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Provisional Peer-Reviewed Toxicity Values for

2-Chlorobenzoic Acid
(CASRN 118-91-2)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 2-CHLOROBENZOIC ACID (CASRN 118-91-2)

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 (http://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.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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

2-Chlorobenzoic acid (CASRN 118-91-2) is an industrial chemical used as a solvent and an intermediate in the manufacture of surfactants, pharmaceuticals, and other organic compounds. The molecular formula of 2-chlorobenzoic acid (also known as ortho-chlorobenzoic acid) is $C_7H_5ClO_2$ (see Figure 1). A list of physicochemical properties is provided in Table 1.

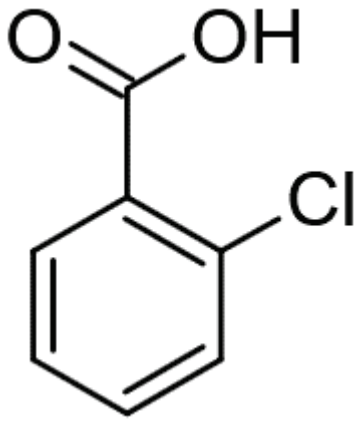

Figure 1. 2-Chlorobenzoic Acid Structure

Table 1. Physicochemical Properties of 2-Chlorobenzoic Acid (CASRN 118-91-2)[a]

Property (unit)	Value
Boiling point (°C)	287
Melting point (°C)	140.2
Density (g/cm^3 at 20°C)	ND
Vapor pressure (mmHg at 25°C)	0.0
pH (unitless)	ND
Solubility in water (mg/L at 25°C)	2,090
Relative vapor density (air = 1)	ND
Molecular weight (g/mol)	156.5675

[a]ChemIDplus (2015).

ND = no data.

Table 2 provides a summary of available toxicity values for 2-chlorobenzoic acid from U.S. EPA and other regulatory agencies or organizations.

Table 2. Summary of Available Toxicity Values for 2-ChlorobenzoicAcid (CASRN 118-91-2)

Source/Parameter[a,b]	Value (applicability)	Reference
Noncancer		
ACGIH	NV	ACGIH (2015)
ATSDR	NV	ATSDR (2015)
Cal/EPA	NV	Cal/EPA (2014); Cal/EPA (2015a); Cal/EPA (2015b)
NIOSH	NV	NIOSH (2015)
OSHA	NV	OSHA (2011), OSHA (2006)
IRIS	NV	U.S. EPA (2015)
DWSHA	NV	U.S. EPA (2012)
HEAST	NV	U.S. EPA (2011)
CARA HEEP	NV	U.S. EPA (1994)
WHO	NV	WHO (2015)
Cancer		
IRIS	NV	U.S. EPA (2015)
HEAST/WOE	NV	U.S. EPA (2011)
IARC	NV	IARC (2015)
NTP	NV	NTP (2014)
Cal/EPA	NV	Cal/EPA (2015a); Cal/EPA (2015b); Cal/EPA (2011)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]Parameters: WOE = cancer weight of evidence (U.S. EPA, 2005).

NV = not available.

Literature searches were conducted on sources published from 1900 through March 2015 for studies relevant to the derivation of provisional toxicity values for 2-chlorobenzoic acid (CASRN 118-91-2). The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for toxicity values or exposure limits: ACGIH, ATSDR, Cal EPA, 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 (NONCANCER AND CANCER)

