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Provisional Peer-Reviewed Toxicity Values for

2-Chloronaphthalene
(CASRN 91-58-7)

Superfund Health Risk Technical Support Center
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Commonly Used Abbreviations

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
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
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
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

PEER-REVIEWED PROVISIONAL TOXICITY VALUES FOR 2-CHLORONAPHTHALENE (CASRN 91-58-7)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) 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) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. 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 U.S. EPA's 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 U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. 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 documents 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 Resource Conservation and Recovery Act (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 document and understand the strengths

and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. 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 U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

A chronic RfD of 8×10^{-2} mg/kg-day is available for 2-chloronaphthalene (chemical structure shown in Figure 1) on IRIS (U.S. EPA, 2009). The RfD is based on a subchronic oral gavage study in mice (U.S. EPA, 1989) that identified a LOAEL of 600 mg/kg-day and a NOAEL of 250 mg/kg-day for dyspnea, abnormal appearance, and liver enlargement. This assessment, which was posted 02/21/1990, is not presented in any other U.S. EPA document. This RfD is not listed in Health Effects Assessment Summary Tables (HEAST, U.S. EPA, 1997) or in the Drinking Water Standards and Health Advisories (DWHA) list (U.S. EPA, 2006). No RfC or cancer assessment for 2-chloronaphthalene is available on IRIS (U.S. EPA, 2009) or in the HEAST (U.S. EPA, 1997) or DWHA list (U.S. EPA, 2006). The only relevant document in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA 1991, 1994) is an Ambient Water Quality Criteria Document (AWQCD) for chlorinated naphthalenes (U.S. EPA, 1980) that includes few data and no assessment for 2-chloronaphthalene. The World Health Organization (WHO, 2001) developed a Concise International Chemical Assessment Document (CICAD) for chlorinated naphthalenes that declined to derive tolerable intakes due to inadequate data. The Agency for Toxic Substances Disease Registry (ATSDR, 2009) has not published a Toxicological Profile for 2-chloronaphthalene. The American Conference of Governmental Industrial Hygienists (ACGIH, 2008), the National Institute for Occupational Safety and Health (NIOSH, 2005), and the Occupational Safety and Health Administration (OSHA, 2009) have not established occupational exposure limits for 2-chloronaphthalene. The carcinogenicity of 2-chloronapthalene has not been assessed by the International Agency for Research on Cancer (IARC, 2009) or by the National Toxicology Program (NTP, 2005, 2009).

Literature searches were conducted from the 1960s through August 2009 for studies relevant to the derivation of provisional toxicity values for 2-chloronaphthalene. Databases searched include MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents (last 6 months).

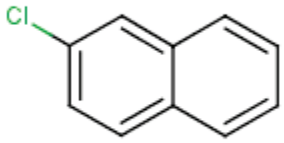

Figure 1. Chemical Structure of 2-Chloronaphthalene

REVIEW OF PERTINENT DATA

Human Studies

No data have been located regarding the effects of 2-chloronaphthalene in humans exposed by any route.

Animal Studies

Oral Exposure

A subchronic study (U.S. EPA, 1989), as cited in IRIS (U.S. EPA, 2009), is the only available study of oral exposure. The following description is reproduced from U.S. EPA (2009):

> "CD-1 mice (20/sex/group) were administered oral gavage dosages of 0, 100, 250, or 600 mg/kg/day beta-chloronaphthalene in corn oil for 13 weeks. Parameters examined included mortality, body and organ weight changes, food consumption, clinical signs, opthalmologic changes, hematology, clinical chemistry, and gross histopathology. Mortality was reported in one male and one female low- dose mice and in three male and two female high-dose mice, although no statistical significance was found when compared with controls. Daily observations revealed dyspnea, rough hair coat, and languid, thin, hunched appearance of high-dose animals; these signs were more prevalent among females than males. Similar symptoms were also observed in other treatment groups, but the incidence was not statistically significant. Although total food consumption was significantly increased in high-dose males throughout the study, this did not result in a significant increase in body weight gain, compared with controls. Absolute and relative liver and gall bladder weights were significantly increased in both sexes at the high-dose level and were accompanied by centrilobular hepatocellular enlargement. Both absolute and relative adrenal weights were significantly increased in low-dose females, but no dose-response relationship could be established, nor was there any corresponding

histopathologic changes. No other effects were observed. The LOAEL was identified as 600 mg/kg/day and the NOAEL was 250 mg/kg/day."

