Mercury
Chemical Summaries

Summary memorandum

Chemical evaluation for:
Mercury (CAS# 7439-97-6)

An ATSDR update toxicological profile for mercury was published in 1999. Update searching for additional information on mercury has been performed through July 2005. Update searches were performed for elemental mercury, inorganic mercury (mercuric[II]chloride, mercuric [II]sulfide, mercurous [I]chloride, mercuric[II]acetate), and organic mercury (methylmercuric chloride, dimethyl mercury, phenylmercuric acetate). Relevant studies identified in updated searches were categorized and scored according to ATSDR protocol. Studies that received high scores for each category were retrieved and examined for information that should be considered when assessing the need to update the most recent toxicological profile. The search results are summarized as follows:

- Two epidemiology studies address data needs for reproductive and developmental effects of mercury.
- Several follow-up studies provide information on ongoing prospective studies (Seychelles cohort and Faroe Islands cohort).
- Many studies provide new information on effects of the various mercurial forms in humans.
- Three animal studies address a data need for reproductive toxicity data; one of these studies might impact the current oral acute- and intermediate-duration MRLs for inorganic mercury.
- Some studies address data needs that include levels of mercury in biological media, quantitative data on absorption of mercury, additional PBPK modeling data, and urinary excretion of mercury from amalgam fillings.
- Nine studies present new information on methods for reducing toxicity.

Detailed scoring results and summaries of relevant information for each category are presented below:

Category	Number of Studies Scored	Highest Score
Epidemiology	185	10
Toxicology	122	17
Potential for Human Exposure	329	7
Supplemental Information	274	5
Total	**910**	**39**

Epidemiology

The highest score is 10 points for filling a data need for two studies that address reproductive and developmental effects of mercury.

- Elghany et al. (1998) provides information on reproductive and developmental effects of vapors of metallic mercury in a group of 46 occupationally exposed women. The current profile notes that there is very limited and unreliable information on this particular topic. The study revealed a higher frequency of adverse reproductive/developmental outcomes, especially congenital anomalies, among the women exposed to mercury vapor levels at or substantially lower than 0.6 mg/m^3; no significant differences in the stillbirth or miscarriage rates were noted.
- Itai et al. (2004) provides information on rates of fetal death, stillbirths, and spontaneous abortions among Japanese women living in areas with heavy methylmercury contamination.

The second highest score is 8 for new epidemiology studies that explored associations between mercury and adverse cardiac effects (myocardial infarction, coronary heart disease), hematological parameters, Alzheimer's disease, or hypothyroidism. Five studies received this score.

- Guallar et al. (2002) reported a positive association between toenail mercury level and risk of myocardial infarction in a study of 684 men from eight European countries and Israel with first diagnosis of myocardial infarction, compared to 724 controls selected to represent similar populations.
- Yoshizawa et al. (2002) found no association between total mercury exposure and the risk of coronary heart disease among 33,737 subjects in a nested case-control design study.
- Zabinski et al. (2000) studied a group of 46 workers exposed to mercury vapors for periods between 7 months and 32 years and found that exposure induce changes in the activity of several red cell enzymes as well as in various hematological parameters.
- Saxe et al. (1999) found no significant association of Alzheimer's disease with the number, surface area, or history of having dental amalgam restorations; the study comprised 68 subjects with Alzheimer's disease and 33 control subjects.
- Li et al. (2004) reported three cases of hypothyroidism induced by cosmetics containing mercury. An abstract is not available for this study, which was published in Chinese.

The remaining studies in this category provide confirmatory information.

Toxicology

The highest score is 17 points for an animal study that addresses a data need for reproductive toxicity data for inorganic mercury and might serve as the basis of an intermediate-duration oral MRL that is lower than the current one for inorganic mercury.

