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Provisional Peer-Reviewed Toxicity Values for

Methyl phosphonic acid
(CASRN 993-13-5)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR METHYL PHOSPHONIC ACID (CASRN 993-13-5)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths

and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Methyl phosphonic acid (MPA) is an environmental hydrolysis product of the chemical warfare nerve agents VX, GB (sarin), and GD (soman) (Munro et al., 1999). MPA has been detected in VX-contaminated soil, presumably as a hydrolysis product of ethyl methyl phosphonic acid, which is, itself, a hydrolysis product of VX at low (<6) or high (>10) pH (Munro et al., 1999). MPA is also formed very slowly in the environment from the hydrolysis of isopropyl methyl phosphonic acid (IMPA), which is a hydrolysis product of GB (Munro et al., 1999). In addition, a small number of bacteria species are capable of metabolizing IMPA to MPA (Zhang et al., 1999; Schowanek and Verstraete, 1990). The chemically related compound, diisopropyl methyl phosphonate (DIMP) is a by-product of the manufacture of GB (ATSDR, 1999; Munro et al., 1999). Sega et al. (1998) reported that the abiotic degradation of DIMP in groundwater resulted in IMPA and MPA, providing another source of MPA in the environment. The slow hydrolysis of pinacolyl methyl phosphonic acid (the primary product of GD hydrolysis) results in MPA formation from the environmental release of GD (Munro et al., 1999). MPA may also be found in the environment as a breakdown product of methyl phosphonate-containing pesticides and flame retardants (Munro et al., 1999).

In the environment, MPA is fairly stable because it is resistant to hydrolysis, photolysis, and thermal decomposition (Munro et al., 1999). Its high solubility, low vapor pressure, low K_{oc}, and low Henry's law constant indicate that MPA will be highly mobile in soils and will exist primarily in aqueous compartments (Munro et al., 1999). Figure 1 shows the chemical structure of MPA.

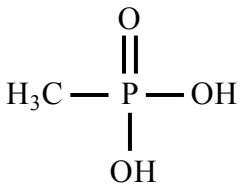

Figure 1. Structure of Methyl Phosphonic Acid

No chronic RfD, RfC, oral slope factor, or inhalation unit risk for MPA is available on the U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) (U.S. EPA, 2009), Drinking Water Standards and Health Advisories list (U.S. EPA, 2006a), or Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997). No documents for MPA are included on the Chemical Assessment and Related Activities (CARA) list (U.S. EPA, 1991, 1994). The U.S. Army (1999) derived an estimated RfD of 5.7×10^{-2} mg/kg-day for MPA based on a quantitative structure-activity relationship (QSAR) estimate of the chronic rat LOAEL of 566 mg/kg-day from TOPKAT® (Accelrys, Inc.), a commercial software program. Munro et al. (1999) mentioned the U.S. Army (1999) QSAR-based RfD but preferred a different RfD value of 2×10^{-2} mg/kg-day for MPA based on the subchronic rat NOAEL of 279 mg/kg-day for the closely related compound IMPA (Bausum et al., 1999). ATSDR (2007), NTP (2007), IARC (2007), and the WHO (2007) have not reviewed the toxicity of MPA. MPA is not included in the National Toxicology Program's (NTP's) 11th Report on Carcinogens (NTP, 2005). The American Conference of Governmental Industrial Hygienist (ACGIH, 2007), Occupational Safety and Health Administration (OSHA, 2007), and National Institute for Occupational Safety and Health (NIOSH, 2007) have not established occupational health standards for MPA. A U.S. Army (1975) review later summarized by Williams et al. (1987) and a review of chemical warfare agent degradation products (Munro et al., 1999) were consulted for relevant information.

To identify toxicological information pertinent to the derivation of provisional toxicity values for MPA, literature searches were initially conducted in January 2007 using the following databases: MEDLINE, TOXLINE Special, TSCATS/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS (these were not date limited); BIOSIS (from August 2000 to January 2007); and Current Contents (previous 6 months only). A final search for published studies was conducted for the period from July 2008 through March 2009.

