

Provisional Peer-Reviewed Toxicity Values for  
  
2-Chlorobenzoic Acid  
(CASRN 118-91-2)

Superfund Health Risk Technical Support Center  
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This document was externally peer reviewed under contract to

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## COMMONLY USED ABBREVIATIONS AND ACRONYMS

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

## **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.

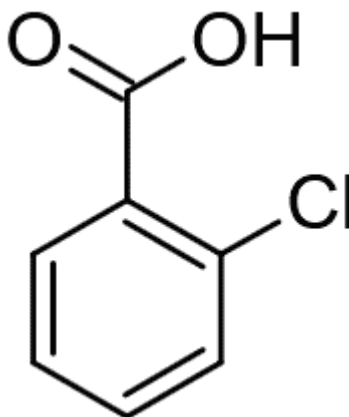


Figure 1. 2-Chlorobenzoic Acid Structure

Table 1. Physicochemical Properties of 2-Chlorobenzoic Acid (CASRN 118-91-2) <sup>a</sup>	
Property (unit)	Value
Boiling point (°C)	287
Melting point (°C)	140.2
Density (g/cm <sup>3</sup> 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

<sup>a</sup>[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-Chlorobenzoic Acid (CASRN 118-91-2)**

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

<sup>a</sup>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.

<sup>b</sup>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, ANEUP, 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 *Protothoxops flavoviridis* venom-induced hemorrhagic lesion formation. The only in vivo toxicological data available are median lethal dose (LD<sub>50</sub>) 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<sub>50</sub> 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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