- Khan et al. (2004) conducted a follow-up of the Atkinson et al. (2001) study. Male mice were dosed throughout mating and females throughout mating, gestation, and lactation with 0, 0.25, 0.5, or 1.0 mg/kg/day (mercuric chloride) by gavage (0.19, 0.37, 0.74 mg

Hg/kg/day). Fertility indices, gestation, parturition, live birth litter size, survival indices, and implantation efficiency were recorded. The fertility index was significantly reduced in the treated groups. Exposure of mice to mercuric chloride did not affect their litter size. No evidence of mercury induced target organ toxicity was seen in either the clinical pathology parameters or histomorphologic evaluations. However, in treated females, ovary weights were significantly different from controls. There were no histomorphologic or clinical pathology effects induced by mercuric chloride. These results suggested that oral exposure to 0.25-1.00 mg/kg/day of mercuric chloride produced adverse effects on the reproductive performance of mice in the absence of overt mercury toxicity. The LOAEL of 0.25 mg/kg/day dose of mercuric chloride is almost the same as the 0.23 mg/kg/day NOAEL that ATSDR used as basis for deriving an intermediate-duration oral MRL for mercuric chloride. However, the fertility index [(number of females delivering/number of females cohabited) x 100] was significantly lower in all treated groups (44 for controls and 16 in each of the treated groups), which may represent a serious LOAEL.

The second highest score for this category is 9 for two animal studies that address a data need for additional reproductive toxicity data for inorganic mercury.

- Atkinson et al. (2001) conducted a 2-generation reproductive toxicity study in male and female before mating and during cohabitation. Dosing was via gavage 7 days/week. The lowest dose level tested (0.5 mg/kg/day in males and 0.75 mg/kg/day in females; 0.37 mg Hg/kg/day and 0.56 mg Hg/kg/day) caused a significant reduction in the number of pregnancies and fertility index and was the study LOAEL. These doses are very close to the NOAEL of 0.23 mg Hg/kg/day that was used to derive an intermediate-duration oral MRL for mercuric chloride (Dieter et al 1992; NTP 1993), but higher than the LOAEL identified in the study of Khan et al. (2004) that received a score of 17.
- Orisakwe et al. (2001) assessed testicular effects of mercuric chloride in mice exposed to the test compound in the drinking water for 12 weeks. The only dose level tested was 4 ppm in water, which the authors state provided a mercury intake of 0.65 mg/kg (it is assumed that they refer to 0.65 mg Hg/kg/day and not to the total dose for the 12-week dosing period; if the latter were the case, the daily dose of Hg would be approximately 0.007 mg/kg/day). Dosing caused a significant reduction in absolute and relative testes weight, reduced epididymal sperm number, disintegration of spermatocytes from the basement membrane and necrosis.

The third highest score for this category is 6 for two new animal studies.

- Al-Saleh et al. (2003) observed histopathological effects in the liver, kidneys, and brain from mice that received skin applications of a rose skin-lightening cream containing mercury for at various intervals during a period of one month. The severity of the effects increased with increasing the number of applications.
- Ramalingam et al. (2003) assessed the affects of mercuric chloride on levels of circulating hormones (testosterone, luteinizing hormone, follicle stimulating hormone, and prolactin) in mature male albino rats following daily oral administration for 30 days

at dose levels of 0, 0.5 or 1.0 mg/kg/day (0, 0.37, or 0.74 mg Hg/kg/day, respectively).

The fourth highest score is 5 for a study (Herr et al. 2004) that appears to refute findings of neurodevelopmental effects in offspring of laboratory animals exposed to mercury vapors during gestation.

The remaining studies received a score of 2 for confirmatory animal data or studies that employed an exposure route other than inhalation, oral, or dermal routes.

One study that was scored as confirmatory animal data presented information that appeared to demonstrate adverse male reproductive effects at a dose level that is several orders of magnitude lower than the NOAEL of 0.93 mg Hg/kg/day in rats from NTP (1993) that ATSDR used to derive an acute-duration oral MRL for mercuric chloride.

