03-08-05

Provisional Peer Reviewed Toxicity Values for

Dimethyl sulfide
(CASRN 75-18-3)

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

03-08-05

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR DIMETHYL SULFIDE (CASRN 75-18-3)
Derivation of a Subchronic and 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 dimethyl sulfide 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). The CARA list (U.S. EPA, 1991, 1994) includes a Reportable Quantity Document (U.S. EPA, 1988) for dimethyl sulfide that was reviewed for relevant information. Dimethyl sulfide is approved for use as a food additive (synthetic flavoring agent) by U.S. FDA (2003). Reviews have been performed by WHO (2000a,b), Shertzer (2001), NIOSH (1978), and Opdyke (1979). No documents for this chemical are available from ATSDR (2003), NTP (2003), or IARC (2003). Literature searches for dimethyl sulfide were conducted for the period from 1965 to December 2004 in the following databases: TOXLINE (including NTIS and BIOSIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, EMIC/EMICBACK,

DART/ETICBACK, RTECS, and TSCATS. Additional literature searches for oral studies on dimethyl sulfoxide (DMSO) were conducted in TOXLINE and MEDLINE (1995-July, 2003).

Dimethyl sulfide [$(CH_3)_2S$, MW = 62.14] is a volatile liquid with a strong unpleasant odor (Budavari, 2001). Industrial sources include wood pulp and petroleum processing plants and sewage treatment plants (Kangas et al., 1984; Jaakkola et al., 1990; Water Pollution Control Federation, 1990). Dimethyl sulfide is emitted from decomposition of plant and animal matters. It is one of the metabolic products of many biosystems. Crude oil containing sulfur and some natural gas also emit this compound (HSDB, 2003). The chemical is found naturally in a wide variety of foods (HSDB, 2003; Sinki and Schlegel, 1990) and is also used as a food additive (U.S. FDA, 2003). Dimethyl sulfide is produced endogenously in mammals during metabolism of methionine and related substances (Blom et al., 1988, 1989; Al Mardini et al., 1984), and by bacteria in the mammalian gut and mouth (e.g., De Boever et al., 1994; Hiele et al., 1991; Yaegaki and Suetaka, 1989). High levels of dimethyl sulfide were detected in the breath of patients with advanced liver disease (Tangerman et al., 1994).

REVIEW OF PERTINENT LITERATURE

Human Studies

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

Animal Studies

Limited data are available regarding the oral toxicity of dimethyl sulfide in animals. Butterworth et al. (1975) administered dimethyl sulfide in corn oil by gavage at 0, 2.5, 25, or 250 mg/kg-day to groups of 15 male and 15 female Wistar SPF rats daily (7 days/week) for 14 weeks. Additional groups of five rats of each sex were administered daily gavage doses of 0, 25, or 250 mg/kg-day for 2 or 6 weeks. Endpoints evaluated included: body weight (recorded initially and then weekly throughout the study), food and water consumption (measured over 24 hours before weighing), urinalysis (urine collected from rats during weeks 2, 6, and 14 and evaluated for volume, specific gravity, glucose, ketones, bile salts, and blood content), hematology and serum chemistry (blood collected from the aorta at the conclusion of the 2-, 6-, or 14-week study period), gross necropsy, organ weights (brain, pituitary, thyroid, heart, liver, stomach, small intestine, cecum, spleen, kidneys, adrenals and gonads), and histopathology (tissue samples of the weighed organs and the salivary gland, trachea, esophagus, colon, rectum, lymph nodes, lung, aorta, pancreas, urinary bladder, uterus, and skeletal muscle were fixed and stained for microscopic examination; only tissue samples from animals with gross abnormalities, rats administered the high dose of 250 mg/kg-day, and one-half of the control rats were examined).

No effects of dimethyl sulfide treatment on body weight gain, food and water consumption, hematological values, serum enzyme levels, or urinalysis parameters were reported in any group at any time period. Gross observations at necropsy showed occasional pitting of the kidney cortex and pallor of the liver. Histopathological evaluation reported some degree of liver cell fatty degeneration and some chronic inflammation in lungs and kidneys; however, incidence and severity of these findings were comparable in the treated and control groups. A few statistically significant differences in absolute and relative organ weights were recorded for treated rats as compared to the control group; however, these differences were not dose-related. The high dose of 250 mg/kg-day is a NOAEL for this study.

In a drinking water study, Wood et al. (1971) administered dimethyl sulfide at 0 or 2% in the drinking water to groups of 10 New Zealand white rabbits (males and females combined) for 13 weeks. Based on daily fluid intake, the investigators estimated the dose of dimethyl sulfide in the treated group to be 2000 mg/kg-day. Baseline body weight, retinoscopy, ophthalmoscopy and biomicroscopy were performed. At necropsy, organs were weighed and examined for gross pathology. The focus of the study was potential changes in the lens of the eye, which are known to occur during oral treatment with dimethyl sulfoxide (of which dimethyl sulfide is a metabolite). Terminal body weights were unaffected (3110 g for dimethyl sulfide-treated versus 3290 g for controls). The lung-to-body weight ratios of treated rabbits were greater than those of controls. On gross examination, pulmonary congestion with some hemorrhagic spots and renal pyelonephritis were seen in the treated rabbits. Histopathological examinations were not performed, and additional details of incidence or severity were not reported. No retinoscopic or microscopic changes in the eye occurred with dimethyl sulfide treatment.

