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Provisional Peer Reviewed Toxicity Values for

Mercuric sulfide
(CASRN 1344-48-5)

Derivation of a Chronic Oral RfD

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 Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

An RfD for mercuric sulfide (HgS) is not available on IRIS (U.S. EPA, 2002) or in the HEAST (U.S. EPA, 1997a). Although mercuric sulfide is not included on IRIS, elemental mercury and mercuric chloride are listed (U.S. EPA, 2001). IRIS reports an RfD of 0.0003 mg/kg-day for mercuric chloride based on immuno-glomerulonephritis in rats exposed by oral gavage to mercuric chloride. The source document for this assessment was a Drinking Water Criteria Document for Inorganic Mercury (U.S. EPA, 1988). This RfD value is reported for inorganic mercury in the Drinking Water Standards and Health Advisories list; however, no drinking water standards or health advisories have been established specifically for mercuric sulfide (U.S. EPA, 2000). An RfD for elemental mercury is not available on IRIS (U.S. EPA, 2001). ATSDR (1999) derived acute and intermediate-duration oral MRLs of 0.007 and 0.002

mg mercury/kg-day, respectively, based on effects in rats exposed to mercuric chloride by oral gavage; however no MRLs were derived based on exposures to mercuric sulfide.

The following sources were also consulted for relevant information: CARA list (U.S. EPA, 1991, 1994), Mercury Study Report to Congress (U.S. EPA, 1997b), Health Issue Assessment Document for Mercury (U.S. EPA, 1984a), Health Effects Assessment (HEA) for Mercury (U.S. EPA, 1984b), NTP (2001), IARC (1993, 2001), and WHO (WHO, 1991). Computer searches of TOXLINE (1965-1993), TOXLIT (1965-1993), NAPRALERT (through 1993), CHEM ID, RTECS, HSDB, MBASE (1974-1993), and TSCATS were conducted in 1993. Update searches of the following databases were conducted from 1993 to August 2001 for relevant studies: TOXLINE, MEDLINE, TSCATS, GENETOX, HSDB, CANCERLIT, CCRIS, RTECS, EMIC/EMICBACK and DART/ETICBACK.

REVIEW OF PERTINENT LITERATURE

The toxicity of mercuric salts appears to be related to cationic mercury (Hg^{2+}), while solubility and tissue distribution is dependent on the valency state and anionic component of the mercuric compound (Goyer, 1996). Distribution data from parallel experiments with mercuric chloride and mercuric sulfide suggest that mercury, administered as mercuric sulfide is less absorbed than when given as mercuric chloride (Ryan et al., 1991; Sin et al., 1983). For these reasons, mercuric chloride is regarded as being more toxic than mercuric sulfide. Irrespective of the route of exposure, the kidney is the critical organ of injury after exposure to mercuric chloride (Goyer, 1996). High doses of mercuric chloride are directly toxic to renal tubular lining cells, while chronic low-dose exposure may induce an immunologic glomerular disease (Goyer, 1996; Henry et al., 1988). Pharmacokinetic studies suggested that once mercuric sulfide has been absorbed, mercury tends to accumulate in the kidney, liver, and brain (Ryan et al., 1991; Sin et al., 1990; Yeoh et al., 1986, 1989). These data suggest that exposure to mercuric sulfide may cause renal effects similar to those observed with mercuric chloride exposure; however, there are no experimental data to support this contention.

Human Studies

The only information regarding the toxic effects of mercuric sulfide in humans comes from case studies of patients (1 adult and 1 child) who ingested patent medicines containing both mercuric sulfide and mercurous chloride (Hg_2Cl_2) (Kang-Yum and Oransky, 1992). Drooling, dysphagia, irregular arm movements, impaired gait, and convulsions were effects noted following ingestion. The study provided limited exposure data. Blood mercury levels of 39-2800 µg/L in 24 hr urine were reported. Definitive conclusions regarding the connection between these effects and exposure to mercuric sulfide in these patients cannot be made due to concurrent exposure to multiple mercury compounds.