REVIEW OF PERTINENT DATA

Human Studies

No data regarding human toxicity resulting from oral or inhalation exposure to MPA were identified in the available reviews or the literature searches.

Animal Studies

Oral Exposure

No chronic, subchronic, developmental, or reproductive toxicity studies conducted by the oral route of exposure were located for MPA.

Inhalation Exposure

No chronic, subchronic, developmental, or reproductive toxicity studies conducted by the inhalation route of exposure were located for MPA.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC TOXICITY VALUES FOR METHYLPHOSPHONIC ACID (RfDs, RfCs)

Due to a lack of data, no chronic or subchronic RfDs or RfCs are developed. However, the Appendix of this document contains a Screening Value for oral toxicity (RfD) based on an analog approach, which may be useful in certain instances. Please see the attached Appendix for details.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR METHYL PHOSPHONIC ACID

Weight-of-Evidence Descriptor

Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is "*Inadequate Information to Assess the Carcinogenic Potential*" of MPA; there are no human epidemiology studies, chronic toxicity studies, or carcinogenicity assays.

Quantitative Estimates of Carcinogenic Risk

The lack of data on the carcinogenicity of MPA precludes the derivation of quantitative estimates of risk for either oral (p-OSF) or inhalation (p-IUR) exposure.

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APPENDIX: DERIVATION OF A SCREENING VALUE FOR METHYL PHOSPHONIC ACID

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for methyl phosphonic acid. However, limited information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

Past efforts to derive RfDs for MPA employed quantitative structure-activity relationships (QSAR) to predict the toxicity of MPA (U.S. Army, 1999). The U.S. Army (1999) used a commercial software program TOPKAT® to predict a rat chronic LOAEL of 566 mg/kg-day, and, from this calculation, derive a chronic RfD of 0.057 mg/kg-day for MPA. In its review of a DuPont (2004) report, the ATSDR (2004) considered acute toxicity predictions for MPA based on the TOPKAT program. The ATSDR (2004) concluded that TOPKAT predictions for MPA were "not reliable because the query structures are poorly represented in the…database." Because the training set in the TOPKAT database is unpublished, it was not possible to verify ATSDR's concern or to validate this predicted chronic RfD for MPA.

Oral Toxicity Value

Screening Chronic and Subchronic RfD

Based on the consensus of results from the two independent approaches (see **Approaches 1 and 2**), the surrogate candidate with the most conservative RfD and highest similarity score would be recommended as the final surrogate for MPA. Therefore, for MPA, the provisional chronic and subchronic RfD for DMMP (6×10^{-2} or 0.06 mg/kg-day), derived by the U.S. EPA (2006b), and based on male reproductive toxicity in a rat study (Dunnick et al., 1984a), is recommended as a screening RfD, for MPA, based on the surrogate analyses (most conservative RfD and highest similarity score) presented here. The peer-reviewed document uses a LOAEL of 250 mg/kg-day (179 mg/kg-day after TWA adjustment) and includes a composite UF of 3,000 (10 for interspecies extrapolation, 10 for intraspecies extrapolation, 10 for use of a LOAEL, and 3 for DMMP database uncertainties). These UFs, described in the PPRTV for DMMP (U.S. EPA, 2006b), have been retained for the MPA assessment.

The **screening chronic and subchronic RfD** for MPA based on DMMP is derived as follows:

Screening Chronic and Subchronic RfD = LOAEL ÷ UF
= 179 mg/kg-day ÷ 3,000
= **0.06 mg/kg-day or 6×10^{-2} mg/kg-day**

Confidence in the critical reproductive study and database is the same as stated in the PPRTV for DMMP (see U.S. EPA, 2006b). Confidence in the overall surrogate approach is medium because the structural similarity is reasonably high between MPA and DMMP and because the physicochemical properties and the LD_{50} data among the potential surrogates and MPA are generally comparable (see Tables 1 and 2). In addition, the screening RfD calculated for MPA compares favorably with most of the available noncancer toxicity values of the potential surrogates identified herein (see Table 2). However, due to the high inherent uncertainty in the overall surrogate approach, confidence in the screening chronic and subchronic p-RfD is low.

