12-20-04

Provisional Peer Reviewed Toxicity Values for

Methyl Mercaptan

(CASRN 74-93-1)

Derivation of Subchronic and Chronic Oral RfDs

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	**provisional inhalation unit risk**
p-OSF	**provisional oral slope factor**
p-RfC	**provisional inhalation reference concentration**
p-RfD	**provisional oral reference dose**
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	**Provisional Peer Reviewed Toxicity Value**
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

12-20-04

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR METHYL MERCAPTAN (CASRN 74-93-1)
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 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 to OSRTI.

INTRODUCTION

A subchronic or chronic RfD for methyl mercaptan is not available on IRIS (U.S. EPA, 2003), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). NTP (2003), IARC (2003), and WHO (2003) have not produced documents for this chemical. ATSDR (1992) produced a toxicological profile for methyl mercaptan, but did not derive oral MRL values for any exposure duration. Review documents by Shertzer (2001) and Santodonato (1985) were consulted. Literature searches of the following databases were conducted from 1965 through June 2003 in order to locate relevant studies: TOXLINE (supplemented with BIOSIS and NTIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. Additional literature

searches from June 2003 through October 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

Methyl mercaptan occurs in foods (onion, garlic, meat, bread, fish), sometimes as a result of microbial activity (Shertzer, 2001; Sinki and Schlegel, 1990; Budavari, 2001). It is approved for use as a food additive (synthetic flavoring agent) by the FDA [21 CFR 172.515] (U.S. FDA, 2003).

Methyl mercaptan is produced endogenously in mammals during metabolism of methionine and related substances (Blom et al., 1988, 1989; Al Mardini et al., 1984; Shertzer, 2001), and by bacteria in the mammalian gut and mouth (Budavari, 2001; De Boever et al., 1994; Hiele et al., 1991; Yaegaki and Sanada, 1992a,b). High levels of methyl mercaptan have been detected in the breath and urine of some patients with advanced liver disease (Shertzer, 2001; Tangerman et al., 1994). A number of studies and reviews explored the possibility that methyl mercaptan may play a role in the pathogenesis of encephalopathy resulting from hepatic failure (Al Mardini et al., 1984; Blom et al., 1988, 1989; Zieve, 1981; Zieve et al., 1974, 1984). These authors concluded that methyl mercaptan may interact (mechanism unknown) with ammonia and fatty acids to possibly exacerbate the encephalopathy in human hepatic failure.

REVIEW OF PERTINENT DATA

Human Studies

No data regarding the toxicity of methyl mercaptan to humans following oral exposure were located.

Animal Studies

No data regarding the toxicity of methyl mercaptan to animals following oral exposure were located.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfDs FOR METHYL MERCAPTAN

The lack of subchronic or chronic oral toxicity data for humans or animals precludes derivation of a subchronic or chronic p-RfD for methyl mercaptan.

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). 1992. Toxicological Profile for Methyl Mercaptan. U.S. Department of Health and Human Services, Public Health Service. Atlanta, GA. PB93/110799/AS. Online. http://www.atsdr.cdc.gov/toxprofiles/tp139.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. Biochim. 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. 2001. The Merck Index. Thirteenth edition. 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.

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

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

Shertzer, H.G. 2001. Organic Sulfur Compounds. Methyl Mercaptan. In: Patty's Toxicology, Fifth edition. Vol. 7. E. Bingham, B. Cohrssen and C.H. Powell, Ed. John Wiley & Sons, NY. p. 687-690.

Santodonato, J., S. Bosch, W. Meylan et al. 1985. Monograph on human exposure to chemicals in the workplace: Mercaptans. Center for Chemical Hazard Assessment, Syracuse Research Corporation, Syracuse, New York. SRC-TR-85-187.

Sinki, G.S. and W.A. Schlegel. 1990. Flavoring Agents. In: Food Science and Technology, Vol. 35, Food Additives, A.L. Branen, P.M. Davidson, and S. Salminen, Ed. 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. 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. Online. 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. 21 CFR172.515. Department of Health and Human Services, Washington, DC. Online. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=172.515

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

Yaegaki, K. and K. Sanada. 1992a. Volatile sulfur compounds in mouth air from clinically healthy subjects and patients with periodontal disease. J. Period. Res. 27(4 Pt 1): 233-238.

Yaegaki, K. and K. Sanada. 1992b. Biochemical and clinical factors influencing oral malodor in periodontal patients. J. Periodont. 63(9): 783-789.

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.

Zieve, L. 1981. The mechanism of hepatic coma. Hepatology. 1: 360-365.

Zieve, L., W.M. Doizaki and C. Hyftogt. 1984. Brain methanethiol and ammonia concentrations in experimental hepatid coma and coma induced by injections of various combinations of these substances. J. Lab. Clin. Med. 104(5): 655-664.