Other Studies

No developmental or reproductive toxicity studies of dimethyl sulfide by any route of exposure were located.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR DIMETHYL SULFIDE

The database for dimethyl sulfide is inadequate for derivation of a p-RfD. No human data were located. The rat study by Butterworth et al. (1975) examined a wide array of toxicological endpoints using adequate numbers of animals and dose groups, but is not useful for risk assessment because a LOAEL was not identified (proximity of the free-standing NOAEL of 250 mg/kg-day to the toxicity threshold cannot be assessed). The rabbit study by Wood et al. (1971) is inadequate because a single dose level was tested, groups were small and of mixed sexes, few endpoints were examined, results were reported in insufficient detail (e.g., no data on incidence or severity of reported gross lesions), and statistical analysis was not performed.

Derivation of an p-RfD by analogy to a surrogate chemical was considered. A potential surrogate is dimethyl sulfoxide [DMSO, $(CH_3)_2SO$, MW = 78.13); dimethyl sulfide [$(CH_3)_2S$, MW = 62.14] is a metabolite of and can be metabolized to DMSO (Brayton, 1986; Williams et al., 1966). The effects of these two chemicals were totally different in the studies that compared their toxicity, but only one dose level of each was tested, and the doses were not equivalent on a g/kg-day or (by inspection, given the similarity of the molecular weights) on a mole/kg-day basis. Dimethyl sulfide given in the drinking water to rabbits at 2 g/kg-day was reported to produce some lung and kidney pathology, but no changes in the lens of the eye and no effect on body weights in rabbits treated subchronically (Wood et al., 1971). Dimethyl sulfoxide at 10 g/kg-day produced changes in the lens and depressed terminal body weights, but was not reported to affect the lung or kidney. In another study, dimethyl sulfide at 0.25% in the drinking water delayed the onset and decreased the incidence of diabetes in genetically susceptible mice, whereas dimethyl sulfoxide at 2.5% in the drinking water accelerated the onset and increased the incidence of diabetes (Klandorf et al., 1989). Dimethyl sulfide at approximately 1/10th of the dose of DMSO reduced motor activity in mice, whereas DMSO did not (Kocsis et al., 1975). Therefore, the data do not support the use of dimethyl sulfoxide as a surrogate for derivation of a provisional RfD for dimethyl sulfide by analogy.

In conclusion, the available data are inadequate for derivation of a provisional RfD for dimethyl sulfide directly or by analogy to the potential surrogate chemical dimethyl sulfoxide.

REFERENCES

Al Mardini, H., K. Bartlett and C.O. Record. 1984. Blood and brain concentrations of mercaptans in hepatic and methanethiol induced coma. Gut. 25(3): 284-290.

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

Blom, H.J., J.P. van den Elzen, S.H. Yap and A. Tangerman. 1988. Methanethiol and dimethylsulfide formation from 3-methylthiopropionate in human and rat hepatocytes. Biochem. Biophys. Acta. 972(2): 131-136.

Blom, H.J., G.H. Boers, J.P. van den Elzen et al. 1989. Transamination of methionine in humans. Clin. Sci. 76(1): 43-49.

Brayton, C.F. 1986. Dimethylsulfoxide (DMSO): A review. Cornell Vet. 76: 61-90.

Budavari, S., Ed. 2001. The Merck Index, 13th ed. Merck & Co. Inc., Whitehouse Station, NJ. p. 1091.

Butterworth, K.R., F.M.B. Carpanini, J.R. Gaunt et al. 1975. Short-term toxicity of dimethyl sulfide in the rat. Food Cosmet. Toxicol. 13: 15.

De Boever, E.H., M. De Uzeda and W.J. Loesche. 1994. Relationship between volatile sulfur compounds, BANA-hydrolyzing bacteria and gingival health in patients with and without complaints of oral malodor. J. Clin. Dent. 4(4): 114-119.

Hiele, M., Y. Ghoos, P. Rutgeerts et al. 1991. Influence of nutritional substrates on the formation of volatiles by the fecal flora. Gastroenterology. 100(6): 1597-1602.

HSDB (Hazardous Substances Data Bank). 2003. Dimethyl Sulfide. National Library of Medicine. Online. http://toxnet.nlm.nih.gov

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

Jaakkola, J.J., V. Vilkka, O. Marttila et al. 1990. The South Karelia air pollution study. The effects of malodorous sulfur compounds from pulp mills on respiratory and other symptoms. Am. Rev. Respir. Dis. 142(6 Pt 1): 1344-1350.

