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ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

File # 1F1091

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 information.

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

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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

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

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NATIONAL AGRICULTURAL CHEMICALS ASSOCIATION

THE MADISON BUILDING • 1155 FIFTEENTH ST., N.W.
WASHINGTON, D. C. 20005

CABLE: NAGRCHEM PH: 202 • 296-1585

April 25, 1972

45th DAY

Mr. Lee A. Farbush
Petition Control Officer
Pesticides Tolerances Division
Environmental Protection Agency
Washington, D. C. 20460

Subject: Pesticide Petition No. 1F1091

Dear Mr. Farbush:

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 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,

Denis Hurley
Secretary & Treasurer

Enclosures

cc: [illegible]
Mr. A. D. Lindquist
Mr. J. Marshall Horner

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

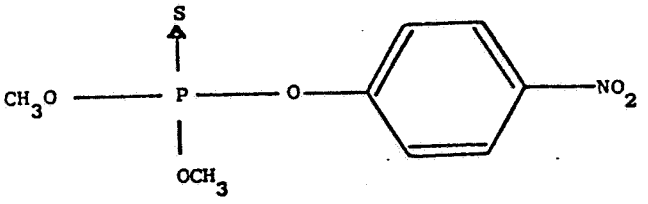
Chemical name

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

Synonyms

Metaphos, Folidol M, E 605, Nitrox, Wofatox

Formula



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., 1958).

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 4×10^{-8} (Davison, 1955).

Acute toxicity

Animal	Route	LD_{50} (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

...ntionable at the 20 ppm level and no significant anti-...terase activity was found in the 5 ppm group.

...n studies

No information available.

...l 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 ... 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_{1a}, F_{1b} and F_{2a} generations at 30 ppm, and in F_{3a} generation at 10 ppm, increased stillbirth rate in F_{1b} and F_{3a} generations at 30 ppm, and F_{3a} at 10 ppm; reduced mean weanling rate in F_{2a} generation at 30 ppm, and F_{1b} generation at 10 ppm. Reduced reproductive performance in F_{1a}, F_{1b}, F_{2a} and F_{3b} 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, 1963). 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 ...lium 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 ...y-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 ...minutes after administration of parathion-methyl. Ataxia and

paralysis of ve... saliva and tear... vulsions. So... Food and water ... four days and t... malformations w... suppression of ... higher dosage. ... incidence of wi... in other experi... vertebrae and ... group treated w...

Observations in...

Normal le... were establish... were given para... 3.5 mg/day for ... cholinesterase ... effects, were o...

In a second... parathion-methyl ... days followed b... mg/day for 28 d... group, 6.5 mg/d... maximum depress... approximately 1... beforehand (Moel...

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

Comments

Teratogen... parenteral admi... studies in rats ... reproductive p... evaluate this ... change the ac... daily intake.

Estimate of t...

0-0.01 m...

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