Since the available QSAR predictions of the toxicity of MPA could not be appropriately validated, two approaches were applied for possible derivation of toxicity values for MPA. Approach 1 was to identify chemicals from the same chemical class (i.e., phosphonic acid; phosphonate) as MPA that have U.S. EPA toxicity values (e.g., RfD) and use those as surrogates for MPA toxicity. Approach 2 was to identify chemicals with U.S. EPA toxicity values that have sufficient structural similarity to serve as surrogates for MPA toxicity. The structure-activity relationships (SAR) examined in Approach 2 include both a chemical similarity search and a comparison of physicochemical properties. Chemical similarity is based on the hypothesis that similar compounds have similar biological activities or toxicities. Both approaches are presented and discussed in detail to support the final selection of DMMP as the most appropriate surrogate for MPA.

Approach 1—Chemical-Class Relationships

Precursor and Biodegradation Products

The search for chemically related analogs of MPA started with an examination of chemical precursors and degradation products. As mentioned in the Introduction, MPA is an environmental hydrolysis or abiotic degradation product of chemical warfare nerve agents or their by-products. Initially, a literature search was conducted for potential analogs that may form MPA in the environment or in mammalian systems. Given the criterion, isopropyl phosphonic acid (IMPA), ethyl methylphosphonic acid (EMPA), and diisopropyl methyl phosphonate (DIMP) were considered as potential analogs. However, no toxicological data were located for EMPA in the IRIS, ATSDR, NTP, HSDB, ESIS, and TSCATS databases, as well as MedLine and Toxline, thus ruling out EMPA as a potential surrogate for MPA in this analysis. Only IMPA and DIMP have available oral toxicity information relevant for provisional oral toxicity values for MPA and were, therefore, considered further as potential surrogates.

Chemical Class Analogs

Since MPA belongs to the chemical class of phosphonic acid, an initial search was conducted on the databases for chemicals within this chemical class, which also had available oral toxicity information. Some unique features within the chemical class have been reported. Williams et al. (1987) noted that MPA contains a unique structural property in the nonreactive carbon-phosphorus (C-P) bond. According to Williams et al. (1987), this bond is resistant to hydrolysis, thermal degradation, and photolysis, and this bond is largely responsible for the persistence of compounds such as MPA in the environment. Because of its unique properties, the C-P bond is considered as an essential feature in the selection of potential analogs for the chemical class. Only chemicals possessing a nonreactive phosphorus-carbon bond, similar to MPA, are identified as potential analogs.

In addition to the C-P bond requirement, evaluation of potential analogs was further conducted in a tiered fashion. The first group (Group 1) of potential analogs included the C-P bond and short-chain alkyl substitutions for the methyl group of MPA (indicated by -R for Group 1 in Figure 2). Group 1 was preferred for identifying potential analogs because they were considered to possess similar biological activity or toxicity with respect to MPA. Search results identified ethyl phosphonic acid, 1-propyl phosphonic acid, and isopropyl phosphonic acid. To be considered for further surrogate selection, a literature search was conducted specifically for the oral route of exposure, but no toxicity values were located for these compounds.

Since no suitable analogs were identified in the first group, a second group with less stringent criteria (more substitutions) was applied to the same databases. The second group of potential analogs included short-chain alkyl monoester substitutions for one of the hydroxyl moieties of MPA and expanded the chemical class to include phosphonates (Group 2 in Figure 2). Compounds identified as potential analogs in this group included monomethyl methylphosphonate, as well as EMPA and IMPA (identified in ***Precursor and Biodegradation Products***). Because toxicological data for monomethyl methylphosphonate were not identified, no further consideration as a surrogate was possible.

