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11-23-2004

Provisional Peer Reviewed Toxicity Values for

Benzothiazole

(CASRN 95-16-9)

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

11-23-2004

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR BENZOTHIAZOLE (CASRN 95-16-9)
Derivation of a Subchronic or Chronic Oral RfD

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

A subchronic or chronic RfD for benzothiazole is not available on IRIS (U.S. EPA, 2002a), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002b). No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). The Office of Drinking Water produced a Toxicological Profile for benzothiazole (U.S. EPA, 1989) that provided a synopsis of toxicological information for the chemical, but no risk assessment. Neither ATSDR (2002), NTP (2002), IARC (2002), nor WHO (2002) have produced documents regarding benzothiazole. Literature searches of the following databases were conducted from 1965 through May 2004 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS.

REVIEW OF PERTINENT DATA

Human Studies

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

Animal Studies

No data regarding the toxicity of benzothiazole to animals following chronic or subchronic oral exposure were located. The only data found were acute animal studies. Investigators reported oral LD_{50} values of 380-492 mg/kg for benzothiazole in male and female Fischer 344 (Mayhew and Muni, 1986) and Sprague-Dawley (Younger Laboratories, 1964, 1976) rats, and an oral LD_{50} of 375 mg/kg in male rats of an unspecified strain (Lorke, 1983). A dermal LD_{50} of 126-200 mg/kg was found for male and female New Zealand Albino rabbits (Younger Laboratories, 1976). Benzothiazole was a mild to moderate skin irritant and a severe eye irritant in rabbits (Younger Laboratories, 1964, 1976).

FEASIBILITY OF DERIVING A PROVISIONAL SUBCHRONIC OR CHRONIC RfD FOR BENZOTHIAZOLE

The lack of chronic or subchronic oral toxicity data for humans or animals precludes derivation of a subchronic or chronic p-RfD for benzothiazole. It was considered that systemic toxicity values might be obtained by analogy to 2-mercaptobenzothiazole (MBT), which has toxicity and carcinogenicity information. However, the pharmacokinetic data on MBT (Colucci and Buyske, 1965; El Dareer et al., 1989; Larsen et al., 1988; Nagamatsu et al., 1979) do not suggest that biotransformation to benzothiazole would occur, and no obvious pathways for biotransformation of benzothiazole to MBT were identified. In addition, there is some evidence that the sulfur-containing mercapto group is involved in MBT carcinogenicity (NTP, 1988) and other aspects of MBT toxicity (Feinman, 1987).

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NTP (National Toxicology Program). 1988. Technical Report on the Toxicology and Carcinogenesis Studies of 2-Mercaptobenzothiazole (CAS No. 149-30-4) in F344/N Rats and B6C3F1 Mice. National Toxicology Program, Research Triangle Park, NC. NTP TR 332. NTIS PB 88245154. Online.
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Provisional Peer Reviewed Toxicity Values for

Benzothiazole

(CASRN 95-16-9)

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
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

11-23-2004

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR BENZOTHIAZOLE (CASRN 95-16-9)
Derivation of a Subchronic or Chronic Inhalation RfC

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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   - 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

A subchronic or chronic RfC for benzothiazole is not available on IRIS (U.S. EPA, 2002) or in the HEAST (U.S. EPA, 1997). No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). The Office of Drinking Water produced a Toxicological Profile for benzothiazole (U.S. EPA, 1989) that provided a synopsis of toxicological information for the chemical, but no risk assessment. ACGIH (2001), NIOSH (2002) and OSHA (2002) have not recommended occupational exposure limits for benzothiazole. ATSDR (2002), NTP (2002), IARC (2002), and WHO (2002) have not produced documents for this chemical. Literature searches of the following databases were conducted from 1965 through May 2004 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS.