Animal Studies

Data from a pharmacokinetic study demonstrated that exposure to mercuric sulfide or mercuric chloride resulted in a greater accumulation of mercury in the kidneys than in the liver or the brain (Ryan et al., 1991). In this study, groups of 3-9 female Swiss albino mice received a single oral dose of 6 or 324 mg mercury/kg body weight as mercuric sulfide or a single oral dose of 0.6 or 6 mg mercury/kg body weight as mercuric chloride in distilled water. At 24 hours, the mice were sacrificed and tissue samples were analyzed for mercury. Greater concentrations of mercury were recovered in blood, brain, liver, and kidneys in mercuric chloride-treated mice than in mercuric sulfide-treated mice and in controls; this included comparison of the low dose of mercuric chloride with the high dose of mercuric sulfide.

In another animal study, groups of 6 young adult female Swiss albino mice received doses of 6 mg mercury/kg body weight as mercuric chloride or mercuric sulfide once a day for 10 days via oral gavage (Sin et al., 1990). A significantly higher ($p<0.05$) concentration of mercury accumulated in the liver, kidney, and brain of mercuric chloride-treated mice than in mercuric sulfide-treated mice. In both mercuric chloride- and sulfide-treated groups, liver glutathione (GSH) content was slightly, but not significantly lower than controls; whereas kidney GSH content in mercuric chloride-treated mice, but not mercuric sulfide-treated mice, was significantly higher than controls. In mercuric chloride-treated mice, brain GSH content was slightly, but not significantly higher than controls, while a level comparable to controls was measured in mercuric sulfide-treated mice. Because GSH is known to be involved in the metabolism and detoxification of endogenous and exogenous substances, plasma concentrations of thyroid hormones (T_4 and T_3) were measured. Plasma thyroid hormone T_4 and T_3 levels were significantly lower ($p<0.05$) in mercuric chloride-treated mice than in the controls, whereas only the T_3 level was significantly reduced in mercuric sulfide-treated mice. A previous study by Sin et al. (1989), demonstrated that a significantly ($p<0.01$) greater concentration of mercury was recovered in the kidneys of mercuric chloride-treated mice than in the mercuric sulfide-treated mice and the concentrations of mercury at 3, 6, 24 and 72 h after treatment in the kidney were greater than in the liver. In this study, groups of 4 adult female Swiss albino mice were given 6 or 324 mg mercury/kg-day for 4 days by oral gavage as mercuric sulfide or 6 mg mercury/kg-day as mercuric chloride. Renal GSH levels were also significantly ($p<0.01$) elevated in mercuric chloride-fed mice, as well as in mice fed only the highest dose of mercuric sulfide.

Revis et al. (1990) reported that mice absorbed 0.4% and 2.1% of a single dose of mercuric sulfide and mercuric chloride, respectively. A single dose of 0.3 mL of a slurry containing 1E-5 distintegrations per minute (dpm) of ^{203}mercuric chloride or ^{203}mercuric sulfide was administered by oral gavage to groups of 5 male mice. Fecal samples were collected for 10 days and the mice were then sacrificed and the intestinal tract removed. The amount of radioactive mercury absorbed was calculated as the difference between the amount intubated and the amount measured in the feces and intestinal tract. However, there was no account of mercury

in other tissues, or biliary excretion, a known homeostatic mechanism for Hg (Goyer, 1996). The interpretation of the authors that 0.4% and 2.1% of mercuric sulfide and mercuric chloride, respectively, was absorbed appears to be incorrect for the following reasons. The study design was inappropriate for determining absorption of a chemical such as mercury, some of which may be distributed to the intestinal mucosa or eliminated by the biliary route and excreted into the feces following absorption (ATSDR, 1999; U.S. EPA, 1988; WHO, 1991). In addition, the data do not show significant differences attributable to absorption between compounds. For mercuric sulfide, for example, the total mercury intubated was 336,580 ± 39,304 dpm (mean ± SD), and the total mercury in feces and intestinal tract was 335,276 ± 46,498 dpm. From this set of values the 0.4% absorption was calculated. However, because the standard deviations are greater than 10% of the mean values, a 0.4% difference between means is statistically meaningless. The same argument applies to the absorption fraction calculated from mercuric chloride measurements. For mercuric chloride, the total mercury intubated was 441,220 ± 68,185 dpm and the total mercury in feces and intestinal tract was 432,915 ± 49,113 dpm. These results indicate that not only was there no meaningful difference between the sulfide and chloride, but that the data provide no evidence of absorption of either salt, as differences between 0.4%, 2.1% and 0% are not statistically significant.

