

Diisopropyl methylphosphonate (DIMP); CASRN 1445-75-6

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 DIMP

File First On-Line 03/01/1989

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	04/01/1989
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	03/01/1989

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Diisopropyl methylphosphonate (DIMP)
CASRN —1445-75-6
Last Revised — 04/01/1989

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
No effects related to treatment	NOEL: 3000 ppm diet (75 mg/kg/day)	1000	1	8E-2 mg/kg/day
90-Day Dog Feeding Study	LOAEL: None			
U.S. DOD, 1980				

* Conversion Factors: Assumed dog food consumption = 2.5% bw/day

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

U.S. Department of Defense. 1980. AD-A082 685. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

The U.S. DOD (1980) evaluated the effects of subchronic feeding of DIMP (96% pure) mixed in the diets of purebred beagle dogs (4/sex/level) for 90 days at doses of 0, 150, 1500, or 3000 ppm. Assuming that a dog consumes approximately 2.5% of its body weight in food/day, these doses would be equivalent to approximately 0, 3.75, 37.5, or 75 mg/kg/day. The dogs were observed daily for general condition and signs of toxicity, and food intake and body weight were recorded weekly. Water was allowed ad libitum throughout. During the course of the experiment, all dogs were treated for intestinal parasites with sulfamethazine and quinacrine hydrochloride. A complete blood count (CBC), hemoglobin, hematocrit and an extensive clinical chemistry analysis were performed at the start of the experiment and at 4, 8, and 13 weeks. Initial and 13-week ophthalmological examinations were conducted. At termination, the animals were sacrificed by intravenous injection of barbiturate and a gross necropsy was performed. The liver, brain, thyroid, kidneys, adrenal glands, testes, ovaries, heart and spleen were weighed and these tissues, as well as others, were prepared for histological examination which was carried out on the control and high-dosed animals.

Feeding of DIMP to dogs in the diet at concentrations up to 3000 ppm (75 mg/kg/day) did not cause any toxic effects clearly related to its ingestion. Mean body weight and food intake levels did not differ significantly between treatment and control groups. No dose-related effects were seen in hematological parameters, urinalysis or clinical chemistry data. Mean clotting times likewise showed no dose-related pattern but were significantly increased at the 4-week interval in males receiving the 1500 ppm dose. Phosphorous levels were significantly decreased at 8 weeks in males on all three treated diets but the mean values, relative to those at other time intervals, were not unusual. No clearly dose-related effect was seen in plasma and red blood cell (RBC) cholinesterase activity although there appeared to be a tendency toward slight inhibition of plasma cholinesterase (16 to 20%) in the high-dosed group at week 4 when compared with week 0 values. Values for this parameter were not consistently time- nor dose- related. Interpretation of the results was complicated by inadequate control data.

Mean values for the absolute organ weights did not differ significantly from control. Mean relative weight of the ovaries from females ingesting the middle dose level were significantly increased. Ophthalmologic examination revealed no abnormal findings. Histopathological examination of the major organs in the control and high-dosed groups revealed changes commonly encountered in dogs. Two males in the high-dosed group displayed changes in the small intestine, described as cystic crypts of Lieberkuhn, commonly resulting from diarrhea associated with hypermotility of the intestines. This finding corresponded to soft, watery stools in both dogs during most of the study. While reported as being possibly related to DIMP ingestion, this condition was also found in one of the control males similarly afflicted with diarrhea. Based on the available data, the dose of 75 mg/kg/day may be considered a NOEL in dogs ingesting DIMP in the diet for 90 days. Considering there were no clear adverse effect levels in the 90-day studies, the conservative approach of selecting 75 mg/kg/day as the NOEL was selected.

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

UF — The UF of 1000 allows for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10A), uncertainty in the threshold for sensitive humans (10H), and uncertainty in the effect of duration when extrapolating from subchronic to chronic exposure (10S).

