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

FEB 19 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Methidathion

FROM: Esther Rinde, Ph.D. E. Rinde 12/30/87
Scientific Mission Support Staff (TS-769c)

TO: Dennis H. Edwards
Product Manager #12
Registration Division (TS-767c)

The Toxicology Branch Peer Review Committee met on Oct. 15, 1987 to discuss and evaluate the weight-of-the-evidence on Methidathion, with particular reference to its oncogenic potential.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Theodore M. Farber — Theodore M. Farber
William L. Burnam — Wm L Burnam
Reto Engler — Reto Engler
Marion Copley — Marion P. Copley
Kerry Dearfield — Kerry L Dearfield
Judith Hauswirth — Judith W. Hauswirth
Richard Levy — Richard A. Levy
Jack Quest — John A. Quest
Esther Rinde — Esther Rinde

A. 2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Marion Copley

Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Anne Barton

Richard Hill/Don Barnes

Robert Beliles

Diane Beal

4. Other Attendees:

George Ghali (TOX), and Joan Kennedy (RD) also attended.

B. Material Reviewed:

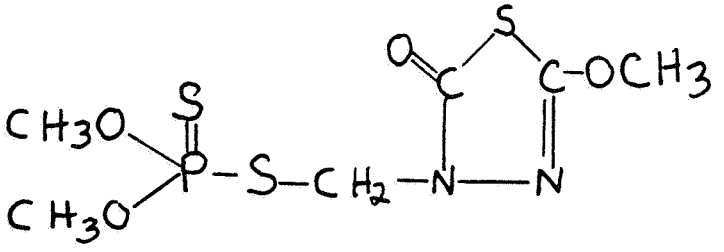
The material available for review consisted of DER's, one-liners, and other data summaries prepared by Dr. Copley; Tables and statistical analysis by B. Fisher. The material reviewed is attached to the file copy of this report.

C. Background Information:

Methidathion [O,O-dimethyl phosphorodithioate S-ester with 4(mercaptomethyl)-2-methoxy-delta 2-1,3,4-thiadiazolin-5-one] is an organophosphate insecticide-acaracide used on several agricultural crops. An IBT mouse oncogenicity study cited in RS-83 [EPA Guidance for Registration of Pesticide Products containing Methidathion, 1/13/1983] showed an increased incidence of male mouse liver tumors associated with dietary administration of Methidathion; however, the study was invalid. A new IRDC study (discussed under Section D) showed a statistically significant treatment-related increase in benign and malignant liver tumors in male CD-1 mice.

A Final Registration Standard and Tolerance Reassessment (FRSTR) is scheduled for completion in May 1988.

Structure of Methidathion:



D. Evaluation of Oncogenicity Evidence for Methidathion:

1. Rat Oncogenicity Study

Reference: MIN 832001; Ciba-Geigy Corp., Summit, N.J., 1986.

Technical Methidathion was administered in the diet to groups of 65 male and 65 female Sprague/Dawley [Crl:COBS CD(SD)BR] rats at 0,4,40 or 100 ppm (equivalent to 0,0.2,2 or 5 mg/kg/day, respectively) for two years.

There were no treatment-related increases in the incidence of neoplastic lesions at any dose.

The MTD was approached at 40 ppm, based on chemical and neurologic signs of cholinesterase inhibition (serum, RBC and brain) in both males and females. In females, the MTD may have been exceeded at 100 ppm (HDT) based on 12-21% decrease in body weight gain, compared to concurrent controls.

2. Mouse Oncogenicity Study

Reference: IRDC # 382-087; IRDC, Mattawan, Mich., Study Termination Date: 1984; Study Report: 1986.

Technical Methidathion was fed in the diet to groups of 50 male and 50 female Chr-CD-1 mice at 0,3,10,50,or 100 ppm (equivalent to 0, 0.46, 1.6, 7.5 or 16.1 mg/kg/day, respectively) for 2 yrs.

Neoplastic lesions:

In the livers of male mice only: adenomas were significantly increased at all doses; carcinomas were increased at 50 ppm (exceeding also the historical control incidence), but were significant only at 100 ppm (HDT), and combined adenoma/carcinoma were significantly increased at 50 and 100 ppm. There was also a significant dose related trend ($p<0.01$) for carcinoma, adenoma and adenoma/carcinoma combined. In female mice, there were no significant treatment-related increases in the incidence of liver tumors.