The available data on 2-chlorobenzoic acid primarily focuses on its biodegradation and biotransformation by microorganisms and its synthesis and use in the development of analytical methods. No information is available regarding repeated-dose oral or inhalation exposure of humans or animals to 2-chlorobenzoic acid. A genetic toxicology study was conducted in *Salmonella* (Zeiger et al., 1992), which was negative. The chemical is being tested as part of Tox 21 and is in the NTP 1408 compound library. However, these tests are mechanistic studies and, do not provide endpoints that are currently usable for identifying a point of departure (POD). PubChem lists 263 in vitro assays, in which the only positive result was for antihemorrhagic activity in ddY mouse assessed as inhibition of *Protobothrops flavoviridis* venom-induced hemorrhagic lesion formation. The only in vivo toxicological data available are median lethal dose (LD_{50}) values in rats of >500 mg/kg oral (NRC, 1953) (Verschueren, 1983), although some references cite this value as being from rabbits, and 2,300 mg/kg intraperitoneally in rabbits (Carminati et al., 1973). There are also Draize test results in rabbits, where 20 mg was scored moderate in the eye test and 500 mg was scored as mild in the skin test (ChemCas, 2015). There is also some information about metabolism and excretion (Blackledge et al., 2000).

DERIVATION OF PROVISIONAL VALUES

DERIVATION OF ORAL REFERENCE DOSES

Feasibility of Deriving Subchronic and Chronic Provisional Reference Doses (p-RfDs)

No subchronic-duration, chronic-duration, developmental toxicity, reproductive toxicity, or carcinogenicity studies on 2-chlorobenzoic acid via the oral route have been identified. Thus, no oral reference doses can be derived. However, as noted below, a computational toxicological surrogate approach was attempted.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Feasibility of Deriving Subchronic and Chronic Provisional Reference Concentrations (p-RfCs)

No subchronic-duration, chronic-duration, developmental toxicity, reproductive toxicity, or carcinogenicity studies on 2-chlorobenzoic acid via the inhalation route have been identified. Thus, no inhalation reference doses can be derived. However, as noted below, a computational toxicological surrogate approach was attempted.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Limitations in the available data preclude development of a weight-of-evidence (WOE) descriptor.

MODE-OF-ACTION (MOA) DISCUSSION

Limitations in the available data preclude determination of a mode of action (MOA) discussion.

ALTERNATIVE METHODS

The surrogate approach allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable. Details regarding searches and methods for surrogate analysis are presented in Wang et al. (2012). Three types of potential surrogates (structural, metabolic, and toxicity) are identified to facilitate the final surrogate chemical selection. The surrogate approach may or may not be route-specific or applicable to multiple routes of exposure. All information has been considered together as part of the final WOE approach to select the most suitable surrogate, both toxicologically and chemically.

An initial surrogate search focused on identifying structurally similar chemicals with toxicity values from the Integrated Risk Information System (IRIS), PPRTV, and Health Effects Assessment Summary Tables (HEAST) databases to take advantage of the well-characterized chemical-class information. This task was accomplished by searching the U.S. EPA's DSSTox database (DSSTox, 2012) at similarity levels >60% and the National Library of Medicine's ChemIDplus database (ChemIDplus, 2015) at similarity levels >80%. The search revealed several structurally related chemicals could serve as potential surrogates for 2-chlorobenzoic acid. DSS-Tox identified several related chemicals: (1) four dichlorobenzoic acid isomers (2,3-; 2,4-; 2,5-; and 2,6-); (2) two monochlorobenzoic acid isomers (3- and 4-); (3) 2,3,6-trichlorobenzoic acid; and (4) chlorobenzaldehyde. These eight unique compounds had similarity scores over 70%. ChemIDplus identified three others, including 2-iodobenzoic acid, 2-fluorobenzoic acid, and 2-bromobenzoic acid. However, there is no in vivo repeated-dose information on any of these closely related compounds to compare with 2-chlorobenzoic acid for matching health effects. Because 2-chlorobenzoic acid is primarily excreted in the urine as the glycine conjugate (Blackledge et al., 2000), no other metabolic surrogates are available. The only data available are LD_{50} values. Due to a lack of repeated-dose toxicity information for any of the potential structural surrogates, derivation of risk values (e.g., oral reference dose [RfD], inhalation reference concentration [RfC], and oral cancer slope factor [OSF]) based on the computational toxicological surrogate approach (Wang et al., 2012) is not feasible for 2-chlorobenzoic acid.

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