MF — None

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

In a 90-day toxicity study conducted in ARS/Sprague-Dawley rats (32/sex/group) were fed diets containing DIMP blended in Purina rat chow at levels of 0, 300, 1000, or 3000 ppm (U.S. DOD,

1976a). Assuming that the rats consumed approximately 5% of their body weight in food each day, these doses are equivalent to 0, 15, 50, or 150 mg/kg/day. A planned recovery study proved unnecessary due to the lack of toxic effects in this 90-day feeding study. Inhibition of cholinesterase was evaluated and there were no treatment related effects. Based on the available data, a dose of 150 mg/kg/day, at the highest dose tested, may be considered a NOEL for DIMP in rats.

In a similar study in ICR Swiss albino mice (30/sex/group), effects were evaluated following dietary intake of DIMP blended in Purina rodent chow at levels of 0, 210, 700, or 2100 ppm over 90 days (U.S. DOD, 1976a). Assuming that the mouse consumes approximately 15% of its body weight in food/day, these doses are equivalent to 0, 31.5, 105 and 315 mg/kg/day. Cholinesterase inhibition was not measured. No signs of toxicity were observed in any of the treated mice. Based on this limited data in mice, a NOEL of 315 mg/kg/day, the highest dose tested, is determined.

The U.S. DOD (1978) commissioned a study to evaluate the toxicity of DIMP administered to male and female Sprague-Dawley rats (20/sex/level) continuously for 26 weeks in drinking water at concentrations intended to be 1000 or 10 ppm and 6 or 0.6 ppb. These levels were prepared as dilutions equivalent to approximately 7.36, 0.0736, 0.000044 and 0.0000044 mg/L, respectively. It had been determined that the conversion from mg/L to ppm was incorrectly made using the conversion factor for air; the targeted dose levels were, therefore, not reached. Based on these data, the high-dose level of approximately 0.8 mg/kg/day (calculated from the author's data on mean cumulative milligrams consumed/gram of animal over the 26-week period), may be considered a NOEL for DIMP in the drinking water of rats over a 26 week duration. As these doses were well below the intended exposure level, the lack of observed effects is not surprising.

Male and female Sprague-Dawley rats (30/sex/level) were exposed to DIMP in laboratory water at intended levels of 0, 10 or 1000 ppm for 10 weeks prior to the initiation of a one-generation screening study for the effects of DIMP on the reproduction process (U.S. DOD, 1976b). Exposure to DIMP was continued in males through the mating period and in females through the end of lactation, for a maximum total exposure of approximately 13 to 19 weeks for males and females, respectively. The design of the study allowed for the evaluation of potential adverse effects of DIMP on the various phases of reproduction. A reported concentration of (actually 2.36 mg/L) DIMP in drinking water, equivalent to approximately 0.8 mg/kg/day (based on the author's data for the mean cumulative intake in milligrams/gram of animal over the first 10-week portion of the study), may be considered a NOEL for reproductive effects in rats. This study was conducted in the same laboratory as the U.S. DOD (1978) study and the same dose calculation error was made.

The U.S. DOD (1980) commissioned a study to examine the effects of DIMP on the reproductive capacity of Sprague-Dawley CD rats (10 males and 20 females/group) over a 3-generation (two matings/generation) study. The DIMP (96% pure) was suspended in 300 mL of PEG 400 and blended into Purina laboratory chow at levels of 300 and 3000 ppm. A level of 3000 ppm in the diet, equivalent to an intake of approximately 135 mg/kg/day for adult rats, may be considered a NOEL in this reproduction study. In the same study, female Charles River CD rats (20/level) received DIMP (96% pure) suspended in PEG 400 and blended into the diet at levels of 0, 100, 300, or 3000 ppm on days 6 through 15 of gestation. Assuming that the rat consumes approximately 5% of its weight in food/day, these levels would be equivalent of 0, 5, 15, or 150 mg/kg/day. No DIMP-related teratogenic effect was indicated. A dose of 150 mg/kg/day may be considered a NOEL for developmental effects.

The U.S. DOD (1979) evaluated the toxic effects of chronic DIMP ingestion by a dark variety of mink (6 males and 24 females/dose) at dietary levels of 0, 50, 150, or 450 ppm. Daily intakes were estimated to be 0, 11, 37, and 95 mg/kg/day based on mean feed consumption for 8 measurements over 4 months and mean body weight for 18 measurements over 12 months. These initially sexually immature animals were treated through one reproduction season or for approximately 12 months total duration. There were no reproductive effects; however, there was significant mortality in high-dose females. Mortality rates of 9, 12.5, and 21% in females at low-, mid-, and high-dose, respectively, were reported. The biological significance of this result is questionable because of the lack of other toxic effects in this study. Individuals were contacted regarding these data for clarification. Nationally, mortality for first-year mink in commercial fur ranch operations approaches 6% annually.