Kangas, J., P. Jappinen and H. Savolainen. 1984. Exposure to hydrogen sulfide, mercaptans and sulfur dioxide in pulp industry. Am. Ind. Hyg. Assoc. J. 45(12): 787-790.

Klandorf, H., A.R. Chirra, A. DeGrucci and D.F. Girman. 1989. Dimethyl sulfoxide modulation of diabetes onset in NOD mice. Diabetes. 38(2): 194-7.

Kocsis, J.J., S. Harkaway, and R. Snyder. 1975. Biological effects of the metabolites of dimethyl sulfoxide. Ann. N.Y. Acad. Sci. 243: 104-109.

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a Recommended Standard: Occupational Exposure to n-Alkane Mono Thiols, Cyclohexanethiol, and Benzenethiol. U.S. DHEW, Rockville, MD. NTIS PB81-225609.

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

Opdyke, D.L.J. 1979. Fragrance raw material monographs. Dimethyl sulfide. Food Cosmet. Toxicol. 17: 365-368.

Shertzer, H.G. 2001. Organic sulfer compounds. In: Patty's Toxicology, 5th ed. Bingham, E., B. Cohrssen, and C.H. Powell, Ed. John Wiley and Sons, New York. 7: 730-731.

Sinki, G.S. and W.A. Schlegel. 1990. Flavoring agents. In: Food Science and Technology, Food Additives, Branen, A.L., P.M. Davidson and S. Salminen, Ed. Marcel Dekker, New York. 35: 195-258.

Tangerman, A., M.T. Meuwese-Arends and J.B. Jansen. 1994. Cause and composition of foetor hepaticus [letter]. Lancet. 343(8895): 483.

U.S. EPA. 1988. Reportable Quantity Document for Dimethyl Sulfide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

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 PB97-921199.

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

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/

U.S. FDA. 2003. Code of Federal Regulations. Title 21 Food and Drugs. 21CFR.172.515. Online. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=172.515

Water Pollution Control Federation. 1990. Operation of Municipal Water Treatment Plants Manual of Practice No. II, Vol. I: Chapter 3 Odor Control. Water Pollution Control Federation, Alexandria, VA. p. 351-408.

Williams, K.I.H., S.H. Burstein and D.S. Layne. 1966. Metabolism of dimethyl sulfide, dimethyl sulfoxide and dimethyl sulfone in the rabbit. Arch. Biochem. Biophys. 117: 84-87.

WHO (World Health Organization). 2000a. Evaluation of Certain Food Additives and Contaminants. Fifty-third Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 896. Geneva, Switzerland.

WHO (World Health Organization). 2000b. Safety Evaluation of Certain Food Additives and Contaminants. WHO Food Additives Series No. 44. Geneva, Switzerland.

Wood, D.C., N.V. Wirth, F.S. Weber and M.A. Palmguise. 1971. Mechanism considerations of dimethyl sulfoxide (DMSO) - Lenticular changes in rabbits. J. Pharmc. Exp. Ther. 177: 528-535.

Yaegaki, K. and T. Suetaka. 1989. The effect of mouthwash on oral malodour production. Shigaku. 76(7): 1492-1500. (MEDLINE abstract)

03-10-05

Provisional Peer Reviewed Toxicity Values for

Dimethyl sulfide
(CASRN 75-18-3)

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

03-10-05

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR DIMETHYL SULFIDE (CASRN 75-18-3)
Derivation of a Subchronic and 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:

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 RfC for dimethyl sulfide is not available on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997). The CARA list (U.S. EPA, 1991, 1994) includes a Reportable Quantity Document (U.S. EPA, 1988) for dimethyl sulfide that was reviewed for relevant information. ACGIH (2003), NIOSH (2003), and OSHA (2003) have not proposed occupational exposure limits for dimethyl sulfide. Dimethyl sulfide is approved for use as a food additive (synthetic flavoring agent) by U.S. FDA (2003). Reviews have been performed by WHO (2000a,b), Shertzer (2001), NIOSH (1978), and Opdyke (1979). No documents for this chemical are available from ATSDR (2003), NTP (2003), or IARC (2003). Literature searches for dimethyl sulfide were conducted for the period from 1965 to December 2004 in the following databases: TOXLINE (including NTIS and BIOSIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, EMIC/EMICBACK, DART/ETICBACK, RTECS, and TSCATS.

Additional literature searches for inhalation studies on dimethyl sulfoxide (DMSO) were conducted in TOXLINE and MEDLINE (1995-July, 2003).