The third group has the least restriction, allowing short-chain alkyl diester substitutions for both hydroxyl moieties (Group 3 in Figure 2). Compounds identified as potential analogs included dimethyl methylphosphonate (DMMP), diethyl methylphosphonate, dipropyl methylphosphonate, and DIMP (identified in ***Precursor and Biodegradation Products***). Repeated-dose oral toxicity data were located for DMMP, thus identifying DMMP as an additional potential surrogate.

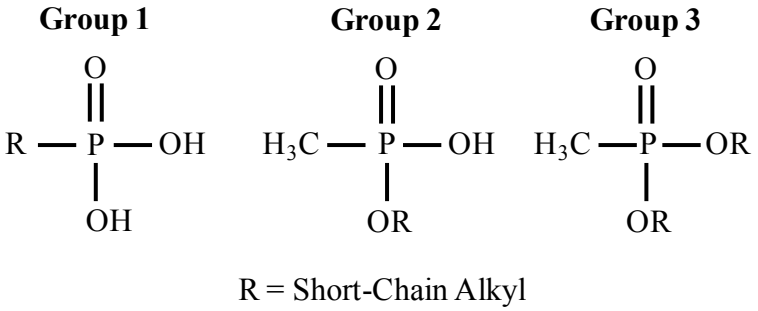


Figure 2. Representation of Analogs in Phosphonic Acid or Phosphonate Chemical Class

As a final check on the search for potential analogs, the databases above (IRIS, ATSDR, NTP, HSDB, ESIS, and TSCATS) were searched for the terms "phosphonate" and "phosphonic acid" in order to ensure that all potential analogs with repeated-dose toxicity data were identified. The search of ESIS identified data for phosphonic acid; however, there were no repeated-dose toxicity data by any route of exposure.

Overall, based on this tiered evaluation within the chemical class, IMPA, DMMP, and DIMP were identified as analogs that were further considered as potential surrogates with available oral toxicity information relevant for deriving a Screening Value of RfD for MPA. IMPA and DIMP were also identified as potential surrogates based on the biodegradation data in the previous section. Comparison of these compounds is provided below on the basis of toxicokinetics, acute lethality, and other available toxicity data.

Comparison of Potential Chemical Class Surrogates

Toxicokinetics

MPA is eliminated via the urine. Following intraperitoneal administration of ^{32}P MPA (31 mg) to a single adult male Wistar rat, 92% of the dose was excreted unchanged in the urine within 48 hours (Hoskin, 1956a). No phosphoric acid was observed in chromatographs of the urine, indicating that MPA is not metabolized to phosphoric acid in the rat.

The available information on the kinetics of DIMP, IMPA, and DMMP suggest that DIMP has extensive metabolism. ATSDR (1999) reviewed the toxicokinetics of DIMP and reported that low doses of DIMP are rapidly and completely metabolized to IMPA, which is the principal urinary metabolite in mice, rats, dogs, mink, and cattle. Male rats have been shown to convert DIMP to IMPA more rapidly than females; plasma elimination rates of 45 and 250 minutes have been estimated for males and females, respectively (ATSDR, 1999). In contrast to DIMP, IMPA is not hydrolyzed in the rat, but is excreted largely unchanged. Hoskin (1956b) administered 285 mg ^{32}P IMPA to 2 rats subcutaneously over a 48-hour span of time. Analysis of urine collected over 72 hours indicated that most of the radioactivity was excreted as unchanged IMPA (85.1%, with total recovery of 96.5%). Only trace amounts of MPA were detected (0.3%) (Hoskin, 1956b).

In rats orally exposed to doses of 50 or 100 mg/kg DMMP, the urine was shown to contain unchanged DMMP and its main metabolite, methyl methyl phosphonate (Blumbach et al., 2000). Within 24 hours after dosing, 58−68% of the administered dose was recovered in the urine of males, while 88−93% of the administered dose was recovered in the urine of females (Blumbach et al., 2000).