The incidences of male liver tumors are given in Table 1. Historical Control values for other studies conducted in the same laboratory are summarized in Table 2. Concurrent controls in the present study had an unusually low adenoma incidence; also, the adenoma incidences at all dose levels below 100 ppm fell within the range for historical controls*. Thus for adenoma per se, the only dose level at which the Committee considered the incidence to be biologically significant, was 100 ppm.

*Since these data are from the performing laboratory, the Committee agreed that this comparison was appropriate.

TABLE 1

Methidathion - Chr-CD-1 Mouse Study
Male Liver Tumor

(Carcinoma and/or Adenoma) Ratest† and Cochran-Armitage
Trend Test and Fisher's Exact Test Results

Liver Tumor	Dose (ppm)				
	0	3	10	50	100
Adenoma only	1/46 (2)**	9/45 (20)**	7/47 (15)*	8/43 (19)**	21/45 (47)a**
Carcinoma	8/46 (17)**	6/45 (13)	4/47 (9)	13/43 (30)	17/45 (38)*
Carcinoma and/or Adenoma	9/46 (20)**	15/45 (33)	11/47 (23)	21/43 (49)**	38/45 (84)**

† Tumor-bearing animals/animals at risk (excludes all animals that died before appearance of the first tumor).
( ) = Percent.
[a] Appearance of first liver tumor - week 63.
Significance of trend analysis denoted at Control.
Significance of pairwise comparison with control denoted at Dose level.

* $p < .05$ ** $p < .01$

Table 2

HISTORICAL CONTROL DATA
Male Chr-CD-1 Mouse

Studies terminated between[1]:

1978 and 1983 (11 studies)

Liver tumors	mean %	(range)
Adenomas	11	(0 - 26.7)
Carcinomas	5.7	(0 - 14.3)
Adenoma/Carcinoma[2]	16.7	(5.0 - 26.7)

1984 and 1985 (3 studies)

Liver tumors	mean %	(range)
Adenomas	14.8	(8.0 - 24.0)
Carcinomas	6.9	(3.3 - 10.0)
Adenoma/Carcinoma[2]	20.0	(13.3 - 32.0)

[1]The Methidathion study (dated 3/7/86) was terminated in 1984.

[2]Animals counted only once.

D. 2. Mouse Oncogenicity Study (continued)

Non-Neoplastic Effects:

These were lesions in the liver and gall bladder (primarily), and included bile duct hyperplasia, cholangiofibrosis, gall bladder epithelial hyperplasia and chronic hepatitis, in both sexes. In females only, there was a decrease in RBC cholinesterase. In males, at 100 ppm, there was also increased mortality; increases in platelets, leukocytes, AST/ALK and plasma cholinesterase; decreased brain cholinesterase; increased absolute and relative spleen weight and EMH, and decreased hepatic EMH. In females, at 100 ppm, additional effects included decreased brain cholinesterase, and cholecystitis.

The MTD appears to have been exceeded in males at 100 ppm (HDT) based on a statistically significant decrease in survival* (24% vs 56% in concurrent controls); other effects included plasma and brain cholinesterase inhibition, and non-neoplastic lesions in the liver. In the female, the MTD appears to have been approached at the HDT, based on decreased brain and RBC cholinesterase and non-neoplastic lesions in the liver.

E. Additional Toxicology Data on Methidathion:

1. Metabolism

No acceptable metabolism studies have been reviewed by TOX. A new metabolism study has been received by RD and will be reviewed by TOX as soon as it is submitted (requested from RD 8/21/87). Figure 1 summarizes what is known about Methidathion metabolism in the rat [RS-83].

