United States
Environmental Protection
Agency

EPA/690/R-04/009F
Final
11-23-2004

Provisional Peer Reviewed Toxicity Values for

2-Fluorophenol
(CASRN 367-12-4)

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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Derivation of Subchronic and Chronic Oral RfDs

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

A subchronic or chronic RfD for 2-fluorophenol is not available on IRIS (U.S. EPA, 2003), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). 2-Fluorophenol is not listed in the HSDB. No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). Neither ATSDR (2003), NTP (2003), IARC (2003), nor WHO (2003) have produced documents regarding 2-fluorophenol. Literature searches of the following databases were conducted from 1965 through January 2003 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. Additional literature searches were conducted by the NCEA-Cincinnati from February 2003 through May 2004 using TOXLINE, MEDLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

No data regarding the toxicity of 2-fluorophenol to humans following chronic or subchronic oral exposure were located.

Animal Studies

No data regarding the toxicity of 2-fluorophenol to animals following chronic or subchronic oral exposure were located. Available data include acute toxicity studies examining oral (Olin Corp., 1973; Tai et al., 1986) and dermal (Olin Corp., 1973) exposures in which a limited number of endpoints were examined. In an LD_{50} study, groups of 3 male and 2 female Sprague Dawley rats were administered single doses of 2-fluorophenol via gavage (vehicle, dose ranges, and controls not specified) that determined an LD_{50} of 1326 mg/kg (95% confidence limits of 1186 to 1483 mg/kg) (Olin Corp., 1973). The length of the observation period was not reported. The animals died 3 to 6 hours after exposure and clinical signs such as tremors, salivation, and chromodacryorrhea were observed. No other endpoints (including gross and microscopic pathology) were examined.

An LD_{50} of 450 mg/kg (range 390 to 520 mg/kg) was determined in a group of 10 seven-week-old Wistar (SPF) rats administered doses of 0.5 to 1.5 ml/100 g body weight of 2-fluorophenol via gavage (Tai et al., 1986). Treated animals were observed hourly up to 8 hours post-dosing for symptoms of poisoning or mortality, and body weight was recorded for 7 days. The investigators reported acute symptoms in rats administered 2-fluorophenol that included: violent convulsions and death in rats administered high doses; transient tremors in animals that received lower doses; and severe decrease in body weight for 3 days following treatment.

Increased mortality was also observed in New Zealand rabbits dermally exposed to 2000 mg/kg of 2-fluorophenol for 24 hours via an occlusive patch (Olin Corp., 1973). Within 6 to 48 hours of exposure, 5 of 6 rabbits died; salivation, difficulty in standing, and convulsions were observed. No other endpoints were examined. In primary skin and eye irritation studies (no details on the protocol or concentration were provided), marked skin and eye irritation was observed in New Zealand rabbits following dermal or ocular exposure to 2-fluorophenol (Olin Corp., 1973).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR 2-FLUOROPHENOL

The database for 2-fluorophenol is inadequate for derivation of an p-RfD. The derivation of an p-RfD by analogy to 4-fluorophenol or 2-chlorophenol was considered. No subchronic or chronic data examining effects of oral exposure to 4-fluorophenol were located. There is an RfD of 5E-3 mg/kg-day for 2-chlorophenol on IRIS (U.S. EPA, 2003). The RfD is based on a NOAEL of 5 mg/kg-day for reproductive effects; an increase in conception rate and number of stillborns and a decrease in litter size were observed in rats exposed to 50 mg/kg-day during a 10-week pre-mating period and during mating, gestation, and weaning.

The selection of a surrogate involves a comparison of toxicological and pharmacokinetic data to determine if the two compounds have similar toxic effects, mechanisms of action, pharmacokinetic properties, and potency. The limited data from the acute toxicity studies of 2-fluorophenol would not adequately support such a comparison. Therefore, a derivation by analogy is not recommended.

The lack of subchronic or chronic oral toxicity data for humans or animals and the lack of data to support a derivation by analogy to structurally related chemicals precludes derivation of a subchronic or chronic p-RfD for 2-fluorophenol.