Mice were treated with either 0.1 or 1.0 g mercuric sulfide/kg-day or 0.2, 2.0 or 10 mg methyl-mercury (MeHg)/kg-day by gastric gavage for 7 consecutive days (Chuu et al., 2001a). Analysis of auditory brainstem response (ABR) indicated that significant elevation of the physiological hearing threshold, as well as significant prolongation of interwave latency I-V, was observed for MeHg (2.0 and 0.2 mg/kg-day) or the high-dose mercuric sulfide-treated mice. Further, both MeHg- and mercuric sulfide-treated animals demonstrated a significant prolongation of interwave latency I-V that increased with an increasing mean blood-Hg level. The oto-neurotoxicity of MeHg (2.0 mg/kg-day) persisted to at least 11 weeks subsequent to the cessation of its administration. The toxic effect of mercuric sulfide, however, disappeared completely 5 weeks subsequent to the cessation of its administration. These results suggest a correlation between the Hg-elicited hearing dysfunction and the availability of mercury in brain tissue. Both inhibition of Na^+/K^+-ATPase activity and overproduction of nitric oxide in the brainstem are consistent with an analysis of the physiological hearing threshold and latencies of ABR waveform at all time points throughout the experimental process. The authors proposed that high-dose mercuric sulfide or MeHg intoxication is associated with a decrease in functional Na^+/K^+-ATPase activity in the brainstem of affected animals, presumably arising via excessive nitric oxide production, and suggesting that brainstem damage may play a role in mercury-induced hearing loss. However, in another study in which nitric oxide synthase (NOS) activity in rat brain homogenates was monitored in the presence and absence of five mercury salts, all five salts inhibited NOS with sensitivities in the following order: MeHg > mercuric nitrate> mercuric iodide > mercuric oxide >mercuric chloride (Desaiah and Roa, 1994).

Chuu et al. (2001b) assessed the neurobehavioral toxicities of three mercurial compounds, MeHg, mercuric sulfide and cinnabar (naturally occurring mercuric sulfide). These compounds were administered intraperitoneally (MeHg, 2 mg/ kg-day) or orally (mercuric sulfide and cinnabar, 1.0 g/kg-day) to male rats for 13 consecutive days with assays conducted during or after discontinuous administration at 1 h, 2, 8 and 33 weeks. Neurotoxicity was assessed based on the active avoidance response and locomotor activity. The results obtained showed that MeHg and cinnabar prominently and irreversibly caused a decrease in body weight, prolongation of latency for escape from electric shock, a decrease in the percentage for the conditioned avoidance response (CAR) to electric shock, impairment of spontaneous locomotion, and inhibition of Na^+/K^+-ATPase activity of the cerebral cortex. Mercuric sulfide reversibly inhibited spontaneous locomotion and Na^+/K^+-ATPase activity, and significantly decreased the latency of escape from electric shock during the administration period, which lasted for 33 weeks after discontinuous administration. Pretreatment with arecoline (a cholinergic receptor agonist) but not fipexide (a dopaminergic receptor agonist) significantly shortened the prolonged latency for escape caused by MeHg and cinnabar, suggesting that the deficit in the active avoidance response was perhaps, at least in part, mediated by the dysfunction of the cholinergic rather than the dopaminergic system. Determination of the Hg levels of the whole blood and cerebral cortex revealed that the tissue mercury content was highly correlated with the degree of neurobehavioral toxicity of these Hg compounds. These findings suggest that insoluble mercuric sulfide and cinnabar can be absorbed from the G-I tract and distributed to the brain. The possibility that contamination due to other minerals in the cinnabar was responsible for the greater neurotoxic effects compared to mercuric sulfide was to be investigated in future studies.

