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Provisional Peer Reviewed Toxicity Values for

1,2-Dinitrobenzene (*o*-Dinitrobenzene)

(CASRN 528-29-0)

Superfund Health Risk Technical Support Center
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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
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
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose

MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
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
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

7-31-2006

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 1,2-DINITROBENZENE (*o*-DINITROBENZENE) (CASRN 528-29-0)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in 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 EPA's Integrated Risk Information System (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 EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. 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 manuscripts 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 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 manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

INTRODUCTION

The HEAST (U.S. EPA, 1997) lists a subchronic RfD of 4E-3 mg/kg-day and a chronic RfD of 4E-4 mg/kg-day for 1,2-dinitrobenzene derived by analogy to 1,3-dinitrobenzene (m-dinitrobenzene). The assessment for 1,3-dinitrobenzene was based on a subchronic NOAEL of 0.4 mg/kg-day and LOAEL of 1.1 mg/kg-day for increased splenic weight in rats, and included an uncertainty factor (UF) of 100 (10 for extrapolation from animal data and 10 for sensitive individuals) for the subchronic RfD, and 1000 (including an additional UF of 10 for the use of a subchronic study) for the chronic RfD. The source document was a Health and Environmental Effects Profile (HEEP) for dinitrobenzenes (U.S. EPA, 1985) that derived a chronic allowable

daily intake (ADI) for 1,2-dinitrobenzene by analogy equal to the chronic ADI for 1,3-dinitrobenzene. Because the HEAST derivations did not employ UFs for database deficiencies, the RfDs for 1,2-dinitrobenzene in the HEAST are higher than the current RfD for 1,3-dinitrobenzene on IRIS (1E-4 mg/kg-day), which added a database uncertainty factor of 3 (total UF = 3000) to the previous assessment (U.S. EPA, 2006). The HEAST (U.S. EPA, 1997) does not list an RfC or cancer assessment for 1,2-dinitrobenzene. On IRIS (U.S. EPA, 2006), 1,2-dinitrobenzene is assigned to cancer weight-of-evidence Group D, not classifiable as to human carcinogenicity, based on a lack of evidence in humans or animals by any route of exposure and negative results in a few bacterial genotoxicity assays. This assessment was derived in a Health and Environmental Effects Document (HEED) for dinitrobenzenes (U.S. EPA, 1991a). 1,2-Dinitrobenzene is not listed on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). Aside from the HEEP, no additional relevant documents are included in the CARA list (U.S. EPA, 1991b, 1994).

ACGIH (2001a,b) established a TLV-TWA of 0.15 ppm (1 mg/m^3) for all three isomers of dinitrobenzene to protect against anoxia resulting from methemoglobin formation. The TLV-TWA also includes a note recognizing that all three isomers are readily absorbed through the skin. This value was based on the TLV-TWA of 2 ppm (7.6 mg/m^3) for aniline (ACGIH, 2001c) and the relatively higher methemoglobin-producing capacity of dinitrobenzenes compared to aniline. The NIOSH (2002) REL-TWA for 1,2-dinitrobenzene is also 1 mg/m^3 with a skin notation to protect against methemoglobinemia and effects on the liver, cardiovascular system, eyes, skin and central nervous system. OSHA (2002a,b) established a PEL-TWA of 1 mg/m^3 with a skin notation for all dinitrobenzenes to protect against the same effects and, in addition, kidney damage.

