United States
Environmental Protection
Agency

EPA/690/R-05/007F
Final
3-15-2005

Provisional Peer Reviewed Toxicity Values for

Anilinobenzothiazole

(CASRN 1843-21-6)

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

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-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
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
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

03-15-05

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ANILINOBENZOTHIAZOLE (CASRN 1843-21-6)
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 anilinobenzothiazole 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). Neither ATSDR (2002), NTP (2002), IARC (2002), nor WHO (2002) have produced documents regarding anilinobenzothiazole. Literature searches of the following databases were conducted from 1965 through July 2002 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. An updated literature search was conducted through April 2004 and no relevant information was found.

REVIEW OF THE PERTINENT DATA

Human Studies

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

Animal Studies

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

FEASIBILITY OF DERIVING A PROVISIONAL SUBCHRONIC OR CHRONIC RfD FOR ANILINOBENZOTHIAZOLE

The lack of chronic or subchronic oral toxicity data for humans or animals precludes derivation of a subchronic or chronic RfD for anilinobenzothiazole. 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 anilinobenzothiazole would occur, and no obvious pathways for biotransformation of anilinobenzothiazole to MBT were identified. In addition, there is some evidence that the sulfhydryl group is involved in MBT carcinogenicity (NTP, 1988) and other aspects of MBT toxicity (Feinman, 1987).

REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 2002. Toxicological Profile Information Sheet. Online. http://www.atsdr.cdc.gov/toxpro2.html

Colucci, D.F. and D.A. Buyske. 1965. The biotransformation of a sulfonamide to a mercaptan and to mercapturic acid and glucuronide conjugates. Biochem. Pharmacol. 14: 457-466.

El Dareer, S.M., J.R. Kalin, K.F. Tillery et al. 1989. Disposition of 2-mercaptobenzothiazole and 2-mercaptobenzothiazole disulfide in rats dosed intravenously, orally and topically and in guinea-pigs dosed topically. J. Toxicol. Environ. Health. 27(1): 65-84.

Feinman, S.E. 1987. Sensitivity to rubber chemicals. J. Toxicol.- Cut. Ocular Toxicol. 6(2): 117-153.

IARC (International Agency for Research on Cancer). 2002. IARC Agents and Summary Evaluations. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

Larsen, G.L., J.E. Bakke, V.J. Feil and J.K. Huwe. 1988. In vitro metabolism of the methylthio group of 2-methylthiobenzothiazole by rat liver. Xenobiotica. 18(3): 313-322.

Nagamatsu, K., Y. Kido, G. Urakubo et al. 1979. Absorption, distribution, excretion and metabolism of 2-mercaptobenzothiazole in guinea pig. Eisei Kagaku. 25: 59-65. (Cited in NTP, 1988)

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.
http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

NTP (National Toxicology Program). 2002. Management Status Report. Online.
http://ntp-server.niehs.nih.gov/

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS 97-921199.

U.S. EPA. 2002a. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online.
http://www.epa.gov/iris/

U.S. EPA. 2002b. 2002 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA 822-R-02-038. Online.
http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

WHO (World Health Organization). 2002. Online Catalogs for the Environmental Criteria Series. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

03-15-05

Provisional Peer Reviewed Toxicity Values for

Anilinobenzothiazole

(CASRN 1843-21-6)

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

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-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
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
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

03-15-05

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ANILINOBENZOTHIAZOLE (CASRN 1843-21-6)
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).

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 RfC for anilinobenzothiazole 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). ACGIH (2001), NIOSH (2002) and OSHA (2002) have not recommended occupational exposure limits for anilinobenzothiazole. 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 July 2002 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. An updated literature search was conducted through April 2004 and no relevant information was found.

REVIEW OF THE PERTINENT DATA

Human Studies

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

Animal Studies

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

FEASIBILITY OF DERIVING A PROVISIONAL SUBCHRONIC OR CHRONIC RfC FOR ANILINOBENZOTHIAZOLE

The lack of chronic or subchronic inhalation data for humans or animals precludes derivation of a subchronic or chronic RfC for anilinobenzothiazole. 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 anilinobenzothiazole would occur, and no obvious pathways for biotransformation of anilinobenzothiazole to MBT were identified. In addition, there is some evidence that the sulfhydryl group is involved in MBT carcinogenicity (NTP, 1988) and other aspects of MBT toxicity (Feinman, 1987).

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. 2001 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2002. Toxicological Profile Information Sheet. Online. http://www.atsdr.cdc.gov/toxpro2.html

Colucci, D.F. and D.A. Buyske. 1965. The biotransformation of a sulfonamide to a mercaptan and to mercapturic acid and glucuronide conjugates. Biochem. Pharmacol. 14: 457-466.