The effects of mercury on renal and hepatic UDP-glucuronyltransferase (UDPGT) activity were studied in mice (Tan et al., 1990). Young adult female Swiss-mice were administered 6 mg Hg^{2+}/kg-day as mercuric chloride or mercuric sulfide orally for 10 days. They were killed 24 hours after the last dose and the livers and kidneys were removed and weighed and assayed for mercury and UDPGT. Renal and hepatic mercury concentrations and UDPGT activity in mercuric sulfide-treated mice were not significantly different from those of the controls; however they were significantly increased in mice given mercuric chloride. The maximum velocities of glucuronidation were significantly increased in mercuric chloride-treated mice. The authors concluded that the increase in renal UDPGT activity induced by mercuric chloride appears to be associated with increased deposition of mercury in renal tissue. The biological significance of the increase in renal UDPGT activity is unknown. The lack of an effect of mercuric sulfide on renal UDPGT may reflect poor absorption due to its low solubility.

In one study, groups of 20 young female Swiss albino mice were given a dose of 0 or 6 μg Hg^{2+}/g body weight (7 mg mercuric sulfide/kg body weight) in distilled water once a day for 4 weeks by oral gavage (Sin and Teh, 1992). Five mice from each group were sacrificed at 1, 2, 3, and 4 week intervals after the last treatment. Mercuric sulfide caused a decrease in plasma T_3 and T_4 levels when data were compared with controls. The decrease in T_4 levels was statistically

significant ($p<0.05$) at weeks 1 and 4. Body weights of the test group were comparable to those of the control group at the various time intervals. GSH levels in the kidney and liver from mercuric sulfide-treated mice were not significantly different from the controls. Despite this, GSH levels in the brain of mercuric sulfide-treated mice were significantly elevated at week 2 ($p<0.05$) and week 3 ($p<0.01$). Analysis of kidney, liver, and brain tissues revealed very low (not statistically significantly elevated) levels of mercury. The authors proposed that although low levels of mercuric sulfide were absorbed, this small quantity of mercuric sulfide might interfere with the normal activities of thyroidal cells or the hypothalamus-pituitary axis.

In another study, groups of 6-12 female Swiss albino mice were fed water containing 0 or 100 ppm of mercuric sulfide (0.23 mg Hg^{2+}/kg-day) or mercuric chloride for 55 days (Ryan et al., 1991). Mercuric chloride-fed mice showed significantly ($p<0.05$) higher mercury levels in the brain, lymphoidal tissue, liver, and spleen as compared to both the control and the mercuric sulfide-fed mice. The mercury content of these organs and tissues from mercuric sulfide-treated mice were comparable to controls. At 50 days, the antibody production of mercuric sulfide-fed mice in response to sheep red blood cells (SRBC) was significantly ($p<0.05$) enhanced compared to both control and the mercuric chloride-fed mice. Mercuric sulfide-fed mice also had significantly ($p<0.05$) higher white blood cell (WBC) counts compared to other treatment groups. However, RBC, hemoglobin, body weight, and food consumption determinations were comparable between the different treatment groups.