12-20-04

Provisional Peer Reviewed Toxicity Values for

Methyl Mercaptan
(CASRN 74-93-1)

Derivation of Subchronic and Chronic Inhalation RfCs

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	**provisional inhalation unit risk**
p-OSF	**provisional oral slope factor**
p-RfC	**provisional inhalation reference concentration**
p-RfD	**provisional oral reference dose**
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	**Provisional Peer Reviewed Toxicity Value**
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

12-20-04

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR METHYL MERCAPTAN (CASRN 74-93-1)
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 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 to OSRTI.

INTRODUCTION

A subchronic or chronic RfC for methyl mercaptan is not available on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997). No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994a). NTP (2003), IARC (2003), and WHO (2003) have not produced documents for this chemical. ATSDR (1992) produced a toxicological profile for methyl mercaptan, but did not derive inhalation MRL values for any duration. Recommended occupational exposure limits for methyl mercaptan, to protect against acute sensory irritation, headache, nausea, and the strong unpleasant odor, include a TLV-TWA of 0.5 ppm (1 mg/m^3) (ACGIH, 2003); a REL for 15-minute ceiling limit of 0.5 ppm (NIOSH, 2003); and a PEL of 10 ppm (20 mg/m^3) (OSHA, 2003). Review documents by Shertzer (2001) and Santodonato (1985) were consulted. Literature searches of the following databases were conducted from 1965 through June 2003 in order to locate relevant studies: TOXLINE (supplemented with BIOSIS and

NTIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. Additional literature searches from June 2003 through October 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

Methyl mercaptan (CH_3SH, MW = 48.11) is a gas with a strong unpleasant odor of rotting cabbage (Budavari, 2001). Natural sources of methyl mercaptan include vegetation, animal waste, microbial degradation, crude oils containing sulfur, and the "sour" natural gas of West Texas (ATSDR, 1992; Budavari, 2001; Rose, 1983; Santodonato et al., 1985). Industrial sources include wood pulp, oil shale, petroleum processing plants, and sewage treatment plants (ATSDR, 1992). Although some other mercaptans are used as odorants in natural and liquified petroleum gas or in commercial, industrial, and residential natural gas, methyl mercaptan is not used for this purpose (ATSDR, 1992; Cain and Turk, 1985; Shertzer, 2001; Santodonato et al., 1985).

Methyl mercaptan occurs in foods (onion, garlic, meat, bread, fish), sometimes as a result of microbial activity (Shertzer, 2001; Sinki and Schlegel, 1990; Budavari, 2001). It is approved for use as a food additive (synthetic flavoring agent) by the FDA [21 CFR 172.515] (U.S. FDA, 2003).

Methyl mercaptan is produced endogenously in mammals during metabolism of methionine and related substances (Blom et al., 1988, 1989; Al Mardini et al., 1984, Shertzer, 2001), and by bacteria in the mammalian gut and mouth (Budavari, 2001; De Boever et al., 1994; Hiele et al., 1991; Yaegaki and Sanada, 1992a,b). High levels of methyl mercaptan have been detected in the breath and urine of some patients with advanced liver disease (Shertzer, 2001; Tangerman et al., 1994). A number of studies and reviews explored the possibility that methyl mercaptan may play a role in the pathogenesis of encephalopathy resulting from hepatic failure (Al Mardini et al., 1984; Blom et al., 1988, 1989; Zieve, 1981; Zieve et al., 1974, 1984). These authors concluded that methyl mercaptan may interact (mechanism unknown) with ammonia and fatty acids to possibly exacerbate the encephalopathy in human hepatic failure.

REVIEW OF THE PERTINENT DATA

Human Studies

Low-level ambient air concentrations of methyl mercaptan have been reported to produce symptoms in exposed workers that include: eye and mucous membrane irritation, dizziness, staggering gait, nausea, and vomiting. Respiratory tract irritation can progress to pulmonary edema, and hepatic and renal damage have been reported (Key et al., 1977). Sources of

information regarding the toxicity of methyl mercaptan to humans are limited to a few case reports of acute inhalation exposures and several epidemiological studies involving a mixture of chemical exposures. Estimates of exposure levels for the accidental case reports and the epidemiological studies were not available.

Shults et al. (1970) reported the case of a 53-year old black man who was found unconscious after exposure to volatilized methyl mercaptan while emptying metal gas cylinders containing methyl mercaptan. A vaporizing liquid was observed on asphalt pavement near him. Upon medical examination, he exhibited tachycardia, elevated blood pressure, persistent coma, and methemoglobinemia. He developed severe acute hemolytic anemia. A deficiency in glucose-6-phosphate dehydrogenase (G6PD) was suspected as the mechanism of the hemolytic episode due to the oxidant effect of methyl mercaptan. Despite medical intervention, the patient's condition deteriorated and he died 28 days after accidental exposure. Autopsy determined the cause of death was due to a massive embolus which occluded both main pulmonary arteries. Bilateral polycystic kidneys were found. No gross or microscopic abnormalities were seen in the brain.