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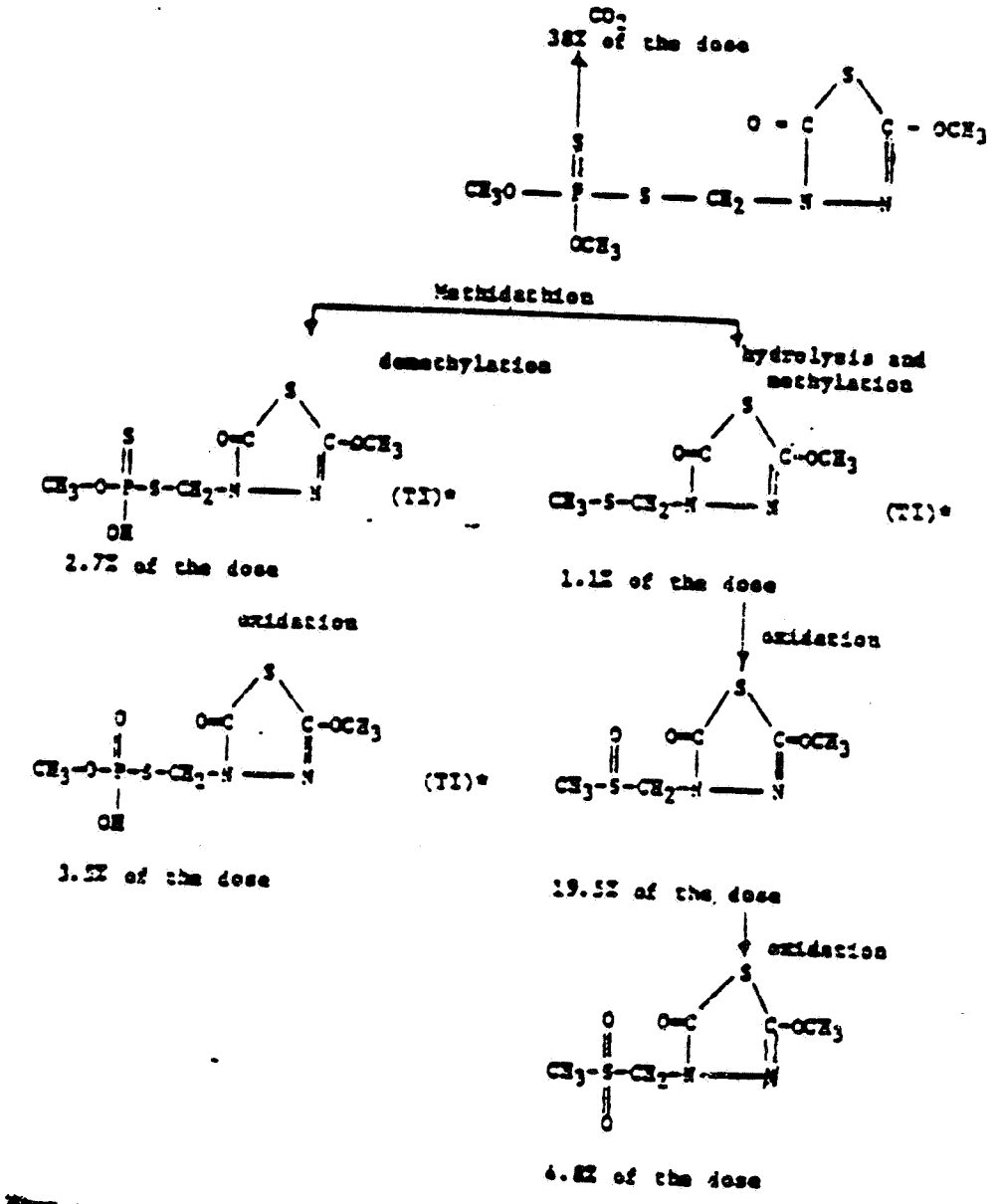
*These excess deaths occurred mainly during the last few weeks of the study; nevertheless, it was suggested that animals at the 100 ppm dose level may have been excessively stressed throughout the study. However, there was a statistically significant increase in combined adenoma/carcinoma even at 50 ppm, where the MTD was not exceeded.

FIGURE 1



*II is tentative identity.

