12-1-04

Provisional Peer Reviewed Toxicity Values for

Dimethylmercury

(CASRN 593-74-8)

Derivation of Subchronic and Chronic Oral RfDs

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

Acronyms and Abbreviations

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

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

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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 dimethylmercury is not available on IRIS (U.S. EPA, 2003), the HEAST (U.S. EPA, 1997a), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). No relevant documents for dimethylmercury were located in the CARA lists (U.S. EPA, 1991, 1994); however, several documents regarding mercury were listed, including a Health Issue Assessment (U.S. EPA, 1984a), Health Effects Assessment (U.S. EPA, 1984b), Drinking Water Criteria Document (U.S. EPA, 1988), and Ambient Water Quality Criteria Document (U.S. EPA, 1989). None of these documents derived an RfD for dimethylmercury. The Mercury Study Report to Congress (U.S. EPA, 1997b) was also consulted. ATSDR prepared a Toxicological Profile on Mercury (ATSDR, 1999) but did not derive acute, intermediate, or chronic oral MRL values for dimethylmercury. IARC (1993) produced a document for Mercury and Mercury Compounds where the Working Group

considered methylmercury compounds including dimethylmercury *possibly carcinogenic to humans* (Group 2B), based on evidence that all methylmercury compounds are similar with regard to absorption, distribution, metabolism, excretion, genotoxicity, and other forms of toxicity. Neither NTP (2003) nor WHO (2003) have produced documents specific to dimethylmercury. Literature searches of the following databases were conducted in 1993 for dimethylmercury: TOXLIT (1985-1993), TOXLINE (1985-1993), HSDB, RTECS, TSCATS, and CHEMID. Update literature searches were conducted from 1993 through October 2004: TOXLINE (supplemented with BIOSIS and NTIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS.

Alkylmercury compounds, such as dimethylmercury, are especially hazardous because of their volatility, ability to penetrate epithelial and blood brain barriers, and their persistence *in vivo* (Gosselin et al., 1984). Dimethylmercury is an extremely volatile liquid (boiling point = 96 °C) (Budavari, 2001) that forms a toxic vapor. The vapor pressure of dimethylmercury at 23.7 °C is 58.8 mm; a cubic meter of saturated air could hold more than 600 g of mercury (Toribara et al., 1997). Oral toxicity assessments have been developed for a number of mercury compounds, including, for example, mercuric chloride (CASRN 7487-94-7) (U.S. EPA, 2003) and methylmercury (CASRN 22967-92-6) (U.S. EPA, 2003; ATSDR 1999).

REVIEW OF PERTINENT DATA

Human Studies

No data regarding the toxicity of dimethylmercury to humans following oral exposure were located. However, several lethal accidental poisonings in humans exposed to dimethylmercury by inhalation and/or dermal contact have been reported.

Dimethylmercury is highly lipophilic and rapidly absorbed through skin and semi-permeable barriers, such as latex gloves (Blayney et al., 1997). Dimethylmercury is lethal at doses of approximately 400 mg of Hg (equivalent to a few drops) or 5 mg/kg body weight (Gosselin et al.,1984; Nierenberg et al., 1998).

Five fatalities involving 2 scientists and 3 technicians exposed to dimethylmercury have occurred in chemical research laboratories. Subjects were exposed to dimethylmercury transdermally while "handling" the mercuric compound or via inhaling the highly volatile vapors. Although these accidental poisonings represent acute exposures, the delayed onset of neurological symptoms post exposure and rapid demise thereafter, highlights the highly toxic nature of this substance.