A Romanian refinery worker inhaled an unknown amount of methyl mercaptan that rendered him unconscious for 9 hours (Cristescu, 1941). The worker was not reported dyspneic, but was cyanotic and experienced convulsions. Hemoglobin value and red cell count were normal, but a determination for methemoglobin was not indicated in this report. Ten days later, the patient was hospitalized for a lung abscess from which he recovered.

Mixed exposures to methyl mercaptan and other sulfur compounds, including ethyl mercaptan, dimethyl sulfide and acrylonitrile, have occurred in industrial accidents (Allied Chemical Corp., 1978; Syntex Corp., 1979). In two separate accidents, a total of four workers were found unconscious after exposure to such a mixture occurred in the work area of a chemical plant. In one accident, a worker was found unconscious and later died after a gas mixture containing in excess of 10,000 ppm of methyl mercaptan was emitted from a pipe into his work area (Syntex Corp., 1979). Autopsy indicated that the immediate cause of death was acute congestive heart failure (this worker had a pre-existing heart condition). In a second accident, three workers recovered after being found unconscious, although one developed pulmonary edema (Allied Chemical Corp., 1978). The workers in the second accident did not report any odor and did not experience symptoms of eye, nose, or throat irritation (they were wearing goggles that may have protected against eye irritation).

Garrettson and Warren (1990) described the adverse effects of exposure to intermittent high levels of methyl mercaptan in a 59-year-old plumber's helper who had pumped 3 school kitchen grease traps daily for 3 weeks, 3 times a year, for 15 years via septic tank pumping rig and manual stirring, without using respiratory protection. Symptoms while on the job included a throbbing headache that intensified over that work day and waned over the following 3-4 day

period, nausea and vomiting, eye irritation, tightness in chest, wheezing, dizziness and double vision to the extent that it impaired his ability to drive and delayed him 1 to 2 hours prior to driving to the next site. After 10 years, the worker developed a limited pulmonary reserve and productive cough. His FVC and $FEV_{1,}$ presumably after 15 years, were 72% and 77% of predicted. The pump exhaust discharged near the cab was found to contain high levels of a substance "comparable with" methyl mercaptan. High concentrations of methyl mercaptan and lower levels of ethyl mercaptan were identified by GC-CS analysis of material from the traps at several sites.

The information that can be obtained for epidemiological studies regarding methyl mercaptan yield only limited information. This is due to the fact that under most situations, exposure occured to a mixture of chemicals. No good exposure assessments were available and information on potentially adverse health effects relied mostly on self-reported symptoms. Most of the studies focused on workers in the paper pulp industry or on populations located near pulp mills, exposed to several sulfur compounds, including hydrogen sulfide, methyl mercaptan, dimethyl sulfide, dimethyl disulfide, and sulfur dioxide. Increases in headaches in workers (Kangas et al., 1984), changes in heme synthesis or iron metabolism in workers (Klingberg et al., 1988; Tenhunen et al., 1983), and eye and respiratory symptoms reported by residents of communities located near the paper pulp mills (Jaakkola et al., 1990; Martilla et al., 1995; Partti-Pellinen et al., 1996) were attributed to exposure to the sulfur compound mixtures (described above). An increase in respiratory infections was reported in children exposed to sulfur compounds from pulp plants and to oxides of nitrogen released from a chemical plant (Jaakkola et al., 1991). Studies of respiratory endpoints in pulp mill workers, however, found decrements only in the workers exposed to chlorine during the bleach process of production (Enarson and Yeung, 1985; Kennedy et al., 1991).

Animal Studies

No chronic inhalation studies for methyl mercaptan were located. Two subchronic studies are available; one continuous inhalation study examining the effects of methyl mercaptan exposure in monkeys, rats, and mice and one intermittent exposure toxicity study in rats. Several acute inhalation exposure studies are also available.

An LC_{50} of 675 ppm (1328 mg/m^3) for methyl mercaptan was determined in male and female Sprague-Dawley rats exposed for 4 hours (Tansy et al., 1980, 1981). Rats that survived the first 24 hours post-exposure survived the full 14-day observation period. There was no evidence of bleeding from any orifice of exposed animals; no other endpoints were indicated. An LC_{50} of 1680 ppm was reported for a 1-hour exposure in rats (ELF Atochem, 1977). Mice appear to be somewhat less sensitive to methyl mercaptan lethality than rats. A 4-hour LC_{50} of 1664 ppm was reported in this species (Horiguchi, 1960).