El Dareer, S.M., J.R. Kalin, K.F. Tillery et al. 1989. Disposition of 2-mercaptobenzothiazole and 2-mercaptobenzothiazole disulfide in rats dosed intravenously, orally and topically and in guinea-pigs dosed topically. J. Toxicol. Environ. Health. 27(1): 65-84.

Feinman, S.E. 1987. Sensitivity to rubber chemicals. J. Toxicol.- Cut. Ocular Toxicol. 6(2): 117-153.

IARC (International Agency for Research on Cancer). 2002. IARC Agents and Summary Evaluations. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

Larsen, G.L., J.E. Bakke, V.J. Feil and J.K. Huwe. 1988. In vitro metabolism of the methylthio group of 2-methylthiobenzothiazole by rat liver. Xenobiotica. 18(3): 313-322.

Nagamatsu, K., Y. Kido, G. Urakubo et al. 1979. Absorption, distribution, excretion and metabolism of 2-mercaptobenzothiazole in guinea pig. Eisei Kagaku. 25: 59-65. (Cited in NTP, 1988)

NIOSH (National Institute for Occupational Safety and Health). 2002. NIOSH Pocket Guide to Chemical Hazards. Online. http://www.cdc.gov/niosh/npg/.html

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.
http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

NTP (National Toxicology Program). 2002. Management Status Report. Online.
http://ntp-server.niehs.nih.gov/

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

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS 97-921199.

U.S. EPA. 2002. 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). 2002. Online Catalogs for the Environmental Criteria Series. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

03-15-05

Provisional Peer Reviewed Toxicity Values for

Anilinobenzothiazole

(CASRN CASRN 1843-21-6)

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

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-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
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
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

03-15-05

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ANILINOBENZOTHIAZOLE (CASRN 1843-21-6)
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).

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 carcinogenicity assessment of anilinobenzothiazole 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). Neither ATSDR (2002), NTP (2002), IARC (2002), nor WHO (2002) have produced documents regarding anilinobenzothiazole. Literature searches of the following databases were conducted from 1965 through July 2002 in order to locate relevant studies: TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. An updated literature search was conducted through April 2004 and no relevant information was found.

REVIEW OF THE PERTINENT DATA

Human Studies

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

Animal Studies

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

Other Studies

No data regarding the genotoxicity of anilinobenzothiazole were located.

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

No information was located regarding the carcinogenicity or genotoxicity of anilinobenzothiazole. 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 anilinobenzothiazole would occur, and no obvious pathways for biotransformation of anilinobenzothiazole to MBT were identified. In addition, there is some evidence that the sulfhydryl 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 for anilinobenzothiazole are inadequate for an assessment of human carcinogenic potential.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

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

REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 2002. Toxicological Profile Information Sheet. Online. http://www.atsdr.cdc.gov/toxpro2.html

Colucci, D.F. and D.A. Buyske. 1965. The biotransformation of a sulfonamide to a mercaptan and to mercapturic acid and glucuronide conjugates. Biochem. Pharmacol. 14: 457-466.

El Dareer, S.M., J.R. Kalin, K.F. Tillery et al. 1989. Disposition of 2-mercaptobenzothiazole and 2-mercaptobenzothiazole disulfide in rats dosed intravenously, orally and topically and in guinea-pigs dosed topically. J. Toxicol. Environ. Health. 27(1): 65-84.

Feinman, S.E. 1987. Sensitivity to rubber chemicals. J. Toxicol.- Cut. Ocular Toxicol. 6(2): 117-153.

IARC (International Agency for Research on Cancer). 2002. IARC Agents and Summary Evaluations. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

Larsen, G.L., J.E. Bakke, V.J. Feil and J.K. Huwe. 1988. In vitro metabolism of the methylthio group of 2-methylthiobenzothiazole by rat liver. Xenobiotica. 18(3): 313-322.

Nagamatsu, K., Y. Kido, G. Urakubo et al. 1979. Absorption, distribution, excretion and metabolism of 2-mercaptobenzothiazole in guinea pig. Eisei Kagaku. 25: 59-65. (Cited in NTP, 1988)

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.
http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

NTP (National Toxicology Program). 2002. Management Status Report. Online.
http://ntp-server.niehs.nih.gov/

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS 97-921199.

U.S. EPA. 1999. Proposed Guidelines for Cancer Risk Assessment. July. Office of Research and Development, National Center for Environmental Assessment, Washington, DC.

U.S. EPA. 2002a. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/

U.S. EPA. 2002b. 2002 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA 822-R-02-038. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

WHO (World Health Organization). 2002. Online Catalogs for the Environmental Criteria Series. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html