

Public Health Goal for Inorganic Mercury In Drinking Water

Prepared by

**Office of Environmental Health Hazard Assessment
California Environmental Protection Agency**

**Pesticide and Environmental Toxicology Section
Anna M. Fan, Ph.D., Chief**

**Deputy Director for Scientific Affairs
George V. Alexeeff, Ph.D.**

February 1999

LIST OF CONTRIBUTORS

PHG PROJECT MANAGEMENT	REPORT PREPARATION	SUPPORT
<p style="text-align: center;"><i>Project Director</i> Anna Fan, Ph.D.</p> <p style="text-align: center;"><i>Workgroup Leaders</i> Joseph Brown, Ph.D. Robert Howd, Ph.D. Lubow Jowa, Ph.D. David Morry, Ph.D. Rajpal Tomar, Ph.D.</p> <p style="text-align: center;"><i>Public Workshop</i> Rajpal Tomar, Ph.D. Coordinator Judy Polakoff, M.S. Juliet Rafol</p> <p style="text-align: center;"><i>Report Template/Reference Guide</i> Hanafi Russell Yi Wang</p> <p style="text-align: center;"><i>Revisions/Responses</i> Joseph Brown, Ph.D. Michael DiBartolomeis, Ph.D.</p>	<p style="text-align: center;"><i>Author</i> Lubow Jowa, Ph.D.</p> <p style="text-align: center;"><i>Primary Reviewer</i> Jim Donald, Ph.D.</p> <p style="text-align: center;"><i>Secondary Reviewer</i> Rajpal Tomar, Ph.D.</p> <p style="text-align: center;"><i>Final Reviewers</i> George Alexeeff, Ph.D. Michael DiBartolomeis, Ph. D. Anna Fan, Ph.D.</p> <p style="text-align: center;"><i>Education and Outreach/Summary Documents</i> David Morry, Ph.D. Hanafi Russell Yi Wang, Ph.D.</p> <p style="text-align: center;">Format/Production Edna Hernandez Hanafi Russell</p>	<p style="text-align: center;"><i>Administrative Support</i> Edna Hernandez Coordinator Juliet Rafol Genevieve Vivar</p> <p style="text-align: center;"><i>Library Support</i> Charleen Kubota, M.L.S. Mary Ann Mahoney, M.L.I.S. Valerie Walter</p> <p style="text-align: center;"><i>Website Posting</i> Edna Hernandez Laurie Monserrat</p>

We thank the U.S. EPA (Office of Water; Office of Prevention, Pesticides and Toxic Substances; National Center for Environmental Assessment) and the faculty members of the University of California with whom OEHHA contracted through the UC Office of the President for their peer reviews of the PHG documents, and gratefully acknowledge the comments received from all interested parties.

PREFACE

**Drinking Water Public Health Goals
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency**

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

TABLE OF CONTENTS

LIST OF CONTRIBUTORS.....	II
PREFACE.....	III
TABLE OF CONTENTS.....	V
PUBLIC HEALTH GOAL FOR INORGANIC MERCURY IN DRINKING WATER.....	1
SUMMARY	1
INTRODUCTION.....	1
CHEMICAL PROFILE	2
Chemical Identity	2
Physical and Chemical Properties.....	2
Production and Uses.....	2
Sources	3
ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE	6
Air.....	6
Soil	6
Water	7
Food.....	7
Other Sources	8
METABOLISM AND PHARMACOKINETICS	8
Absorption.....	8
Distribution	8
Metabolism.....	9
Excretion	9
Physiological/Nutritional Role.....	10
TOXICOLOGY.....	10
Toxicological Effects in Animals.....	10
Acute Toxicity	10
Subchronic Toxicity	10
Cardiac Toxicity	10

