

DIMETHRIN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

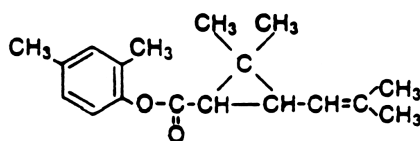
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAS are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 70-38-2

Structural Formula



2,4-Dimethylbenzyl-2,2-dimethyl-3-(2-methylpropenyl)-cyclopropane carboxylate

Synonyms

- ENT 21,170; Chrysanthemumic acid; 2,4-Dimethylbenzylester.

Uses

- Insecticide for use in ponds and swamps as a mosquito larvicide (Meister, 1986).

Properties

Chemical Formula	C ₁₈ H ₂₄ O ₂
Molecular Weight	286.39 (Ambrose, 1964)
Physical State (25°C)	Amber liquid
Boiling Point	175°C
Melting Point	
Density	
Vapor Pressure (25°C)	
Specific Gravity	0.98
Water Solubility (25°C)	Insoluble (further details not provided)
Log Octanol/Water Partition Coefficient	
Taste Threshold	
Odor Threshold	
Conversion Factor	

Occurrence

- No information is available on the occurrence of dimethrin in water.

Environmental Fate

- No information is available on the environmental fate of dimethrin.

III. PHARMACOKINETICSAbsorption

- In a preliminary metabolic study by Ambrose (1964), four rabbits were given 5 mL/kg (5 mg/kg) of undiluted dimethrin by intubation. Urine was collected every 24 hours over a 72-hour period. Identification of two possible metabolites in the urine indicated that dimethrin was absorbed. Sufficient data were not available to quantify the extent of absorption.

Distribution

- No information on the distribution of dimethrin was found in the available literature.

Metabolism/Excretion

- Information presented by Ambrose (1964) indicates that dimethrin (5 mg/kg), administered by intubation to rabbits, is metabolized (by reduction) and excreted in the urine as chrysanthemumic acid and the glucuronic ester of 2,4-dimethyl benzoic acid. Sufficient information was not presented to determine if these are the only metabolites of dimethrin or if any unchanged dimethrin is excreted.

IV. HEALTH EFFECTSHumans

- No information on the health effects of dimethrin in humans was found in the available literature.

Animals

Short-term Exposure

- The acute oral LD50 value of dimethrin for male and female Sherman rats was reported to be >15,000 mg/kg (Gaines, 1969).
- Ambrose (1964) conducted an acute oral study in which male and female albino rabbits (two/sex/dose) and male albino Wistar-CWL rats (five/dose) were given a single dose of 10 or 15 mL/kg (9.8 or 14.7 mg/kg) of technical-grade dimethrin (98% pure) by gavage. Albino guinea pigs (four/sex) received a single dose of 10 mL/kg (9.3 mg/kg) by gavage. No effects were observed in rats or rabbits during a 2-week observation period. (Specific parameters observed were not identified). In guinea pigs, the only effect reported during a similar observation period was a refusal to eat or drink for 24 hours following dosing.
- Ambrose (1964) administered 10 mL/kg (9.8 mg/kg) of technical-grade dimethrin (98% pure) to 15 male albino Wistar-CWL rats by gavage, 5 days per week for 3 weeks. This corresponds to an average daily dose of 7 mg/kg. No adverse effects, as judged by general appearance, behavior and growth, were observed. At necropsy, no gross abnormalities were observed. No histopathological examinations were performed.

Dermal/Ocular Effects

- Ambrose (1964) conducted a dermal irritation study in which dimethrin (98% pure) was applied at a dose level of 10 mL/kg (9.8 mg/kg) to the intact or abraded skin of four albino rabbits (two/sex) for a 24-hour exposure period. No skin irritation was observed immediately after the removal of the dimethrin or during a 2-week observation period.
- Ambrose (1964) reported that single or multiple (3 consecutive days) instillations of 0.1 mL of undiluted dimethrin (98% pure) into the conjunctival sac of eight albino rabbits caused no visible irritation or chemosis and no injury to the cornea as detectable by means of fluorescein staining. When 0.2 mL of dimethrin was applied to the penile mucosa of five albino rabbits on two occasions 6 days apart, no irritation or sloughing of the mucosa was observed during a 1-week observation period.
- Masri et al. (1964) applied 3 mL of undiluted dimethrin to the shaved back and sides of three albino rabbits 10 times over a 2-week period (frequency of application not specified). The only reported reaction was the development of a slight scaliness which disappeared after cessation of application.
- Ambrose (1964) applied dimethrin (98% pure) to the skin of albino rabbits (five/dose) 5 days per week for 13 weeks (65 applications). Doses administered were 0.5 mL/kg undiluted dimethrin or 0.5 mL/kg of a 50% solution of dimethrin in cottonseed oil (equivalent to 0.25 mL/kg of dimethrin); controls received 0.5 mL/kg of cottonseed oil only. No evidence of any cutaneous reaction was observed. Occasionally, a slight, nonpersistent erythema was observed in all groups of rabbits. At necropsy, all organs from treated animals were indistinguishable from the controls. No histopathological differences between control and treated animals were observed.