REVIEW OF THE PERTINENT DATA

Human Studies

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

Animal Studies

No data regarding the toxicity of benzothiazole to animals following chronic or subchronic inhalation exposure were located. An acute inhalation study was conducted in which four male Sprague-Dawley rats survived a 6-hour exposure to a concentrated vapor of benzothiazole (Younger Laboratories, 1964). The exposure concentration was not estimated.

FEASIBILITY OF DERIVING A PROVISIONAL SUBCHRONIC OR CHRONIC RfC FOR BENZOTHIAZOLE

The lack of chronic or subchronic inhalation data for humans or animals precludes derivation of a subchronic or chronic p-RfC for benzothiazole. It was considered that systemic toxicity values might be obtained by analogy to 2-mercaptobenzothiazole (MBT), which has toxicity and carcinogenicity information. However, the pharmacokinetic data on MBT (Colucci and Buyske, 1965; El Dareer et al., 1989; Larsen et al., 1988; Nagamatsu et al., 1979) do not suggest that biotransformation to benzothiazole would occur, and no obvious pathways for biotransformation of benzothiazole to MBT were identified. In addition, there is some evidence that the sulfur-containing mercapto group is involved in MBT carcinogenicity (NTP, 1988) and other aspects of MBT toxicity (Feinman, 1987).

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NTP (National Toxicology Program). 2002. Management Status Report. Online.
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OSHA (Occupational Safety and Health Administration). 2002. OSHA Standard 1910.1000 TableZ-1. Part Z, Toxic and Hazardous Substances. Online.
http://www.osha-slc.gov/OshStd_data/1910_1000_TABLE_Z-1.html

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Provisional Peer Reviewed Toxicity Values for

Benzothiazole

(CASRN 95-16-9)

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
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
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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

11-23-2004

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR BENZOTHIAZOLE (CASRN 95-16-9)
Derivation of a Carcinogenicity Assessment

Background

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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 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

A carcinogenicity assessment of benzothiazole is not available on IRIS (U.S. EPA, 2002a), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002b). No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). A toxicological profile on benzothiazole prepared by the Office of Drinking Water (U.S. EPA, 1989) did not locate carcinogenic study data for benzothiazole in humans or animals, but did include mutagenicity assay results in bacteria (Sano and Korte, 1985). Neither ATSDR (2002), NTP (2002), IARC (2002), nor WHO (2002) have produced documents regarding benzothiazole. Literature searches of the following databases were conducted from 1965 through May 2004 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS.

REVIEW OF THE PERTINENT DATA

Human Studies

No data regarding the possible carcinogenicity of benzothiazole in humans were located.

Animal Studies

No reports of animal studies examining the carcinogenicity of benzothiazole by any route of exposure were located.

Supporting Studies

Data regarding the genotoxicity of benzothiazole are limited to two reports of testing in the Ames assay. Benzothiazole did not induce an increase in revertant colony counts with or without an S-9 metabolic activation system in *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537, and TA1538 exposed to concentrations ranging from 3.2×10^{-4} to 1 µl/plate (Sano and Korte, 1985). In another study, benzothiazole was reported to have induced reverse mutations in strain TA1537 in the presence of an S-9 metabolic activation system, but the study was presented in an abstract that did not include any experimental details (Kinae et al., 1981).

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

There are no data on the carcinogenicity of benzothiazole in humans or animals and only limited genotoxicity data. It was considered that cancer toxicity values might be obtained by analogy to 2-mercaptobenzothiazole (MBT), which has toxicity and carcinogenicity information. However, the pharmacokinetic data on MBT (Colucci and Buyske, 1965; El Dareer et al., 1989; Larsen et al., 1988; Nagamatsu et al., 1979) do not suggest that biotransformation to benzothiazole would occur, and no obvious pathways for biotransformation of benzothiazole to MBT were identified. In addition, there is some evidence that the sulfur-containing mercapto group is involved in MBT carcinogenicity (NTP, 1988) and other aspects of MBT toxicity (Feinman, 1987). Under the proposed U.S. EPA (1999) cancer guidelines, the available data are inadequate for an assessment of human carcinogenic potential.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

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

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