A chronic oral exposure study (Revis et al., 1989) was located that examined the effects of soil contaminated with mercury. However, in addition to mercury, the soil was contaminated with other metals. In this study, 30 groups of 40 male and 40 female Swiss mice received diets containing soil contaminated with selenium, zinc, arsenic, lead, cadmium, and mercury for 6, 12, or 20 months. The authors of this study did not report the use of a control group. The metals-contaminated soil and sediment were obtained from 30 different sites and added individually to Purina mouse chow to give a total concentration of 5% soil or sediment per diet. The mercury compound distribution of soil samples consisted of 88% mercuric sulfide, 7% elemental mercury, and 0.01% organic mercury. The concentration of mercury in soil ranged from 0.59-1799 ppm. The investigators measured the daily intake of metals-contaminated soil and determined that male mice received mercury doses in the range of 0.11-392 μg Hg^{2+}/day and that female mice received 0.07-282 μg Hg^{2+}/day. Five to 10 animals were sacrificed at 6, 12, or 20 months and a gross necropsy and histopathological examination of the kidneys were performed. Body weights were determined and a swim test was used to examine neurological effects. Data showed that the experimental diets did not affect mortality, the growth of the mice, or liver and kidney weights. Exposure to metals-contaminated soil appeared to have caused only minor proximal tubular lesions in the kidney. However, because no controls were used in this study, it is not known if proximal tubule lesions were treatment-related. Metals-contaminated soil did not appear to cause neurological effects, as determined by the swim test. However, the authors recognized that the swim test is not capable of detecting subtle neurological effects.

In a related experiment, developmental toxicity of the metals-contaminated soil was assessed (Revis et al., 1989). Three pairs of Swiss mice from the above study exposed for 6 months were time-mated. The litter size was determined at 24 and 96 hours postdelivery. Exposure had no effect on litter size. Changes in the number of digits of the hand and foot, apparent neurological effects, and cleft palate were not observed in offspring from soil-exposed dams. As noted above, there were no controls.

No conclusions regarding the connection between effects or lack of effects noted and exposure to mercuric sulfide can be made from these chronic studies (Revis et al., 1989) due to concurrent exposure to multiple metal compounds.

Other Studies

Mercuric chloride was found to elicit an autoantibody response that predominantly targets fibrillarin, a protein component of many small nucleolar ribonucleoproteins particles (Pollard et al., 1997). Addition of mercuric chloride to isolated rat liver nuclei resulted in aberrant SDS-PAGE migration of fibrillarin, but not other nuclear autoantigens. Interaction of mercury with the two cysteines in the fibrillarin sequence was suggested by the differential sensitivity of the mercuric chloride-induced modification of fibrillarin to 2-methoxyethanol, iodoacetamide, and hydrogen peroxide, and confirmed by mutation of the cysteines to alanines, which abolished the aberrant migration of fibrillarin in the presence of mercuric chloride. Immunoprecipitation by anti-fibrillarin autoantibodies suggested that unmodified fibrillarin is a B cell antigen, whereas mercury-modified fibrillarin is the source of T cell antigenicity. These observations suggest a plausible mechanism of toxicity for mercury-induced immunological effects (immuno-glomerulonephritis) in rats orally gavaged with mercuric chloride (Andres, 1984).

PROVISIONAL RfD FOR MERCURIC SULFIDE

While altered plasma T_4 levels and brain GSH levels were measured in mice treated by oral gavage with mercuric sulfide (Sin and Teh, 1992), the mechanisms and significance of the alterations remain unknown, and therefore these data are inadequate bases for derivation of a p-RfD for mercuric sulfide. In the study by Ryan et al., (1991), the significance of the elevated WBC count in relation to mercuric sulfide exposure is unknown, and it also not known whether the heightened WBC count is responsible for the increased antibody production. As stated previously, no conclusions regarding the toxicity of mercuric sulfide can be made from the study by Revis et al. (1989) due to concurrent exposure to multiple metal compounds. The lack of data in humans and of adequate subchronic or chronic oral data in animals precludes derivation of a provisional RfD for mercuric sulfide.

