Isopropyl methyl phosphonic acid (IMPA); CASRN 1832-54-8

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 IMPA

File First On-Line 03/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	06/01/1992*
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	03/01/1991*

*A comprehensive review of toxicological studies was completed (05/27/05) - please see sections I.A.6. and II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Isopropyl methyl phosphonic acid (IMPA)
CASRN — 1832-54-8
Last Revised — 06/01/1992

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 adverse effects observed **Rat Drinking Water Study 90-day** **Mecler, 1981**	NOAEL: 3000 ppm (279 mg/kg-day) LOAEL: None	3000	1	1E-1 mg/kg-day

*Conversion Factors: Dose in mg/kg-day based on actual water consumption.

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

Mecler, F.J. 1981. Mammalian toxicological evaluation DIMP and DCPD (Phase 3 - IMPA). Litton Bionetics, Inc. Contract No. DAMD 17-77-X-7003. U.S. Army Medical Research and Development Command, Ft. Detrick, Frederick, MD. (Final report).

Concentrations of 0, 300, 1000, and 3000 ppm sodium IMPA were given in drinking water to groups of 20 Sprague-Dawley rats/sex for 90 days (U.S. DOD, 1981). Based on body weight and fluid consumption data, the female rats were exposed to an average of 0, 34, 137.4, or 399.1 mg/kg-day and the male rats to doses of 0, 25, 92.4, or 278.5 mg/kg-day. The animals were observed daily for gross signs of toxicity and weighed weekly. Food and water intake records were noted weekly. Blood samples were analyzed for standard hematological parameters at 4, 8, and 12 weeks. Blood chemistry measurements were determined only at the end of the study. After 90 days the animals were sacrificed. All tissues for the control and 3000-ppm groups were examined histologically and selected body organs were weighed.

No statistically significant effects of exposure were noted. In the 3000- ppm group there was a slight, insignificant decrease in body weight. The decrease was less than 10% for both males and females. The NOEL is 279 mg/kg-day based on no effects on body weight, clinical chemistry, hematology, or histological examinations. There is no LOAEL for this study.

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

UF — An uncertainty factor of 3000 reflects 10 each for intra- and interspecies variability, 10 for the use of a subchronic study for chronic RfD derivation, and an additional 3 to account for the lack of a toxicity study in a second specie, developmental toxicity studies, and a reproductive study.

MF — None

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

Isopropyl methylphosphonic acid also exists as the sodium salt, isopropyl methylphosphonate (CASRN 6838-92-3).

The application of an additional uncertainty factor was considered to compensate for the uncertainty attributable to the existence of only one long-term IMPA study. However, since IMPA is a mammalian metabolic product of diisopropyl methylphosphonic acid (DIMP), and more than 90% of DIMP is rapidly (within 24 hours) converted to IMPA (Ivie, 1980; Hart, 1976; Hart, 1980), the DIMP database can be used to support conclusions about IMPA (see following). In studies conducted in rats, mice, dogs, and mink, as well as in quail and ducks, for periods ranging from 90 days to 26 weeks, and in a 3-generation rat reproduction study, DIMP was relatively nontoxic to all species (U.S. EPA, 1988). No unequivocal systemic effect nor sign of toxicity was evident in any species. Since DIMP is rapidly and mostly metabolized to IMPA, it is reasonable to assume that the DIMP administered to mammals in these studies was metabolized to IMPA; therefore, the absence of effects from DIMP also may be considered to indicate a lack of effects from IMPA.

In a 90-day toxicity study, ARS/Sprague-Dawley rats (32/sex/dose) were fed diets containing DIMP blended in Purina rat chow at levels of 0, 300, 1000, or 3000 ppm (Hart, 1976). 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. Inhibition of cholinesterase was evaluated and there were no treatment related effects. Based on the available data, a dose of 150 mg/kg-day, the highest dose tested, may be considered a NOAEL for DIMP in rats.

In a similar study with ICR Swiss albino mice (30/sex/dose), 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 (Hart, 1976). 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 NOAEL of 315 mg/kg-day, the highest dose tested, is determined.