ATSDR (2002) and the WHO (2002) have not published toxicological reviews on 1,2-dinitrobenzene; ATSDR (1995) published a toxicological profile on 1,3-dinitrobenzene, but this document has no information about 1,2-dinitrobenzene. IARC (2002) and the NTP (2002) have not evaluated the carcinogenicity of 1,2-dinitrobenzene. Toxicity reviews on aromatic nitro compounds (Benya and Cornish, 1994; Weisburger and Hudson, 2001) were consulted for relevant information. Literature searches were conducted for the period from 1984 to December 2001 to identify data relevant for the derivation of a provisional RfD, RfC and cancer assessment for 1,2-dinitrobenzene. The following databases were searched: TOXLINE, MEDLINE, CANCERLIT, TOXLIT/BIOSIS, RTECS, HSDB, GENETOX, CCRIS, TSCATS, EMIC/EMICBACK and DART/ETICBACK.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No data were located regarding oral exposure of humans to 1,2-dinitrobenzene or subchronic or chronic inhalation exposure of humans to 1,2-dinitrobenzene where the levels of exposure were known. In general, occupational incidents involved combined inhalation and dermal exposure and exposure levels were not reported (ACGIH, 2001b). Cyanosis and methemoglobinemia were the major reported health effects. Following chronic exposures to dinitrobenzenes, anemia and sometimes hepatic injury, impaired vision, and yellow discoloration of the conjunctiva and sclera of the eye were observed.

Animal Studies

No data were located on the toxicity of 1,2-dinitrobenzene to animals following chronic or subchronic oral or inhalation exposure.

Similarity to 1,3-Dinitrobenzene

Data on physical and chemical properties, pharmacokinetics and acute effects suggest that toxic effects from chronic oral exposure to 1,2-dinitrobenzene will be similar to that of 1,3-dinitrobenzene, although the 1,2- isomer appears to be less potent. The physical and chemical properties of the two isomers are generally similar, except that the 1,2-isomer is considerably more soluble in water (Table 1).

Pharmacokinetic data suggest a similar fate for all of the dinitrobenzenes in mammalian systems (U.S. EPA, 1991a). Gavage studies of dinitrobenzenes in rats and rabbits showed a high degree of absorption by the gastrointestinal tract and urinary excretion as the major route of elimination; significant biliary excretion was reported.. In rabbits gavaged with single doses of 50-100 mg/kg of 1,3-dinitro-[^{14}C]-benzene, absorption was $\geq$95% of the dose. Recovery of radioactivity over 48 hours accounted for 65-93% of the dose in urine and $\leq$5% in feces. In rats given single doses of 25.2 mg/kg of radiolabeled isomer, absorption was at least 92.4% for 1,2-dinitrobenzene, 82.6% for 1,3-dinitrobenzene and 91.3% for 1,4-dinitrobenzene. Over 48 hours, radioactivity in urine accounted for 81.3, 63.2 and 75.1% of the dose, and in feces, 7.6, 17.4 and 8.7% of the dose for 1,2-, 1,3- and 1,4-dinitrobenzene, respectively.

Analysis of urinary metabolites in rats gavaged with dinitrobenzenes revealed some differences in metabolic pathways (U.S. EPA, 1991a; Benya and Cornish, 1994). The major urinary metabolites of 1,2-dinitrobenzene were *S*-(2-nitrophenyl)-*N*-acetylcysteine (42%), 2-nitroaniline-*N*-glucuronide (4%), 2-amino-3-nitrophenyl sulfate (1.5%) and 2-(*N*-hydroxylamine)-nitrobenzene (1-2%). The major urinary metabolites of 1,3-dinitrobenzene were 3-aminoacetanilide (22%), 4-acetamidophenyl sulfate (6%), 1,3-diacetamidobenzene (7%)

Table 1. Selected Properties of Dinitrobenzenes (U.S. EPA, 1985, 1991a; O'Neil et al., 2001)

Physical Property	1,2-Dinitrobenzene	1,3-Dinitrobenzene
Physical state	white crystals	yellowish crystals
Melting point °C	117.9	89.9
Boiling point °C	319 (at 773 mm Hg)	291 (at 756 mm Hg)
Specific gravity	1.565	1.546
Vapor pressure (mm Hg)	1.60×10^{-4}	2.23×10^{-4}
Water solubility (mg/L)	2100 at 25°C	500 at 25°C
Log octanol/water partition coefficient	1.58	1.49

and 3-nitroaniline-*N*-glucuronide. The major urinary metabolites of 1,4-dinitrobenzene were 2-amino-5-nitrophenyl sulfate (35%), *S*-(4-nitrophenyl)-*N*-acetylcysteine (13%) and 1,4-diacetamidobenzene (7%). These results indicate that 1,3-dinitrobenzene was metabolized exclusively by reduction of the nitro groups to amines, which were subsequently acetylated. No direct conjugation to glutathione was detected for 1,3-dinitrobenzene, whereas that process was the major metabolic pathway for 1,2-dinitrobenzene. 1,4-Dinitrobenzene was metabolized by both of these pathways, but its major pathway involved reduction of a nitro group followed by hydroxylation of the phenyl ring and sulfate conjugation of the phenol.