REFERENCES

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

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11-23-04

Provisional Peer Reviewed Toxicity Values for

2-Fluorophenol
(CASRN 367-12-4)

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

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
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FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
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LEL	lowest-effect level
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LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
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m	meter
MCL	maximum contaminant level
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MF	modifying factor
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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

11-23-04

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2-FLUOROPHENOL (CASRN 367-12-4)
Derivation of Subchronic and Chronic Inhalation RfCs

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).

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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

A subchronic or chronic RfC for 2-fluorophenol is not available on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997). 2-Fluorophenol is not listed in the HSDB. No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). ACGIH (2002), NIOSH (2003), and OSHA (2003) have not recommended occupational exposure limits for 2-fluorophenol. ATSDR (2003), NTP (2003), IARC (2003), and WHO (2003) have not produced documents for this chemical. Literature searches of the following databases were conducted from 1965 through January 2003 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and

TSCATS. Additional literature searches were conducted by the NCEA-Cincinnati from February 2003 through May 2004 using TOXLINE, MEDLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT DATA

Human Studies

No data regarding the toxicity of 2-fluorophenol to humans following chronic or subchronic inhalation exposure were located.

Animal Studies

No data regarding the toxicity of 2-fluorophenol to animals following chronic or subchronic inhalation exposure were located. In one acute study, Olin Corp. (1973a) reported no overt signs of toxicity or deaths in 5 male and 5 female Sprague Dawley rats exposed by inhalation to 200 ppm of 2-fluorophenol for 1 hour. Exposure to 20,000 ppm of 2-fluorophenol for 1 hour resulted in convulsions during and after exposure and death in 2/5 male and 5/5 female rats (Olin Corp., 1973b). No other endpoints were examined in either inhalation study.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR 2-FLUOROPHENOL

The database for 2-fluorophenol is inadequate for derivation of an p-RfC. The derivation of an p-RfC by analogy to 4-fluorophenol or 2-chlorophenol was considered, but no subchronic or chronic data are available for either possible surrogate chemical via the inhalation route of exposure.

The lack of chronic or subchronic inhalation data for humans or animals preclude derivation of a subchronic or chronic p-RfC for 2-fluorophenol.

REFERENCES

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

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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

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11-23-04

Provisional Peer Reviewed Toxicity Values for

2-Fluorophenol
(CASRN 367-12-4)

Derivation of a Carcinogenicity Assessment

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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CNS	central nervous system
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UF	uncertainty factor
µg	microgram
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VOC	volatile organic compound

11-23-04

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2-FLUOROPHENOL (CASRN 367-12-4) Derivation of a Carcinogenicity Assessment

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INTRODUCTION

A carcinogenicity assessment for 2-fluorophenol is not available on IRIS (U.S. EPA, 2003), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). 2-Fluorophenol is not listed in the HSDB. No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). Neither ATSDR (2003), NTP (2003), IARC (2003), nor WHO (2003) have produced documents regarding 2-fluorophenol. Literature searches of the following databases were conducted from 1965 through January 2003 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. Additional literature searches were conducted by the NCEA-Cincinnati from February 2003 through May 2004 using TOXLINE, MEDLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT DATA

Human Studies

No data regarding the possible carcinogenicity of 2-fluorophenol in humans were located.

Animal Studies

No animal studies examining the carcinogenicity of 2-fluorophenol by any route of exposure were located.

Other Studies

One *in vitro* mutagenicity study was located in the CCRIS database that reported positive results with 2-fluorophenol in a mouse lymphoma assay (NCI, 1989). However, additional study information was not provided.

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

No studies examining the carcinogenic potential of 2-fluorophenol in humans or animals were located. As the available data are insufficient to assess carcinogenic potential in animals or humans, they are consistent with the hazard descriptor, "*inadequate information to assess carcinogenic potential*," as specified by the updated U.S. EPA (1999) Proposed Guidelines for Cancer Risk Assessment.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for 2-fluorophenol is precluded by the lack of data demonstrating carcinogenicity associated with 2-fluorophenol exposure.

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