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Provisional Peer Reviewed Toxicity Values for

2-Fluorobiphenyl
(CASRN 321-60-8)

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

12-20-04

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2-FLUOROBIPHENYL (CASRN 321-60-8)
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-fluorobiphenyl 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). 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-fluorobiphenyl. 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 NCEA-Cincinnati from February 2003 through May 2004 using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

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

Animal Studies

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

Other Studies

Borlakoglu and Wilkins (1993), in their *in vitro* study, identified hydroxylated metabolites of 2-fluorobiphenyl formed by hepatic microsomal preparations both with and without metabolic activation from control rats, pigeons, and rabbits. The investigators reported that *para*-hydroxylation was the predominant route of metabolism for 2-fluorobiphenyl in *in vitro* mammalian assays. 2-Fluorobiphenyl is not likely to bioaccumulate due to rapid oxidation.

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

The database for 2-fluorobiphenyl is inadequate for derivation of a p-RfD and the derivation of a p-RfD by a surrogate chemical was considered. However, 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 lack of toxicological data for 2-fluorobiphenyl precludes comparison with potential surrogates.

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-fluorobiphenyl.

REFERENCES

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

Borlakoglu, J.T. and J.P.G. Wilkins. 1993. Microsomal oxidation of bromo-, chloro-, and fluorobiphenyls. Comp. Biochem. Physiol. 105C (1): 119-125.

IARC (International Agency for Research on Cancer). 2003. IARC Agents and Summary Evaluations. Online. http://www-cie.iarc.fr/

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

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U.S. EPA. 2003. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/

WHO (World Health Organization). 2003. Online Catalogs for the Environmental Criteria Series. Online. http://www.who.int/pcs/pubs/pub_ehc_alph.htm

12-20-04

Provisional Peer Reviewed Toxicity Values for

2-Fluorobiphenyl
(CASRN 321-60-8)

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
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
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L	liter
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
MCLG	maximum contaminant level goal
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mg	milligram
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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

12-20-04

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2-FLUOROBIPHENYL (CASRN 321-60-8) 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:

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Questions Regarding PPRTVs

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INTRODUCTION

A subchronic or chronic RfC for 2-fluorobiphenyl is not available on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997). 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-fluorobiphenyl. 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 NCEA-Cincinnati from February 2003 through May 2004 using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT DATA

Human Studies

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

Animal Studies

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

Other Studies

Borlakoglu and Wilkins (1993), in their *in vitro* study, identified hydroxylated metabolites of 2-fluorobiphenyl formed by hepatic microsomal preparations both with and without metabolic activation from control rats, pigeons, and rabbits. The investigators reported that *para*-hydroxylation was the predominant route of metabolism for 2-fluorobiphenyl in *in vitro* mammalian assays. 2-Fluorobiphenyl is not likely to bioaccumulate due to rapid oxidation.

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

The database for 2-fluorobiphenyl is inadequate for derivation of a p-RfC and the derivation of a p-RfC by a surrogate chemical was considered. However, 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 lack of toxicological data for 2-fluorobiphenyl precludes comparison with potential surrogates.

The lack of subchronic or chronic inhalation 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-RfC for 2-fluorobiphenyl.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2002. 2002 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

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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12-20-04

Provisional Peer Reviewed Toxicity Values for

2-Fluorobiphenyl
(CASRN 321-60-8)

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

bw	body weight
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CNS	central nervous system
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NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
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OSF	oral slope factor
p-IUR	**provisional inhalation unit risk**
p-OSF	**provisional oral slope factor**
p-RfC	**provisional inhalation reference concentration**
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PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	**Provisional Peer Reviewed Toxicity Value**
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RCRA	Resource Conservation and Recovery Act
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REL	relative exposure level
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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

12-20-04

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2-FLUOROBIPHENYL (CASRN 321-60-8) Derivation of a Carcinogenicity Assessment

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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INTRODUCTION

A carcinogenicity assessment of 2-fluorobiphenyl 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). 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-fluorobiphenyl. 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 NCEA-Cincinnati from February 2003 through May 2004 using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT DATA

Human Studies

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

Animal Studies

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

Other Studies

Borlakoglu and Wilkins (1993), in their *in vitro* study, identified hydroxylated metabolites of 2-fluorobiphenyl formed by hepatic microsomal preparations both with and without metabolic activation from control rats, pigeons, and rabbits. The investigators reported that *para*-hydroxylation was the predominant route of metabolism for 2-fluorobiphenyl in *in vitro* mammalian assays. 2-Fluorobiphenyl is not likely to bioaccumulate due to rapid oxidation.

2-Fluorobiphenyl was not mutagenic in *in vitro* bacterial assays but showed mutagenic effects in one mammalian assay with metabolic activation. No significant increases were observed in the number of revertants in *Salmonella typhimurium* strains TA98 or TA100 with or without metabolic activation (Glatt et al., 1992) or in *Salmonella typhimurium* strains TA98, TA100, TA 1535, TA1537, or TA1538 with or without activation. The details of these data were not reported in the NCI (1989) report. In cultured Chinese hamster V79 cells, 2-fluorobiphenyl produced a mutagenic effect with metabolic activation that was not seen in the absence of activation (Glatt et al., 1992).

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

No studies examining the carcinogenic potential of 2-fluorobiphenyl in humans or animals were located. *In vitro* mutagenicity studies for 2-fluorobiphenyl were negative in bacterial assays, but positive results were seen in one mammalian cell assay following metabolic activation. 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 proposed U.S. EPA (1999) Guidelines for Cancer Risk Assessment.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

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

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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