Comparative *in vitro* analysis of the metabolites in rat erythrocytes or hepatocytes exposed for 30 minutes also demonstrated differences and similarities among the isomers (U.S. EPA,1991a; Rickert, 1987). In erythrocytes, 37% of added 1,2-dinitrobenzene was conjugated to glutathione and 24% was conjugated to macromolecules. In erythrocytes treated with 1,3-dinitrobenzene, no metabolites were detected, but 2% was covalently bound to macromolecules. In erythrocytes treated with 1,4-dinitrobenzene, 6% was conjugated to glutathione, 10% was reduced to 4-nitrophenylhydroxylamine and 40% was covalently bound to erythrocyte macromolecules. In hepatocytes, a significant proportion of all three isomers was converted to the related nitroaniline (30% 2-nitroaniline, 74% 3-nitroaniline and 81% 4-nitroaniline) and no covalent binding of any isomer was detected. Glutathione conjugation represented 48% of the 1,2-dinitrobenzene added to rat hepatocytes. These experiments indicate that all dinitrobenzene isomers, to some degree, covalently bind to macromolecules in erythrocytes and are metabolized to another methemoglobin-producing compound (nitroaniline) in the liver (see below).

Acute oral exposure to dinitrobenzene isomers causes methemoglobinemia in humans and animals (U.S. EPA, 1985, 1991a). An acute oral LD_0 of 28 mg/kg has been reported for 1,3-

dinitrobenzene in humans (U.S. EPA, 1991a). The acute oral LD_0s in rats were 250, 27 and 29 mg/kg for 1,2-, 1,3- and 1,4-dinitrobenzene, respectively (Watanabe et al., 1976; U.S. EPA, 1991a). In rats injected i.p. with 100 μM dinitrobenzene isomer, methemoglobin levels five hours after injection were 13.1, 25.5 and 29.5% for 1,2-, 1,3- and 1,4-dinitrobenzene, respectively (Watanabe et al., 1976). In single-dose studies in rats, treatment with ≥16 mg/kg of 1,3-dinitrobenzene caused testicular lesions that were not caused by the other dinitrobenzenes (U.S. EPA, 1991a).

In vitro studies demonstrated that 1,4-dinitrobenzene was about ten times more potent than 1,2-dinitrobenzene in inducing methemoglobin formation in freshly-drawn sheep erythrocytes (French et al., 1995); 1,3-dinitrobenzene was not effective in sheep erythrocytes. Methemoglobin levels about four times higher than control were produced by treatment with 0.005 mM 1,4-dinitrobenzene or 0.05 mM 1,2-dinitrobenzene. The related nitroanilines were also significant inducers of methemoglobin formation, but their effect required the presence of an NADP bioactivation system. 4-Nitroaniline was more potent than 2- or 3-nitroaniline; approximately four-fold increases in methemoglobin were induced by 0.005 mM 4-nitroaniline, 0.25 mM 3-nitroaniline or 0.05 mM 2-nitroaniline.

The available *in vitro* evidence suggests that 1,2-dinitrobenzene is less genotoxic than 1,3-dinitrobenzene (U.S. EPA, 1985, 1991a). Neither isomer induced reverse mutations in *Salmonella typhimurium* strains TA1537 or TA100NR3 (nitroreductase-deficient) with or without metabolic activation. 1,2-Dinitrobenzene did not induce reverse mutations in TA98, TA1535 or TA1538 with or without metabolic activation, or in strain TA100 without activation, whereas 1,3-dinitrobenzene generally tested positive in these strains (U.S. EPA, 1985, 1991a). Positive results occurred when strain TA100 was tested with 1,2-dinitrobenzene in the presence of S9 from Kanechlor 500-induced rat liver (Kawai et al., 1987); S9 from Arochlor-induced rat liver was not effective (U.S. EPA, 1991a; Assmann et al., 1997). 1,2-Dinitrobenzene, as well as the 1,3- and 1,4- isomers, induced chromosomal aberrations in peripheral lymphocytes obtained from a human male donor (Huang et al., 1996); in this study, all three isomers tested positive at concentrations of ≥1 mmol/l.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 1,2-DINITROBENZENE BY ANALOGY TO 1,3-DINITROBENZENE