A study evaluating the toxicity of DIMP administered in drinking water to Sprague-Dawley rats (20/sex/dose) found no effects (HDT = 0.8 mg/kg/day) (U.S. DOD, 1978). The low dose rates were a result of a calculation error prior to dose administration. A one-generation reproduction study (Sprague-Dawley rats) in the same lab, with the same dose-calculation error, found no effects on a variety of male and female reproduction endpoints (NOEL=0.8 mg/kg/day) (U.S. DOD, 1976b). These data are of little use for derivation of the RfD as much higher NOELs have been established for this species and strain.

I.A.5. Confidence in the Oral RfD

Study — Low
Database — Low
RfD — Low

The principal study was adequate in design for a 90-day dog study, but failed to identify an effect level, and was complicated by concomitant treatment of the animals for parasites. Although

many toxicological endpoints have been evaluated for DIMP, no study has established a LOAEL. The mortality observed for mink is of questionable significance. Available long-term studies were poorly executed. Confidence in the RfD is rated low because of the likelihood of change with additional data.

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 — U.S. EPA, 1989

Agency Work Group Review — 05/25/1988

Verification Date — 05/25/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Diisopropyl methylphosphonate (DIMP) conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

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 — Diisopropyl methylphosphonate (DIMP)

CASRN —1445-75-6

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Diisopropyl methylphosphonate (DIMP)

CASRN —1445-75-6

Last Revised — 03/01/1989

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 — D; not classifiable as to human carcinogenicity.

Basis — No data from cancer bioassays or epidemiological studies are available.

II.A.2. Human Carcinogenicity Data

None.

Diisopropyl methylphosphonate was first introduced into the environment as a by-product or contaminant in the effluent from the manufacture of the nerve gas, GB. There are no human studies.

II.A.3. Animal Carcinogenicity Data

There are no lifetime (chronic) bioassays evaluating carcinogenicity.

II.A.4. Supporting Data for Carcinogenicity

No mutagenic activity was detected in a series of in vitro microbial assays (Salmonella) reported by the U.S. Department of Defense (DOD, 1976, 1980). Purified DIMP (>99.9%) dissolved in dimethylsulfoxide at concentrations ranging from 0.001 to 5 uL/plate was tested, in the presence or absence of the rat liver activation system, using Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 and Saccharomyces cerevisiae strain D4.

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, 1989

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

Agency Work Group Review — 09/22/1988

Verification Date — 09/22/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Diisopropyl methylphosphonate (DIMP) conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

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 — Diisopropyl methylphosphonate (DIMP)
CASRN —1445-75-6

VI.A. Oral RfD References

U.S. Department of Defense. 1976a. AD-A058 323. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1976b. AD-A040 454. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1978. AD-A054 733. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1979. AD-A087 257/2. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1980. AD-A082 685. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. EPA. 1989. Drinking Water Health Advisory for Diisopropyl Methyl- phosphonate. Office of Drinking Water, Washington, DC.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

U.S. Department of Defense. 1976. AD-A058 323. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1980. AD-A082 685. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. EPA. 1989. Health Advisory on Diisopropyl methylphosphonate. Office of Drinking Water, Washington, DC.

VII. Revision History

Substance Name — Diisopropyl methylphosphonate (DIMP)
CASRN —1445-75-6

Date	Section	Description
03/01/1989	II.	Carcinogen summary on-line
04/01/1989	I.A.	Oral RfD summary on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Diisopropyl methylphosphonate (DIMP)

CASRN —1445-75-6

Last Revised — 03/01/1989

- 1445-75-6
- diisopropyl methanephosphonate
- Diisopropyl methylphosphonate
- DIMP
- phosphonic acid, methyl-, bis(1-methylethyl) ester
- phosphonic acid, methyl-, diisopropyl ester