Gastrointestinal Toxicity	11
Renal Toxicity	11
Genetic Toxicity	12
Developmental and Reproductive Toxicity	13
Immunotoxicity	13
Neurotoxicity	14
Chronic Toxicity/ Carcinogenicity	14
Toxicological Effects in Humans	16
Acute Toxicity	16
Subchronic Toxicity	16
Genetic Toxicity	17
Developmental and Reproductive Toxicity	17
Immunotoxicity	17
Neurotoxicity	18
Chronic Toxicity	18
Carcinogenicity	18
DOSE-RESPONSE ASSESSMENT	18
Noncarcinogenic Effects	18
Carcinogenic Effects	19
CALCULATION OF PHG	20
Noncarcinogenic Effects	21
RISK CHARACTERIZATION	22
OTHER GUIDANCE VALUES AND REGULATORY STANDARDS	24
REFERENCES	25

PUBLIC HEALTH GOAL FOR INORGANIC MERCURY IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.0012 mg/L (1.2 ppb) has been developed for inorganic mercury compounds in drinking water. There are a variety of effects from exposure of humans and animals to mercury-containing compounds. For inorganic mercury compounds, the predominant effect is toxicity to the kidney. Inadequate information exists on the chronic effects of inorganic mercury in either animals or humans. Therefore, individual health-based concentrations were computed based on slight kidney toxicity in a short-term study. In this study, rats were administered 0, 0.23, 0.46, 0.92, 1.8 or 3.7 mg Hg/kg-day by gavage for six months. The decrease in body weight gains and increases in absolute and relative kidney weights at doses of 0.46 mg Hg/kg-day and above were sufficient to designate the dose of 0.46 mg Hg/kg-day as the LOAEL. Therefore, the dose of 0.23 mg Hg/kg-day would be a NOAEL. Using the subchronic study, a health-based concentration was computed based on an adult body weight of 70 kg, a consumption of 2 L of water per day, an inter- and intraspecies uncertainty factor of 100, a source contribution factor of 20%, and an additional uncertainty factor of 10 to extrapolate chronic effects from subchronic observations. Based on these considerations, the Office of Environmental Health Hazard Assessment (OEHHA) adopts a PHG of 0.0012 mg/L (1.2 ppb) for inorganic mercury in drinking water.

INTRODUCTION

The purpose of this document is to develop a PHG for inorganic mercury. At present, mercury and mercury compounds can be categorized into three groups: mercury (metallic or elemental), inorganic and organic mercury compounds. Based on the chemical, biological and environmental fate characteristics of all these forms, inorganic mercury is the form most likely to pose a hazard by drinking water. For that, reason, federal and state drinking water regulations for mercury in drinking water have been based on the hazards of inorganic mercury. A Maximum Contaminant Level (MCL) of 0.002 mg/L was established by the California Department of Health Services (DHS) in 1995 (22 CCR 64431). This level is the same as the federal Maximum Contaminant Level Goal (MCLG) and MCL of 0.002 mg/L for mercury (U.S. EPA, 1997a).

Inorganic mercury has been evaluated for carcinogenic potential. Mercuric chloride has been classified by the U.S. Environmental Protection Agency (U.S. EPA) as a possible human carcinogen, Group C (IRIS, 1998).

In this document, we focus on evaluating the available data on the toxicity of inorganic mercury. To determine a public health-protective level of inorganic mercury in drinking water, sensitive groups were identified and considered, and relevant studies were identified, reviewed and evaluated.

CHEMICAL PROFILE

Chemical Identity

Mercury is an element with an atomic number of 80 on the periodic table. Mercury has three valence states: 0, +1, +2. Besides elemental mercury, many mercury-containing compounds are available which are broadly divided into inorganic and organic forms. Organic mercury compounds are defined as compounds in which the mercury is bound covalently to at least one carbon atom (WHO, 1991). Thus, mercuric complexes with organic acids, for example, mercuric acetate, are classified as inorganic forms and their data is presented in inorganic mercury discussions.

Other information related to the identity of mercury and selected inorganic compounds, mercuric chloride and mercuric sulfide, is provided in Table 1. Mercuric chloride and mercuric sulfide are presented as representatives of the class of inorganic mercury compounds as they are some of the most environmentally available mercury compounds.