- Nagar and Bhattacharya (2001) described adverse histological effects in the testes from mice exposed to mercuric chloride for 7, 14, or 21 days. Alterations involving the seminiferous tubules, spermatogonia, spermatocytes, spermatids, Sertoli and Leydig cells were already seen after 7 days of treatment. The report states that the mice were administered 0.5 ml/day of a 0.5 ppm (0.5 mg/L) solution of mercuric chloride, which results in a daily intake of 0.00025 mg/day. Assuming that the mice weighed 0.030 kg, the resulting dose would be 0.0000075 mg/kg/day or approximately 0.000006 mg Hg/kg/day. NTP (1993) identified a NOAEL of 0.93 mg Hg/kg/day in rats, which ATSDR used to derive an acute-duration oral MRL for mercuric chloride. It should be pointed out that there was no evidence of testicular damage in rats or mice in the 16-day, 6-month, or 2-year NTP (1993) studies. The report of Nagar and Bhattacharya (2001) does not specify the exposure route. Furthermore, reported sperm parameters were often reported to be significantly different from controls only at some of the assessed time points. Based on study limitations, the results are questionable and are not considered to be adequate for purposes of risk assessment.

Potential for Human Exposure

The highest score is 7 points and was given to 13 studies for providing data that address data needs, which include levels of mercury in biological media, quantitative data on oral absorption of mercury, additional PBPK modeling data, and urinary excretion of mercury from amalgam fillings.

Levels in biological tissues:

- CDC (2001) provides updated information on blood and hair levels of mercury in young children and women of childbearing age. The report presents preliminary estimates of blood and hair Hg levels from the 1999 National Health and Nutrition Examination Survey (NHANES 1999) and compares them with a recent toxicological review by the National Research Council (NRC). The findings suggest that mercury levels in young children and women generally are below those considered hazardous.

- Kurttio et al. (1998) monitored levels of mercury in the hair from subjects living near a hazardous-waste-treatment plant before and 10 years after the plant began operation. During the 10-y period, median hair total mercury concentrations increased by 0.35 mg/kg in workers (n = 11); by 0.16 mg/kg, 0.13 mg/kg, and 0.03 mg/kg in individuals who lived 2 km (n = 45), 2-4 km (n = 38), and 5 km (n = 30) from the plant, respectively; and by 0.02 mg/kg in the reference group (n = 55).

Quantitative data on oral absorption of mercury:

- Geijersstam et al. (2001) present quantitative data on oral absorption of mercury in humans. The study investigates gastrointestinal uptake of mercury in eleven volunteers after intake of a single dose of 1 gram of amalgam powder and pharmacokinetic analysis of the data. The mean half-life of the terminal phase of Hg in plasma for the population was 37 days and the absorbed fraction of the administered dose was estimated to be about 0.04%.

PBPK modeling data:

- Carrier et al. (2001, two studies) developed a new PBPK model for predicting the distribution of elimination of methylmercury and its metabolite, inorganic mercury, under a variety of exposure scenarios in rats.
- Jonsson et al. (1999) developed a 4-compartment model for kinetics of mercury vapor in humans.
- Leggett et al. (2001) proposed a revised model that is more consistent with current knowledge regarding the fate of inhaled mercury vapor in animals and humans. The revised model predicts lower deposition in the upper respiratory tract, greater deposition in the lower respiratory tract, and a different pattern of absorption to blood.

Urinary excretion of mercury from amalgam fillings:

- Kingman et al. (1998) examined the association between mercury concentrations in blood and urine and amalgam exposure in a U.S. military population (non-occupationally exposed).
- Halbach et al. (1997, 1998, 2000) presented information that included urinary levels of mercury released from amalgam.
- Khordi-Mood et al. (2001) presented information on urinary excretion of mercury following amalgam filling in children.
- Dye et al. (2005) used results of NHANES (1999-2000) to assess potential associations between urinary mercury concentrations and dental restorations in U.S. women of reproductive age.

One study received a score of 6 for new information on monitoring mercury levels in groundwater collected from wells on and near an NPL waste site (Cizdziel 2004).