Since data are inadequate for mercuric sulfide for derivation of a p-RfD, consideration was given to the similarity of mercuric sulfide to other inorganic mercury salts such that a p-RfD might be derived based on common properties of inorganic species, or by analogy to another inorganic mercury salt, such as mercuric chloride. Data from several animal studies demonstrated that mercuric chloride is a more bioavailable salt than mercuric sulfide (U.S. EPA, 1993). Additional animal studies have also demonstrated that oral administration of mercuric chloride resulted in higher concentrations of mercury in the kidney than when mercuric sulfide was administered (Sin et al., 1983, 1989, 1990). These data suggest that a larger oral dose of mercuric sulfide compared to mercuric chloride may be required to produce a similar toxic effect in the kidney. Therefore, based on the limited available pharmacokinetic data for mercuric sulfide, the RfD for mercuric chloride (0.0003 mg/kg-day) could be considered protective for mercuric sulfide. It is likely that the actual RfD for mercuric sulfide would be higher by a factor of at least 10 when compared to that of mercuric chloride, based on their relative bioavailability.

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Provisional Peer Reviewed Toxicity Values for

Mercuric sulfide
(CASRN 1344-48-5)

Derivation of a Chronic Inhalation RfC

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

09-25-02

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR MERCURIC SULFIDE (CASRN 1344-48-5)
Derivation of a Chronic Inhalation RfC

Background

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

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

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

An RfC for mercuric sulfide (HgS) is not available on IRIS (U.S. EPA, 2002) or in the HEAST (U.S. EPA, 1997a). Although mercuric sulfide is not included on IRIS, elemental mercury and mercuric chloride are listed (U.S. EPA, 2002). IRIS reports an RfC of 0.3 μg Hg/m^3 for elemental mercury based on exposures in humans to metallic mercury vapor. An RfC for mercuric chloride is not available on IRIS (U.S. EPA, 2002). ATSDR (1999) derived a chronic inhalation MRL of 0.2 μg Hg/m^3 for metallic mercury; however no MRLs were derived based on exposures to mercuric sulfide. ACGIH (2001), NIOSH (2001), and OSHA (2001) have not assessed the toxicity of mercuric sulfide; however these agencies report exposure limits for inorganic mercury based on studies of mercuric chloride.

The following sources were also consulted for relevant information: CARA list (U.S. EPA, 1991, 1994), Mercury Study Report to Congress (U.S. EPA, 1997b), Health Issue Assessment Document for Mercury (U.S. EPA, 1984a), Health Effects Assessment (HEA) for Mercury (U.S. EPA, 1984b), NTP (2001), IARC (1993, 2001), and WHO (1991). Computer searches of TOXLINE (1965-1993), TOXLIT (1965-1993), NAPRALERT (through 1993), CHEM ID, RTECS, HSDB, MBASE (1974-1993), and TSCATS were conducted in 1993. Update searches of the following databases were conducted from 1993 to August 2001 for relevant studies: TOXLINE, MEDLINE, TSCATS, GENETOX, HSDB, CANCERLIT, CCRIS, RTECS, EMIC/EMICBACK and DART/ETICBACK.

REVIEW OF PERTINENT LITERATURE

Human Studies

While data exist on inhalation exposure to metallic mercury vapor, the available reviews (U.S. EPA, 1984a,b, 1997b; ATSDR, 1999; IARC, 1993; WHO, 1991) found no toxicity studies of mercuric sulfide or other inorganic mercury salts in humans following inhalation exposure. The literature search identified no new studies regarding toxicity of mercuric sulfide in humans following inhalation exposure.

Animal Studies

The available reviews (U.S. EPA, 1984a,b, 1997b; ATSDR, 1999; IARC, 1993; WHO, 1991) found no toxicity studies of mercuric sulfide in animals following inhalation exposure. The literature search identified no new studies regarding the toxicity of mercuric sulfide in animals following inhalation exposure.

FEASIBILITY OF DERIVING A PROVISIONAL RfC FOR MERCURIC SULFIDE

The lack of data in humans and in animals following inhalation exposure precludes derivation of a provisional RfC for mercuric sulfide.

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Provisional Peer Reviewed Toxicity Values for

Mercuric sulfide
(CASRN 1344-48-5)

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
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MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
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MRL	minimal risk level

MTD	maximum tolerated dose
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NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
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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

09-25-02

PROVISIONAL PEER REVIEWED TOXICITY VALUES
MERCURIC SULFIDE (CASRN 1344-48-5)
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:

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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.

