United States
Environmental Protection
Agency

EPA/690/R-07/005F
Final
6-19-2007

Provisional Peer Reviewed Toxicity Values for

p-Chlorobenzoic acid

(CASRN 74-11-3)

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

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
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
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

6-19-2007

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR p-CHLOROBENZOIC ACID (CASRN 74-11-3)

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.

INTRODUCTION

The HEAST (U.S. EPA, 1997) lists subchronic and chronic RfD values for p-chlorobenzoic acid of 2E-0 and 2E-1 mg/kg-day, respectively. The source document for this assessment was a Health and Environmental Effects Document (HEED) (U.S. EPA, 1987). Both RfD values were based on a free-standing NOAEL of 26 mg/day (173 mg/kg-day) in a 5-month study in rats (Kieckebusch et al., 1960); uncertainty factors of 100 and 1000 were used to derive the subchronic and chronic RfD, respectively. No RfD assessment for p-chlorobenzoic acid is available on IRIS (U.S. EPA, 2005a) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). Other than the HEED discussed above, the CARA list (U.S. EPA, 1991, 1994) does not include any relevant documents. The toxicity of p-chlorobenzoic acid has not been evaluated by ATSDR (2003) or WHO (2003).

An RfC for p-chlorobenzoic acid is not available on IRIS (U.S. EPA, 2005a) or in the HEAST (U.S. EPA, 1997). The HEED reports that there were no available inhalation toxicity data in humans or animals when the document was prepared. Occupational exposure limits for p-chlorobenzoic acid have not been derived by ACGIH (2003), NIOSH (2003), or OSHA (2003).

The HEED (U.S. EPA, 1987) assigned p-chlorobenzoic acid to cancer weight of evidence Group D (not classifiable as to human carcinogenicity) based on lack of data via any exposure route. A cancer assessment for p-chlorobenzoic acid is not available on IRIS (U.S. EPA, 2005a) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). The carcinogenicity of p-chlorobenzoic acid has not been assessed by NTP (2003) or IARC (2003).

Literature searches were conducted from 1986 through September, 2003 for studies relevant to the derivation of provisional toxicity values for p-chlorobenzoic acid. Databases searched included: TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART, EMIC/ EMICBACK, HSDB, and GENETOX.

REVIEW OF PERTINENT DATA

Human Studies

No data regarding the toxicity of p-chlorobenzoic acid in humans were located.

Animal Studies

Several studies of limited value for toxicity evaluation of p-chlorobenzoic acid have been conducted in laboratory animals (Kieckebusch et al., 1960; Wuehrer, 1931; D'eng et al., 1983). Kieckebusch et al. (1960) maintained young (unspecified age) Elberfeld rats (20 per sex and dose) on commercial feed supplemented with p-chlorobenzoic acid (unspecified purity) at 0%, 0.1%, or 0.2% (w/w) for 5 months (0, 13, or 26 mg/day of p-chlorobenzoic acid, as calculated by the researchers). Dividing by the estimated rat mean body weight of 0.15 kg (based on rat body weights at the start and end of the study) yields average estimated doses of 0, 87, or 173 mg/kg-day. Body weight, food consumption, and protein efficiency (weight gain per gram of food consumed) were reported for two-week intervals for the first 8 weeks of treatment; values for these parameters were not reported at time intervals after week 8. Mortality and clinical signs of toxicity appeared to be evaluated; however, specifics regarding scheduled clinical observations were not included in the study report. Animals were mated after the first 8 weeks of treatment and again 2 months later to evaluate the effects of treatment on reproductive ability. The following reproductive parameters were evaluated: percentage of sterile females, percentage of females with delayed sexual maturity, number of littered pups per female, survival of pups to 21

days of age, and pup weight at 21 days of age. Urine was collected from all treated and control animals "towards the end" of the 5-month exposure period and examined for protein and sugar content. Urine sediment was also microscopically examined. All animals were then sacrificed; the liver, kidneys, heart, spleen, and testes were weighed, and the liver and kidneys were microscopically examined. The authors reported that no treatment-related effects were observed on any of the endpoints evaluated. Although they indicated an increase in the percentage of treated females with delayed sexual maturity in the treated groups (5%, 40%, and 40% in the control, low-, and high-dose groups, respectively), the study authors concluded that the number of treated animals was not sufficient to evaluate whether this was a treatment-related effect.

Kieckebusch et al. (1960) reproductive effects study, although limited in several aspects, was strong in several respects. The number of animals was sufficient (20 rats per group). There were 3 dose levels including the control (0, 0.1% = 87 mg/kd-day, and 0.2% = 173 mg/kg-day). The duration of exposure was adequate (5 months). Endpoints included in the study were weight gain, feed utilization, general health, number of litter young, histological examination of the liver and kidneys, and organ weight.