Other acute inhalation studies examined endpoints in addition to lethality. Zieve et al. (1974) reported that rats (3-5/group) exposed to 2000 ppm of methyl mercaptan became comatose, but coma was not induced in any of the rats exposed to 1200 ppm for up to 15 minutes. Ljunggren and Norberg (1943) exposed rats (1 female per group) to levels of methyl mercaptan ranging from 500 to 10,000 ppm for 30-35 minutes, followed by a 24-hour observation period. No overt effects were seen at 500 ppm, signs of fatigue were observed at 700 ppm, prostration and trembling were observed at 1500 ppm, and death occurred at 10,000 ppm after 14 minutes. Microscopic examination revealed pulmonary edema in the rats exposed to 1500 and 10,000 ppm. Male rats exposed to methyl mercaptan at 250 to 500 ppm for 4-hour periods exhibited clinical signs of irritation of the eyes and nose and at autopsy showed pulmonary congestion and edema (Haskell Laboratory, n.d.). In subacute inhalation studies, ten 6-hour exposures at 100 ppm were not lethal, but similar exposure to 200 ppm resulted in death to 1 of 4 rats in each of two experiments. At necropsy, rats that had died during the exposure or were killed at the end of the study were found to have pneumonia, but there were no controls with which to compare. The authors concluded that the pathological changes were suggestive of an irritant effect of methyl mercaptan, which could have predisposed the animals to a pneumonia infection (Haskell Laboratory, n.d.).

A 2-month intermittent inhalation exposure study of a relatively high concentration of methyl mercaptan was conducted in mice by Horiguchi (1960). In this study, 11 male white mice were exposed to 300 ppm of methyl mercaptan for 2 hours/day, 3 days/week, for up to 2 months. Six mice died after 15 exposures, and all the remaining mice were dead after 25 exposures. Additional details were not available.

A 3-month intermittent inhalation study of methyl mercaptan in young adult male Charles River Sprague-Dawley rats was conducted by Tansy and coworkers (Tansy et al., 1980, 1981). Groups of 31 rats were exposed to 0, 2, 17 or 57 ppm (0, 4, 33 or 112 mg/m^3) of methyl mercaptan, 7 hours/day, 5 days/week for 3 months. The rats from the 0 and 57 ppm exposure groups were selected from a different shipment of rats than the rats from the 2 or 17 ppm exposure groups. Observations made on all animals included: oxygen consumption, blood clinical chemistry, organ weights, and complete histopathological liver examinations. Ten rats/group were observed for metabolic performance and systolic blood pressure, and 5 rats/group were subjected to histopathological examination of the heart, lungs, small intestine, and kidneys.

Little evidence of toxicity was seen in the study (Tansy et al., 1980, 1981). No deaths occurred. During the exposures to 57 ppm, the rats huddled in small groups toward the periphery of the chamber with noses pointed outward. This behavior did not occur in the sham exposures: it is unclear whether and to what extent it may have occurred in the 2 or 17 ppm groups. Time courses of weight-normalized metabolic parameters were analyzed by regression analysis. Results indicate that rates of change in food intake and in wet and dry fecal weight increases were not affected. Other metabolic performance parameters were statistically significantly

different in the 2 and 17 ppm groups, but not the 57 ppm exposure group, as compared to controls (i.e., fecal pellet count increases and water intake rate increases were lower and urine output increases were higher in the 2 and 17 ppm groups). There were no significant differences in intestinal transit parameters. The mean terminal body weights of the exposed groups were depressed; the weights were statistically significantly different from controls at the 57 ppm level (~15% lower) and showed a statistically significant dose-related trend. Similar results were seen for the average rates of body weight gain for the subset groups, as determined by regression analysis. Some statistically significant (but small) differences in mean organ weights were seen, but there was no dose-related trend and the investigators suggested that the precision of organ removal was such that these differences may not have been biologically significant. No consistent patterns were found for systolic blood pressure and no consistent statistically significant differences were found for oxygen consumption (data not provided). Some statistically significant differences between treated and control groups were seen in the clinical chemistry findings, but none of these demonstrated a statistically significant dose-related trend. Total serum proteins were similar in all three exposed groups and significantly higher than in controls. Serum albumin levels were similar in the three exposed groups and significantly lower than in controls. Lactate dehydrogenase (LDH) activities were lower in the exposed groups than in the control groups. Increases in serum bilirubin were seen in the 2 and 17 ppm groups, but not the 57 ppm group, as compared to controls. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were similar in all groups.

Histological evidence of liver involvement was reported, but the report does not explicitly describe the liver histology of controls (Tansy et al., 1980, 1981). The investigators stated that the pathologist could not predict whether a liver sample was from an exposed or control rat on a blind basis, indicating that differences between liver histology in exposed and control rats were negligible. Hyperplastic nodules were found in livers of a few rats from the control-, 2-, and 57-ppm-groups and a hepatic carcinoma was found in a liver from a 17-ppm rat; these findings, while not associated with exposure, were unexpected in rats of this age. Evidence of pneumonia, emphysematic changes, and occasional fibrosis were seen in the lungs of rats from all groups, including the control group. Actual incidences of histopathological effects were not reported.