In a separate pharmacokinetics study, Hart (1976) gave mice, rats, and dogs a single oral dose of 225 mg/kg 14C-DIMP. Samples of blood, urine, feces, and expired CO2 (except dogs) were collected for up to 72 hours and analyzed for radioactivity. Rodent blood samples were taken when 3 mice and 2 rats were sacrificed at interval sampling times. Dog samples were taken from the femoral vein. Tissue samples were taken and analyzed when the animals were sacrificed. The detectable radiation declined to low levels within 24 hours. Within 24 hours approximately 90% of the recoverable radiation was in the urine when compared with the feces, carcass, and gastrointestinal tract.

Hart (1980) fed purebred beagle dogs (4/sex/dose) DIMP (96% pure) mixed in the diets for 90 days at concentrations 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. Concentrations of DIMP 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. Organ weights and histopathology were not affected by DIMP. Two males in the high-dose group displayed changes in the small intestine, described as cystic crypts of Lieberkuhn, commonly resulting from diarrhea associated with hypermotility of the intestines. While reported as being possibly related to DIMP ingestion, this condition was also found in one of the control males. Considering there were no clear adverse effect levels in the 90-day studies and using the conservative approach, 75 mg/kg-day was selected as the NOAEL.

The effects of DIMP on the reproductive capacity of Sprague-Dawley CD rats (10 males and 20 females/dose) over 3-generations (two matings/generation) was studied (Hart, 1980). DIMP (96% pure) was 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 NOAEL in this reproduction study. In the same study, female Charles River CD rats (20/dose) received DIMP (96% pure) blended into the diet at levels of 0, 100, 300, or 3000 ppm on days 6-15 of gestation. Assuming that the rat consumes approximately 5% of its weight in food/day, these levels would be equivalent to 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 NOAEL for developmental effects.

Hart (1980) continued a previous metabolism study (Hart, 1976), by analyzing 0-24-hour urine samples from mice, rats, and dogs. Thin-layer chromatography and gas-liquid chromatography/mass spectrometry showed that IMPA was the major product in the urine of all three species, following the administration of 14C-DIMP. This metabolite accounted for 93-99% of the recoverable radioactivity. The remaining metabolites were not identified.

Biskup et al. (1978) administered DIMP to male and female Sprague-Dawley rats (20/sex/dose) 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. The conversion from mg/L to ppm was made incorrectly; therefore, 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 NOAEL for DIMP in the drinking water of rats over 26 weeks. As these doses were well below the intended exposure level, the lack of observed effects is not surprising. A 1-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 reproductive endpoints (NOAEL = 0.8 mg/kg-day). These data are of little use for deriving the RfD, as much higher NOAELs have been established for this species and strain.

Hardisty (1976) exposed male and female Sprague-Dawley rats (30/sex/dose) to DIMP in laboratory water at intended levels of 0, 10 or 1000 ppm for 10 weeks prior to initiating of a 1-generation screening study on the reproductive effects of DIMP. 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 and 19 weeks for males and females, respectively. The design of the study allowed the researchers to evaluate the potential adverse effects of DIMP on the various phases of reproduction. A concentration of 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 NOAEL for reproductive effects in rats. This study was conducted in the same laboratory as the Biskup et al. (1978) study and the same dose calculation error was made.

Aulerich et al. (1979) fed DIMP to 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 doses, respectively, were reported. The biological significance of this result is questionable because of the lack of other toxic effects in this study.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Low
RfD — Low

The 90-day study in rats had an adequate number of animals of both sexes and evaluated a variety of gross, histological, hematological, and clinical endpoints. The study is weakened because blood chemistries were performed only at the end of the study rather than throughout it. The database is rated low because there is only one subchronic study in one species. The medium ratings for the study and the low rating for the database result in a low level of confidence in the RfD.

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

Source Document — U.S. EPA, 1992

Other EPA Documentation — None

Agency Work Group Review — 08/14/1991

Verification Date — 08/14/1991

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfD for Isopropyl methyl phosphonic acid and a change in the RfD is not warranted at this time. For more information, IRIS users may contact 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 — Isopropyl methyl phosphonic acid (IMPA)
CASRN — 1832-54-8

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Isopropyl methyl phosphonic acid (IMPA)
CASRN — 1832-54-8
Last Revised — 03/01/1991

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 — Based on no data in humans and animals.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

None.

