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Methidathion; CASRN 950-37-8

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Methidathion

File First On-Line 08/22/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/22/1988
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	05/01/1989

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Methidathion

CASRN — 950-37-8

Last Revised — 08/22/1988

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver toxicity	NOEL: 4 ppm (0.1 mg/kg/day)	100	1	1E-3 mg/kg/day
2-Year Dog Feeding Study	LEL: 16 ppm (0.4 mg/kg/day)			
Ciba-Geigy, 1967				

* Conversion Factors: 1 ppm = 0.025 mg/kg/day (assumed dog food consumption)

I.A.2. Principal and Supporting Studies (Oral RfD)

Ciba-Geigy Corporation. 1967. MRID No. 00011839. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Methidathion was administered in the diet at 0, 4, 16, or 64 ppm (0.1, 0.4, or 1.6 mg/kg/day) to 3 males and 3 females per dose group for 2 years.

Signs of toxicity noted at the mid and high doses were: increased alkaline phosphatase and SGPT, as well as histologic liver alterations including pigmentation (porphyrin), serositis, fibrosis, nodularity, and phlebitis. RBC cholinesterase inhibition was only observed at the high dose. Based on liver pathology and related enzyme changes, the NOEL and LEL for systemic toxicity are 4 and 16 ppm (0.1 and 0.4 mg/kg/day), respectively.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 100 was used, 10 each to account for the inter- and intraspecies differences.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Data Considered for Establishing the RfD

- 1) 2-Year Feeding - dog: Principal study - see previous description; core grade minimum
- 2) 2-Year Feeding (oncogenic) - rat: Systemic NOEL=4 ppm (0.2 mg/kg/day); Systemic LEL=40 ppm (2 mg/kg/day) (inhibition of RBC and brain ChE, alopecia and neurologic signs); core grade guideline (Ciba-Geigy Corp., 1986a)
- 3) 2-Generation Reproduction - rat: Maternal NOEL=5 ppm (0.25 mg/kg/day); Maternal LEL=25 ppm (1.25 mg/kg/day) (tremors and decreased food consumption during lactation); Reproductive NOEL=5 ppm (0.25 mg/kg/day); Reproductive LEL=25 ppm (1.25 mg/kg/day) (unthrifty in the pups while nursing); core grade minimum (Ciba-Geigy Corp., 1986b)
- 4) Teratology - rat: Maternal NOEL=1 mg/kg/day; Maternal LEL=2.25 mg/kg/day (clinical signs of cholinesterase inhibition); Developmental NOEL=2.25 mg/kg/day (HDT); Developmental LEL=none; core grade minimum (Ciba-Geigy Corp., 1987a)
- 5) Teratology - rabbit: Maternal NOEL=6 mg/kg/day; Maternal LEL=12 mg/kg/day (clinical signs of cholinesterase inhibition); Developmental NOEL=12 mg/kg/day (HDT); Developmental LEL=none; core grade minimum (Ciba-Geigy Corp., 1987b)

Other Data Reviewed:

- 1) 2-Year Feeding (oncogenic) - mice: Systemic NOEL=10 ppm (1.6 mg/kg/day); Systemic LEL=50 (7.5 mg/kg/day) (nonneoplastic liver alterations in males, RBC ChE inhibition in females); core grade minimum (Ciba-Geigy Corp., 1986c)

Data Gaps: None

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — High

RfD — High

The critical study is of adequate quality and is given a medium confidence rating. Additional studies are supportive and of good quality and therefore, the database is given a high confidence rating. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — Pesticide Registration Files

Agency Work Group Review — 01/21/1988

Verification Date — 01/21/1988

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Methidathion

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Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Methidathion

CASRN — 950-37-8

Last Revised — 05/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk

Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen.

Basis — increased incidence of liver adenomas, carcinomas, and combined adenomas and carcinomas in male mice. There was no shortening of time to tumor. Short-term tests and structure/activity study were not supportive of a higher classification.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. Both chronic rat and chronic mouse bioassays have been conducted (Ciba-Geigy, 1986a,b). Technical methidathion was fed in the diet to 50 Cbr- CD-1 mice/sex/group at levels of 0, 3, 10, 50, or 100 ppm for 2 years (Ciba- Geigy, 1986a). An increased incidence of liver adenomas was observed in each dose group in male mice; however, the incidence was within the range of values measured for historical controls (14 studies from the same laboratory) in all but the 100 ppm (HDT) group. The adenoma incidence of 21/45 at 100 ppm vs. 1/46 in the male concurrent controls was statistically significant by the OPP Peer Review Committee. In male mice, there was also a statistically significant increase in hepatic carcinomas at the 100 ppm dose (17/45) as compared with the controls (8/46) and in carcinomas and/or adenomas in the 40 and 100 ppm dose groups (21/47 and 38/45, respectively), as compared with the controls (9/46). There were also statistically significant dose-related trends for carcinoma, adenoma, and adenomas and/or carcinomas combined for male mice. No significant treatment-related trend or increases in the incidence of tumors was observed in female mice.