The results of the study by Tansy et al. (1980, 1981) suggest that 7 ppm (33 mg/m^3) is a NOAEL and 57 ppm (112 mg/m^3) is a LOAEL for body-weight-depression in male rats exposed subchronically to methyl mercaptan for 7 hours/day, 5 days/week.

In a continuous inhalation exposure study, 10 male rhesus monkeys, 50 male Sprague-Dawley rats, and 100 male Porten-Woods mice were exposed to methyl mercaptan at 50 ppm (98 mg/m^3) (as part of a mixture of indole, skatole, hydrogen sulfide, and methyl mercaptan) while housed in cages located in a large exposure chamber for 90 days (Sandage, 1961). Controls were housed in the room that contained the exposure chamber. Endpoints included: hematology, blood chemistry and urinalysis in all species, liver function tests in monkeys, stress tests

(swimming) in 50% of the surviving animals, and necropsy and histopathological examinations of major organs in all monkeys and in 25% of the surviving rats and mice.

Although the experimental protocol and the findings of the study are described only in very broad terms, it appears that some of the rats and mice that died during the exposure period were necropsied and examined histopathologically (Sandage, 1961). This study included groups exposed to three other chemicals or to a mixture. The reporting of the data was relatively nonspecific, with little tabulation of the numerical data, so that meaningful comparisons between methyl mercaptan-exposed and control animals are possible only for mortality. For example, the pathology data were reported in a summary table as per cent of necropsied animals having any gross or microscopic pathology findings in each organ examined (heart, lung, liver, kidneys, brain), with no indication of the specific lesions or their incidences. Some sporadic discussion of specific findings is presented in the text, but the discussion by the author is frequently inconsistent with the comments of the pathologist, which are included in the report.

For methyl mercaptan, the data presentation (in Sandage, 1961) is insufficient to support any independent conclusions. Terminal body weights were lower in monkeys and unaffected in rats and mice compared statistically to those in controls (data not presented). Increased mortality was seen in the exposed groups (4/10 monkeys, 5/50 rats, 43/100 mice) as compared to controls (0/9 monkeys, 2/50 rats, 16/100 mice), and was significantly different from controls in the monkeys and mice. According to the author, the above tests and examinations did not reveal a probable cause for the mortality in monkeys exposed to methyl mercaptan. Rather, the results were said to be similar to those for a group of monkeys exposed to hydrogen sulfide (20 ppm), in which there were no deaths. The pathologist's comments mention a mild-to-moderate edema in the lungs of 12 of the 14 monkeys that died during the exposure to any of the tested chemicals or the mixture, but do not specifically discuss findings for methyl mercaptan. In addition, the pathologist mentions that many of the surviving monkeys had recent mild inflammation of the lungs, probably resulting from the swimming test (i.e., not chemical-related). The pathology data table does not differentiate between these conditions, and shows a 40% occurrence of lung pathology in control monkeys, all of which survived.

The author ascribed the increased mortality in methyl mercaptan-exposed mice to hepatitis, whereas the pathologist's comments (included in the report) stated that "most of the mice and rats were normal, except for the persistent hepatitis in mice," a statement that does not seem to ascribe that lethality was significantly associated with hepatitis (Sandage, 1961). In addition, the pathologist noted that there was "some hepatitis" in the controls. The author stated that, in rats, methyl mercaptan perhaps was associated with lung damage: 16% in exposed versus 0% in controls. These incidences are unlikely to be statistically significantly different, because the number of exposed rats examined histopathologically is approximately 16 (5 that died during exposure plus 25% of the surviving 45), so the number with lung effects may have been only 2 or 3; similarly, the number of controls examined was probably approximately 14. In addition, the

pathologist's comments do not include any mention of adverse lung effects in the rats exposed to methyl mercaptan.

The hematological tests revealed some statistically significant differences in red cell parameters in rats and mice exposed to methyl mercaptan, but the actual data were not presented (Sandage, 1961). The author considered the results indicative of an adverse effect in these species. Performance of the methyl mercaptan-exposed groups in the swim test was better in monkeys, not different in rats, and worse in mice, as compared statistically with performance in controls (data not shown).

The deficiencies in experimental design and the reporting of results in the study by Sandage (1961) compromise a quality assessment for inhalation toxicity of methyl mercaptan in the exposed animals. It appears that the animals tested were exposed to a mixture of gases, from which severity of effects could not be attributed exclusively to methyl mercaptan. Although the reported results seem to indicate that rats may be less sensitive than monkeys or mice to continuous exposure at 50 ppm methyl mercaptan, confidence in this study is very low, and the results from a single exposure level are not necessarily predictive of a dose-response at lower exposure levels.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfCs FOR METHYL MERCAPTAN

The inhalation data base for methyl mercaptan is inadequate for p-RfC derivation. Two subchronic inhalation studies are available, but were of inadequate design for use in derivation of provisional toxicity values. The minimal database requirement for derivation of an RfC is a well-conducted subchronic inhalation bioassay that evaluated a comprehensive array of endpoints, including adequate evaluation of the respiratory tract, and established an unequivocal NOAEL and LOAEL (U.S. EPA, 1994b).