METABOLIC PATHWAY OF METHIDATHION IN THE RAT

E. 2. Mutagenicity

The following acceptable studies [RS-83] were negative for mutagenicity:

1) in vitro bacterial assays: S. typhimurium, (point mutations, strains TA98, TA100, TA1535, TA1537, TA1538 ± activation); E. coli (point mutations, strain B/r WP2 ± activation); B. subtilis (rec assay, strains H17 and M45).
2) host-mediated assays: S. typhimurium in Swiss Webster mice and in albino mice; mouse lymphoma (mammalian cell line) cells in DBA/Bom/SPF mice.
3) nuclear anomalies assay: in vivo assay for clastogenicity in Chinese hamster bone marrow.
4) sister-chromatid exchange (SCE): Chinese hamster bone marrow
5) dominant lethal assay: albino male mice.

3. Structure-Activity Correlations

No structurally related chemicals with oncogenic concerns were identified in a search of data bases in Chemical Information Systems, Inc. and NLM's TOXLINE AND TOXLIT65. Two pesticides (Prothidathion and Lythidathion) with similar structures, listed in the Farm Chemical Handbook, do not have readily available toxicity information, since they are not registered in the USA.

Oxadiazone, reported to be oncogenic to the liver in two rodent species, and a proposed metabolism scheme by which a hydrazine might be generated, were also discussed (Memo: G.Ghali to M.Copley, 9/28/87). The Committee, however, did not feel that Oxadiazone was a very good analog for Methidathion.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on Methidathion to be of importance in a weight-of-the evidence determination of oncogenic potential.

Methidathion fed to CD-1 mice resulted in statistically significant increases in the incidence of both benign and malignant liver tumors in males only.

Carcinomas were increased at 50 ppm (exceeding also the historical control incidence), but were significant only at 100 ppm (HDT), and occurred with a significant ($p<0.01$) dose-related trend.

Adenomas were significantly increased at 100 ppm, but the Committee concluded that at doses below 100 ppm, adenomas per se were not biologically significant, based on the low incidence in concurrent controls, and by comparison to historical control incidences.

Combined adenoma/carcinoma were significant ($p<0.01$) at 50 and 100 ppm and occurred with a significant ($p<0.01$) dose-related trend.

The incidences of both tumor types, individually and combined were unusually high at 100 ppm compared to that of historical controls from the same laboratory.

It was also determined that the proportion of malignant tumors was not increased in a dose-related fashion and there was no apparent shortening of time to appearance of tumor.

Methidathion fed to Sprague-Dawley rats was not oncogenic in either sex at doses up to 100 ppm.

Methidathion was not mutagenic in several acceptable studies (in vitro point mutations assays, both mammalian and bacterial; nuclear anomaly test; SCE; dominant lethal test).

There were no close structural analogs with oncogenic concerns identified.

G. Classification of Oncogenic Potential:

Criteria contained in the EPA Guidelines [FR51: 33992-34003, 1986] for classifying a carcinogen were considered.

Dietary administration of Methidathion was associated with benign and malignant liver tumors in only one species (mouse), and only 1 sex (male).

Adenomas, although increased at all doses, were only considered to be biologically relevant at 100 ppm (HDT); carcinomas were increased at 50 ppm (exceeding also the historical control incidence), but were significant only at 100 ppm; combined adenoma/carcinoma were significantly increased at 50 and 100 ppm.

The MTD appeared to have been exceeded in males at 100 ppm; but at 50 ppm, where the MTD was not exceeded, combined adenoma/carcinoma were significantly increased (21/47 vs 9/46 in concurrent controls, at $p<0.01$).

The incidence of both benign and malignant tumors at 100 ppm was unusually high, but there was no dose-related increase in the proportion of tumors that were malignant, or dose-related shortening of time to appearance of tumors, and Methidathion was negative in a spectrum of short-term mutagenicity studies.

The Peer Review Committee agreed that the above constituted only limited evidence of carcinogenicity, particularly since the only oncogenic response was in the male mouse liver, and classified Methidathion as a Group C, Possible Human Carcinogen. Additional evidence from short-term tests or structure-activity relationships were not supportive of a higher classification.

The evidence as a whole (ie: 1 species, 1 sex, common tumor; no increase in proportion of malignant tumors, or apparent shortening of time to tumor; lack of mutagenicity or SAR) was not considered strong enough to warrant a quantitative estimation of human risk.