Subject: Parathion-methyl parathion residue tolerance requests.

To: Mr. Drew M. Baker, Chief
   Petitions Control Branch
   Pesticides Tolerances Division

   Pesticide Petition No. 1F1091

   0.1 ppm (negligible) almonds, filberts, white & sweet potatoes, pecans, safflower, sorghum, sugar beets, sugarcane, and walnuts.

   0.5 ppm rye (graia)

In TB's 5 January 1972 memo conclusions, a safety evaluation was not possible due to lack of certain information.

The lacking information included:


2) Specifications or details of composition of methyl parathion.

3) Knowledge concerning which "inerts" or adjuvants of the 100 formulations of parathion and methyl parathion listed in this petition are cleared for use under Federal regulation.

The petitioner, by supplement, (5 June, 19 May, 30 May, 20 April) has furnished this lacking data.

The WHO/FAO reproduction question was about effects noted in a 3 generation rat study that has been furnished to TB by the petitioner. The examination of the data of
this study revealed a REL of 10 ppm. This information is judged adequate in response to the FAO/WHO discussion referred to in the TB 5 January 1972 memo.

The provided supplementary information on the composition of methyl parathion is judged adequate and furnishes the lacking information.

CB will examine the adjuvant and inert list for clearance of use. Any material not cleared will be considered apart from this petition.

**CONCLUSION**

Available parathion-methyl parathion toxicity data and TS requested supplementary data adequately support the safety of the requested residue tolerances of this petition (CB considerations permitting).

George E. Whitmore, D.V.M.
Section Chief
Toxicology Branch
Pesticides Tolerances Division

GEWhitmore:km 08-25-72

cc: JGCummings
PRD/EPA
Perrine Branch
Atlanta Branch (CLeavis)
Division Reading File
Branch Reading File
PP No. 1F1091

Init: C.H. Williams
April 26, 1972

Mr. Joe L. Turlough
Petition Control Officer
Pesticides Tolerance Division
Environmental Protection Agency
Washington, D.C. 20469

Subject: Pesticide Petition No. 1r1891

Dear Mr. Turlough:

Relative to your letter dated January 26, 1972, pertaining to Pesticide Petition No. 1r1891, enclosed is the information requested:


2) Characterization of Technical Methyl Parathion.

3) Enclosed are copies of letters to various inert ingredient manufacturers requesting formula disclosures for the inert ingredients.

We trust that the above information, submitted on behalf of the Industry Task Force for Parathion and Methyl Parathion, will support the continued review of this petition.

Very truly yours,

[Signature]

Chris Neeley
Secretary & Treasurer

Inclinations

cc: R.W.J.
Mr. R. E. Lehnweber
Mr. J. H. Willard

BEST AVAILABLE COPY

May 4, 1972
PARATHION-METHYL

This pesticide was evaluated for acceptable daily intake under the heading "Methyl parathion" by the Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues (FAO/WHO, 1965).

Since that time additional toxicological data have become available as well as data on its residues in food and their evaluation. The earlier monograph is now rendered obsolete and a completely revised monograph is presented in its entirety below.

IDENTITY

Chemical name

O,0-dimethyl O-(4-nitrophenyl) phosphorothioate (IUPAC)

Synonyms

Metaphos, Folidol M, E 605, Nitox, Wofatox

Formula

\[
\begin{align*}
\text{S} \\
\text{CH}_3\text{O} \\
\text{P} \\
\text{O} \\
\text{NO}_2 \\
\text{OCH}_3
\end{align*}
\]

Other information on identity and properties

Typical analyses of technical parathion-methyl are not available. In 1966 the world production of parathion-methyl was 31,700 metric tons (United States of America production, 14,800 metric tons).

EVALUATION FOR ACCEPTABLE DAILY INTAKE

Biochemical aspects

When \(^{32}\)P-labelled parathion-methyl was administered orally to guinea-pigs, the phosphorus was found to enter the organs almost immediately, and the maximum tissue level was attained in one to two hours. A high degree of absorption was found in the liver (Gar et al., 1959).
Parathion-methyl is biologically similar to parathion and is metabolized to its oxygen analogue, paraoxon-methyl (Augustinsson and Jonsson, 1957).

Parathion-methyl is an in vivo cholinesterase inhibitor (Williams et al., 1959). It also inhibits this enzyme in vitro, however it is weaker in this respect than its ethyl analogue, parathion (DuBois and Coon, 1952). The same is true of the respective oxygen metabolites; paraoxon-methyl being a weaker cholinesterase inhibitor than paraoxon. The in vitro molar \( \text{LD}_{50} \) value for paraoxon-methyl, using rat brain cholinesterase, is \( 4 \times 10^{-6} \) (Davison, 1955).