Kieckebusch et al. (1960) described a study (Wuehrer, 1931) that evaluated the toxicity of p-chlorobenzoic acid in dogs. Wuehrer (1931) maintained one dog (unspecified breed) on a diet supplemented with 3 g per day of p-chlorobenzoic acid for just over a year (≈13 months) and maintained two dogs on a diet supplemented with 1.5 g per day of the substance for almost two years (20.5 months). Histological examinations were conducted at the end of the exposures (gastric and intestinal mucosa, unspecified organs). No effects were observed in any of the treated dogs.

D'eng et al. (1983) reported decreased protein synthesis in the liver and increased levels of urokaninase (urocanate hydratase) and histidase (markers for liver damage) in the serum of animals (unspecified species) treated with unspecified oral doses of p-chlorobenzoic acid (equivalent to 1/10 of the LD_{50} or 1/50 of the LD_{50}) for up to 2 months. No further details were available in the English abstract of this study from the Russian literature.

Other Studies

p-Chlorobenzoic acid was negative in *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98, TA100, and TA104 and E. coli WP2UvrA with or without addition of exogenous metabolic activation (S9) (Zeiger et al., 1992; Ohkubo et al., 1996). Genotoxicity studies using other test systems were not located.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR p-CHLOROBENZOIC ACID

No relevant data were located regarding the human toxicity of p-chlorobenzoic acid following oral exposure. Wuehrer (1931) found no effects in one dog treated with 3 g per day of p-chlorobenzoic acid for just over a year (≈13 months) and two dogs treated with 1.5 g per day of the substance for almost two years (20.5 months). D'eng (1983) identified the liver as a target for p-chlorobenzoic acid, but experimental details were not available. The oral toxicity studies of p-chlorobenzoic acid in animals are of limited utility for risk assessment. Kieckebusch et al. (1960) found no effects in rats treated with p-chlorobenzoic acid in the diet for 5 months at doses up to approximately 159 mg/kg-day, but only a limited array of endpoints were assessed. The primary limitations of this study were the lack of detail on general methods and the apparent delayed sexual maturity, lack of histology on organs other than liver and kidney, and lack of methods for calculating exposure. No differences were found in terms of growth, feed utilization and state of health of the dams. The histological examination of the liver and kidneys did not reveal any adverse effects. No histological study was done on the reproductive organs and no endocrine study was done. No differences were found in the number of littered young and their rearing compared to the controls. The authors noted delayed sexual maturity in 40% of the dams for both test groups, as compared with the 5% in the controls. The authors concluded that this effect was not significant because of small sample size but did not report a statistical test. However, subsequent statistical analysis by the U.S. EPA showed statistical significance at the low dose group by a t-test ($p<0.01$) and a statistically-significant trend across all dose groups (Cochran-Armitage trend test; $p<0.01$). Kieckebusch et al. (1960) provided no indication of the severity, duration of the delay of the sexual maturity or how it was observed. The adversity of the reported effect is uncertain given that there were no other reproductive effects that might have resulted from the delay. The RfDs in the HEED (U.S. EPA, 1987) and HEAST (U.S. EPA, 1997) were derived from the freestanding NOAEL in the Kieckebusch et al. (1960) study. The Kieckebusch et al. study, although not sufficiently rigorous for development of PPRTV values, does provide potentially useful information in this regard. However, the Appendix of this document contains a Screening Value that may be useful in certain instances. Please see the attached Appendix for details.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR p-CHLOROBENZOIC ACID

In the absence of subchronic or chronic data on the inhalation toxicity of p-chlorobenzoic acid in humans or animals, derivation of provisional subchronic or chronic RfC values is precluded.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR p-CHLOROBENZOIC ACID

There are no human or animal carcinogenicity data for p-chlorobenzoic acid by any exposure route. The substance is not mutagenic in the Ames test (Zeiger et al., 1992; Ohkubo et al., 1996), and has not been tested for genotoxicity in other systems. Therefore, under the cancer guidelines (2005b) the data provide inadequate information to assess carcinogenic potential for p-chlorobenzoic acid.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2003. 2003 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2003. Internet HazDat-Toxicological Profile Query. Online. http://www.atsdr.cdc.gov/toxpro2.html

D'eng, B., A.I. Nikolaev, P.Z. Khasigov et al. 1983. [Evaluation of the hepatotoxic activity of several chlor-nitro derivatives of benzoic acid.] Vopr. Med. Khim. 29(6): 113-117. (Rus.; Eng. abstract)

IARC (International Agency for Research on Cancer). 2003. Search of IARC Monographs. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

Kieckebusch W., W. Griem and K. Lang. 1960. [The tolerability of p-chlorobenzoic acids.] Arzneimi Hel-Forsch. 10: 999-1001. (Ger.; Eng. trans.)