No data are available for the chronic or subchronic oral toxicity of 1,2-dinitrobenzene in humans or animals. However, a chronic RfD of 1E-4 mg/kg-day is available for

1,3-dinitrobenzene on IRIS (U.S. EPA, 2006) and a related subchronic RfD[1] of 1E-3 is available for 1,3-dinitrobenzene in the HEAST (U.S. EPA, 1997). The chronic RfD was based on increased splenic weight (apparently secondary to erythrocyte effects) in rats treated with 8 ppm of 1,3-dinitrobenzene in drinking water for 16 weeks (Cody et al., 1981). The chronic RfD for 1,3-dinitrobenzene was calculated by applying an uncertainty factor of 3000 (10 for extrapolation from rats to humans, 10 to protect sensitive individuals, 10 for the use of a subchronic study, and 3 for database deficiencies) to the NOAEL of 0.4 mg/kg-day (3 ppm).

In order to derive an oral p-RfD for 1,2-dinitrobenzene by analogy to 1,3-dinitrobenzene, the two isomers must be sufficiently similar in physical properties, fate in the body and nature of their toxic effects to justify the extrapolation. This is largely a matter of judgement. As noted above, the physical and chemical properties are similar for 1,2-dinitrobenzene and 1,3-dinitrobenzene, and both compounds have the ability to convert hemoglobin to methemoglobin. Although there are slight differences in pharmacokinetic pathways, the major hepatic metabolites (nitroanilines) of both compounds are also methemoglobin-producing. The apparent higher acute toxicity of 1,3-dinitrobenzene suggests that RfDs based on 1,3-dinitrobenzene will be sufficiently protective for exposures to 1,2-dinitrobenzene. Therefore, the **chronic RfD of 1E-4 mg/kg-day** for 1,3-dinitrobenzene on IRIS (U.S. EPA, 2006) is adopted as the chronic p-RfD for 1,2-dinitrobenzene. The subchronic p-RfD for 1,2-dinitrobenzene is derived by eliminating the uncertainty factor of 10 for use of the subchronic study, resulting in a **subchronic p-RfD of 1E-3 mg/kg-day** for 1,2-dinitrobenzene. These p-RfD values are lower than those in the HEAST (U.S. EPA, 1997) because the new derivations include uncertainty factors for data base deficiencies.

Confidence in the subchronic and chronic p-RfDs for 1,2-dinitrobenzene is low, as no relevant studies were located and the p-RfDs were derived by analogy to the 1,3-dinitrobenzene isomer.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 1,2-DINITROBENZENE

No data are available for the chronic or subchronic inhalation toxicity of 1,2-dinitrobenzene in humans or animals. In addition, no information is available for 1,3-dinitrobenzene or 1,4-dinitrobenzene. In the absence of compound-specific data or data on close analogs, it is not feasible to derive subchronic or chronic p-RfCs for 1,2-dinitrobenzene.

[1] The HEAST (1997) misstates the uncertainty factor for the subchronic RfD for 1,3-dinitrobenzene; it was 300 and not 100.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,2-DINITROBENZENE

No human or animal carcinogenicity data were located for 1,2-dinitrobenzene. *In vitro* genotoxicity data indicate that this chemical is not mutagenic in bacteria without bioactivation, but that it may induce chromosomal aberrations in human lymphocytes. Under the U.S. EPA (2005) cancer guidelines, the available data are inadequate for an assessment of human carcinogenic potential.

Derivation of quantitative estimates of cancer risk for 1,2-dinitrobenzene is precluded by the absence of carcinogenicity data.

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