

Provisional Peer Reviewed Toxicity Values for

p-Bromofluorobenzene (CASRN 460-00-4)

Derivation of Subchronic and Chronic Oral RfDs

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

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p-BROMOFLUOROBENZENE (CASRN 460-00-4)
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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 HQ 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

An RfD for *p*-bromofluorobenzene (C_6H_4BrF) is not listed on IRIS (U.S. EPA, 2002a), the Drinking Water Standards and Health Advisories table (U.S. EPA, 2002b), or the HEAST (U.S. EPA, 1997). No pertinent documents are listed in the CARA database (U.S. EPA, 1991, 1994). A Drinking Water Toxicity Profile for *p*-bromofluorobenzene (U.S. EPA, 1992) did not contain sufficient information supporting an RfD derivation. ATSDR (2002) has not published a toxicological profile for *p*-bromofluorobenzene and this chemical was not listed in the NTP (2002) Management Status Reports. IARC (2002) and WHO (2002) have not published a review for *p*-bromofluorobenzene. No information pertinent to an RfD derivation for *p*-bromofluorobenzene was found in a review by Leber and Bus (2001). Literature searches of the following databases were conducted from 1994 to September 2002 for relevant studies: TOXLINE, MEDLINE, TSCATS, GENETOX, EMIC/EMICBACK, DART/ETICBACK,

HSDB, RTECS, CCRIS, and BIOSIS. Previous literature searches of TOXLINE (1965-1994), TSCATS and RTECS were conducted in November 1994. An updated literature search was conducted through April 2004 and no relevant information was found. Literature search strategy employed for this compound was based on the CASRN and at least one common name.

REVIEW OF PERTINENT LITERATURE

Human Studies

No studies were located regarding the toxicity of *p*-bromofluorobenzene in humans following oral exposure.

Animal Studies

No studies were located regarding the toxicity of *p*-bromofluorobenzene in animals following subchronic or chronic oral exposure.

One acute oral lethality study was found (DuPont, 1985; U.S. EPA, 2002c). Groups of 10 male Sprague Dawley rats were administered 1000, 2000, 3000, or 5000 mg/kg of *p*-bromofluorobenzene via gavage in corn oil and sacrificed after a 14-day observation period. The LD₅₀ was 2700 mg/kg (95% CI: 2200-3200 mg/kg). At non-lethal doses (specific levels not reported), tremors, limpness, and weight loss (3-19%) were observed 1-2 days after dosing. At lethal doses, death occurred within 3 days of dosing, preceded by tremors, absence of righting and/or grasping reflex, limpness, ataxia, lung noise, clear ocular discharge, and body weight loss (8-21%). No other endpoints (including gross and histological pathology) were examined.

FEASIBILITY OF DERIVING A PROVISIONAL SUBCHRONIC OR CHRONIC RfD FOR *p*-BROMOFLUOROBENZENE

The lack of chronic or subchronic oral toxicity data for humans or animals precludes derivation of a subchronic or chronic p-RfD for *p*-bromofluorobenzene.

REFERENCES

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11-23-2004

Provisional Peer Reviewed Toxicity Values for

p-Bromofluorobenzene
(CASRN 460-00-4)

Derivation of Subchronic and Chronic Inhalation RfCs

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

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INTRODUCTION

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November 1994. An updated literature search was conducted through April 2004 and no relevant information was found. Literature search strategy employed for this compound was based on the CASRN and at least one common name.

REVIEW OF PERTINENT LITERATURE

Human Studies

No studies were located regarding the toxicity of *p*-bromofluorobenzene in humans following inhalation exposure.

Animal Studies

No studies were located regarding the toxicity of *p*-bromofluorobenzene in animals following subchronic or chronic inhalation exposure.