Physical and Chemical Properties

Important physical and chemical properties of elemental mercury, mercuric chloride and mercuric sulfate are provided in Table 2. Mercuric chloride is more soluble than elemental mercury in water.

Production and Uses

Mercury is an element, which is currently found in the earth's crust with an average content of 0.5 ppm. Most of the world's supply of mercury is produced from mercury mines; both open air and underground mines. Most mercury mining in the U.S. is done secondarily to other mining. It is produced as a byproduct of gold mining operations in California, Nevada and Utah. The principal mercury ore is cinnabar, which is predominantly mercuric sulfide (ATSDR, 1997).

Mercury is a very useful component of many items due to its unique properties. It exhibits fluidity at a wide range of temperatures, and a uniform volume expansion over the entire liquid temperature range; thus, it is used in thermometers and other monitoring equipment. It has a high ability to form alloys with many metals, thus its significant use in dental amalgams, which are composed of nearly 50% elemental mercury combined with other metals. Conductivity properties have made mercury an essential component in batteries and switching and wiring devices. Mercury is used in lamps for its high efficiency, long life and high lumen output. The largest single use of mercury for commercial purposes (35% of domestic production) is in the electrolytic production of chlorine and caustic soda. Mercury is also used as a catalyst in the production of vinyl chloride and urethane forms (ATSDR, 1997).

Mercury salts have been components of antiseptics, diuretics, and skin lightening creams and laxatives. Organic mercury compounds were employed in antisyphilitic drugs and some laxatives. Phenyl mercuric acetate has been used as a fungicide, applied to seeds, and as a

bactericide, used in pharmaceuticals. Due to concern over its high toxicity, domestic uses of mercury have been gradually diminished since 1970s. Mercury in pharmaceuticals has been largely eliminated, although in some countries these pharmaceuticals may still be used. Similarly, uses of organic mercury as bactericides and fungicides have been largely phased out for toxicity concerns (ATSDR, 1997).

Sources

Besides mining, mercury is produced from recycling operations. From 1987 to 1991, annual production of mercury from old scrap averaged nearly 180 metric tons in the US (Jasinski, 1993).

Table 1. Chemical Identity of Mercury and Selected Compounds (ATSDR, 1997)

Characteristic	Mercury	Mercuric Chloride	Mercuric Sulfide
Name	Mercury	Mercuric (II) chloride	<i>Mercuric (II) sulfide</i>
Synonym(s)	Colloidal mercury; liquid silver; mercury, metallic (DOT); quicksilver, metallic mercury, elemental mercury, hydrargyrum	Dichloride of mercury, mercury dichloride, mercury chloride, mercury dichloride, mercury perchloride, mercury (II) chloride, corrosive sublimate, corrosive mercury chloride, dichloromercury	Etiops mineral, mercury sulfide, black, vermilion, Chinese red, C.I. Pigment Red 106, C.I. 77766, quicksilver vermilion, red mercury sulfide, artificial cinnabar, red mercury sulfuret
Registered trade names(s)	No data	Calochlor, Fungchex, TL 898	No data
Chemical formula	Hg	HgCl ₂	Hg S
Identification numbers:			
CAS registry	7439-97-6	7487-94-7	1344-48-5
NIOSH/ RTECS	OVA45500000	OVA9100000	No data
U.S. EPA hazardous waste	U151; D009	D009	No data
OHM/TADS	7216782	No data	No data
DOT/UN/NA/IM CO shipping	UN 2024 (mercury compounds, liquid) UN 2025 (mercury compounds solid); IMO 6.1 (mercury compounds, liquid or solid) UN 2809 (DOT)	UN1624 (mercuric chloride) IMO 6.1 (mercuric chloride)	No data

Characteristic	Mercury	Mercuric Chloride	Mercuric Sulfide
HSDB	1208	33	No data
NCI	C60399	C60173	No data