A fatal accidental poisoning occurred when a 48 year-old research chemist spilled several drops of liquid dimethylmercury onto the dorsum of her gloved hand while working under a ventilated fume hood in the laboratory (Nierenberg et al., 1998; Siegler et al., 1999). Five months later, and five days prior to hospital admission, the patient developed deterioration in balance, gait, and speech. In the preceding two months, she had lost 6.8 kg (15 lb) and experienced brief episodes of nausea, diarrhea, and abdominal discomfort. Initial medical evaluation showed moderate upper-extremity dysmetria, dystaxic handwriting, dysarthria, and a broad-based gait. Routine laboratory tests were normal and analyses of cerebrospinal fluid reported clear fluid, protein concentration of 42 mg/dl, and no cells. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head were normal except for the incidental finding of a probable menigioma, 1 cm in diameter. A preliminary whole blood mercury level was 4,000 μ/L (normal range 1 to 10 μ/L) collected 162 days after dimethylmercury exposure. The original body burden was estimated to be 1,344 mg of mercury. Her condition worsened in subsequent days; she described tingling in her fingers, brief flashes of light in her eyes, and soft background noise in her ears that progressed to marked constriction of visual fields and deafness. The patient lapsed into a coma 22 days from presentation of symptoms and died 4 months later, 298 days after dimethylmercury exposure. The investigators attributed this accidental exposure to both transdermal absorption of liquid dimethylmercury (given the lack of protection provided by the disposable latex gloves) and inhalation of vapors (even though the work was conducted under a fume hood). Upon gross examination, the areas of the brain most profoundly affected by dimethylmercury poisoning were the cerebellum and visual cortex (Nierenberg et al., 1998). Microscopic evaluation showed extensive neuronal loss and gliosis bilaterally within the primary visual and auditory cortices, with milder loss of neurons and gliosis in the motor and sensory cortices. There was widespread loss of cerebellar granular-cell neurons, Purkinje cells, and basket-cell neurons, with evidence of loss of parallel fibers in the molecular layer. Bergmann gliosis was well-developed and widespread.

The only previous report of neuropathology of dimethylmercury poisoning was by Pezderová et al. (1974, as cited in Siegler et al., 1999), who reported the autopsy findings of a 28-year old chemist who had prepared 6000 grams of dimethylmercury over a 3 month period. Additional exposure information was not provided. Neuropathologic damage included massive Purkinje cell loss, temporal lobe damage, and slight degenerative changes of the granular layer, but no changes in the cerebellar white matter.

Edwards (1865, 1866, as cited in Hunter et al., 1940) reported the poisoning of 3 laboratory technicians exposed to dimethylmercury while engaged in research. The route of exposure was not provided, but is assumed to be primarily via inhalation with some dermal exposure indicated for the second fatality. Two of the three technicians died. The first case, a 30-year old male, had been exposed to dimethylmercury for 3 months, when he began to complain of numbness of the hands, deafness, poor vision, and sore gums. Symptoms exhibited were described as “slow and dull in manner, unsteady in gait, and inability to stand without

support." His condition deteriorated rapidly, including restlessness, unresponsiveness to questions, urinary incontinence, and coma. The first technician died 2 weeks after reported onset of symptoms. The second technician, a 23-year old male, had worked in the laboratory for 12 months and had reportedly "handled" dimethylmercury 3 months previous for a 2 week period. One month after this exposure, he began complaining of sore gums, salivation, numbness of the feet, hands and tongue, and dimness of vision. The second technician experienced similar symptoms as the first in that he answered questions "only very slowly and with indistinct speech," and was ataxic. After 3 weeks, the man had difficulty in swallowing, was incontinent, unable to speak, and often restless and violent. He remained "in a confused state" until his death due to pneumonia 12 months later. The third technician was described as having similar, less severe symptoms, with eventual recovery.

Animal Studies

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

Two abstracts were located regarding a study or studies of the toxicity of dimethylmercury following intramuscular administration to rats (Koya and Kudo, 1986; Koya et al., 1986). Both abstracts were presented at the same scientific meeting in Tokyo, Japan, and were very poorly translated; full reports of the studies do not appear to have been published. The first abstract reported that 7 male Wistar rats were treated with 16 daily doses (route of treatment not reported, but specified as intramuscular in the following abstract) of 1 mg Hg/rat/day as dimethylmercury (Koya and Kudo, 1986). Following treatment, the rats were observed for 2 to 13 months. Neurological symptoms included ataxic gait, tremor, hypermetria, and loss of equilibrium. Other effects included crossing of the hind limbs induced by holding the rat upside down, twisting of the body, stretched knee and ankle junction, and raised and stiff tail. Muscle atrophy and increased length of the hind limb claws were also reported. Examination of the brain after sacrifice revealed a lesion described as focal calcification in the rostral vermis of the cerebellum in the middle to basal part of the granular layer. The authors attributed the ataxia in the rats to dimethylmercury-induced damage in this area of the brain. The second abstract by the same authors describes a study essentially identical in protocol, and specifies the route of administration as intramuscular injection (Koya et al., 1986). This abstract mentions an ataxic gait, but focuses on histopathological findings. The brain lesions were as reported by Koya and Kudo (1986): focal calcification in the rostral vermis of the cerebellum in the middle to basal part of the granular layer. However, additional details were reported regarding the exact location of the damage and the size of the calcified deposits. In addition, degeneration of the spino-cerebellar and sensory tracts, and peripheral nerves was reported, with this damage possibly occurring before that observed in the brain (Koya et al., 1986).

