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 RC-72 SRMD/Reregistration (H750SC)

FROM: David S. Lien, Ph.D., Section II, Toxicology Branch II/HERD (H750SC)

THROUGH: K. Clark Sventzel, Section Head Section II, Toxicology Branch II/HERD (H750SC)

and

Marcia van Gemert, Ph.D., Branch Chief Toxicology Branch II/HERD (H750SC)

MRID No.: 422356-01
Caswell No.: 372
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 SCC (Research and Consulting Company - Permacor Laboratory) and submitted by Jellinek, Schwartz, Cosmolloy & Frekman, Inc. on behalf of Chaminova Agro A/S, Submitter/Sponsor.
a. Maternal Clinical Observations (Appendix E)

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. E)

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

<table>
<thead>
<tr>
<th>Non-ossified Skeleton</th>
<th>0 mg/kg day</th>
<th>3 mg/kg day</th>
<th>1 mg/kg day</th>
<th>3 mg/kg day</th>
<th>Historical Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd Cervical Vertebral</td>
<td>8%</td>
<td>21%</td>
<td>0%</td>
<td>35%</td>
<td>8 - 27%</td>
</tr>
<tr>
<td>Prox. Phalanx Right Digit 2</td>
<td>46%</td>
<td>54%</td>
<td>50%</td>
<td>75%**</td>
<td>64 - 79%</td>
</tr>
<tr>
<td>Metatarsal 1, Right</td>
<td>17%</td>
<td>29%</td>
<td>46%*</td>
<td>50%**</td>
<td>40 - 59%</td>
</tr>
<tr>
<td>Tarsal 1, Right</td>
<td>17%</td>
<td>29%</td>
<td>46%*</td>
<td>50%**</td>
<td>40 - 59%</td>
</tr>
</tbody>
</table>

@ = consists of 144 litters from 6 studies conducted in 1987.
* = statistically significant at p < 0.05.

In the original study report (NCRDS 411361-01), the investigators concluded that "...the incompletely ossified cervical vertebrae, phalangeal nuclei and metatarsals 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 statistical 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:

- The non-ossified 3rd cervical vertebra in the high-dose group was outside the historical control range.
- 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 biological 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 MRIDS#411361-01 and the current supplementary data MRIDS#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:

- 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.

- 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 (MRIDS# 4113610-01) is now upgraded to core-minimum.
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 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.

____ The document is a duplicate of page(s) ________.
____ The document is not responsive to the request.

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