CAS= Chemical Abstracts Service; DOT/UN/NA/IMO= Dept. of Transportation/ United Nations/North America/ International Maritime Dangerous Goods Code; EPA = U.S. Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/ Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 2. Chemical and Physical Properties of Mercury and Selected Compounds (From ATSDR, 1998)

Property	Mercury	Mercuric chloride	Mercuric Sulfide
Molecular weight	200.59	271.52	232.68
Color	Silver-white	white	Black or grayish black(mercuric sulfide, black), also bright scarlet-red, blackens on exposure to light (mercuric sulfide, red)
Physical state	Heavy, mobile, liquid metal , solid mercury is ductile, malleable	Crystals, granules or powder, rhombic crystals, crystalline solid	Heavy amorphous powder, also occurs as black cubic crystals (mercuric sulfide, black), powder, lumps, hexagonal crystals (mercuric sulfide, red)
Melting point	-38.87°C	277°C	Transition temp (red to black) 386°C, sublimes at 446°C (mercuric sulfide black) and 583°C (mercuric sulfide, red)

Property	Mercury	Mercuric chloride	Mercuric Sulfide
Boiling point	356.72°C	302 °C	No data
Density at °C	13.534 g/cm ³ at 25°C	5.4 g/cm ³ at 25 °C	7.55-7.70 (mercuric sulfide, black), 8.06-8.12 g/cc (mercuric sulfide, red)
Odor	Odorless	Odorless	Odorless
Odor threshold (Water/Air)	No data	No data	No data
Solubility: water	0.28 µmoles/L at 25 °C	1 g/35 mL, 1 g/2.1 mL boiling H ₂ O; 6.9 g/100cc H ₂ O at 20 °C, 48 g/100 cc at 100 °C	Insoluble (mercuric sulfide, black), soluble in aqua regia with separation of S in warm hydriodic acid with evolution of H ₂ S (mercuric sulfide, red)
Partition Coefficient			
log K _{ow}	5.95	No data	No data
log K _{oc}	No data	No data	No data
Vapor Pressure	2 x 10 ⁻³ mm Hg at 25°C	1 mm Hg at 136.2 °C	No data
Henry's Law Constant	No data	No data	No data
Conversion factors:			
ppm (v/v) to mg/m ³ in air at 25°C	1 ppm = 8.18 mg/m ³	No data	No data
mg/m ³ to ppm (v/v) in air at 25°C	1 mg/m ³ = 0.122 ppm	No data	No data
Valence states	0,+1, +2	+2	+2

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Mercury is an element commonly found in the environment. It is released into the environment by the natural weathering of rocks, soils, volcanic activity and decay processes. There are also anthropogenic releases; the most significant of which are chlor-alkali plants, paper mills, fossil fuel combustion and waste disposal. There is a natural biogeochemical cycling of mercury, which consists of the degassing of elemental mercury from soils and surface waters, followed by oxidation in the atmosphere and then deposition of mercury back onto the water and soils. Once in the soils it can be reduced to the elemental form and volatilize again.

Most of the atmospheric mercury (mostly elemental), 50-75%, appears to be from anthropogenic sources (U.S. EPA, 1997b). Releases from anthropogenic sources are mostly from mining and manufacturing operations, which can account for 2,00-4500 metric tons per year. Significant emissions also occur from coal-fired power plants; this as well as other fossil fuels account for nearly 25% of mercury emissions to the atmosphere (WHO, 1991).