Long-term Exposure

- Masri et al. (1964) administered dimethrin to male (five/dose) and female (six/dose) weanling albino rats for 16 weeks at dietary levels of 0, 0.2, 0.6, 1.5 or 3.0%. Based on food consumption and body weight data presented in the study, these dietary levels of dimethrin were calculated to correspond to about 0, 120, 320, 1,000 or 2,300 mg/kg/day for males, and 0, 130, 400, 1,100 or 2,500 mg/kg/day for females. Results indicated a significant reduction in body weight in males

- receiving 0.6 or 3.0% and females receiving 1.5 or 3.0%. Absolute liver weight and liver-to-body weight ratios were significantly higher in both the male and female 1.5- and 3.0%-dose groups. Kidney-to-body weight ratios were also significantly higher for these groups. Scattered gross pathologic changes did not appear to bear a relationship to dose. Histopathological examination revealed dose-related morphological changes in the liver that consisted of a round eosinophilic ring in the cytoplasm, approximately the size of the nucleus. Amorphous material within the ring stained less densely than the rest of the cytoplasm. Also, many hepatic cells of rats receiving 1.5 or 3.0% dimethrin appeared larger than those of controls and had less distinct basophilic cytoplasmic particles. Hepatic changes were less pronounced in the 0.6% group. No cell inclusions were seen in rats receiving 0.2% dimethrin. The effects of increased liver and kidney-to-body weight ratios as well as histopathological changes in the liver were shown to be reversible after withdrawal of dimethrin. The No-Observed-Adverse-Effect Level (NOAEL) identified in this study was 0.2% dimethrin (120 mg/kg/day for males; 130 mg/kg/day for females).
- Ambrose (1964) administered dimethrin to male and female albino Wistar-CWL rats (10/sex/dose) for 52 weeks at dietary levels of 0, 0.05, 0.1, 0.5, 1.0 or 2.0%. These dietary levels correspond to 0, 30, 60, 300, 600 or 1200 mg/kg/day. The only statistically significant effect reported in this study was an increase in the liver-to-body weight ratios in both male and female animals receiving 1.0 or 2.0% dimethrin. Withdrawal of dimethrin from the diet for 6 weeks resulted in return of liver weights to levels indistinguishable from the controls. No differences in hemoglobin parameters were noted between the treated and control animals at any time during the 52-week period. Histologically, no significant changes or lesions that could be attributed to dimethrin in the diet were observed in any of the test groups of animals. A NOAEL of 300 mg/kg was identified from this study.
 - As described in a review by Cohen and Grasso (1981), dimethrin has been implicated as a hypolipidemic agent and causes an increase in hepatic peroxisome proliferation. Dietary administration of certain hypolipidemic agents to rodents has resulted in the induction of liver carcinomas.

Reproductive Effects

- No information on the reproductive effects of dimethrin was found in the available literature.

Developmental Effects

- No information on the developmental effects of dimethrin was found in the available literature.

Mutagenicity

- No information on the mutagenicity of dimethrin was found in the available literature.

Carcinogenicity

- No information on the carcinogenicity of dimethrin was found in the available literature. However, the report by Cohen and Grasso (1981) implicating dimethrin as a hypolipidemic agent may indicate that dimethrin has carcinogenic potential in rodents. (It should be noted that the relationship between hypolipidemic agents and liver carcinomas in rodents has not been observed in humans.)