In a more recent study from the same laboratory, Mori et al. (2000) administered 5 mg/kg of dimethylmercury daily via intramuscular injection for 12 consecutive days to 20 adult female Wistar rats, of which two were selected for sacrifice on each of days 1, 4, 7, 10, 12, 24, 32, 49, 100 and 140 post treatment. Of the total three control rats treated with sesame oil, one was sacrificed on each of days 7, 24, and 100. On day 4, pyknotic neurons were found in the dorsal root ganglia, cerebellar cortex, cerebral cortex and thalamus of treated rats. On day 10, necrotic neurons were also found in the dorsal caudate nucleus, putamen and anterior horn of the spinal cord. Neurohistological examination identified widespread calcium deposition in the nervous system of treated rats as early as 4 days post-treatment. Behavioral observations in treated rats were hind limbs that showed flexion and/or crossing on day 4, and from day 14, ataxic gait that worsened over time.

No information or toxicological studies regarding the reproductive or developmental effects of dimethylmercury were located.

Other Studies

Oyama et al. (1998) compared the reactivity of methylmercury, methylmercury conjugated to L-cysteine, and dimethylmercury *in vitro* via flow cytometry methods. Reactivity was measured by changes in intracellular calcium concentrations indicative of cell viability in rat cerebellar neurons dissected from 10 to 14 day old Wistar rats treated with respective mercurial compounds. Intracellular calcium was released from treated cerebellar neurons by methylmercury and to a lesser extent by methylmercury-cysteine conjugate, but not by dimethylmercury, including that it does not decrease viability in this assay.

Aggregating cell cultures of fetal rat telencephalon treated continuously with dimethylmercury preferentially affected the mature cells compared to immature cells by measurement of enzymatic activities and change in total protein content (Monnet-Tschudi et al., 1993), although the toxicological significance of this finding *in vivo* is not known. Dimethylmercury (10^{-6} M) preferentially affected the differentiated cells from the aggregating cell cultures during the range of culture days 24 to 34 (period of advanced development), producing a 30% reduction in 2' 3' -cyclic nucleotide 3'-phosphohyrolase (CNP) activity. In the immature cultures, days 5 to 14 (period of cell proliferation and early differentiation), dimethylmercury treatment (10^{-7} to 10^{-8}) resulted in an approximate 60% increase in CNP activity. Selective changes in the mature (fetal rat) cultures suggests dimethylmercury interferes with neurological development at more advanced stages.

Östland (1969; cited in Nierenberg et al., 1998) reported on the metabolism of methylmercury and dimethylmercury in mice. Results indicated that dimethylmercury does not enter the brain until metabolized over a period of days to monomethylmercury, which is capable of binding to cellular proteins.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR DIMETHYLMERCURY

The database for dimethylmercury is inadequate for derivation of a p-RfD. No data on the effects of oral exposure to dimethylmercury in animals or humans were located.

Derivation of a p-RfD for dimethylmercury by analogy to methylmercury was considered. Limited data suggest that dimethylmercury does not enter the brain until metabolized to monomethylmercury, which may produce toxicity by binding to cellular proteins (Östland, 1969). Support for methylmercury as the proximal toxicant in dimethylmercury poisoning comes from Oyama et al. (1998), who found that methylmercury, but not dimethylmercury, was toxic to cerebellar neurons *in vitro*. However, the human data suggest that dimethylmercury is more acutely toxic than methylmercury. Methylmercury poisonings generally show gliosis of both the cerebral and cerebellar cortices and damage consistent with granule and Golgi cell loss in the cerebellum (Verity, 1997), but they do not show the massive Purkinje cell loss and temporal lobe damage observed in the victims of dimethylmercury poisoning. The difference in neuropathology may reflect differences in route and duration of exposure (the methylmercury poisonings resulted from repeated consumption of contaminated food, in contrast to the dimethylmercury poisonings, which resulted from single or short-term dermal/inhalation exposure), or differences in toxicity between methyl and dimethylmercury. Additional data on toxicity, toxicokinetics, and mode of action for both methyl and dimethylmercury would be needed to support use of methylmercury as a surrogate for derivation of an p-RfD for dimethylmercury.