Dimethyl sulfide [$(CH_3)_2S$, MW = 62.14] is a volatile liquid with a strong unpleasant odor (Budavari, 2001). Industrial sources include wood pulp and petroleum processing plants and sewage treatment plants (Kangas et al., 1984; Jaakkola et al., 1990; Water Pollution Control Federation, 1990). Dimethyl sulfide is emitted from decomposition of plant and animal matters. It is one of the metabolic products of many biosystems. Crude oil containing sulfur and some natural gas also emit this compound (HSDB, 2003). The chemical is found naturally in a wide variety of foods (HSDB, 2003; Sinki and Schlegel, 1990) and is also used as a food additive (U.S. FDA, 2003). Dimethyl sulfide is produced endogenously in mammals during metabolism of methionine and related substances (Blom et al., 1988, 1989; Al Mardini et al., 1984), and by bacteria in the mammalian gut and mouth (e.g., De Boever et al., 1994; Hiele et al., 1991; Yaegaki and Suetaka, 1989). High levels of dimethyl sulfide were detected in the breath of patients with advanced liver disease (Tangerman et al., 1994).

REVIEW OF PERTINENT LITERATURE

Human Studies

Information regarding the toxicity of dimethyl sulfide to humans is limited to a case report and a few epidemiological studies involving mixed exposures.

The case report involved a man who had entered a storage tank in a paper manufacturing plant, collapsed immediately and was dead when removed (duration of exposure was not specified) (Terazawa et al., 1991a,b). Autopsy revealed congestion of the internal organs and pulmonary edema. Sampling and analysis of the atmosphere in the tank at an unspecified interval after the accident revealed no detectable hydrogen sulfide, methyl mercaptan at <10 ppm, dimethyl sulfide at "several ppm" and dimethyl disulfide at 1 ppm. Death was attributed to dimethyl sulfide (possibly combined with hypoxia) because GC-MS analysis of headspace gas from blood and organ samples revealed a single peak identified as dimethyl sulfide. The samples, however, were taken 27 hours after the accident and were heated to 60°C for 30 minutes prior to analysis of the headspace gas. The delay in obtaining samples and conditions of analysis may have afforded opportunity for microbial degradation of the cadaver tissue releasing dimethyl sulfide.

Several epidemiological studies were conducted on workers in the paper pulp industry and populations located near pulp mills. Exposure was to a mixture of sulfur compounds, including dimethyl sulfide, but also hydrogen sulfide, methyl mercaptan, dimethyl disulfide, and sulfur dioxide. Effects attributed to exposure to the mixed sulfur compounds were headaches in

workers (Kangas et al., 1984), altered heme synthesis and iron metabolism in workers (Klingberg et al., 1988; Tenhunen et al., 1983), and eye and respiratory symptoms in residents of communities located near the paper pulp mills (Jaakkola et al., 1990; Partti-Pellinen et al., 1996). A study of symptoms and neuropsychological test results in a small number of former workers and neighbors located geographically downwind of an oil refinery (who were exposed to hydrogen sulfide, unspecified mercaptans, ethane, propane and other chemicals, in addition to dimethyl sulfide) reported significant differences in the exposed groups, as compared with a control group consisting of friends and relatives nominated by the exposed group (Kilburn and Warshaw, 1995). It is not possible to draw any conclusions regarding dimethyl sulfide from these data, as subjects were exposed in each case to a mixture of chemicals. The studies were also limited by lack of quantitative exposure assessment and reliance on self-reported symptoms.

Animal Studies

Acute inhalation studies in animals show that brief exposure to high levels of dimethyl sulfide in air can produce nasal and respiratory irritation, CNS depression, and death. An unpublished study by Dow Chemical (1957) reported that exposure of 3 rats to a "saturated" atmosphere of dimethyl sulfide for 3 minutes resulted in labored breathing, nasal irritation, and unconsciousness, but no deaths; similar exposure for 9 minutes resulted in the death of 2/3 rats. Pathology results were reported to be negative, but the extent of the examination is unclear. The progression of effects resulting from exposure to dimethyl sulfide levels ranging from 1100 to 54,000 ppm was described by Ljunggren and Norberg (1943). No overt effects were seen in exposed rats at 1100 ppm for up to 35 minutes. Observations at higher concentrations were: closed eyes (2 minutes) and lay down (10 minutes) at 5600 ppm; closed eyes (immediately) and slow, irregular respiration at 13,000 ppm; prostration with dyspnea at 29,000 and 31,000 ppm; and dyspnea (2 minutes), nasal discharge of fluid (5 minutes), and death (15 minutes) at 54,000 ppm. Rats exposed to $\leq$31,000 ppm recovered once removed from the exposure chamber. No macroscopic changes were seen at necropsy. Irritation to mucous membranes, evidenced by secretion from the eyes and nose, was observed, but the exposure levels for this effect were not reported. An EC_{50} of 96,000 ppm was estimated for production of coma in rats exposed to dimethyl sulfide vapor for 15 minutes (Zieve et al., 1974). A 4-hour study in rats found no lethality at 24,000 ppm, a minimum lethal level of 36,000 ppm (2/10 died) and an LC_{50} of 40,250 ppm (Tansy et al., 1980, 1981). Dimethyl sulfide concentrations of 68,000 ppm and above were fatal to mice within 8 minutes (Terazawa et al., 1991a).