U.S. EPA (1980) reported ambient air concentrations of mercury of 10-20 ng/m³ with higher values in industrialized areas. Point emission sources for mercury include mines, refineries and agricultural fields treated with mercury fungicides. Mercury can also be present in a particulate phase in the atmosphere. Particulate phase mercury levels in rural areas of the Great Lakes and Vermont ranged from 1-86 pg/m³, while urban and industrial areas were in the range of 15-1,200 pg/m³ (ATSDR, 1997)

Soil

Mercury can exist in the mercuric Hg⁺² or mercurous Hg₂⁺² state naturally in soils containing ores. These ores are found in nearly all classes of rock. The highest mercury-containing ore is cinnabar, which consists of 86% mercuric sulfide. Mercury is found in virgin and cultivated surface soils in average concentrations of 20-625 ng/g (Andersson, 1979). Higher concentrations of mercury are found in urban soils and soil, which have a high mineral over organic content. All mercury forms appear to have a high sorption rate to soils and sediments and are not easily dislodged by leaching. The mobilization of sorbed mercury requires chemical or biological reduction to metallic mercury or conversion to organic forms by microbial processes (ATSDR, 1997).

Anthropogenic sources of mercury to soils include direct application of inorganic and organic fertilizers (sewage, sludge and compost), lime and fungicides containing mercury (Andersson, 1979). Other anthropogenic sources of mercury include disposal of mercury-containing products into landfills. Landfills also receive fly ash from municipal incinerators which also contain significant amounts of mercury (ATSDR, 1997).

Water

As with soils, mercury can exist in the mercuric Hg^{+2} or mercurous Hg_2^{+2} state in a number of complex ions with varying water solubilities. At a pH of 4-9 and normal sulfide concentration, mercury will form mercuric sulfide. Mercuric mercury is probably the predominant form found in surface waters; however, the predominant form of mercury in ore (mercuric sulfide) shows virtually no water solubility.

The important transformation process in the environmental fate of mercury in sediments of surface waters is the biotransformation of mercuric ions into methyl mercury by sulfur-reducing bacteria. This process is dependent upon concentration of inorganic mercuric ion, methyl cobalamine and oxygen, with the reaction increasing, as conditions become more anaerobic. In addition, under anaerobic conditions, volatile elemental mercury can evolve as with the demethylation of methyl mercury (Regnell and Tunlid, 1991).

Mercury concentrations in rainwater and fresh snow are generally below $0.2\mu\text{g/L}$ (ppb). Fresh water without an obvious source of anthropogenic mercury is estimated to be 5 ng/L (ATSDR, 1997). Of the 6856 sites sampled from California public drinking water, groundwater sources there were 225 positive detections and 27 exceedances of the MCL level of 2 ppb (Storm, 1994). The mean mercury concentration was 6.5 ppb (median, 0.62 ppb; range 0.21 to 300 ppb). Mercury was detected at levels greater than 0.5 ppb in 15-30% of wells tested in some ground water surveys nationwide. Generally, drinking water is assumed to contain less than $0.025\mu\text{g/L}$ (ATSDR, 1997).

Food

The most significant source of mercury in food comes from seafood. Organic mercury, chiefly methyl mercury produced by microorganisms, is very soluble, mobile and enters the aquatic food chain from plankton and is biomagnified in carnivorous fish to 10,000 to 100,000 times that found in ambient waters. Fish appear to accumulate methyl mercury from food sources and the water column. While fish accumulate inorganic mercury as well as methyl mercury, the methyl mercury accumulation is generally higher. Phytoplankton also preferentially accumulate methyl mercury over inorganic mercury because the inorganic form tends to be associated with cell membranes while the methyl mercury partitions to the cytoplasm (ATSDR, 1997).

Mercury has been detected in U.S. FDA Total Diet Study in 129 adult foods with seafood contributing nearly 77% of the total dietary intake ($3.9\mu\text{g}$) for 25-30 year old males (Gundersen, 1988). A survey of 220 cans of tuna conducted in 1991 by the FDA found an average methyl mercury content of 0.17 ppm (as mercury) (Yess, 1993). WHO estimated that nonfish food provides an average daily intake of $3.6\mu\text{g}$ of inorganic mercury while fish provide $0.60\mu\text{g}$ inorganic mercury (ATSDR, 1997).