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FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
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i.m.	intramuscular
i.p.	intraperitoneal
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IRIS	Integrated Risk Information System
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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
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REL	relative exposure level
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RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
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sq.cm.	square centimeters
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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 dimethylmercury is not available on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997a). No relevant documents for dimethylmercury were located in the CARA lists (U.S. EPA, 1991, 1994); however, several documents regarding mercury were listed, including a Health Issue Assessment (U.S. EPA, 1984a), Health Effects Assessment (U.S. EPA, 1984b), Drinking Water Criteria Document (U.S. EPA, 1988), and Ambient Water Quality Criteria Document (U.S. EPA, 1989). None of these documents derived an RfC for dimethylmercury. The Mercury Study Report to Congress (U.S. EPA, 1997b) was also consulted. ATSDR prepared a Toxicological Profile on Mercury (ATSDR, 1999) but did not derive acute, intermediate, or chronic inhalation MRL values for dimethylmercury. IARC (1993) produced a document for Mercury and Mercury Compounds where the Working Group considered methylmercury compounds including dimethylmercury *possibly carcinogenic to*

humans (Group 2B), based on evidence that all methylmercury compounds are similar with regard to absorption, distribution, metabolism, excretion, genotoxicity, and other forms of toxicity. Dimethylmercury is included in the group of the organo (alkyl) mercury compounds for which OSHA (2003) set a TWA-PEL of 0.01 mg/m^3 and ACGIH (2003) adopted a TWA-TLV of 0.01 mg/m^3 as Hg and a STEL of 0.03 mg/m^3 as Hg. NIOSH (2002) has not recommended an exposure limit for this compound. The California Office of Environmental Health and Hazard Assessment (OEHHA, 2002) and the Air Resources Board (ARB) support a chronic inhalation REL of 1.0 µg/m^3 for "methylmercury [CASRN 593-74-8]" based on potential adverse effects to the nervous system. Neither NTP (2003) nor WHO (2003) have produced documents specific to dimethylmercury. Literature searches of the following databases were conducted in 1993 for dimethylmercury: TOXLIT (1985-1993), TOXLINE (1985-1993), HSDB, RTECS, TSCATS, and CHEMID. Update literature searches were conducted from 1993 through October 2004: TOXLINE (supplemented with BIOSIS and NTIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS.

The alkyl mercury compounds, such as dimethylmercury, are especially hazardous because of their volatility, ability to penetrate epithelial and blood brain barriers, and their persistence *in vivo* (Gosselin et al.,1984). Dimethylmercury is an extremely volatile liquid (boiling point = 96° C) (Budavari, 2001) that forms a toxic vapor upon contact with air. The vapor pressure of dimethylmercury at 23.7 °C is 58.8 mm; a cubic meter of saturated air could hold more than 600 g of mercury (Toribara et al., 1997). Dimethylmercury is highly lipophilic and rapidly absorbed through skin and semi-permeable barriers, such as latex gloves (Blayney et al, 1997). Dimethylmercury is lethal at doses of approximately 400 mg of Hg (equivalent to a few drops) or 5 mg/kg body weight (Gosselin et al.,1984; Nierenberg et al., 1998).

REVIEW OF THE PERTINENT DATA

Human Studies

No data regarding the toxicity of dimethylmercury to humans following chronic or subchronic inhalation exposures were located. However, several accidental poisonings in humans by dimethylmercury have been reported.

Five fatalities involving 2 scientists and 3 technicians exposed to dimethylmercury have occurred in chemical research laboratories. Subjects were exposed to dimethylmercury transdermally while "handling" the mercuric compound or via inhaling the highly volatile vapors. Although these accidental poisonings represent acute exposures, the delayed onset of neurological symptoms post exposure and rapid demise thereafter, provides information to the highly toxic nature of this substance.