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\text{L/day})} = \text{mg/L (ug/L)}$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the one-day HA values for dimethrin. It is therefore recommended that the Longer-term HA for a 10-kg child (10 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

No information was found in the available literature that was suitable for determination of the Ten-day HA values for dimethrin. It is therefore recommended that the Longer-term HA for a 10-kg child (10 mg/L, calculated below) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The 16-week rat study by Masri et al. (1964) has been selected to serve as the basis for determination of the Longer-term HA. In this study, male and female rats were administered dimethrin at dietary levels of 0, 0.2, 0.6, 1.5 or 3.0% for 16 weeks. Results of this study indicated a statistically significant reduction in body weights of males receiving 0.6 or 3.0%, and in females receiving 1.5 or 3.0%. Absolute liver weight and liver-to-body weight ratios were significantly higher in the 1.5- and 3.0%-dose groups. Kidney-to-body weight ratios were also significantly higher in those groups. Histopathological examinations revealed dose-related morphological changes in the liver occurring at dose levels as low as 0.6%. A NOAEL of 0.2% dimethrin (120 mg/kg/day for males; 130 mg/kg/day for females) was identified in this study.

Using a NOAEL of 120 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(120 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 12 \text{ mg/L (10,000 ug/L)}$$

where:

120 mg/kg/day = NOAEL, based on absence of hepatic effects in male rats exposed to dimethrin via the diet for 16 weeks.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Using a NOAEL of 120 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(120 \text{ mg/kg/day}) (70 \text{ kg})}{(100) (2 \text{ L/day})} = 42 \text{ mg/L (40,000 ug/L)}$$

where:

120 mg/kg/day = NOAEL, based on absence of hepatic effects in rats exposed to dimethrin via the diet for 16 weeks.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 52-week study in rats by Ambrose (1964) has been selected to serve as the basis for determination of the Lifetime HA for dimethrin. In this study, dimethrin was administered to albino Wistar-CWL rats for 52 weeks at dietary levels of 0, 0.05, 0.1, 0.5, 1.0 or 2.0%. A statistically significant increase in the liver-to-body weight ratio was observed in both male and female rats receiving 1.0 or 2.0% dimethrin (600 and 1,200 mg/kg/day). Histologically, no changes that could be attributed to dimethrin were observed in any of the test groups. No adverse effects were reported in rats receiving dimethrin at 0.5% (300 mg/kg/day for males) or lower.

Using a NOAEL of 300 mg/kg/day, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(300 \text{ mg/kg/day})}{(1,000)} = 0.3 \text{ mg/kg/day}$$

where:

300 mg/kg/day = NOAEL, based on absence of increased liver-to-body weight ratio in rats exposed to dimethrin in the diet for 52 weeks.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.3 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 10.5 \text{ mg/L (10,000 ug/L)}$$

where:

0.3 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (10.5 \text{ mg/L}) (20\%) = 2.1 \text{ mg/L (2,000 ug/L)}$$

where:

10.5 mg/L = DWEL

20% = assumed percentage of daily exposure contributed by ingestion of drinking water.

It should be noted that the Lifetime HA of 2 mg/L apparently exceeds the water solubility of dimethrin (insoluble).

Evaluation of Carcinogenic Potential

- No information on the carcinogenicity of dimethrin was found in the available literature. However, the report by Cohen and Grasso (1981) implicating dimethrin as a hypolipidemic agent may indicate that dimethrin has carcinogenic potential in rodents. (It should be noted that the relationship between hypolipidemic agents and liver carcinomas in rodents has not been observed in humans.)
- The International Agency for Research on Cancer has not evaluated the carcinogenicity of dimethrin.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), dimethrin may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No information on existing criteria, guidance, or standards pertaining to dimethrin was found in the available literature. However, tolerances for pyrethroids, of which dimethrin is a member, range from 0.05 ppm in potatoes (post-harvest) to 3 ppm in wheat, barley, rice and oats (CFR, 1985).

VII. ANALYTICAL METHODS

- Dimethrin is a cyclopropane carboxylate pesticide which, as such, can be analyzed by EPA Method #616 (U.S. EPA, 1984). This method covers CHO pesticides such as cyclopropane and resmethrin, which are chemically identical to dimethrin. The method is similar to other 600 series methods in that 1 liter of sample is extracted with methylene chloride and reduced to 1 mL or less. Analysis is by flame-ionization gas chromatography (FID/GC). A cleanup procedure is provided in case interferences are noted.
- While method #616 can be used for monitoring dimethrin, the analyst should demonstrate precision and accuracy data for this compound before proceeding. An estimated detection limit (EDL) should also be determined as specified by regulation (CFR, 1984). The detection limit should fall into the range of 20 to 50 ug/L.

VIII. TREATMENT TECHNOLOGIES

- The manufacture of this compound was discontinued (Meister, 1986). No information was found in the available literature on treatment technologies capable of effectively removing dimethrin from contaminated water.

IX. REFERENCES

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