**Acute toxicity**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Route</th>
<th>( \text{LD}_{50} ) (mg/kg body-weight)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>oral</td>
<td>32.1</td>
<td>Ikeda, 1962</td>
</tr>
<tr>
<td>Mouse</td>
<td>oral</td>
<td>150</td>
<td>Wills, 1968</td>
</tr>
<tr>
<td>Rat (M)</td>
<td>oral</td>
<td>14</td>
<td>Wills, 1968</td>
</tr>
<tr>
<td>Rat (F)</td>
<td>oral</td>
<td>24</td>
<td>Wills, 1968</td>
</tr>
<tr>
<td>Rat</td>
<td>oral</td>
<td>17.2</td>
<td>Hagan, 1958</td>
</tr>
<tr>
<td>Rat (F)</td>
<td>oral</td>
<td>9.7-14.8</td>
<td>Deichmann et al., 1952</td>
</tr>
<tr>
<td>Rat</td>
<td>i.p.</td>
<td>3.5</td>
<td>DuBois and Coon, 1952</td>
</tr>
<tr>
<td>Rabbit</td>
<td>oral (in oil)</td>
<td>420</td>
<td>Wills, 1968</td>
</tr>
<tr>
<td>Rabbit</td>
<td>oral (undiluted)</td>
<td>1 270</td>
<td>Wills, 1968</td>
</tr>
</tbody>
</table>

**Short-term studies**

**Dog.** Pairs of dogs, comprising one male and one female, were fed parathion-methyl for 12 weeks at dietary levels of 5, 20, and 50 ppm along with four dogs used as controls. In the 20 and 50 ppm group, erythrocyte cholinesterase began to be significantly depressed soon after commencement of the test-diet. The same was true of plasma cholinesterase in the 50 ppm group. Maximum extent of depression was attained at the end of the 12-week period but recovery was complete within four to eight weeks after withdrawal of parathion-methyl. Depression of plasma cholinesterase...
paralysis of vol.
saliva and tear
vulsions. Some
Food and water
four days and the
malformations or
suppression of
higher dosage.
incidence of win:
in other export
vertebrae and the
group treated

Observations in

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were given para:
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effects, were oc.

In a second
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days followed by
mg/day for 28 d
maximum depression
approximately 1%
beforehand (Most

In a conti-
given parathion-
8 mg and 9 mg.
activities were
value (Moller

Comments

Teratogenic:
parenteral admini.
reproductive or
evaluate this to
change the acc.
daily intake.

Estimate of in
0.0101 ml.
paralysis of voluntary muscles were followed by hypersecretion of saliva and tears, urinary incontinence, tremor and general convulsions. Some died and the others recovered by the next day. Food and water intake in rats was noted to be lower for three or four days and there was a weight loss. No external or internal malformations were found. In mice lethality, teratogenicity and suppression of growth were noted in the group treated with the higher dosage. The only malformation was cleft palate, the incidence of which was 0.71 per cent, when used as control groups in other experiments. Retardation of ossification of the caudal vertebrae and increased incidence of cervical rib occurred in the group treated with the higher dose (Tanamura et al., 1967).

Observations in man

Normal levels of red blood cell and plasma cholinesterase were established in 12 human subjects, five of these subjects were given parathion-methyl in dose levels of 3 mg/day for 28 days, 3.5 mg/day for 28 days and 4.0 mg/day for 43 days. No anti-cholinesterase activity in plasma on red blood cells, and no side effects, were observed (Moeller and Rider, 1961).

In a second study, three groups of five subjects were given parathion-methyl. The first group received 4.5 mg/day for 30 days followed by 5.0 mg/day for 29 days; the second group, 5.5 mg/day for 28 days, then 6.0 mg/day for 29 days; and the third group, 6.5 mg/day for 35 days, then 7.0 mg/day for 24 days. The maximum depression of cholinesterase occurred in plasma and was approximately 15 per cent. of the control values established beforehand (Moeller and Rider, 1962).

In a continuing experiment, groups of five subjects were given parathion-cetyl for 30 days at daily doses of 7 mg, 7.5 mg, 8 mg and 9 mg. Plasma and red blood cell cholinesterase activities were within 20 per cent. of the pre-established control values (Moeller and Rider, 1963).

Comments

Teratogenic effects were observed in mice only after parenteral administration, on the other hand the reproduction studies in rats showed some disturbance of the physiology of the reproductive process. It was therefore found necessary to re-evaluate this compound by using a higher safety factor and to change the acceptable daily intake to a temporary acceptable daily intake.

TOXICOLOGICAL EVALUATION

Estimate of temporary acceptable intake

0-0.001 mg/kg body-weight