The only longer-term inhalation study of dimethyl sulfide located was a subchronic study in rats from the Russian literature (Selyuzhitskii, 1972) described in a review article (Opdyke, 1979). Ten groups of 15 rats each were exposed to dimethyl sulfide concentrations ranging from 5 mg/m^3 (2 ppm) to 25 mg/m^3 (10 ppm) 6 hr/day for 6 months. Details regarding experimental protocol and conditions were not provided. Reported effects included: decreased body weight gain, increased heart weight, decreased oxygen consumption, increased serum cholesterol, and a

variety of biochemical changes in whole blood and tissue homogenates. Transient changes were reported to occur at the low concentration of 2 ppm, but a description of these effects was not provided. This study also reported acute inhalation LC_{50} values for dimethyl sulfide of 31.62 mg/m^3 (12 ppm) for 2 hours in mice and 50.12 mg/m^3 (20 ppm) for 4 hours in rats (Selyuzhitskii, 1972). These values are orders of magnitude lower than those reported in other acute studies, described above. Due to the lack of available details regarding experimental methods and results, this study cannot be properly evaluated, although the discrepancy in acute lethality data from the rest of the database suggests that the results are not reliable.

Other Studies

No developmental or reproductive studies of dimethyl sulfide by any route of exposure were located.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR DIMETHYL SULFIDE

The inhalation data base for dimethyl sulfide is inadequate for p-RfC derivation. Exposure to dimethyl sulfide in human studies was unquantified and always in combination with other chemicals. Animal studies were limited to acute studies and one inadequate study of subchronic duration. Other possibilities for p-RfC derivation include route-to-route extrapolation from oral data and derivation by analogy to the toxicity of a surrogate chemical.

Subchronic oral toxicity studies are available for dimethyl sulfide. Oral-to-inhalation extrapolation is not appropriate, however, because the existing inhalation data suggest that portal-of-entry effects may be a sensitive endpoint for inhalation exposure to dimethyl sulfide. Irritant symptoms were reported in some human studies (Jaakkola et al., 1990; Partti-Pellinen et al., 1996), although exposure was not to dimethyl sulfide alone in either case. Irritant symptoms were also observed in acute animal studies (Dow Chemical, 1957; Ljunggren and Norberg,1943). In the Ljunggren and Norberg (1943) study, signs of mucous membrane irritation were observed at concentrations well below those causing mortality (closing of the eyes at $\geq$5600 ppm and secretion from the eyes and nose, possibly at the same exposure levels, but not specified; death occurred at 54,000 ppm). Although evidence of CNS depression was also seen at 5600 ppm, irritant effects occurred earlier in the exposure (2 min vs. 10 min.). Because portal-of-entry effects appear to be a sensitive endpoint for dimethyl sulfide, extrapolation from oral studies would not be appropriate.

A possible surrogate for dimethyl sulfide [$(CH_3)_2S$] is methyl mercaptan (CH_3SH). Dimethyl sulfide is a metabolite of methyl mercaptan (Susman et al., 1978). A comparison of the acute inhalation toxicity of these compounds based on studies that tested both chemicals,

however, indicates that there are significant qualitative and quantitative differences in toxicity. Although these acute studies do not necessarily predict differences that would occur during long-term, low-level exposure, the differences shown in Table 1 below are so striking that they preclude further consideration of derivation of a provisional RfC for dimethyl sulfide by analogy to methyl mercaptan.

Table 1. Comparison of Acute Inhalation Toxicity of Dimethyl Sulfide and Methyl Mercaptan

Endpoint	Dimethyl sulfide	Methyl mercaptan	Reference
highest nonlethal 4-hr exposure (ppm)	24,000	400	Tansy et al., 1981
lowest 4-hr exposure at which deaths occurred (ppm)	36,000	600	
4-hr LC_{50} (ppm)	40,250	675	
15-min E_{50} for coma (ppm)	96,000	1600	Zieve et al., 1974
Threshold blood level for coma (nmole/ml)	7000	0.5	
highest nonlethal 30-min exposure (ppm)	31,000	1500	Ljunggren and Norberg, 1943
lowest 30-min exposure at which death occurred (ppm)	54,000	10,000	
Observations	signs of eye and nose irritation; no lung pathology	no signs of eye or nose irritation; pulmonary edema	

Another potential surrogate is dimethyl sulfoxide [DMSO, $(CH_3)_2SO$, MW = 78.13); dimethyl sulfide [$(CH_3)_2S$, MW = 62.14] is a metabolite of, and can be metabolized to, DMSO (Brayton, 1986; Williams et al., 1966). 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. Inhalation toxicity data for DMSO are not available, precluding further consideration of this chemical as a surrogate. Therefore, a derivation by analogy is not feasible.

In conclusion, the available data are inadequate for derivation of a provisional RfC for dimethyl sulfide directly from the inhalation data, by route-to-route extrapolation from the oral data, or by analogy to the potential surrogate chemicals, methyl mercaptan or dimethyl sulfoxide.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2003. 2003 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

Al Mardini, H., K. Bartlett and C.O. Record. 1984. Blood and brain concentrations of mercaptans in hepatic and methanethiol induced coma. Gut. 25(3): 284-290.