NIOSH (National Institute for Occupational Safety and Health). 2003. NIOSH Pocket Guide to Chemical Hazards. Online. http://www.cdc.gov/niosh/npg/npgd0000.html#F

NTP (National Toxicology Program). 2003. Management Status Report. Online. http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

Ohkubo T., S. Goto, O. Endo et al. 1996. Mutagenicity of chlorinated aromatic hydrocarbons containing oxygen. Kankyo Kagaku. 6(4): 533-540. (Cited in CCRIS database)

OSHA (Occupational Safety and Health Administration). 2003. OSHA Standard 1910.1000 Table Z-1. Part Z, Toxic and Hazardous Substances. Online. http://www.osha-slc.gov/OshStd_data/1910_1000_TABLE_Z-1.html

U.S. EPA. 1987. Health and Environmental Effects Document for p-Chlorobenzoic acid. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA. 2002. 2002 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA 822-R-02-038.
http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

U.S. EPA. 2005a. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online.
http://www.epa.gov/iris/

U.S. EPA. 2005b. Guidelines for Carcinogen Risk Assessment. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/630/P-03/001F.

WHO (World Health Organization). 2003. Online catalogs for the Environmental Health Criteria Series. Online. http://www.who.int/dsa/cat97/zehc1.htm

Wuehrer, J. 1931. [Title not specified]. Arch. Exp. Pathol. Pharmakol. 161: 719. (Cited in Kieckebusch et al., 1960)

Zeiger E., B. Anderson, S. Haworth et al. 1992. Salmonella Mutagenicity Tests: V. Results from the Testing of 311 Chemicals. Environ. Mol. Mutagen. 19(Supplement 21): 2-141.

APPENDIX

DERIVATION OF A SCREENING VALUE FOR P-CHLOROBENZOIC ACID

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for p-chlorobenzoic acid, subchronic RfD. However, 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. In the OSRTI hierarchy, Screening Values are considered to be below Tier 3, "Other (Peer-Reviewed) Toxicity Values."

Screening Values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available. Screening Values may be used, for example, to rank relative risks of individual chemicals present at a site to determine if the risk developed from the associated exposure at the specific site is likely to be a significant concern in the overall cleanup decision. Screening Values are not defensible as the primary drivers in making cleanup decisions because they are based on limited information. Questions or concerns about the appropriate use of Screening Values should be directed to the Superfund Health Risk Technical Support Center.

The Kieckebusch et al. study, although not sufficiently rigorous for development of PPRTV values, does provide potentially useful information in this regard. Thus, this appendix is provided with screening values that could be useful for screening or other limited purposes pursuant to consultation with the Superfund Technical Support Center. Delayed sexual maturity observed in Kieckebusch et al. (1960) rat reproductive effects study would ordinarily be considered adverse, and considering the high incidence in both treatment groups, a LOAEL of 80 mg/kg-day could be established based on food consumption of 13 mg/day and mean body weight of 165 g. The mean body weight value was determined based on integration of the provided body weight data and an assumption of linearity for the 8-20 week period. A **screening subchronic reference dose of 0.08 mg/kg-day** could be derived from the LOAEL of 80 mg/kg-day by applying an uncertainty factor (UF) of 1000. The UF of 1000 includes 3 ($10^{0.5}$) for minimal LOAEL (UF_L), 3 ($10^{0.5}$) for lack of additional reproductive and developmental toxicity data (UF_D), 10 for interspecies extrapolation (UF_A) and 10 for sensitive humans (UF_H).

Subchronic screening reference dose = LOAEL ÷ UF
= 80 mg/kg-day ÷ 1000
= 0.08 (8E-2) mg/kg-day

Confidence for the study is low because of the lack of detail on the critical effect and other deficiencies noted in this document. Given the lack of additional studies, confidence in the database is also low. Thus, confidence in the toxicity value is low.

If subsequent information becomes available indicating that the reported delayed sexual maturity was not biologically significant, an alternative screening subchronic reference dose based on a NOAEL at the highest dose could be derived. In this case, a **screening subchronic reference dose of 0.5 mg/kg-day** can be calculated for a NOAEL of 160 mg/kg-day using a total UF of 300 (UF_A = 10, UF_H = 10, UF_D = 3). Confidence in the study and database would remain low, yielding low confidence in the value. Given current information, however, the preferred approach is the one based on the LOAEL for delayed sexual maturity at the low dose, which is health protective. The quantitative impact of the LOAEL-based approach versus the less-conservative NOAEL-based one is less an order of magnitude.

Regarding the chronic screening reference dose, applying an additional uncertainty factor of 3 to the subchronic values gives **chronic screening values of 0.03 and 0.2 mg/kg-day** respectively, relative to the two subchronic values discussed previously.