A fatal accidental poisoning occurred when a 48 year-old research chemist spilled several drops of liquid dimethylmercury onto the dorsum of her gloved hand while working under a ventilated fume hood in the laboratory (Nierenberg et al., 1998; Siegler et al., 1999). Five months later, and five days prior to hospital admission, the patient developed deterioration in balance, gait, and speech. In the preceding two months, she had lost 6.8 kg (15 lb) and experienced brief episodes of nausea, diarrhea, and abdominal discomfort. Initial medical evaluation showed moderate upper-extremity dysmetria, dystaxic handwriting, dysarthria, and a broad-based gait. Routine laboratory tests were normal and analyses of cerebrospinal fluid reported clear fluid, protein concentration of 42 mg/dl, and no cells. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head were normal except for the incidental finding of a probable menigioma, 1 cm in diameter. A preliminary whole blood mercury level was 4,000 μ/L (normal range 1 to 10 μ/L) collected 162 days after dimethylmercury exposure. The original body burden was estimated to be 1,344 mg of mercury. Her condition worsened in subsequent days; she described tingling in her fingers, brief flashes of light in her eyes, and soft background noise in her ears that progressed to marked constriction of visual fields and deafness. The patient lapsed into a coma 22 days from presentation of symptoms and died 4 months later, 298 days after dimethylmercury exposure. The investigators attributed this accidental exposure to both transdermal absorption of liquid dimethylmercury (given the lack of protection provided by the disposable latex gloves) and inhalation of vapors (even though the work was conducted under a fume hood).

Upon gross examination, the areas of the brain most profoundly affected by dimethylmercury poisoning were the cerebellum and visual cortex (Nierenberg et al., 1998). Microscopic evaluation showed extensive neuronal loss and gliosis bilaterally within the primary visual and auditory cortices, with milder loss of neurons and gliosis in the motor and sensory cortices. There was widespread loss of cerebellar granular-cell neurons, Purkinje cells, and basket-cell neurons, with evidence of loss of parallel fibers in the molecular layer. Bergmann gliosis was well-developed and widespread.

The only previous report of neuropathology of dimethylmercury poisoning was by Pezderová et al. (1974, as cited in Siegler et al., 1999), who reported the autopsy findings of a 28-year old chemist who had prepared 6000 grams of dimethylmercury over a 3 month period. Additional exposure information was not provided. Neuropathologic damage included massive Purkinje cell loss, temporal lobe damage, and slight degenerative changes of the granular layer, but no changes in the cerebellar white matter.

Edwards (1865, 1866, as cited in Hunter et al., 1940) reported the poisoning of 3 laboratory technicians exposed to dimethylmercury while engaged in research. The route of exposure was not provided, but is assumed to be primarily via inhalation with some dermal exposure indicated for the second fatality. Two of the three technicians died. The first case, a 30-year old male, had been exposed to dimethylmercury for 3 months, when he began to

complain of numbness of the hands, deafness, poor vision, and sore gums. Symptoms exhibited were described as “slow and dull in manner, unsteady in gait, and inability to stand without support." His condition deteriorated rapidly, including restlessness, unresponsiveness to questions, urinary incontinence, and coma. The first technician died 2 weeks after reported onset of symptoms. The second technician, a 23-year old male, had worked in the laboratory for 12 months and had reportedly "handled" dimethylmercury 3 months previous for a 2 week period. One month after this exposure, he began complaining of sore gums, salivation, numbness of the feet, hands and tongue, and dimness of vision. The second technician experienced similar symptoms as the first in that he answered questions "only very slowly and with indistinct speech," and was ataxic. After 3 weeks, the man had difficulty in swallowing, was incontinent, unable to speak, and often restless and violent. He remained "in a confused state" until his death due to pneumonia 12 months later. The third technician was described as having similar, less severe symptoms, with eventual recovery.

Animal Studies

No data regarding the toxicity of dimethylmercury to animals following inhalation exposure were located.