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

Blom, H.J., J.P. van den Elzen, S.H. Yap and A. Tangerman. 1988. Methanethiol and dimethylsulfide formation from 3-methylthiopropionate in human and rat hepatocytes. Biochem. Biophys. Acta. 972(2): 131-136.

Blom, H.J., G.H. Boers, J.P. van den Elzen et al. 1989. Transamination of methionine in humans. Clin. Sci. 76(1): 43-49.

Brayton, C.F. 1986. Dimethylsulfoxide (DMSO): A review. Cornell Vet. 76: 61-90.

Budavari, S., Ed. 2001. The Merck Index, 13th ed. Merck & Co. Inc., Whitehouse Station, NJ. p. 1091.

De Boever, E.H., M. De Uzeda and W.J. Loesche. 1994. Relationship between volatile sulfur compounds, BANA-hydrolyzing bacteria and gingival health in patients with and without complaints of oral malodor. J. Clin. Dent. 4(4): 114-119.

Dow Chemical. 1957. Results of range finding toxicological tests on dimethyl sulfide. Submitted by Dow Chemical Company in 1992 under TSCA 8E. OTS Fiche # OTS0538292.

Hiele, M., Y. Ghoos, P. Rutgeerts et al. 1991. Influence of nutritional substrates on the formation of volatiles by the fecal flora. Gastroenterology. 100(6): 1597-1602.

HSDB (Hazardous Substances Data Bank). 2003. Dimethyl Sulfide. National Library of Medicine. Online. http://toxnet.nlm.nih.gov

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

Jaakkola, J.J., V. Vilkka, O. Marttila et al. 1990. The South Karelia air pollution study. The effects of malodorous sulfur compounds from pulp mills on respiratory and other symptoms. Am. Rev. Respir. Dis. 142(6 Pt 1): 1344-1350.

Kangas, J., P. Jappinen and H. Savolainen. 1984. Exposure to hydrogen sulfide, mercaptans and sulfur dioxide in pulp industry. Am. Ind. Hyg. Assoc. J. 45(12): 787-790.

Kilburn, K.H. and R.H. Warshaw. 1995. Hydrogen sulfide and reduced-sulfur gases adversely affect neurophysiological functions. Toxicol. Ind. Health. 11(2): 185-197.

Klingberg, J., A. Beviz, C-G. Ohlson and R. Tenhunen. 1988. Disturbed iron metabolism among workers exposed to organic sulfides in a pulp plant. Scan. J. Work Environ. Health. 14(1): 17-20.

Ljunggren, G. and B. Norberg. 1943. On the effect and toxicity of dimethyl sulfide, dimethyl disulfide, and methyl mercaptan. Acta Physiol. Scand. 5: 248-255.

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a Recommended Standard: Occupational Exposure to n-Alkane Mono Thiols, Cyclohexanethiol, and Benzenethiol. U.S. DHEW, Rockville, MD. NTIS PB81-225609.

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

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

Opdyke, D.L.J. 1979. Fragrance raw material monographs. Dimethyl sulfide. Food Cosmet. Toxicol. 17: 365-368.

OSHA (Occupational Safety and Health Administration). 2003. 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

Partti-Pellinen, K., O. Marttila, V. Vilkka et al. 1996. The South Karelia air pollution study: Effects of low-level exposure to malodorous sulfur compounds on symptoms. Arch Environ. Health. 51(4): 315-320.

Selyuzhitskii, G.V. 1972. Experimental data used to determine the maximum permissible concentration of methyl mercaptan, dimethyl sulfide, and dimethyl disulfide in the air of the production area of paper and pulp plants. Gig. Truda Prof. Zabol. 16: 46-7. (Rus.) (Cited in Opdyke, 1989; Tansy et al., 1981)

Shertzer, H.G. 2001. Organic sulfer compounds. In: Patty's Toxicology, 5th ed. Bingham, E., B. Cohrssen, and C.H. Powell, Ed. John Wiley and Sons, New York. 7: 730-731.

Sinki, G.S. and W.A. Schlegel. 1990. Flavoring agents. In: Food Science and Technology, Food Additives, Branen, A.L., P.M. Davidson and S. Salminen, Ed. Marcel Dekker, New York. 35: 195-258.

Susman, J.L., J.F. Hornig, S.C. Thomas and R.P. Smith. 1978. Pulmonary excretion of hydrogen sulfide, methanethiol, dimethyl sulfide and dimethyl disulfide in mice. Drug Chem. Toxicol. 1: 327-338.

Tangerman, A., M.T. Meuwese-Arends and J.B. Jansen. 1994. Cause and composition of foetor hepaticus [letter]. Lancet. 343(8895): 483.