Overall, DIMP generally undergoes rapid metabolism and forms major metabolites including IMPA, while MPA, IMPA, and DMMP stay relatively intact after excretion and have high recovery in urine after the administered dose.

Acute Lethality

Williams et al. (1987) cited oral lethal doses of 5,000 and >5,000 mg/kg for MPA in rats and mice, respectively. An ATSDR (2004) review of a DuPont (2004) report entitled "Toxicology Assessment of Health Hazard Considerations for Safe Management of Newport Caustic Hydrolysate"[1] identified a recent rat study (Finlay, 2004, as cited in ATSDR, 2004) from which the acute toxicity of MPA was estimated. Efforts to obtain the original report were not successful. ATSDR (2004) reported that the study estimated an approximate lethal dose of 2,300 mg/kg for MPA administered via gavage to rats (strain not specified). According to the

[1]According to the ATSDR review of the DuPont report, Newport Caustic Hydrolysate, or caustic VX hydrolysate, contains 80% water with minor amounts of methyl phosphonic acid and other compounds.

ATSDR summary, MPA was administered to one rat per dose (doses not specified); clinical signs and body weights were observed for 14 days after exposure. ATSDR (2004) noted that the report did not give any indication of the clinical endpoints of acute MPA toxicity.

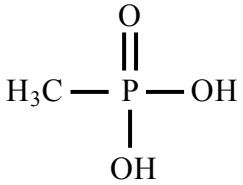
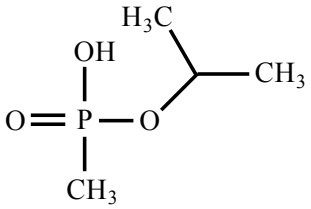
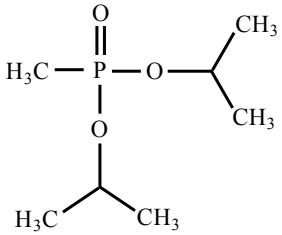
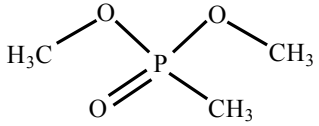
The acute lethality of orally administered MPA does not differ substantially from that of MPA administered intraperitoneally; Williams et al. (1987) reported intraperitoneal LD_{50} values of 2,250 and 3,370 mg/kg-day for rats and mice, respectively. Table 1 contains acute oral toxicity values (LD_{50}) for DIMP, IMPA, DMMP, and MPA. DIMP is more acutely toxic to both rats and mice, while IMPA, DMMP, and MPA have comparable acute oral lethality.

Repeated Oral Dose

In rats exposed to IMPA, only trace amounts of MPA were detected, and IMPA was largely excreted unchanged (Hoskin, 1956b). Furthermore, the only repeated-dose toxicity study of IMPA, a 90-day rat drinking water study (Mecler, 1981), resulted in the identification of a freestanding NOAEL (279 mg/kg-day) and, thus, did not identify a critical toxicological endpoint of IMPA toxicity. The IRIS assessment, as derived in February 1993 for IMPA, cites studies of DIMP (which is rapidly hydrolyzed to IMPA in mammalian systems) as support for the IMPA RfD that is based on this freestanding NOAEL. Similarly, the oral studies as cited in the DIMP IRIS assessment in February 1993 also did not identify a toxicological endpoint for these compounds.

In contrast, the toxicological database for DMMP is more robust, including both subchronic and chronic rodent bioassays (NTP, 1987; Dunnick et al., 1988; Ciba-Geigy 1977) as well as developmental and reproductive toxicity studies (Ciba-Geigy, 1978; Hardin et al., 1987; Dunnick et al., 1984a,b; and Chapin et al., 1984). The U.S. EPA (2006b) calculated provisional subchronic and chronic RfDs for DMMP based on a reproductive toxicity study in rats conducted by Dunnick et al. (1984a). This study identified a LOAEL of 250 mg/kg-day (the lowest dose tested) for increased resorptions in untreated female rats mated with males treated at this dose and higher doses. The increase in resorptions was dose related. The U.S. EPA (2006b) adjusted the LOAEL for continuous exposure (doses were administered by gavage only 5 days per week) to give an adjusted LOAEL of 179 mg/kg-day. A composite uncertainty factor of 3,000, including a 10-fold UF for interspecies extrapolation, a 10-fold UF for human variability, a 10-fold UF for use of a LOAEL, and 3-fold UF for DMMP database limitations, was applied in both the subchronic and chronic RfDs. An uncertainty factor for less-than-chronic duration was not applied because the 84-day exposure period was considered to be chronic for the critical effect, reproductive toxicity.