II.A.4. Supporting Data for Carcinogenicity

Isopropyl methyl phosphonic acid was not mutagenic in five strains (TA98, TA100, TA1535, TA1537 and TA1538) of Salmonella typhimurium when tested according to the Ames protocol, both with and without microsomal activation (U.S. DOD, 1981). Concentrations of 0.5, 1.0, 10, 100, 500, 2500, and 5000 ug/plate were tested. There were signs of compound toxicity in some of the tested strains at doses of 2500 ug/plate or greater.

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

None.

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

None.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1989

The Health Advisory for Isopropyl Methyl Phosphonic Acid has received Agency and external review.

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

Agency Work Group Review — 01/10/1991

Verification Date — 01/10/1991

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the

existing carcinogenicity assessment for Isopropyl methyl phosphonic acid and a change in the assessment is not warranted at this time. For more information, IRIS users may contact 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).

VI. Bibliography

Substance Name — Isopropyl methyl phosphonic acid (IMPA)
CASRN — 1832-54-8

VI.A. Oral RfD References

Aulerich, R.J., T.H. Coleman, D. Polin, R.K. Ringer, K.S. Howell, R.E. Jones and T.J. Kavanaugh. 1979. Toxicology study of diisopropyl methylphosphonate and dicyclopentadiene in mallard ducks, bobwhite quail, and mink. Michigan State University, East Lansing, MI. Contract No. DAMD17-76-C-6054. AD-A087- 257.

Biskup, R.K., J.H. Manthei, J.C. Malloy, J.S. Wiles and E.R. McKinley. 1978. Toxicity study in rats dosed with diisopropyl methylphosphonate (DIMP) in their drinking water for 26 weeks. Technical Report ARCSL-TR-77073. Chemical Systems Laboratory, U.S. Army Armament Research and Development Command, Aberdeen Proving Ground, MD. AD-A054-733.

Hardisty, J.F. 1976. Reproductive studies with diisopropylmethylphosphonate in rats. Biomedical Laboratory, 24 March. AD-A040-454.

Hart, E.R. 1976. Mammalian toxicology study of DIMP and DCPD. Final Report. Litton Bionetics, Inc., Kensington, MD. Contract No. DAMD17-75-C-5068. AD-A058-323.

Hart, E.R. 1980. Mammalian toxicology study of DIMP and DCPD. (Phase 2). Litton Bionetics, Inc., Kensington, MD. Contract No. DAMD17-77-C-7003. AD-A082-685.

Ivie, G.W. 1980. Fate of diisopropyl methylphosphonate (DIMP) in a lactating cow. Bull. Environ. Contam. Toxicol. 24: 40-48.

Mecler, F.J. 1981. Mammalian toxicological evaluation DIMP and DCPD (Phase 3 - IMPA). Litton Bionetics, Inc. Contract No. DAMD 17-77-C-7003. U.S. Army Medical Research and Development Command, Ft. Detrick, Frederick, MD. (Final report).

U.S. EPA. 1988. Health Advisory on Diisopropyl Methylphosphonate (DIMP). Office of Water. U.S. Environmental Protection Agency, Washington, DC.

U.S. EPA. 1992. Health Advisory on Isopropyl Methylphosphonic Acid (IMPA). Office of Water. U.S. Environmental Protection Agency, Washington, DC.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

U.S. Department of Defense. 1981. Available from U.S. Army Medical Research and Development Command. DAMD17-77-C-7003. Ft. Detrick, Frederick, MD 21701.

U.S. EPA. 1989. Drinking Water Health Advisory for Isopropyl Methyl Phosphonic Acid. Office of Drinking Water, Washington, DC. (Draft)

VII. Revision History

Substance Name — Isopropyl methyl phosphonic acid (IMPA)
CASRN — 1832-54-8

Date	Section	Description
03/01/1991	II.	Carcinogenicity assessment on-line
06/01/1992	I.A.	Oral RfD summary on-line

Date	Section	Description
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
06/22/2005	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — Isopropyl methyl phosphonic acid (IMPA)
CASRN — 1832-54-8
Last Revised — 03/01/1991

- 1832-54-8
- Phosphonic acid, methyl-, mono(1-methylethyl) ester
- Phosphonic acid, methyl-, monoisopropyl ester
- 6838-93-3
- Isopropyl methyl phosphonic acid, sodium salt