Inorganic mercury in the soils is not taken up well by plants, although there is some indication that mushrooms can take up substantial quantities (ATSDR, 1997). Mercury can enter meat, poultry and eggs when fishmeal is used in feed. In Germany, poultry and eggs were found to contain average mercury concentrations of 0.04 and 0.03 mg/kg, respectively. In cattle, 0.001-0.02 mg/kg was found in the meat, while cow's milk had 0.01 mg/kg (Hapke, 1991). A survey of raw foods in Germany contained mercury concentrations of 0.005 to 0.05 mg/kg with wild mushrooms contained up to 8.8 mg/kg (Weigert, 1991).

Other Sources

Mercury can also be available from more “localized” sources. Elemental mercury is released during preparation and handling of dental amalgams, exposing dental professionals and patients. The dental amalgam restorations, themselves, appear to be the major contributor to an individual’s body burden of mercury. Broken thermometers and other appliances make mercury available for inhalation and skin contact. Metallic mercury has been used in cultural and religious practices because of its apparent “magical properties” (ATSDR, 1997).

METABOLISM AND PHARMACOKINETICS

Absorption

Metallic mercury appears to be well absorbed following inhalation exposure due to its highly lipophilic nature. This lipophilic nature allows for the rapid diffusion of mercury through alveolar membranes to the blood. Hursh et al. (1976) reported that humans inhaling 0.1-2 mg/m³ of mercury vapor retained from 74-80% of the inhaled dose. Similarly, animals exposed to metallic mercury vapor absorbed high levels of mercury. No information is available concerning absorption of inorganic mercury salts from inhalation, although it is not expected to be great.

In contrast to the pattern of absorption of metallic mercury by inhalation, oral absorption of metallic mercury is poor (ATSDR, 1997). Absorption of mercury salts is limited, but highly variable depending on the nature of the salt and the tested species (ATSDR, 1997). About 15% of mercurous nitrate were absorbed in humans (Rahola et al., 1973). In rats, 3.0-8.7% of orally administered mercuric chloride was absorbed as measured by whole body retention (Piotrowski et al., 1992). Mercuric sulfide was reported to be less absorbable than mercuric chloride in comparative studies, however, no quantitative information was provided (ATSDR, 1997). The available evidence indicates that organic mercury, in particular methyl mercury, is the most absorbable of all forms by ingestion, with 95% of aqueous methylmercuric nitrate being absorbed in humans (Aberg et al., 1969).

Small amounts of metallic mercury are absorbable by dermal exposure. Mercury intoxication has been reported from the application of ointments containing mercuric salts (ATSDR, 1997). Absorption of mercuric chloride can be as much as 6-8% (Berlin, 1986). The extent of inorganic mercury absorption is not known, but is likely to vary with the type of salt as well as the vehicle of application.

Distribution

Distribution of all mercury forms varies with their physical properties. Metallic mercury, due to its lipophilic nature, is distributed throughout the body, and crosses blood-brain and placental barriers. Peak blood levels occur within 24 hours after initial dosing. In the brain, the peak level is reached after 2-3 days (Clarkson, 1989). Similarly, organic mercury is widely distributed. In the blood, organic mercury is oxidized to mercuric mercury then concentrates in the kidneys (Halbach and Clarkson, 1978).

In the plasma, the mercuric ion is mostly nondiffusible and binds to albumins and globulins. Its lack of the strong lipophilic nature results in limited ability to cross the blood brain and placental barriers (Clarkson, 1989). The liver and kidneys had the highest mercury levels 14 days after exposure to a single oral dose of 0.2-20 mg/kg as mercuric chloride in mice (Nielsen et al., 1991). Mercuric chloride administered to mice at 4-5 mg Hg/kg for 2-8 weeks had the highest levels in the kidney (Sin et al., 1983). Thus, the kidney is the single largest depot of mercury in the body: there it is concentrated in the proximal tubule primarily in complex with metallothionein (Piotrowski et al., 1974). Mercury was observed to induce the synthesis of metallothionein, a low molecular weight cytoplasmic protein rich in sulfhydryl groups. The second largest depot of mercury is the liver, with the greatest concentration near the periportal area.