The 90-day continuous inhalation exposure study (Sandage, 1961) exposed monkeys, mice, and rats to a mixture that included methyl mercaptan; determination of adverse effects by a single chemical component was not possible.

The subchronic inhalation study in rats by Tansy et al. (1980, 1981) resulted in body weight depression in male rats exposed to methyl mercaptan 7 hours/day, 5 days/week, for 3 months. No clear evidence of other adverse effects was observed in this study. The study has several limitations that preclude its use as a basis for RfC derivation. Histopathological examinations were performed on a limited number of organs in a small subset of the animals; reporting of these results was not comprehensive. Evidence of pneumonia, emphysematic changes, and occasional fibrosis were seen in the lungs in the subset of rats examined from all

groups, including the control group. The upper respiratory tract of the exposed animals was not evaluated and actual incidences of histopathological effects were not reported. Animals in two of the exposure groups were from a different shipment than animals from the other exposure groups, lowering confidence in the overall experimental design and results.

In conclusion, the lack of adequate chronic or subchronic inhalation data for humans or animals precludes derivation of a subchronic or chronic p-RfC for methyl mercaptan.

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.

Allied Chemical Corporation. 1978. Letter to U.S. EPA submitting a medical review of an incident that occur in one of the plants involving the exposure of methyl mercaptan, dimethyl disulfide, and acetonitrile. Produced by Allied Chemical Corporation 05/19/78. U.S. EPA OPTS Fiche #: OTS0200447. Doc#: 88-7800149.

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). 1992. Toxicological Profile for Methyl Mercaptan. U.S. Department of Health and Human Services, Public Health Service. Atlanta, GA. PB93/110799/AS. Online. http://www.atsdr.cdc.gov/toxprofiles/tp139.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. Biochim. 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. 2001. The Merck Index. Thirteenth edition. Merck & Co., Inc., Whitehouse Station, NJ. p. 1091.

Cain, W.S. and A. Turk. 1985. Smell of danger: An analysis of LP-gas odorization. Am. Ind. Hyg. Assoc. J. 46 (3): 115-126.

Cristescu, V. 1941. A case of poisoning with mercaptan. Med. Bull. Standard Oil Co., N.J. 5: 78-84. (Cited in Shults, 1970)

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.

ELF Atochem. 1977. Unpublished study, Pharmacology Research Inc. (Cited in Shertzer, 2001)

Enarson, D.A. and M. Yeung. 1985. Determinants of changes in FEV_1 over a workshift. Br. J. Ind. Med. 42(3): 202-204.

Garrettson, L.K. and D.A. Warren. 1990. Chronic methanethiol poisoning. American Association of Poison Control Centers, American Academy of Clinical Toxicology, American Board of Medical Toxicology, Canadian Association of Poison Control Centers Scientific Meeting. Tuscon, AZ; September 14-18, 1990. Vet. Hum. Toxicol. 32(4): 365.

Haskell Laboratory. n.d. Toxicity of methyl mercaptan. Medical Research Project No. MR-287. Submitted by Dupont Chemical in 1992 to EPA under TSCA 8E. OTS Fiche #: OTS0571484.

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.

Horiguchi, M.J. 1960. [An experimental study on the toxicity of methylmercaptan in comparison with hydrosulfide.] J. Osaka City Med. Center 9(12): 8, 5357-5393. (Cited in Shertzer, 2001)

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.

Jaakkola, J.J., M. Paunio, M. Virtanen and O.P. Heinonen. 1991. Low-level air pollution and upper respiratory infections in children. Am. J. Pub. Health. 81(8): 1060-1063.

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.

Kennedy, S.M., D.A. Enarson, R.G. Janssen and M. Chan-Yeung. 1991. Lung health consequences of reported accidental chlorine gas exposures among pulpmill workers. Am. Rev. Respir. Dis. 143: 74-79.

Key, M.M., A.F. Henschel, J. Butler et al. 1977. Occupational diseases: A guide to their recognition. U. S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control and Prevention. National Institute for Occupational Safety and Health. DHEW (NIOSH) Pub No. 77-181; NTIS PB83-129-528. Online. http://www.cdc.gov/niosh/pdfs/77-181-g.pdf

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.

Martilla, O., J. Jaakkola, K. Partti-Pellinen et al. 1995. South Karelia air pollution study: Daily symptom intensity in relation to exposure levels of malodorous sulfur compounds from pulp mills. Environ. Res. 71: 122-127.

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/

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.

Rose, V.E. 1983. Thiols. Encyclopedia of Occupational Health and Safety. 2: 2172-2173.