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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 cancer assessment for mercuric sulfide (HgS) is not available on IRIS (U.S. EPA, 2002) or in the HEAST (U.S. EPA, 1997a). Although mercuric sulfide is not included on IRIS, elemental mercury and mercuric chloride are listed (U.S. EPA, 2002). IRIS classifies elemental mercury in cancer weight-of-evidence Group D (not classifiable as to human carcinogenicity) based on inadequate human and animal data, and mercuric chloride in Group C (possible human carcinogen) based on limited animal data showing equivocal evidence for treatment-related tumors in the forestomach, thyroid and kidney in some rodent studies. Quantitative estimates of cancer risk were not derived for mercuric chloride (U.S. EPA, 2002). A Group D classification is reported for inorganic mercury in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2001). Neither IARC (1993) nor ACGIH (2001) have assessed the carcinogenicity of mercuric sulfide. Based on inadequate evidence in humans for the carcinogenicity of mercury

and mercury compounds, inadequate evidence in experimental animals for the carcinogenicity of metallic mercury, and limited evidence in experimental animals for the carcinogenicity of mercuric chloride, IARC (1993) has determined that metallic mercury and inorganic mercury compounds are not classifiable as to their carcinogenicity to humans (Group 3). ACGIH (2001) has assigned elemental and inorganic forms of mercury to carcinogenicity category A4-not classifiable as a human carcinogen.

The following sources were also consulted for relevant information: CARA list (U.S. EPA, 1991, 1994), Mercury Study Report to Congress (U.S. EPA, 1997b), Drinking Water Criteria Document for Inorganic Mercury (U.S. EPA, 1988), Health Issue Assessment Document for Mercury (U.S. EPA, 1984a), Health Effects Assessment (HEA) for Mercury (U.S. EPA, 1984b), Toxicological Profile for Mercury (ATSDR, 1999), NTP (2001), and WHO (WHO, 1991). Computer searches of TOXLINE (1965-1993), TOXLIT (1965-1993), NAPRALERT (through 1993), CHEM ID, RTECS, HSDB, MBASE (1974-1993), and TSCATS were conducted in 1993. Update searches of the following databases were conducted from 1993 to August 2001 for relevant studies: TOXLINE, MEDLINE, TSCATS, GENETOX, HSDB, CANCERLIT, CCRIS, RTECS, EMIC/EMICBACK and DART/ETICBACK.

REVIEW OF PERTINENT LITERATURE

Human Studies

The available reviews (U.S. EPA, 1984a,b, 1988, 1997b; ATSDR, 1999; IARC, 1993; WHO, 1991) found no studies regarding the carcinogenicity of mercuric sulfide in humans. The literature search identified no new studies regarding the carcinogenicity of mercuric sulfide in humans.

Animal Studies

While limited data exist for the carcinogenicity of mercuric chloride in animals (U.S. EPA, 1997b, 2001a), the available reviews (U.S. EPA, 1984a,b, 1988, 1997b; ATSDR, 1999; IARC, 1993; WHO, 1991) found no studies regarding the carcinogenicity of mercuric sulfide in animals. The literature search identified no new studies regarding the carcinogenicity of mercuric sulfide in animals.

Other Studies

While data for genotoxicity of elemental mercury and mercuric chloride exist, no studies were located regarding the genotoxicity of mercuric sulfide.

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

No data were located regarding the carcinogenicity of mercuric sulfide in humans or animals. Following the U.S. EPA (1999) proposed guidelines for carcinogen risk assessment, the data for mercuric sulfide are inadequate for an assessment of human carcinogenic potential.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

The lack of cancer data precludes derivation of a provisional oral slope factor or a provisional inhalation unit risk for mercuric sulfide.

REFERENCES

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

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IARC (International Agency for Research on Cancer). 1993. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry Chemical, Environmental and Experimental Data, Vol. 58. p. 239.

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