Tansy, M.F., R.M. Kendall, J. Fantasia et al. 1980. Acute and subchronic toxicity studies of rats exposed to vapors of methyl mercaptan and other reduced sulfur compounds. RYO Submission FYI-OTS-0680-0080 by the American Paper Institute. OTS Fiche # OTS000080-0.

Tansy, M.F., F.M. Kendall, J. Fantasia et al. 1981. Acute and subchronic toxicity studies of rats exposed to vapors of methyl mercaptan and other reduced-sulfur compounds. J. Toxicol. Environ. Health. 8(1-2): 71-88.

Tenhunen, R., H. Savolainen and P. Jappinen. 1983. Changes in Haem synthesis associated with occupational exposure to organic and inorganic sulphides. Clin. Sci. 64(2): 187-191.

Terazawa, K., K. Mizukami, B. Wu and T. Takatori. 1991a. Fatality due to inhalation of dimethyl sulfide in a confined space: A case report and animal experiments. Int. J. Legal Med. 104(3): 141-4.

Terazawa, K., D. Kaji, H. Akabane and T. Takatori. 1991b. Determination of dimethyl sulphide in blood and adipose tissue by headspace gas analysis. J. Chromatog. 565(½): 453-456. (Cited in Terazawa et al., 1991a)

U.S. EPA. 1988. Reportable Quantity Document for Dimethyl Sulfide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

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 PB97-921199.

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/

U.S. FDA. 2003. Code of Federal Regulations. Title 21 Food and Drugs. 21CFR.172.515. Online. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=172.515

Water Pollution Control Federation. 1990. Operation of Municipal Water Treatment Plants Manual of Practice No. II, Vol. I: Chapter 3 Odor Control. Water Pollution Control Federation, Alexandria, VA. p. 351-408.

Williams, K.I.H., S.H. Burstein, and D.S. Layne. 1966. Metabolism of dimethyl sulfide, dimethyl sulfoxide and dimethyl sulfone in the rabbit. Arch. Biochem. Biophys. 117: 84-87.

WHO (World Health Organization). 2000a. Evaluation of Certain Food Additives and Contaminants. Fifty-third Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 896. Geneva, Switzerland.

WHO (World Health Organization). 2000b. Safety Evaluation of Certain Food Additives and Contaminants. WHO Food Additives Series No. 44. Geneva, Switzerland.

Yaegaki, K. and T. Suetaka. 1989. The effect of mouthwash on oral malodour production. Shigaku. 76(7): 1492-1500. (MEDLINE abstract)

Zieve, L., W.M. Doizaki and F.J. Zieve. 1974. Synergism between mercaptans and ammonia or fatty acids in the production of coma: A possible role for mercaptans in the pathogenesis of hepatic coma. J. Lab. Clin. Med. 83: 16-28.

03-08-05

Provisional Peer Reviewed Toxicity Values for

Dimethyl sulfide
(CASRN 75-18-3)

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

03-08-05

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR DIMETHYL SULFIDE (CASRN 75-18-3)
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 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 for dimethyl sulfide 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). The CARA list (U.S. EPA, 1991, 1994) includes a Reportable Quantity Document (U.S. EPA, 1988) for dimethyl sulfide that was reviewed for relevant information. Dimethyl sulfide is approved for use as a food additive (synthetic flavoring agent) by U.S. FDA (2003). Reviews have been performed by WHO (2000a,b), Shertzer (2001), NIOSH (1978), and Opdyke (1979). No documents for this chemical are available from ATSDR (2003), NTP (2003), or IARC (2003). Literature searches for dimethyl sulfide were conducted for the period from 1965 to December 2004 in the following databases: TOXLINE (including NTIS and BIOSIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, EMIC/EMICBACK, DART/ETICBACK, RTECS, and TSCATS.

Dimethyl sulfide [$(CH_3)_2S$, MW = 62.14] is a volatile liquid with a strong unpleasant odor (Budavari, 2001). Industrial sources include wood pulp and petroleum processing plants and sewage treatment plants (Kangas et al., 1984; Jaakkola et al., 1990; Water Pollution Control Federation, 1990). Dimethyl sulfide is emitted from decomposition of plant and animal matters. It is one of the metabolic products of many biosystems. Crude oil containing sulfur and some natural gas also emit this compound (HSDB, 2003). The chemical is found naturally in a wide variety of foods (HSDB, 2003; Sinki and Schlegel, 1990) and is also used as a food additive (U.S. FDA, 2003). Dimethyl sulfide is produced endogenously in mammals during metabolism of methionine and related substances (Blom et al., 1988, 1989; Al Mardini et al., 1984), and by bacteria in the mammalian gut and mouth (e.g., De Boever et al., 1994; Hiele et al., 1991; Yaegaki and Suetaka, 1989). High levels of dimethyl sulfide were detected in the breath of patients with advanced liver disease (Tangerman et al., 1994).

REVIEW OF THE PERTINENT DATA

Human Studies

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

Animal Studies

No animal studies examining the carcinogenicity of dimethyl sulfide by any route of exposure were located.