Sandage, C. 1961. Tolerance criteria for continuous inhalation exposure to toxic material. II. Effects on animals of 90-day exposure to phenol, CCl_4, and a mixture of indole, skatole, H_2S, and methyl mercaptan. ASD Technical Report 61-519 (II), Biomedical Laboratory, Wright-Patterson Air Force Base, OH. NTIS AD-287-797.

Shertzer, H.G. 2001. Organic Sulfur Compounds. Methyl Mercaptan. In: Patty's Toxicology, Fifth edition. Vol. 7. E. Bingham, B. Cohrssen and C.H. Powell, Ed. John Wiley & Sons, NY. p. 687-690.

Santodonato, J., S. Bosch, W. Meylan et al. 1985. Monograph on human exposure to chemicals in the workplace: Mercaptans. Center for Chemical Hazard Assessment, Syracuse Research Corporation, Syracuse, New York. SRC-TR-85-187.

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

Shults, W.T., E.N. Fountain and E.C. Lynch. 1970. Methanethiol poisoning: Irreversible coma and hemolytic anemia following inhalation. J. Am. Med. Assoc. 211: 2153-2154.

Syntex Corporation. 1979. Summary of accident report on methyl mercaptan fatality with cover letter. Produced 05/15/79. U.S. EPA OPTS Fiche #: OTS0000032-0. Doc#:FYI-AX-0579-0032.

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.

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

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

U.S. EPA. 1994b. Methods of Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, Washington, DC. October 1994. EPA/600/8-90/066F.

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. 21 CFR172.515. Department of Health and Human Services, Washington, DC. Online. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=172.515

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

Yaegaki, K. and K. Sanada. 1992a. Volatile sulfur compounds in mouth air from clinically healthy subjects and patients with periodontal disease. J. Period. Res. 27(4 Pt 1): 233-238.

Yaegaki, K. and K. Sanada. 1992b. Biochemical and clinical factors influencing oral malodor in periodontal patients. J. Periodont. 63(9): 783-789.

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.

Zieve, L. 1981. The mechanism of hepatic coma. Hepatology. 1: 360-365.

Zieve, L., W.M. Doizaki and C. Hyftogt. 1984. Brain methanethiol and ammonia concentrations in experimental hepatid coma and coma induced by injections of various combinations of these substances. J. Lab. Clin. Med. 104(5): 655-664.

12-20-04

Provisional Peer Reviewed Toxicity Values for

Methyl Mercaptan
(CASRN 74-93-1)

Derivation of a Carcinogenicity Assessment

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	**provisional inhalation unit risk**
p-OSF	**provisional oral slope factor**
p-RfC	**provisional inhalation reference concentration**
p-RfD	**provisional oral reference dose**
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	**Provisional Peer Reviewed Toxicity Value**
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

12-20-04

PROVISIONAL PEER REVIEWED TOXICITY VALUE FOR METHYL MERCAPTAN (CASRN 74-93-1)
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 to OSRTI.

INTRODUCTION

A carcinogenicity assessment for methyl mercaptan is not available on IRIS (U.S. EPA, 2003), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). NTP (2003), IARC (2003), and WHO (2003) have not produced documents for this chemical. Review documents by ATSDR (1992), Shertzer (2001), and Santodonato (1985) were consulted. Literature searches of the following databases were conducted from 1965 through June 2003 in order to locate relevant studies: TOXLINE (supplemented with BIOSIS and NTIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. Additional literature searches from June 2003 through October 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

Methyl mercaptan (CH_3SH, MW = 48.11) is a gas with a strong unpleasant odor of rotting cabbage (Budavari, 2001). Natural sources of methyl mercaptan include vegetation, animal waste, microbial degradation, crude oils containing sulfur, and the "sour" natural gas of West Texas (ATSDR, 1992; Budavari, 2001; Rose, 1983; Santodonato et al., 1985). Industrial sources include wood pulp, oil shale, petroleum processing plants, and sewage treatment plants (ATSDR, 1992). Although some other mercaptans are used as odorants in natural and liquified petroleum gas or in commercial, industrial, and residential natural gas; methyl mercaptan is not used for this purpose (ATSDR, 1992; Cain and Turk, 1985; Shertzer, 2001; Santodonato et al., 1985).

Methyl mercaptan occurs in foods (onion, garlic, meat, bread, fish), sometimes as a result of microbial activity (Shertzer, 2001; Sinki and Schlegel, 1990; Budavari, 2001). It is approved for use as a food additive (synthetic flavoring agent) by the FDA [21 CFR 172.515] (U.S. FDA, 2003).