Two abstracts were located regarding a study or studies of the toxicity of dimethylmercury following intramuscular administration to rats (Koya and Kudo, 1986; Koya et al., 1986). Both abstracts were presented at the same scientific meeting in Tokyo, Japan, and were very poorly translated; full reports of the studies do not appear to have been published. The first abstract reported that 7 male Wistar rats were treated with 16 daily doses (route of treatment not reported, but specified as intramuscular in the following abstract) of 1 mg Hg/rat/day as dimethylmercury (Koya and Kudo, 1986). Following treatment, the rats were observed for 2 to 13 months. Neurological symptoms included ataxic gait, tremor, hypermetria, and loss of equilibrium. Other effects included crossing of the hind limbs induced by holding the rat upside down, twisting of the body, stretched knee and ankle junction, and raised and stiff tail. Muscle atrophy and increased length of the hind limb claws were also reported. Examination of the brain after sacrifice revealed a lesion described as focal calcification in the rostral vermis of the cerebellum in the middle to basal part of the granular layer. The authors attributed the ataxia in the rats to dimethylmercury-induced damage in this area of the brain. The second abstract by the same authors describes a study essentially identical in protocol, and specifies the route of administration as intramuscular injection (Koya et al., 1986). This abstract mentions an ataxic gait, but focuses on histopathological findings. The brain lesions were as reported by Koya and Kudo (1986): focal calcification in the rostral vermis of the cerebellum in the middle to basal part of the granular layer. However, additional details were reported regarding the exact location of the damage and the size of the calcified deposits. In addition, degeneration of the spino-cerebellar and sensory tracts, and peripheral nerves was reported, with this damage possibly occurring before that observed in the brain (Koya et al., 1986).

In a more recent study from the same laboratory, Mori et al. (2000) administered 5 mg/kg of dimethylmercury daily via intramuscular injection for 12 consecutive days to 20 adult female Wistar rats, of which two were selected for sacrifice on each of days 1, 4, 7, 10, 12, 24, 32, 49, 100 and 140 post treatment. Of the total three control rats treated with sesame oil, one was sacrificed on each of days 7, 24, and 100. On day 4, pyknotic neurons were found in the dorsal root ganglia, cerebellar cortex, cerebral cortex and thalamus of treated rats. On day 10, necrotic neurons were also found in the dorsal caudate nucleus, putamen and anterior horn of the spinal cord. Neurohistological examination identified widespread calcium deposition in the nervous system of treated rats as early as 4 days post-treatment. Behavioral observations in treated rats were hind limbs that showed flexion and/or crossing on day 4, and from day 14, ataxic gait that worsened over time.

No information or toxicological studies regarding the reproductive or developmental effects of dimethylmercury were located.

Other Studies

Oyama et al. (1998) compared the reactivity of methylmercury, methylmercury conjugated to L-cysteine, and dimethylmercury *in vitro* via flow cytometry methods. Reactivity was measured by changes in intracellular calcium concentrations indicative of cell viability in rat cerebellar neurons dissected from 10 to 14 day old Wistar rats treated with respective mercurial compounds. Intracellular calcium was released from treated cerebellar neurons by methylmercury and to a lesser extent by methylmercury-cysteine conjugate, but not by dimethylmercury.

Aggregating cell cultures of fetal rat telencephalon treated continuously with dimethylmercury preferentially affected the mature cells compared to immature cells by measurement of enzymatic activities and change in total protein content (Monnet-Tschudi et al., 1993). Dimethylmercury (10^{-6} M) preferentially affected the differentiated cells from the aggregating cell cultures during the range of culture days 24 to 34 (period of advanced development), producing a 30% reduction in 2' 3' -cyclic nucleotide 3'-phosphohyrolase (CNP) activity. In the immature cultures, days 5 to 14 (period of cell proliferation and early differentiation), dimethylmercury treatment (10^{-7} to 10^{-8}) resulted in an approximate 60% increase in CNP activity. Selective changes in the mature (fetal rat) cultures suggests dimethylmercury interferes with neurological development at more advanced stages.

Östland (1969; cited in Nierenberg et al., 1998) reported on the metabolism of methylmercury and dimethylmercury in mice. Results indicated that dimethylmercury does not enter the brain until metabolized over a period of days to monomethylmercury, which is capable of binding to cellular proteins.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR DIMETHYLMERCURY

The inhalation data base for dimethylmercury is inadequate for p-RfC derivation. No subchronic or chronic data examining effects of inhalation exposure to dimethylmercury in animals or humans were located.

Derivation of a p-RfC for dimethylmercury by analogy to methylmercury was considered, but no RfC for methylmercury is available on IRIS (U.S. EPA, 2003).