Mercury has an affinity for ectodermal and endodermal epithelial cells such as the epithelial lining of the gastrointestinal tract, squamous epithelium of the hair and skin and glandular tissue such as salivary glands, lacrymal glands, mammary glands, thyroid, pancreas, sweat glands, testicles and the prostate. Many of the above mentioned secretory organs and the skin can also serve to eliminate mercury (Von Berg, 1995).

Metabolism

Both metallic and organic mercury are oxidized to inorganic mercury. Metallic mercury is oxidized by the hydrogen-peroxide catalase pathway occurring primarily in the red blood cells (Clarkson, 1989). It is believed that the rate of oxidation is dependent on concentration of catalase and the endogenous production of hydrogen peroxide. The oxidation pathway of metallic mercury can be inhibited by ethanol since ethanol is a competitive substrate for catalase (Nielsen-Kudsk, 1973). Besides the red cells, the oxidation of metallic mercury may also occur in the brain and liver of adults and fetuses, and probably other tissues as well (Clarkson, 1989).

Inorganic mercury is not transformed appreciably in the body. There is some evidence that mercuric mercury can be reduced to metallic mercury and eliminated. Rats and mice treated parentally with mercuric chloride exhaled metallic mercury vapor (Dunn et al., 1981).

Organic mercury can be converted to inorganic mercury in tissues, specifically the liver. Evidence indicates that rat liver microsomes can degrade methyl mercury into inorganic mercury, and that this was dependent upon hydroxyl radical production (Suda and Hirayama, 1992). Intestinal flora can also convert organic mercury to inorganic mercury, and as such, decreases the amount of relative absorption of mercury (Rowland et al., 1980)

Excretion

The urine and feces are the main excretory pathways of metallic and inorganic mercury in humans, with a body burden half-life of approximately 1-2 months (Clarkson, 1989). An elimination half life from urine was estimated to be 25.6 days following an acute exposure to 13.8 mg/kg of mercuric chloride (Suzuki et al., 1992). Approximately 60-75% of absorbed mercury was excreted as sulfhydryl mercury compounds, primarily with cysteine or N-acetyl cysteine, and little if any metallic mercury was in the urine (Winship, 1985). Urinary excretion involves active tubular transport and glomerular filtration, which is probably passive (Berlin, 1986).

Lesser pathways for elimination include exhalation, secretion in saliva, bile and sweat. Sweating was used since the 18th century as a means of lowering the body burden of mercury in cases of chronic mercury poisoning (Berlin, 1986). Inorganic mercury is also excreted in the breast milk of guinea pigs exposed to metallic mercury vapor. The mercury content of breast milk was less than the plasma levels, so there was no apparent concentration of mercury in breast milk. Another pathway of mercury elimination is through the hair, which can also be used to monitor mercury body burden.

The form of mercury found in the feces is predominantly inorganic form. Intestinal flora can convert organic mercury to inorganic, which then promotes its fecal excretion (Rowland et al., 1980).

Physiological/Nutritional Role

Mercury has always been present in the environment and available for human exposure, yet there has never been identified a physiologic need for this element. It is not a component of any known essential enzyme.

TOXICOLOGY

The toxic effects of inorganic mercury are summarized below:

Toxicological Effects in Animals

Acute Toxicity

Mercury salts are toxic orally to rats with LD₅₀s ranging from 25.9 to 77 mg Hg/kg for mercuric chloride (Kostial et al., 1978; Troen et al., 1951).

Subchronic Toxicity

The kidney is the most prominent site of toxicity from longer-term exposure to inorganic mercury. Other significant toxicities seen with longer-term mercury exposure include that to the developmental, gastrointestinal, cardiac, immunologic and neurologic systems. Extensive and current reviews of these are provided in U.S. EPA (1997; 1994) and ATSDR (1997) and summarized below and in the following organ-specific accounts.