Table 1. Physical-Chemical Properties of MPA and Potential Analogs

	MPA	IMPA	DIMP	DMMP
Structure				
CASRN	993-13-5	1832-54-8	1445-75-6	756-79-6
Molecular formula	CH_5O_3P	$C_4H_{11}O_3P$	$C_7H_{17}O_3P$	$C_3H_9O_3P$
Molecular weight	96.0	138.1	180.2	124.1
Melting point (ºC)	108.5[a]	NA	<25[a]	NA
Boiling point (ºC)	NA	123−125 at 0.2 torr[b]	121.05 at 10 mmHg [a]; 134[b]	181[a]; 174[b]
Vapor pressure (mmHg)	2×10^{-6}[a]	0.0119[a]; 0.0034 at 25 ºC [f]	0.277[b]	0.962[a]
Henry's law constant (atm-m^3/mole)	1.22×10^{-11}[a]	6.88×10^{-9} [a]	4.38×10^{-5}[a]	1.25×10^{-6}[a]
Density (g/mL)	ND	1.1091 at 20 ºC	0.976[b]	1.15 at 20 ºC
Water solubility (g/L)	>20[b]	50[a] ; 48[f]	1−2[b]	1,000[a]
Log Kow	-2.28[c]	-0.54[c]	1.03[a] ; 0.478[f]	-0.61[a]
pKa	2.12[a]; 2.38[c]	1.98[c]	NA	NA
Oral Lethality (LD_{50})				
Rat (mg/kg)	2,300[d], 5,000[e]	7,650 (male), 6,070 (female)[f]	826[f]	>3,000[g]
Mouse (mg/kg)	>5,000[e]	5,620 (male), 6,550 (female)[f]	1,041[f]	>6,000[g]

[a]PhysProp Database
[b]Rosenblatt et al., 1975
[c]Small, 1984
[d]Finlay et al., 2004
[e]Williams et al., 1987
[f]Munro et al., 1999
[g]NTP, 1987

In summary, IMPA, DIMP, and DMMP were considered potential surrogates for MPA based on the biodegradation and chemical class specific information and the availability of repeated-dose oral toxicity data. Ideally, selection of a potential surrogate for MPA would be based on identifying a compound with target organ toxicity similar to MPA; however, there are neither toxicity data nor mechanistic information to predict potential target organs or effects of MPA. In addition, no target organ was identified in toxicological studies of IMPA and DIMP asreviewed in the IRIS (U.S. EPA, 2009) records for these two compounds. The ATSDR (1999) identified hematological effects as the critical endpoint for chronic DIMP toxicity; however, this study was published after the IRIS RfD was posted. U.S. EPA (2006b) identified reproductive toxicity (increased resorptions in rats) as the critical effect of oral exposure to DMMP.

Considering all relevant toxicity information, selection for final surrogate among DMMP, IMPA, and DIMP would be based on most conservative toxicity value due to lack of the mechanistic information. Furthermore, without quantitative assessment of similarity with respect to MPA, an alternative solution for deriving a provisional RfD for MPA would be a range of toxicity values among the three surrogates: 6×10^{-2} to 1×10^{-1} mg/kg-day. A separate approach using structure-activity relationship was applied to facilitate the ranking of identified surrogates and to search for other potential surrogates; details are presented in the next section.

