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Provisional Peer-Reviewed Toxicity Values for

O,O-Diethyl phosphorodithioate
(CASRN 298-06-6)

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TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
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
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
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
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *O,O*-DIETHYL PHOSPHORODITHIOATE (CASRN 298-06-6)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

No reference dose (RfD), reference concentration (RfC), or cancer assessment for *O,O*-diethyl phosphorodithioate is included in the U.S. Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) (U.S. EPA, 2011a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2011b). The Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2011c) does not report any RfD or RfC values. The Chemical Assessments and Related Activities (CARA) list does not include any EPA documents for *O,O*-diethyl phosphorodithioate (U.S. EPA, 1994). The toxicity of *O,O*-diethyl phosphorodithioate has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2011) or the World Health Organization (WHO, 2011). The California Environmental Protection Agency (CalEPA, 2008, 2011) has not derived toxicity values for exposure to *O,O*-diethyl phosphorodithioate. No occupational exposure limits for *O,O*-diethyl phosphorodithioate have been derived or recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute for Occupational Safety and Health (NIOSH, 2007), or the Occupational Safety and Health Administration (OSHA, 2006).

The HEAST (U.S. EPA, 2011c) does not report a U.S. EPA (1986) cancer weight-of-evidence (WOE) classification of *O,O*-diethyl phosphorodithioate. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of *O,O*-diethyl phosphorodithioate. *O,O*-Diethyl phosphorodithioate is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2009) has not prepared a quantitative estimate of the carcinogenic potential of *O,O*-diethyl phosphorodithioate.

Literature searches were conducted on sources published from 1900 through September 2011 for studies relevant to the derivation of provisional toxicity values for *O,O*-diethyl phosphorodithioate, CAS No. (298-06-6). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for risk assessment values: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

No information is available regarding repeat-dose human or animal studies of short–term or chronic duration for *O,O*-diethyl phosphorodithioate. There are a limited number of acute-duration animal studies for *O,O*-diethyl phosphorodithioate that are summarized in Table 1. However, these studies cannot be used for derivation of a reference value because they do not provide repeat-dose toxicity information.

Table 1. Summary of Acute Toxicity Data for *O,O*-Diethyl Phosphorodithioate (CASRN 298-06-6)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry	Effects	Reference (Comments)
Human				
1. Oral (mg/kg-day)				
No studies were located.				
2. Inhalation (mg/m^3)				
No studies were located.				
Animal				
1. Oral (mg/kg)				
Acute	10/10, Sprague-Dawley rat, single gavage followed by a 14-day observation period	1260, 1580, 2000, or 2510	Weight loss, mortality, increasing weakness, collapse, hemorrhagic lungs, liver discoloration, and acute gastrointestinal inflammation	Information from IUCLID (2007); Primary reference for this study is not available
	10/10, Sprague-Dawley rat, single gavage	316, 398, 501, or 631	Tremors, salivation, dyspnea, increasing weakness, and inflammation of the gastric mucosa with renal and liver hyperemia	Information from IUCLID (2007); Primary reference for this study is not available
2. Inhalation (mg/L)				
Acute	30/30, Sprague-Dawley rat, 4 hours followed by a 14-day observation period	0.98, 1.02, 10.4, 1.35, 1.60, or 2.10	Cholinesterase inhibition;, clear nasal discharge; lacrimation; breathing difficulties; hypoactivity; fur discoloration; breathing difficulties; chromodacryorrhea around the mouth, nose, and eyes; weight loss; mortality; tremors; petechial hemorrhage of the thymus and lungs; alopecia	Information from IUCLID (2007); Primary reference for this study is not available
	6/0, Sprague-Dawley rat, 6 hours followed by a 14-day observation period	0.7	Mortality, ocular erythema, increasing weakness , tremors, nasal bleeding, and hemorrhagic lungs	Information from IUCLID (2007); Primary reference for this study is not available

DERIVATION OF PROVISIONAL VALUES

Limitations in the available data preclude development of cancer and noncancer toxicity values.

CANCER WOE DESCRIPTOR

Limitations in the available data preclude development of a WOE descriptor.

MODE-OF-ACTION DISCUSSION

Mutagenicity studies of diethyl phosphorodithioate, technical grade (92%) or the sodium salt, were conducted by FMC Corporation (1985, 1986, 1987) using the Ames assay with or without S-9 metabolic activation at doses ranging from 50 µg to 1000 µg per plate. Technical grade diethyl phosphorodithioate was mutagenic in *Salmonella typhimurium* strain TA1535; the mutagenic response was nearly twice as great without activation (41-fold increase with 1000 µg/plate over solvent controls versus 23.9-fold increase with activation). A repeat experiment produced quantitatively similar results, suggesting that the chemical is detoxified by oxidative metabolism. A positive response was also observed in strain TA100 without activation, although it was of lesser magnitude. No increase in revertant colonies, either with or without metabolic activation, was observed in strains TA98, TA1537, or TA1538, which are sensitive to frame-shift mutagens. No positive responses with the sodium salt of diethyl phosphorodithioate were observed with or without metabolic activation in any of the five strains tested (i.e., TA98, TA100, TA1535, TA1537, TA1538).

These studies (i.e., FMC Corporation, 1985, 1986, 1987) provide information on a possible mode of action for *O,O*-diethyl phosphorodithioate-induced toxicity. However, these studies cannot be used for derivation of a reference value because they do not provide repeat-dose toxicity information.

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