



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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

JUN 2 1992

MEMORANDUM

SUBJECT: Review of Supplementary Data (MRID# 422356-01) to support a Developmental Toxicity Study in Rats (MRID# 411361-01) with Methyl-parathion that was Classified as Core-supplementary.

TO: Mr. Larry Schnaubelt/Robert Richards PM-72
SRRD/Reregistration (H7508W)

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THROUGH: K. Clark Swentzel, Section Head *K. Clark Swentzel 5/26/92*
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and

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MRID No.: 422356-01
Caswell No.: 372

DP Barcode No.: D177992
Submission: S417459

ACTION REQUESTED

Review of Supplementary Data (MRID# 422356-01) that was requested by Toxicology II to support a Developmental Toxicity Study (MRID# 411361-01; memo from Lien to Edwards dated 10/5/90 is attached) with Methyl-parathion that was classified as Core-supplementary in October 5, 1990.

REVIEW OF THE SUPPLEMENTARY DATA

The supplementary data was prepared by RCC (Research and Consulting Company - Performing Laboratory), and submitted by Jellinek, -Schwartz, Connolly & Freshman, Inc. on behalf of Cheminova Agro A/S, Submitter/Sponsor.



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a. Maternal Clinical Observations (Appendix A)

The clinical sign data submitted confirmed that the observed increased incidences of somnolence, ataxia, dyspnea, ventral recumbency, and repeated chewing in the high dose (3 mg/Kg) group were related to treatment.

b. Summary Fetal and Litter Skeletal Ossification Data (App. B)

Statistically significant increased litter incidences of non-ossified skeletal findings in this study as compared to the historical controls are summarized as follows:

Non-ossified Skeleton	0 mg/kg day	.3 mg/kg day	1 mg/kg day	3 mg/kg day	Historical Control ^Q
3rd Cervical Vertebra	8%	21%	0%	35%*	8 - 27%
Prox. Phalanx Right Digit 2	46%	54%	50%	75%*	64 - 79%
Metatarsal 1, Right	17%	29%	46%*	50%*	40 - 59%
Metatarsal 1, Left	17%	29%	46%*	50%*	40 - 59%

^Q = consists of 144 litters from 6 studies conducted in 1987.

* = statistically significant at $p < 0.05$.

In the original study report (MRID#411361-01), the investigators concluded that "...the incompletely ossified cervical vertebrae, phalangeal nuclei and metatarsalia were slightly increased; these findings were due to delayed maturation due to reduced fetal body weight and therefore were not considered compound-related effects". Correlation between fetal body weight reduction and increased incidences of delayed ossification was presented in the supplementary report (Appendix C). This reviewer agrees with the investigators that increased delayed ossifications are generally due to reduced fetal body weights. However, one must also consider other related data in the study. In this study all high-dose statistically significant delayed ossification values noted in the above Table are judged to be related to treatment because it is consistent with treatment-related reduced maternal and fetal body weights in the high-dose group. This is also supported by the following:

- o The non-ossified 3rd cervical vertebra in the high-dose group was outside the historical control range.
- o The high-dose proximal phalanx of the 2nd right digit was at the high end of the historical control range.

As for the increased incidence of un-ossified metatarsal 1, only the high-dose group is considered to be biologically significant, although the mid-dose group was statistically significant and the non-ossified metatarsal 1 showed a dose-related trend. This conclusion is consistent with the statistically significant reduction of the maternal and fetal body weights in the high-dose but not in the mid-dose group (see attached DER dated Oct. 5, 1990). Also, the concurrent control value was well below the historical control range.

CONCLUSIONS

Based on all the data presented (original study MRID#411361-01 and the current supplementary data MRID#422356-01), administration by gavage of 0.3, 1.0, and 3.0 mg/kg/day of methyl-parathion in distilled water to four groups of 25 mated female Wistar rats, produced the following results:

- o The maternal toxicity LOEL is 3.0 mg/kg/day based on the increased maternal mortality, adverse clinical signs (i.e. somnolence, ataxia, dyspnea, ventral recumbency, and repeated chewing) and post-implantation losses, and decreased maternal body weight, body weight gains, and food consumption. Also, at the 3.0 mg/kg/day dose level, the compound induced plasma, erythrocyte, and brain cholinesterase activity inhibition in maternal rats. The maternal toxicity NOEL is 1.0 mg/kg/day.
- o The developmental toxicity LOEL is 3.0 mg/kg/day based on increased delayed ossification of the 3rd cervical vertebra, proximal phalanx of the 2nd right digit, 1st metatarsal of the right and left hindlimbs, and the reduction of fetal body weight. The developmental NOEL is 1.0 mg/kg/day.

Maternal toxicity NOEL = 1.0 mg/kg/day; LOEL = 3.0 mg/kg/day.
Developmental Toxicity NOEL = 1.0 mg/kg/day; LOEL = 3.0 mg/kg/day.

RECOMMENDATION

The developmental toxicity study with E-120 (technical methyl parathion with a purity of 97%) in the rat (MRID# 4113610-01) is now upgraded to core-minimum.

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