



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

JUN 28 1989

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Methyl parathion: supplemental data for a developmental toxicity study in rabbits.

TO: Dennis Edwards PM 12
Registration Division (H7505C)

FROM: K. Clark Swentzel *K. Clark Swentzel 6/26/89*
Acting Section Head
Toxicology Branch II (HFAS)
HED (H7509C)

THRU: Marcia van Gemert, Ph.D. *M. van Gemert 6/26/89*
Chief
Toxicology Branch II (HFAS)
HED (H7509C)

EPA ID No.: 4787-4
Project No.: 9-1416
MRID/Acc. No.: 41046101
Caswell No.: 372
Registrant: A/S Cheminova

Requested Action

Evaluate subject data.

Background

A study [Parathion-methyl (Folidol M active ingredient), Study for embryotoxic effects on rabbits after oral administration. Renhof, M. (Unpublished Report No. 12907, prepared by Bayer AG Institute of Toxicology, Wuppertal, West Germany; submitted by Cheminova, Lemvig, Denmark; dated September 4, 1984). Accession Nos. 259403 through 259405] was previously evaluated by TB (EPA memorandum, Katz, TB, to Allen & Ellenberger, RD, March 19, 1986). There was no evidence of teratogenicity, embryotoxicity or fetotoxicity in this study in which pregnant Himalayan rabbits were administered methyl parathion in 0.5% aqueous Cremophor EL emulsion by gavage on days 6 through 18 of gestation at dosages of 0.3, 1.0 or 3.0 mg/kg/day. One of the deficiencies noted in this evaluation was the absence of induced maternal toxicity at the high dose level. The objective of the subject study was to address this deficiency.

Conclusion

The registrant has successfully demonstrated that the highest dosage administered (3.0 mg/kg/day) to pregnant rabbits in a previously evaluated developmental toxicity study (Report No. 12907) induces maternal toxicity, which was indicated by inhibited plasma and erythrocyte cholinesterase activity in the same species of rabbit under similar experimental conditions. Therefore, it is TB's opinion that the highest dosage administered in the noted study was adequate, however, the

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registrant did not address the other deficiencies noted by the reviewer of Report No. 12907. The reviewer requested 1) individual and group mean absolute body weight data, 2) categorization of dead fetuses with respect to the approximate time of death in utero, 3) a copy of the protocol and a description of any deviations from the protocol, 4) a copy of each of the references (1,3,4 in English), 5) individual clinical observations and necropsy findings for the dams, 6) historical control data with respect to post-implantation losses in rabbits of the same strain, 7) a description of conditions of storage of the test material and dosing mixtures and 8) analytical results with respect to homogeneity, concentration and stability of the test material in the dosing mixtures. This information is required in order for TB to complete its evaluation of the developmental toxicity study.

Core-classification: supplementary data

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Reviewed by: K. Clark Swentzel *K. Clark Swentzel 6/26/89*
Section II, Tox. Branch (H7509C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section II, Tox. Branch (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Teratogenicity/supplemental data TOX. CHEM. NO.: 372

MFID/Accession No.: 41046101

TEST MATERIAL: O,O-dimethyl-O-(4-nitro-phenyl)-monothiophosphate

SYNONYMS: Methyl parathion

STUDY NUMBER(S): T 6025711 (Report no. 16331)

SPONSOR: A/S Cheminova

TESTING FACILITY: Bayer AG

TITLE OF REPORT: Supplement to Methyl Parathion (E120) Study for Embryotoxic Effects
on Rabbits After Oral Administration (Report no. 12907)

AUTHOR(S): M. Renhof

REPORT ISSUED: December 22, 1987

CONCLUSIONS:

The registrant has successfully demonstrated that the highest dosage administered (3.0 mg/kg/day) to pregnant rabbits in a previously evaluated developmental toxicity study (Report No. 12907) induces maternal toxicity, which was indicated by inhibited plasma and erythrocyte cholinesterase activity in the same species of rabbit under similar experimental conditions. Therefore, it is TB's opinion that the highest dosage administered in the noted study was adequate, however, the registrant did not address the other deficiencies noted by the reviewer of Report No. 12907. The reviewer requested 1) individual and group mean absolute body weight data, 2) categorization of dead fetuses with respect to the approximate time of death in utero, 3) a copy of the protocol and a description of any deviations from the protocol, 4) a copy of each of the references (1,3,4 in English), 5) individual clinical observations and necropsy findings for the dams, 6) historical control data with respect to post-implantation losses in rabbits of the same strain, 7) a description of conditions of storage of the test material and dosing mixtures and 8) analytical results with respect to homogeneity, concentration and stability of the test material in the dosing mixtures. This information is required in order for TB to complete its evaluation of the developmental toxicity study.

Core-classification: supplementary data

Quality assurance statement: signed and dated

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Test Material

Methyl parathion technical, 96.8%, white solid crystalline, stored in at 4°C, batch no. 230 606 003.

