings of this study:

Dose (mg/kg/d)	Pregnant/ Mated	Corpora Luteae	Implantations /dam	— Resorptions (%) — Embryonic	Early	Late
0	24/24	16.3	14.7	0.090	0.5	0.0
0.20	23/24	15.7	14.1	0.097	0.4	0.0
0.75	23/24	15.9	15.0	0.051	0.9	0.0
1.00	21/24	14.7	13.4	0.093	0.6	0.1

Dose (mg/kg/d)	Abortions	Live litters	Live Fetuses Fetuses/dam	% Live	Wt (g)	% Male
0	0.0	24	14.1	100	3.41	51
0.20	0.0	23	13.7	100	3.38	51
0.75	0.0	23	14.1	100	3.31	45
1.00	0.0	20	12.7	100	3.49	50

There was an elevated rate of early resorption at the mid-dose level, but since it was not dose-related, it is unlikely that this was a toxic effect. No compound-related reproductive effects or gross lesions were observed. There was no evidence of compound-related external, visceral, or skeletal malformations and variations. A high-dose (1.00 mg/kg/day) dam delivered 9 pups on what was considered to be gestation day 8. Based on the stage of the pups' development, this dam was obviously pregnant earlier than had been assumed. One pup was cannibalized, but the others appeared normal.

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CONCLUSIONS: The defined doses are as follows:

Maternal NOEL =	0.20	mg/kg/day
Maternal LEL =	0.75	mg/kg/day (tremors)
Fetotoxic NOEL	>1.00	mg/kg/day
Embryotoxic NOEL	>1.00	mg/kg/day
Teratogenic NOEL	>1.00	mg/kg/day
A/D Ratio =	<0.75	

STUDY CLASSIFICATION: This study is classified CORE GUIDELINE.

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Section II, Toxicology Branch
Hazard Evaluation Division

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