The remaining studies in this category received scores of 4 for new kinetics or environmental fate data (14 studies); 3 for confirmatory information on levels measured in biological tissues of the

general population, new bioavailability/bioaccumulation data, or new chemical release data (73 studies); 2.5 for confirmatory information on environmental monitoring for the general population or confirmatory information on levels measured in biological tissues of workers (29 studies); 2 for confirmatory information on environmental levels in the workplace, confirmatory environmental fate data, or confirmatory kinetics data (71 studies); 1.5 for confirmatory bioavailability/bioaccumulation data (69 studies); or 0 for monitoring data in a foreign country (59 studies).

Supplemental Information

The highest score is 5 points for new information on methods for reducing toxicity. Nine studies received this score.

- Girardi and Elias (1998) examined the effects of verapamil, a calcium channel blocker, on the renal glomerular structural damage produced by mercuric chloride in rats. Verapamil prevented the glomerular proteinuria observed in $HgCl_2$-treated rats.
- Kim et al. (2000) reported that simultaneous administration of methylmercury and melatonin to mice delayed the neurological effects of methylmercury alone and prevented death of the animals, partly due to antioxidative effects of melatonin in the brain.
- Nava et al. (2000) found that melatonin protects rats from the acute renal effects caused by mercuric chloride and also suggested that melatonin protection is due to its antioxidant properties.
- Lee et al. (1999) found that garlic juice protected pregnant rats against the embryotoxicity of methylmercury chloride; no possible mechanism is discussed in the abstract available.
- Nerudova et al. (2000) evaluated the efficacy of sodium-2,3-dimercapto-1-propane sulfonate (DMPS) for mobilizing mercury from the body in occupationally exposed people and experimental animals. They examined workers of the chloralkali industry, dentists, non-exposed individuals, and rats exposed to mercury vapor for 15 weeks. It was estimated that two doses of DMPS mobilized 17-20% (after oral administration) and 25-30% (after intramuscular administration) of kidney mercury burden, both in the control and exposed subjects.
- Sharma et al. (2002) reported that an aqueous extract from the leaf of *Ocimum sanctum* provides protection against liver toxicity induced by mercuric chloride in mice.
- Passos et al. (2003) presented data indicating that the consumption of fruit resulted in reduced absorption of mercury from contaminated fish. The authors suggested that a number of phytochemicals and nutritional fibers present in fruits might be interacting with Hg in several ways: absorption and excretion, transport, binding to target proteins, metabolism, and sequestration.
- Aikoh et al. (2002) found that a sulfur-bridged molybdenum complex (referred to as the NTA complex) enhanced the excretion of mercury from organs of mice that been exposed to metallic mercury vapor. No possible mechanism is discussed in the abstract available.

- Tiwari and Bhattacharya (2004) demonstrated a protective effect of essential phospholipids against mercuric chloride-induced thyroid effects in mice, presumably via antioxidative action.

The majority of the remaining studies in this category were assigned 4 points providing new information on mechanisms of action, primarily regarding immunological, neurological, or kidney effects.

Additional Information

MRLs

Inhalation

Metallic Mercury

- ATSDR derived a chronic-duration inhalation MRL of 0.0002 mg/m^3 for metallic mercury, based on neurological effects in workers exposed to metallic mercury vapors (Fawer et al. 1983). The MRL was based on a LOAEL of 0.026 mg/m^3, which was adjusted from intermittent to continuous exposure (0.0062 mg/m^3) and divided by an uncertainty factor of 30 (3 for use of a minimal-effect LOAEL and 10 for human variability).

ATSDR did not derive acute- or intermediate-duration inhalation MRLs due to lack of adequate data. No new studies were located that might serve as a basis for deriving acute- or intermediate-duration inhalation MRLs for metallic mercury.

EPA (IRIS 2005) derived an RfC of 0.0003 mg/m^3 for elemental mercury based on the results of the same human occupational inhalation study that was used by ATSDR to derive a chronic-duration inhalation MRL of 0.0002 mg/m^3 Fawer et al. 1983). The values differ slightly due to different approaches used to adjust the workday exposure to a continuous exposure scenario.