Test Animals and Environmental Parameters

Himalayan rabbits, strain- CHBB:HM, supplied by Thomae Co., Biberach a.d. Riss. Sexually mature males > 2500g and females (nulliparous), 1873 - 2559 g were acclimated for at least 7 days. The animals, which were caged singly, were provided with K4 Rabbit Diet (ad libitum?) and tap water ad libitum. Animals were identified individually by cage and ear tattoo. The environmental parameters were: room temperature- $24 \pm 2^\circ\text{C}$, humidity- approximately 65%, forced ventilation- at least 10/hr, light cycle- 12 hr.

Methods

Females were caged with males one to one; the day that mating was observed was considered day 0 of gestation.

The mated females were randomly divided into 4 groups of 5 rabbits. Methyl parathion in 0.5% aqueous Cremophor EL emulsion was administered (constant dosage volume = 5 ml/kg) via gastric intubation on days 6 through 18 of gestation at dose levels of 0.3, 1.0 and 3.0 mg/kg/day. The study included a control group, however, the report did not indicate if vehicle was administered to this group.

The report summary stated that "the dams' body weights, appearance and behaviour were examined." Although a test protocol was not included, the Results section indicated that appearance and behavior examinations were performed daily. It is also evident from tabulated data that body weights were measured daily on days 0-18 of gestation. Evidently, food and water consumption were not quantitated, but subjective observations were included with the Results section of the report.

Blood samples for the determination of plasma and RBC cholinesterase activity were taken from the marginal ear vein before (time interval not given) the first, second and ninth administrations as well as 24 hrs after the last administration of methyl parathion. Brain cholinesterase activity was determined at termination. The investigator used Welch's t test to evaluate differences in cholinesterase activity (test vs control).

Results

None of the treated animals died during the study. There was no evidence of systemic toxicity at any dosage level from examinations of appearance, behavior, clinical signs, food and water consumption, body weight gain or gross necropsy.

Inhibition of plasma and RBC cholinesterase activity (Appended page 1) in high dose (3.0 mg/kg/day) dams was evident before the ninth administration (-29.0 and -25.4% vs baseline, respectively) and after the last administration (-39.1 and -30.0% vs baseline, respectively). The noted reductions in RBC cholinesterase activity were statistically significant ($p < 0.025$ or 0.005) relative to control values (Appended page 2). There was no evidence that brain cholinesterase activity was inhibited in treated animals.

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Conclusions

The registrant has successfully demonstrated that the highest dosage administered (3.0 mg/kg/day) to pregnant rabbits in a previously evaluated developmental toxicity study (Report No. 12907) induces maternal toxicity, which was indicated by inhibited plasma and erythrocyte cholinesterase activity in the same species of rabbit under similar experimental conditions. Therefore, it is TB's opinion that the highest dosage administered in the noted study was adequate, however, the registrant did not address the other deficiencies noted by the reviewer of Report No. 12907. The reviewer requested 1) individual and group mean absolute body weight data, 2) categorization of dead fetuses with respect to the approximate time of death in utero, 3) a copy of the protocol and a description of any deviations from the protocol, 4) a copy of each of the references (1,3,4 in English), 5) individual clinical observations and necropsy findings for the dams, 6) historical control data with respect to post-implantation losses in rabbits of the same strain, 7) a description of conditions of storage of the test material and dosing mixtures and 8) analytical results with respect to homogeneity, concentration and stability of the test material in the dosing mixtures. This information is required in order for TB to complete its evaluation of the developmental toxicity study.

Core-classification: supplementary data

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Page _____ is not included in this copy.

Pages 6 through 7 are not included in this copy.

The material not included contains the following type of information:

- _____ Identity of product inert ingredients.
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 - _____ Description of the product manufacturing process.
 - _____ Description of quality control procedures.
 - _____ Identity of the source of product ingredients.
 - _____ Sales or other commercial/financial information.
 - _____ A draft product label.
 - _____ The product confidential statement of formula.
 - _____ Information about a pending registration action.
 - ☒ FIFRA registration data.
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Tox Chem No. 372

File Last Updated

Current Date 6/23/89

EPA

MRID/Acc.

No.

Results:

LD50, LC50, PIS, NOEL, LEL

TOX

Category

CORE Grade/

Doc. No.

Material

Study/Lab/Study #/Date

Ms. parathion
tech.
96.8%Supplemental study
(Teratology study in
rabbits, Report no.
12907, 9/4/84)/Bayer AG/
T 6025711/Dec. 22, 1987Pregnant Himalayan rabbits admin.
0.3, 1.0 & 3.0 mg/kg/day, days 6-
18 of gestation.Plasma & REC cholinesterase inhib.
at 3.0 mg/kg/day. Therefore,
high dose in terato. study
(Report no. 12907) was adequate

supplementary

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