A significant upward trend in the mortality of male mice was observed to be due to the large number of deaths in the 100 ppm-dose group. No effect on mortality in female mice was seen. In males, the MTD appears to have been exceeded at 100 ppm based on the increased mortality; other effects included plasma and brain cholinesterase inhibition and nonneoplastic lesions in the

liver. In females, the dose selection appears to have been adequate and an MTD achieved, based on observation of decreased body weight gain and water consumption.

Technical methidathion was fed in the diet to groups of 80 male and 80 female Sprague-Dawley rats of the CrI:COBS CD (SR)BR strain at 0, 4, 40, or 100 ppm for 2 years. The population was reduced by 10 rats/sex/dose at week 52 and 5 rats/sex/dose at week 93. There was no indication of oncogenic potential at any dose level (Ciba Geigy, 1986b).

No treatment-related mortality was observed for either sex. The MTD was achieved in both sexes at 40 ppm based on chemical (serum, RBC, and brain) and neurologic signs of cholinesterase inhibition in both sexes. In the females, the MTD may have been exceeded at 100 ppm (HDT) since there was a 12 to 21% decrease in body weight gain compared with concurrent controls.

II.A.4. Supporting Data for Carcinogenicity

Methidathion was tested in five studies for genotoxic effects with negative results. These studies include mutagenicity assays using *S. typhimurium* (with and without hepatic homogenates); mutagenicity assays in mouse lymphoma cells; a DNA damage test Chinese hamster bone marrow cells; and a sister-chromatid exchange test in Chinese hamster bone marrow.

Studies of structurally related chemicals have not demonstrated carcinogenicity.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA. 1987. Office of Pesticides Program Peer Review memoranda of 9/10/87, 10/13/1987 and 11/10/1987.

The OPP Peer Review Group and the Science Advisory Panel reviewed data on methidathion.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 01/04/1989

Verification Date — 01/04/1989

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Methidathion

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VI.A. Oral RfD References

Ciba-Geigy Corporation. 1967. MRID No. 00011839. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1986a. Accession No. 263322-6. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1986b. MRID No. 40079812, 40079813. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1986c. Accession No. 262098-106. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1987a. MRID No. 40079807, 40079808. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1987b. MRID No. 40079809, 40079810. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Ciba-Geigy Corporation. 1986a. Accession No. 262098-106. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1986b. Accession No. 263322-6. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

U.S. EPA. 1987. Office of Pesticides Program Peer Review memoranda of 9/10/87, 10/13/1987 and 11/10/1987.

VII. Revision History

Substance Name — Methidathion
CASRN — 950-37-8

Date	Section	Description
08/22/1988	I.A.	Oral RfD summary on-line
05/01/1989	II.	Carcinogen summary on-line

VIII. Synonyms

Substance Name — Methidathion

CASRN — 950-37-8

Last Revised — 08/22/1988

- 950-37-8
- Ciba-Geigy GS 13005
- DMTP
- ENT 27193
- Fisons NC 2964
- Geigy 13005
- GS 13005
- Methidathion
- methidathion 50S
- OMS 844
- O,O-dimethyl-s-(2-methoxy-1,3,4-thiadiazol-5(4H)-onyl-(4)-methyl)phosphorodithioate
- O,O-dimethyl-S-((2-methoxy-1,3,4 (4H)-thiadiazol-5-on-4-yl)-methyl)-dithiofosfaat
- (O,O-dimethyl)-S-(-2-methoxy-delta(sup 2)-1,3,4-thiadiazolin-5-on-4-ylmethyl)dithiophosphate
- O,O-dimethyl S-(5-methoxy-1,3,4-thiadiazoliny-3-methyl) dithiophosphate
- O,O-dimethyl-S-(2-methoxy-1,3,4-thiadiazol-5-on-4-ly)-methyl-dithiophosphat
- O,O-dimethyl-S-(2-methoxy-1,3,4-thiadiazol-5-(4H)-onyl-(4)-methyl)-dithiophosphat
- O,O-dimetil-S-((2-metossi-1,3,4-(4H)-tiadiazol-5-on-4-il)-metil)-ditifosfato
- S-(2,3-dihydro-5-methoxy-2-oxo-1,3,4-thiadiazol-3-methyl) dimethyl phosphorothiolothionate
- S-2,3-dihydro-5-methoxy-2-oxo-1,3,4-thiadiazol-3-ylmethyl O,O-dimethylphosphorodithioate
- S-((5-methoxy-2-oxo-1,3,4-thiadiazol-3(2H)-yl)methyl) O,O-dimethyl phosphorodithioate
- S-2-metoksy-1,3,4-tiadiazolo-5-on-N-metylo-O,O-dwumetylowy
- somonil
- supracid
- supracide
- ultracid 40
- ultracide