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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Methyl Parathion: Supplemental Data for a Developmental Toxicity Study in Rabbits; Report No. 12907, September 4, 1987; Acession Nos. 259403 through 259405.

TO: Dennis Edwards PM 12
Registration Division (H7505C)

FROM: K. Clark Swentzel, Section Head K. Clark Swentzel 11/8/89
Toxicology Branch II (HFAS)
HED (H7509C)

THRU: Marcia van Gemert, Ph.D. Marcia Gemert 11/9/89
Chief
Toxicology Branch II (HFAS)
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EPA ID No. 4787-4
Project No. 9-1967
Caswell No. 372
Registrant: A/S Cheminova

Requested Action

Review data

Submission

The submission contains supplemental data for the following studies:

1) Machemer, L. Parathion-methyl, Evluation for embryotoxic and teratogenic effects on rats following oral adminsitration. (Unpublished Report No. 6825 prepared by Bayer AG Institute of Toxicology, Wuppertal, West Germany; submitted by Cheminova, Lemvig, Denmark; dated June 3, 1977). Accession No. 257512.

2) Renhof, M. Parathion-methyl (Folidol M active ingredient), Study for embryotoxic effects on rabbits after oral administration. (Umpublished 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.

3) Bonhard, et al. E 605-methyl chronic toxicological study on rats. Unpublished study Nos. 9889 and 12559 prepared by Bayer AG Institute of Toxicology, Wuppertal, West Germany; submitted by Cheminova, Lembig, Denmark; dated March 31, 1981). Accession Nos. 257513 and 257514.

Response

Study No. 1

The following deficiencies, included among those indicated by the TB reviewer(memorandum, Katz, HED, to Allen and Ellenberger, RD, March 19, 1986), have not been satisfied: a test protocol was not submitted, the individual clinical observations and necropsy findings were not adequately reported, analytical data for the stability and content of the test material were not provided and storage conditions for the test material were not given. Therefore, this study can not be upgraded.

A new developmental toxicity study in rats has been submitted to the Agency and is currently being reviewed by TB II (EPA ID No. 4787-4, MRID No. 41136101).

Study No. 2

The registrant's response to the Agency's toxicology review is discussed below.

Study No. 3

The registrant's response to the toxicology review was previously addressed by TB (memorandum, Swentzel, HED, to Edwards, RD, November 13, 1987). TB concluded that the Core-classification could not be upgraded because of the deficiencies that remain in the study.

Response to the TB review of Study No. 2 (Katz to Allen and Ellenberger, March 19, 1986)

The deficiencies in this study, indicated by Katz, and the registrant's response to each, with TB's current comments, are given below.

Deficiency

Since maternal toxicity was not demonstrated in this study, even at the high dose, the registrant should explain the rationale for the selection of doses.

Response

The selection of doses was based on the oral LD_{50} as well as the level which inhibits cholinesterase in rabbits. Additionally, this deficiency was previously addressed by submitting a study (MRID No. 41046101) which showed that the high dose used in the subject study (3.0 mg/kg/day) is capable of inducing maternal toxicity (inhibited plasma and RBC cholinesterase). This submission has been evaluated by TB (memorandum, Swentzel, HED, to Edwards, RD, June 29, 1989).

Deficiency

Individual body weight data were not submitted.

Response

Individual as well as mean absolute body weight data were included in the present

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submission. These data show that treatment did not have and adverse effect on maternal body weights or body weight gain during gestation.

Deficiency

In utero data should be presented in a manner which would allow evaluation of possible treatment-related differences with respect to the approximate time (early or late gestation) of death.

Response

These data, which were reorganized as requested and provided in this submission (appended page 1), show that treatment had no apparent effect on the incidence of either early or late resorptions.

Deficiency

Submit a test protocol and describe deviations from that protocol.

Response

A summarized test protocol was submitted (appended pages 2,3 & 4). The only deviation noted was "the formulation for the top dose group must be mixed daily, since the substance precipitates after about 24 hours." However, the protocol did not give the proposed frequency of prepartation for any of the formulations (dosing suspensions).

Deficiency

A copy of each of the three references should be provided in English.

Response

Reprints of the references were provided in the original language (German) only. The submission indicated that English translations are forthcoming.

Deficiency

Individual clinical observations and necropsy findings for the dams are needed.

Response

The submitted data consisted primarily of deviations in food and water consumption. No necropsy data were submitted even though the cover letter indicated that they were located in Appendix 2.D. No treatment-related effects were apparent from the observations provided.

Deficiency

Historical data, with respect to post-implantation losses in rabbits of the same strain, should be submitted.

Response

No data were provided, however, the submission stated that "during the study period in

six tests with a total of 88 dams, averages of 6.0 fetuses" (live?), "0.3 early resorptions and 0.7 late resorptions per dam were found in the control group." The early resorption rate in the concurrent controls of the subject study (1.36/dam) was not in line with the historical data, however, early and late resorption rates in the treated groups were comparable to the historical data (appended page 1). As indicated earlier, inter-group comparisons of resorption data did not reveal a treatment-related effect.

Deficiency

A description of conditions of storage of the test material and dosing mixtures should be provided.

Response

The submission referred to the test protocol on appended pages 2, 3 and 4 which indicated that the test "substance" and "formulation" were stored in a refrigerator (temperature not given).

Deficiency

The original report did include analytical results with respect to homogeneity, concentration and stability of the test material in the dosing mixtures.

Response

Analytical data for active ingredient and stability were provided, but not for homogeneity in the dosing mixtures.

Purity given (technical): 95.7% a.i.

Dosing mixtures (all): 88-104% of nominal value at 5 days
84-90% of nominal value at 7 days

		% of nominal
High-dose:	5 days =	88
	7 days =	84%
Low-dose:	5 days =	104%
	7 days =	90%

Conclusion

Although the data/information provided in this submission did not satisfy every deficiency noted in the original TB review (Katz, March 19, 1986), it is TB II's opinion that, based on the critical deficiencies that were adequately addressed by the registrant, this study should be upgraded to Core-minimum.

Methyl parathion toxicology review

Page _____ is not included in this copy.

Pages 5 through 8 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product 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

X FIFRA registration data

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