Inorganic Mercury

ATSDR did not derive inhalation MRLs for inorganic mercury due to lack of adequate data. No new relevant information was located.

EPA (IRIS 2005) does not list an RfC for inorganic mercury compounds on IRIS.

Organic Mercury

ATSDR did not derive inhalation MRLs for organic mercury, due to lack of adequate data. No new relevant information was located.

EPA (IRIS 2005) does not list an RfC for organic mercury compounds on IRIS.

Oral

Metallic Mercury

ATSDR did not derive oral MRLs for metallic mercury, due to lack of adequate data. No new information was located that could be used for derivation of oral MRLs for metallic mercury.

EPA (IRIS 2005) does not list an RfD for metallic mercury on IRIS.

Inorganic Mercury

- ATSDR derived an acute-duration oral MRL of 0.007 mg/kg/day for inorganic mercury, based on a NOAEL of 0.93 mg/kg/day for renal effects in rats (NTP 1993). The dose was duration-adjusted for a 5-day/week exposure and divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for sensitive individuals).

- ATSDR derived an intermediate-duration oral MRL of 0.002 mg/kg/day for inorganic mercury, based on a NOAEL of 0.23 mg/kg/day for renal effects in rats (Dieter et al. 1992; NTP 1993). The dose was duration-adjusted for a 5-day/week exposure and divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for sensitive individuals). The study of Khan et al. (2004) may impact both the acute- and intermediate-duration oral MRLs for inorganic mercury.

ATSDR did not derive a chronic-duration oral MRL for inorganic mercury, due to lack of adequate data. No new information was located that could be used for derivation of a chronic-duration oral MRL for inorganic mercury.

EPA (IRIS 2005) derived an RfD of 0.0003 mg/kg/day for mercuric chloride (verified 11/16/1988) based on a recommended Drinking Water Equivalent Level (DWEL) of 0.01mg/L, which had been recommended based on the results of oral and subcutaneous injection studies performed in rats (Andres 1984; Bernaudin et al. 1981; Druet et al. 1978). Reference human daily water consumption (2 L/day) and reference adult male bodyweight (70 kg) were used to calculate the RfD as follows: 0.01 mg/L x (2 L/day/70 kg) = 0.003 mg/kg/day.

Organic Mercury

ATSDR derived a chronic-duration oral MRL for organic mercury of 0.0003 mg/kg/day, based on a NOAEL of 0.0013 mg/kg/day for neurodevelopmental effects in children (The Seychelles prospective study) exposed *in utero* (Davidson et al. 1998). An uncertainty factor of 3 was applied to account for human pharmacokinetic and pharmacodynamic variability; a modifying factor of 1.5 was applied to account for domain-specific findings in the Faroe study). New

information is available regarding this cohort (Axtell et al. 2000; Myers et al. 2000; Palumbo et al. 2000). In addition, Crump et al. (2000) used benchmark analysis on the Seychelles data as an alternate approach for estimating an MRL.

No new adequate information was located for derivation of acute- and intermediate-duration oral MRLs for organic mercury.

EPA (IRIS 2005) derived an RfD of 0.0001 mg/kg/day for methyl mercury based on developmental neuropsychological impairment reported in epidemiological studies (Budtz-Jørgensen et al. 1999; Grandjean et al. 1997). Maternal daily dietary intake levels were used as the dose surrogate for the observed developmental effects in children exposed *in utero*. Daily dietary intake levels were calculated from blood concentrations measured in the. Benchmark dose analysis was used to analyze the neurological effects in the children. This approach resulted in a $BMDL_{05}$ range of 46-79 ppb in maternal blood for different neuropsychological effects in the offspring at 7 years of age, corresponding to a range of maternal daily intakes of 0.857-1.472 µg/kg/day. An uncertainty factor of 10 was applied to the maternal daily intake to account for human variability.