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12-1-04

Provisional Peer Reviewed Toxicity Values for

Dimethylmercury
(CASRN 593-74-8)

Derivation of a Carcinogenicity Assessment

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

Acronyms and Abbreviations

bw	body weight
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

PROVISIONAL PEER REVIEWED TOXICITY VALUE FOR DIMETHYLMERCURY (CASRN 593-74-8)
Derivation of a Carcinogenicity Assessment

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

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.

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Questions Regarding PPRTVs

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INTRODUCTION

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humans (Group 2B), based on evidence that all methylmercury compounds are similar with regard to absorption, distribution, metabolism, excretion, genotoxicity, and other forms of toxicity. Neither NTP (2003) nor WHO (2003) have produced documents specific to dimethylmercury. Literature searches of the following databases were conducted in 1993 for dimethylmercury: TOXLIT (1985-1993), TOXLINE (1985-1993), HSDB, RTECS, TSCATS, and CHEMID. Update literature searches were conducted from 1993 through October 2004: TOXLINE (supplemented with BIOSIS and NTIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS.

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REVIEW OF THE PERTINENT DATA

Human Studies

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

Animal Studies

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

Other Studies

Dimethylmercury induced chromosomal aberrations and aneuploidy in cultured human lymphocytes (Betti et al., 1992), and DNA damage (DNA fragmentation measured via single-cell microgel electrophoresis) in human lymphocytes, rat lymphocytes, and rat gastric mucosa cells *in vitro* (Betti et al., 1993). Dimethylmercury also induced chromosomal aberrations in cultured CHO cells, but did not potentiate the clastogenic effects of mitomycin c, cisplatin, 4-nitroquinoline 1-oxide, or methyl methanesulfonate in this test system (Yamada et al., 1993).

In vivo and *in vitro* studies examining the effects of mercury on meiosis (Jagiello and Lin, 1973) were conducted in the ova removed from random bred Swiss/Webster female mice. Ova were treated *in vitro* with 0, 2.5, 5, 10, or 25 µg/ml of dimethylmercury for 5 hours to obtain first metaphase meiotic figures or 14 hours to obtain second metaphase with polar body. An increased number of abnormal divisions occurred in the second metaphase in cultures containing 10 µg dimethylmercury; no cell division occurred in cultures with 25 µg. Treatment of 6 female mice via intravenous administration of 1400 µg Hg/g body weight of dimethylmercury did not result in an increased number of abnormalities in either stage of meiosis in the ova removed from donor females, cultured, and examined for meiotic figures 24 hours post treatment. The U.S. EPA's Gene-Tox Program (U.S. EPA, 1981) Work Group evaluated the findings of Jagiello and Lin (1973) and concluded that they were qualitatively negative for clastogenic effects (Preston et al., 1981).

A dominant lethal assay was conducted in 20 random bred Swiss male mice injected intraperitoneally with 50 mg dimethylmercury/kg;10 males were injected with the vehicle, petroleum, and served as controls (Varma et al., 1974). An increased mutagenicity index (MI) occurred in the post-meiotic stages of spermatogenesis, indicative of genetic damage to spermatozoa and spermatids; this resulted in reduced fertility and decreased number of implants per pregnancy. The Gene-Tox Work Group on the Dominant Lethal Assay (U.S. EPA, 1985) evaluated the experimental protocol for *in vivo* mammalian genotoxicity studies based on established criteria. The Work Group concluded the findings by Varma et al. (1974) indicate a borderline response (considered positive in the estimation of correlation between mutagenicity and carcinogenicity) (Green et al., 1985).

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

No studies examining the carcinogenic potential of dimethylmercury in humans or animals were located. Limited genotoxicity data indicate dimethylmercury can produce DNA damage and chromosomal aberrations *in vitro*, but these effects have not been demonstrated *in vivo*. As the available data are insufficient to assess carcinogenic potential in animals or humans, they are consistent with the hazard descriptor, "*inadequate information to assess carcinogenic potential*," as specified by the proposed U.S. EPA (1999) Guidelines for Carcinogen Risk Assessment. It should be noted that methylmercury was determined to be a possible human carcinogen in the Mercury Study Report to Congress (U.S. EPA, 1997b).

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

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

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