Methyl mercaptan is produced endogenously in mammals during metabolism of methionine and related substances (Blom et al., 1988, 1989; Al Mardini et al., 1984; Shertzer, 2001), and by bacteria in the mammalian gut and mouth (Budavari, 2001; De Boever et al., 1994; Hiele et al., 1991; Yaegaki and Suetaka, 1992a,b). High levels of methyl mercaptan have been detected in the breath and urine of some patients with advanced liver disease (Shertzer, 2001; Tangerman et al., 1994). A number of studies and reviews explored the possibility that methyl mercaptan may play a role in the pathogenesis of encephalopathy resulting from hepatic failure (Al Mardini et al., 1984; Blom et al., 1988, 1989; Zieve, 1981; Zieve et al., 1974, 1984). These authors concluded that methyl mercaptan may interact (mechanism unknown) with ammonia and fatty acids to possibly exacerbate the encephalopathy in human hepatic failure.

REVIEW OF THE PERTINENT DATA

Human Studies

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

Animal Studies

No animal studies examining the carcinogenicity of methyl mercaptan by any route of exposure were located.

Other Studies

Methyl mercaptan was mutagenic in an *in vivo* assay in *Drosophila melanogaster* (Garrett and Fuerst, 1974) and elicited a weak positive response in a bone marrow micronucleus assay conducted by inhalation exposure in mice (ELF Atochem, 1996, 1997).

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

No studies examining the carcinogenic potential of methyl mercaptan in humans or animals were located. Available genotoxicity data are positive, but limited to only two assays. The available data are insufficient to assess carcinogenic potential in animals or humans as specified by the proposed U.S. EPA (1999) Guidelines for Carcinogen Risk Assessment.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for methyl mercaptan is precluded by the lack of data to assess carcinogenicity associated with methyl mercaptan 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). 1992. Toxicological Profile for Methyl Mercaptan. U.S. Department of Health and Human Services, Public Health Service. Atlanta, GA. PB93/110799/AS. Online. http://www.atsdr.cdc.gov/toxprofiles/tp139.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. Biochim. 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. 2001. The Merck Index. Thirteenth Edition. Merck & Co. Inc., Whitehouse Station, NJ. p. 1091.

Cain, W.S. and A. Turk. 1985. Smell of danger: An analysis of LP-gas odorization. Am. Ind. Hyg. Assoc. J. 46 (3): 115-126.

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.

ELF Atochem North America, Inc. 1996. Bone Marrow Micronucleus Assay in Male and Female Swiss-Webster Mice Following Acute Nose-Only Inhalation Exposure to Methyl Mercaptan. Produced: 07/09/96. U.S. EPA/OPTS Fiche #: OTS0558450-1. Doc#: 89960000185.

ELF Atochem North America, Inc. 1997. Letter from ELF Atochem North America, Inc. to U.S. EPA Regarding Bone Marrow Micronucleus Assay of Methyl Mercaptan; Amended Final Report No. 1. Produced: 02/19/97. U.S. EPA/OPTS Fiche #: OTS0558450-1. Doc#: 89970000087.

Garrett, S. and R. Fuerst. 1974. Sex-linked mutations in *Drosophila* after exposure to various mixtures of gas atmospheres. Environ. Res. 7: 286-93.

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.

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

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

Rose, V.E. 1983. Thiols. Encyclo. Occup. Health Saf. 2: 2172-2173.

Shertzer, H.G. 2001. Organic Sulfur Compounds. Methyl Mercaptan. In: Patty's Toxicology, Fifth edition. Vol. 7. E. Bingham, B. Cohrssen and C.H. Powell, Ed. John Wiley & Sons, NY. p. 687-690.

Santodonato, J., S. Bosch, W. Meylan et al. 1985. Monograph on human exposure to chemicals in the workplace: Mercaptans. Center for Chemical Hazard Assessment, Syracuse Research Corporation, Syracuse, New York. SRC-TR-85-187.

Sinki, G.S. and W.A. Schlegel. 1990. Flavoring agents. In: Food Science and Technology, Vol. 35, Food Additives, A.L. Branen, P.M. Davidson, and S. Salminen, Ed. 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. 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. Proposed Guidelines for Cancer Risk Assessment. July 1999. Office of Research and Development, National Center for Environmental Assessment, Washington, DC.

U.S. EPA. 2002. 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

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. 21 CFR.172.515. Department of Health and Human Services, Washington, DC. Online.
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=172.515

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

Yaegaki, K. and K. Sanada. 1992a. Volatile sulfur compounds in mouth air from clinically healthy subjects and patients with periodontal disease. J. Period. Res. 27(4 Pt 1): 233-238.

Yaegaki, K. and K. Sanada. 1992b. Biochemical and clinical factors influencing oral malodor in periodontal patients. J. Periodont. 63(9): 783-789.

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.

Zieve, L. 1981. The mechanism of hepatic coma. Hepatology. 1: 360-365.

Zieve, L., W.M. Doizaki, and C. Hyftogt. 1984. Brain methanethiol and ammonia concentrations in experimental hepatid coma and coma induced by injections of various combinations of these substances. J. Lab. Clin. Med. 104(5): 655-664.