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## ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D. C. 20560

Date: August 25, 1972

Reply to  
Attn of:

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 (grain)

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

The lacking information included:

- 1) Detailed information respecting alleged adverse effect  
of methyl parathion on reproduction and its teratogenic  
potential, as discussed in FAO/WHO "1968 Evaluations  
of Some Pesticide Residues in Food," pp 242-5.
- 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

AUG 28 1972

Page 2 - PP No. 1F1091

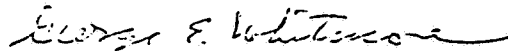
this study revealed a NEL of 10 ppm. This information is judged adequate in response to the FAO/WHO discussion referred to in the TB 5 January 1972 memo.

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 TB 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 (CLewis)  
Division Reading File  
Branch Reading File  
PP No. 1F1091

Init: C.H. Williams

2

NATIONAL AGRICULTURAL CHEMICALS ASSOCIATION

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April 25, 1972

45th DAY

Mr. Lee L. Terburgh  
Petitions Control Officer  
Pesticides Tolerances Division  
Environmental Protection Agency  
Washington, D. C. 20460

Subject: Pesticide Petition No. 1F1091

Dear Mr. Terburgh:

Relative to your letter dated January 26, 1972,  
pertaining to Pesticide Petition No. 1F1091, enclosed  
is the information requested:

- 1) Three copies of the FAO/WHO "1968  
Evaluations of Some Pesticide Residues  
in Food", pages 242-245.
- 2) Characterization of Technical Methyl  
Parathion.
- 3) Enclosed are copies of letters to various  
inert ingredient manufacturers requesting  
formula disclosures for the inert ingre-  
dients.

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,

Denis Hawley  
Secretary & Treasurer

Encl.  
Enclosures

cc: Mr. J. L. Lindquist  
Mr. J. L. Lindquist  
Mr. J. L. Lindquist

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- 212 -

## 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).

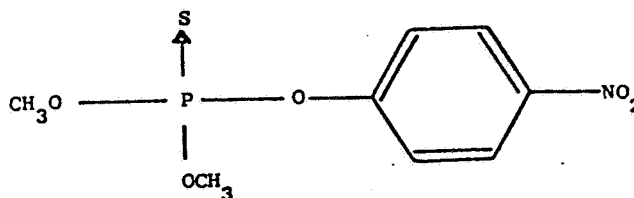
Since that time additional toxicological data have become available as well as data on its residues in food and their evaluation. The earlier monograph is now rendered obsolete and a completely revised monograph is presented in its entirety below.

IDENTITYChemical name

OO-dimethyl O-(4-nitrophenyl) phosphorothioate (IUPAC)

Synonyms

Metaphos, Folidol M, E 605, Nitrox, Wofatox

FormulaOther 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 INTAKEBiochemical aspects

When <sup>32</sup>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., 1958).

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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  $I_{50}$  value for paraoxon-methyl, using rat brain cholinesterase, is  $4 \times 10^{-8}$  (Davison, 1955).

#### Acute toxicity

Animal	Route	LD <sub>50</sub> (mg/kg body-weight)	References
Mouse	oral	32.1	Ikeda, 1962
Mouse	oral	150	Wills, 1968
Rat (M)	oral	14	Wills, 1968
Rat (F)	oral	24	Wills, 1968
Rat	oral	17.2	Hagan, 1958
Rat (F)	oral	9.7-14.8	Deichmann et al., 1952
Rat	i.p.	3.5	DuBois and Coon, 1952
Rabbit	oral (in oil)	420	Wills, 1968
Rabbit	oral (un- diluted)	1 270	Wills, 1968

#### 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

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- 244 -

questionable at the 20 ppm level and no significant anticholinesterase activity was found in the 5 ppm group.

#### Other studies

No information available.

#### Other studies

#### (a) Reproduction

A three-generation reproduction study using 10 male and 20 female rats per dose level for each generation, at 0, 10 and 30 ppm parathion-methyl, and comprising two litters per generation, revealed no consistent effect on the number of live or stillbirths, birth weights, physical structure of newborn, litter size, weanling weights or percentage survival to weaning.

Sporadic effects included lower weanling survival rate in F<sub>1a</sub>, F<sub>1b</sub> and F<sub>2a</sub> generations at 30 ppm, and in F<sub>3a</sub> generation at 10 ppm, increased stillbirth rate in F<sub>1b</sub> and F<sub>3a</sub> generations at 30 ppm, and F<sub>3a</sub> at 10 ppm; reduced mean weanling rate in F<sub>2a</sub> generation at 30 ppm, and F<sub>1b</sub> generation at 10 ppm. Reduced reproductive performance in F<sub>1a</sub>, F<sub>1b</sub>, F<sub>2a</sub> and F<sub>3b</sub> generations at 30 ppm, was the only parameter consistently affected. No such activity was evident at the 10 ppm level (Woodard Research Corp., 1966).

#### (b) Teratogenicity

Some cases of foetal deaths and malformations have been reported in Japan and may possibly be related to the use of organo-phosphorus insecticides in the field (Ogi and Hamada, 1965). Parathion was identified in a human term foetus whose mother had used it to commit suicide (Le Breton et al., 1963). No significant developmental defects in rats whose mothers had been injected intraperitoneally with methyl parathion was observed (Fish, 1966).

Because of these reports, the effect on organogenesis in the rat and mouse was studied by injecting intraperitoneally parathion-methyl suspended in a 0.5 per cent. aqueous solution of sodium carboxymethyl cellulose once on day 12 of gestation in rats and once on day 10 in mice. The dosage was 5 to 15 mg/kg of body-weight in rats and 20 to 60 mg/kg in mice. The animals were killed near term on day 21 in rats and on day 18 in mice. The foetuses were examined for intrauterine death, external malformations, internal abnormalities and skeletal abnormalities. All animals of both species showed signs of toxicity about 30 minutes after administration of parathion-methyl. Ataxia and

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saliva and tear  
vulsions. Some  
Food and water  
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#### Observations in

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In a conti  
given parathion-  
8 mg and 9 mg.  
activities were  
values (Moeller

#### Comments

Teratogen  
parenteral admin  
studies in rats  
reproductive pr  
evaluate this c  
change the acc  
daily intake.

#### Estimate of the

C-0.001 mg  
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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 (Tanimura 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-methyl 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

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