Approach 2—Structure-Activity Relationships

Structure-activity relationship (SAR) is a means by which the effect of a toxic chemical on an animal, a human, or the environment can be related to its molecular structure. Traditionally, this type of relationship may be assessed by considering a series of chemicals, making gradual changes to them, and noting the effect of each change on their biological activity. This process is very similar to the search performed earlier (tiered evaluation as described in Chemical Class Analogs) in identifying potential analogs within a chemical class (e.g., phosphonic acid). Alternatively, it may be possible to assess similarity by using software programs or models to try to establish a relationship. One publicly available program, ChemIDplus (http://chem.sis.nlm.nih.gov/chemidplus/), part of National Library of Medicine Web site, can provide quantitative assessment (similarity score) for identifying and ranking of potential structural analogs.

A structural analog was considered a potential surrogate if it was structurally related (≥50% similarity in ChemIDplus score) and had toxicity values derived from repeated-dose oral toxicity data. The threshold of ≥50% was chosen to identify all relevant structural analogs in both 2-dimensional and 3-dimensional aspects of a chemical. When combining Similarity Search under the Structure Search Options on the National Library of Medicine ChemIDplus with the availability of oral toxicity data of these analogs on the IRIS, ATSDR, NTP, HSDB, ESIS, and TSCATS databases, three potential surrogates were identified: DMMP, IMPA, and DIMP. These three potential surrogates are identical to the ones identified in the first approach. No other potential surrogates were located by the SAR approach.

In addition to ChemIDplus, other programs were also used. DMMP was also identified as a potential analog using two independent commercial software packages: Leadscope® (Leadscope, Inc., http://www.leadscope.com) and TOPKAT® (Accelrys, Inc., http://www.accelrys.com/products/topkat/index.html/,

http://accelrys.com/products/discovery-studio/toxicology/index.html). The consensus among the three similarity search programs provides high confidence that the identified structural analog (DMMP) can be considered as a potential surrogate.

Table 1 shows a comparison between the physicochemical properties and acute oral lethality data for MPA, IMPA, DIMP, and DMMP. The table indicates that, while physical-chemical properties of these compounds are generally similar (all have high water solubility and low log Kow, vapor pressure and Henry's Law constants), DIMP is more toxic to both rats and mice than the other compounds based on a comparison of acute lethality data. In contrast, the LD_{50} data for MPA, IMPA, and DMMP are generally comparable. These similar physicochemical properties and acute oral lethality data for MPA and three structural analogs reinforce the appropriateness of IMPA, DIMP, and DMMP as potential surrogates.

Table 2 summarizes all chronic oral noncancer toxicity values for MPA and the three potential surrogates (DMMP, IMPA, DIMP). Based upon both the most conservative chronic oral noncancer toxicity values (mg/kg-day) and the highest structural similarity (NLM ChemIDplus similarity %), the current provisional noncancer oral reference dose (p-RfD) of 6×10^{-2} (U.S. EPA, 2006b) for DMMP may serve as a conservative estimate (surrogate) for oral toxicity for MPA. Given the high level of uncertainty associated with derivation of chemical surrogate toxicity values, molecular weight-based adjustment to surrogate values is not appropriate.

Table 2. Comparison of Chronic Oral Noncancer Toxicity Values for MPA and Potential Surrogates

	U.S. EPA Provisional RfD (mg/kg-day)	IRIS RfD (mg/kg-day)	ATSDR MRL (mg/kg-day)	U.S. Army (1999) QSAR-based RfD (mg/kg-day)	NLM ChemIDplus Similarity (%)
MPA	ND	ND	ND	6×10^{-2}	100
DMMP	**6×10^{-2}**	ND	ND	ND	**72**
IMPA	ND	1×10^{-1}	ND	ND	68
DIMP	ND	8×10^{-2}	6×10^{-1}	ND	56

ND = No Data

Using information from Approaches 1 and 2, the three top candidates with available RfDs were selected: DMMP, IMPA, and DIMP.