Inhalation Exposure

No data have been located regarding inhalation exposure of animals to 2-chloronaphthalene.

Other Studies

Parenteral Exposure

In an acute hepatoxicity study of halogenated aromatic hydrocarbons, Brodie et al. (1971) injected male Sprague-Dawley rats (180 g) intraperitoneally with saline or 80 mg phenobarbital/kg bw for 3 successive days, followed by an injection of 100 mg (555 mg/kg bw) 2-chloronaphthalene the next day. Livers were removed 24 hours after the injection of 2-chloronaphthalene and examined. "Extensive" to "massive" necrosis was found in the rats pretreated with phenobarbital. Only occasional glycogen loss was noted in rats pretreated with saline.

Genotoxicity

2-Chloronaphthalene (99% purity) did not induce mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA1535, TA1537, or TA1538 with or without metabolic activation (Zeiger et al., 1992).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 2-CHLORONAPHTHALENE

Subchronic p-RfD

Only one study (i.e., U.S. EPA, 1989, as cited in U.S. EPA, 2009) potentially suitable for derivation of a subchronic p-RfD for 2-chloronaphthalene has been located. As described by U.S. EPA (2009), the study was a 13-week subchronic exposure study in CD-1 mice (20/sex/dose). The NOAEL and LOAEL values are 250 and 600 mg/kg-day, respectively. The basis for the LOAEL includes dyspnea, abnormal appearance, and liver enlargement. Use of this study based on the description provided by U.S. EPA (2009) is limited by incomplete reporting of methods and results. Because the data are not shown, it was not possible to use benchmark dose modeling to derive a point of departure (POD). Therefore, the NOAEL (250 mg/kg-day) has been selected as the POD.

The **subchronic p-RfD** is calculated as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 50 \text{ mg/kg-day} \div 1000 \\ &= \mathbf{0.2 \text{ mg/kg-day or } 2 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

The composite uncertainty factor of 1000 is composed of the following:

- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient.

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
- UF_D: A factor of 10 is applied for database inadequacies because data for evaluating developmental and reproductive toxicity are not available.

As reported on IRIS (U.S. EPA, 2009), confidence in the principal study is medium. The study is well-designed and identified both a LOAEL and NOAEL for multiple endpoints using CD-1 mice (20/sex/group) at 4 dose levels including one control group. The liver effects seen at the LOAEL are also supported by the liver toxicity observed by Brodie et al. (1971). Confidence in the database is low because developmental, reproductive, and other long-term toxicity following oral exposure to beta-chloronaphthalene have not been tested. Confidence in the RfD is accordingly low.

Chronic p-RfD

A chronic oral RfD of 8×10^{-2} mg/kg-day for 2-chloronapthalene is available on IRIS (U.S. EPA, 2009) based on the subchronic mouse study (U.S. EPA, 1989).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 2-CHLORONAPHTHALENE

Provisional RfC values for 2-chloronaphthalene cannot be derived because of the lack of human and animal inhalation data.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2-CHLORONAPHTHALENE

Weight-of-Evidence Descriptor

Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is "*Inadequate Information to Assess* [the] *Carcinogenic Potential*" of 2-chloronaphthalene based on the lack of carcinogenicity studies.

Quantitative Estimates of Carcinogenic Risk

There are no data with which to quantify estimates of carcinogenic risk for 2-chloronaphthalene.

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