Two acute inhalation studies were found (DuPont, 1985; Rhone-Poulenc, 1987; U.S. EPA, 2002b). Groups of 10 male Sprague-Dawley rats were exposed to 7.1, 14, 19, 22, or 26 mg/L air of *p*-bromofluorobenzene for 4 hours and sacrificed after a 14-day observation period (DuPont, 1985). The LC₅₀ was 18 mg/L (95% CI: 15-21 mg/L). Exposure to 14 mg/L or greater resulted in loss of righting reflex, diminished startle response, lethargy, tremors, spasms, labored or rapid breathing, red nasal discharge, and darkened eyes. A slight-to-moderate body weight loss (up to 8%) was observed in rats exposed to 7.1 mg/L and a slight-to-severe weight loss (4.1-17.5%) was observed in the rats exposed to 14 mg/L or greater. No other endpoints (including gross and histopathology) were examined. The second study was conducted at a lower concentration. Groups of 10 albino Wistar rats (5/sex/group) were exposed (whole-body as opposed to nose only) to 0 (clear air control) or 5.95 mg/L of *p*-bromofluorobenzene for 4 hours (Rhone-Poulenc, 1987). There were no deaths during the study. Clinical signs during exposure were consistent with a mildly irritant vapor and included abnormal respiratory pattern and body posture. During the post exposure observation period, signs included abnormal respiratory pattern and fascicular tremors. Four of five female rats exposed to *p*-bromofluorobenzene developed hair loss from the back during the observation period, compared to a single female with hair loss from the head. Food and water consumption, body weight and relative lung weight were unaffected by exposure to *p*-bromofluorobenzene. There were no macroscopic or microscopic findings attributable to exposure to *p*-bromofluorobenzene.

FEASIBILITY OF DERIVING A PROVISIONAL SUBCHRONIC OR CHRONIC RfC FOR *p*-BROMOFLUOROBENZENE

The lack of chronic or subchronic inhalation toxicity data for humans or animals precludes derivation of a subchronic or chronic *p*-RfC for *p*-bromofluorobenzene.

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11-23-2004

Provisional Peer Reviewed Toxicity Values for

p-Bromofluorobenzene
(CASRN 460-00-4)

Derivation of a Carcinogenicity Assessment

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
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Cincinnati, OH 45268

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Derivation of a Carcinogenicity Assessment**

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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

A carcinogenicity assessment for *p*-bromofluorobenzene (C_6H_4BrF) is not listed on IRIS (U.S. EPA, 2002a), the Drinking Water Standards and Health Advisories table (U.S. EPA, 2002b), or the HEAST (U.S. EPA, 1997). No documents for this chemical are listed in the CARA database (U.S. EPA, 1991, 1994). A Drinking Water Toxicity Profile for *p*-bromofluorobenzene (U.S. EPA, 1992) contained no relevant information. ATSDR (2002) has not published a toxicological profile for *p*-bromofluorobenzene and this chemical was not listed in the NTP (2002) Management Status Reports. ACGIH (2002), IARC (2002) and WHO (2002) have not assessed the carcinogenicity of *p*-bromofluorobenzene. No information pertinent to a carcinogenicity assessment for *p*-bromofluorobenzene was found in a review by Leber and Bus (2001). Literature searches of the following databases were conducted from 1994 to September 2002 for relevant studies: TOXLINE, MEDLINE, TSCATS, GENETOX, EMIC/EMICBACK,

DART/ETICBACK, HSDB, RTECS, CCRIS, and BIOSIS. Previous literature searches of TOXLINE (1965-1994), TSCATS and RTECS were conducted in November 1994. An updated literature search was conducted through April 2004 and no relevant information was found. Literature search strategy for this compound was based on the CASRN and at least one common name.

REVIEW OF PERTINENT LITERATURE

Human Studies

No studies of the potential carcinogenicity of *p*-bromofluorobenzene in humans were located.

Animal Studies

No studies of the potential carcinogenicity of *p*-bromofluorobenzene in animals were located.

Other Studies

No genetic toxicity data were located for *p*-bromofluorobenzene.

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

Under the proposed U.S. EPA (1999) guidelines, the data are inadequate for an assessment of human carcinogenic potential.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for *p*-bromofluorobenzene is precluded by the lack of data regarding carcinogenicity of this chemical.

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