Other Studies

Dimethyl sulfide did not induce *umu* gene expression in a test for SOS induction in *Salmonella typhimurium* TA1535/pSK1002 (Nakamura et al., 1990).

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

No studies examining the carcinogenic potential of dimethyl sulfide in humans or animals were located. Genotoxicity data are limited to one assay. Under the proposed U.S. EPA (1999) guidelines, the data for these chemicals are inadequate for an assessment of human carcinogenic potential.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for dimethyl sulfide is precluded by the lack of data to assess carcinogenicity associated with dimethyl sulfide exposure.

REFERENCES

Al Mardini, H., K. Bartlett and C.O. Record. 1984. Blood and brain concentrations of mercaptans in hepatic and methanethiol induced coma. Gut. 25(3): 284-290.

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

Blom, H.J., J.P. van den Elzen, S.H. Yap and A. Tangerman. 1988. Methanethiol and dimethylsulfide formation from 3-methylthiopropionate in human and rat hepatocytes. Biochem. Biophys. Acta. 972(2): 131-136.

Blom, H.J., G.H. Boers, J.P. van den Elzen et al. 1989. Transamination of methionine in humans. Clin. Sci. 76(1): 43-49.

Budavari, S., Ed. 2001. The Merck Index, 13th ed. Merck & Co. Inc., Whitehouse Station, NJ. p. 1091.

De Boever, E.H., M. De Uzeda and W.J. Loesche. 1994. Relationship between volatile sulfur compounds, BANA-hydrolyzing bacteria and gingival health in patients with and without complaints of oral malodor. J. Clin. Dent. 4(4): 114-119.

Hiele, M., Y. Ghoos, P. Rutgeerts et al. 1991. Influence of nutritional substrates on the formation of volatiles by the fecal flora. Gastroenterology. 100(6): 1597-1602.

HSDB (Hazardous Substances Data Bank). 2003. Dimethyl Sulfide. National Library of Medicine. Online. http://toxnet.nlm.nih.gov

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

Jaakkola, J.J., V. Vilkka, O. Marttila et al. 1990. The South Karelia air pollution study. The effects of malodorous sulfur compounds from pulp mills on respiratory and other symptoms. Am. Rev. Respir. Dis. 142(6 Pt 1): 1344-1350.

Kangas, J., P. Jappinen and H. Savolainen. 1984. Exposure to hydrogen sulfide, mercaptans and sulfur dioxide in pulp industry. Am. Ind. Hyg. Assoc. J. 45(12): 787-790.

Nakamura, S., Y. Oda and M. Ugawa. 1990. Induction of *umu* gene expression in *Salmonella typhimurium* TA1535/pSK1002 by dimethyl sulfoxide (DMSO). Mutat. Res. 229: 11-15.

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a Recommended Standard: Occupational Exposure to n-Alkane Mono Thiols, Cyclohexanethiol, and Benzenethiol. U.S. DHEW, Rockville, MD. NTIS PB81-225609.

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

Opdyke, D.L.J. 1979. Fragrance raw material monographs. Dimethyl sulfide. Food Cosmet. Toxicol. 17: 365-368.

Shertzer, H.G. 2001. Organic sulfer compounds. In: Patty's Toxicology, 5th ed. Bingham, E., B. Cohrssen, and C.H. Powell, Ed. John Wiley and Sons, New York. 7: 730-731.

Sinki, G.S. and W.A. Schlegel. 1990. Flavoring agents. In: Food Science and Technology, Vol. 35, Food Additives (Branen, A.L., P.M. Davidson and S. Salminen, Eds.), Marcel Dekker, New York. p. 195-258.

Tangerman, A., M.T. Meuwese-Arends and J.B. Jansen. 1994. Cause and composition of foetor hepaticus [letter]. Lancet. 343(8895): 483.

U.S. EPA. 1988. Reportable Quantity Document for Dimethyl Sulfide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

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 PB97-921199.

U.S. EPA. 1999. Guidelines for Carcinogen Risk Assessment. Review Draft. Risk Assessment Forum, Washington, DC. July.

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

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/

U.S. FDA. 2003. Code of Federal Regulations. Title 21 Food and Drugs. 21CFR.172.515. Online. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=172.515

Water Pollution Control Federation. 1990. Operation of Municipal Water Treatment Plants Manual of Practice No. II, Vol. I: Chapter 3 Odor Control. Water Pollution Control Federation, Alexandria, VA. p. 351-408.

WHO (World Health Organization). 2000a. Evaluation of Certain Food Additives and Contaminants. Fifty-third Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 896. Geneva, Switzerland.

WHO (World Health Organization). 2000b. Safety Evaluation of Certain Food Additives and Contaminants. WHO Food Additives Series No. 44. Geneva, Switzerland.

Yaegaki, K. and T. Suetaka. 1989. The effect of mouthwash on oral malodour production. Shigaku. 76(7): 1492-1500. (MEDLINE abstract)