Cardiac Toxicity

Increased blood pressure and changes in the contractility of the heart were reported in two chronic studies conducted in eight Sprague Dawley and Wistar rats exposed to mercuric chloride, ad lib in drinking water. Rats given 7 mg Hg/kg-day (as HgCl₂) for 350 days showed increase blood pressure and positive inotropic response (Carmignani et al., 1989). An increase in blood pressure with a negative inotropic response (not significant) was seen in eight weanling male rats given 28 mg Hg/kg-day (as HgCl₂) for 180 days, but not in controls (Carmignani et al., 1992).

However, in these studies a small number of animals were tested and no explanation was given for the differences in effects.

Gastrointestinal Toxicity

Limited information is available concerning gastrointestinal toxicity in animals, which has been better described in exposed humans. In a range-finding study, B6C3F₁ mice were exposed to 0, 3.7, 7.4, 14.8, 29 or 59 mg HgCl₂/kg-day by gavage for 14 days. Stomach inflammation and necrosis were observed at the 59 mg/kg-day dose (NTP, 1993). In the following two-year study, B6C3F₁ mice had forestomach epithelial hyperplasia at the 1.8 mg/kg-day dose (males) and 3.7 mg/kg-day dose (females) (NTP, 1993).

Renal Toxicity

The kidney appears to be the critical organ of toxicity following inorganic mercury exposures. Renal toxicity was observed in many animal studies with inorganic mercury compounds. In two experiments (Jonker et al., 1993), groups of five male or female Wistar rats were given 4, 16, 64 ppm or 75, 150 and 300 ppm mercuric chloride (0, 0.56, 4.4 or 2.8, 5.6 and 11.1 mg Hg/kg-day) in feed ad lib for four weeks. Ketonuria was reported at all levels in males and increased kidney weights at all levels for females and at levels of 75 ppm and above for males.

In the NTP study (1993), Fisher 344 rats and B6C3F₁ mice were given by gavage mercuric chloride at varying doses for acute, intermediate- and chronic-duration exposures. In a 14-day study in rats, relative and absolute kidney weights were increased in males at the 1.847 mg/kg-day dose level. Increased tubular necrosis was observed at 3.7 mg Hg/kg-day. Similarly in both sexes of mice, relative and absolute kidney weights were increased at a dose of 3.693 mg Hg/kg-day and acute renal necrosis appeared at 59 mg Hg/kg-day. Mice receiving mercuric chloride in drinking water for 7 weeks showed slight degeneration of the tubular epithelial cells at 2.9 mg Hg/kg-day. Minimal renal nephropathy (dilated tubules and either flattened eosinophilic epithelial cells or large cytomegalic cells with foamy cytoplasm) was observed at 14.3 mg Hg/kg-day (Dieter et al., 1992).

With chronic duration exposure studies, subtle to moderate pathology can be observed. Mercuric chloride was given to male Sprague Dawley rats in drinking water (28 and 7 mg/kg-day), for periods of 180 and 360 days, respectively (Carmignani et al., 1992; 1989). Renal toxicity was observed, consisting of hydrophobic degeneration of tubular cells, IgM deposition in glomeruli, decreased urinary kallikrein and creatinine, decreased plasma renin, and increased plasma angiotensin converting enzyme. Mercuric chloride given by gavage for two years to Fischer 344 rats resulted in thickening of glomerular and tubular basement membranes, degeneration and atrophy of tubular epithelium at a dose of 1.8 mg/kg (NTP, 1993). B6C3F₁ mice, treated similarly as the Fischer rats, had an increase number of foci in the proximal tubule with thickened basement membrane and basophilic cells with scant cytoplasm at a dose of 3.7 mg Hg/kg-day (NTP, 1993).

The renal damage seen following mercury exposure is thought to be the result of two mechanisms based on the site of injury (ATSDR, 1997). Renal tubular toxicity appears to be the predominant form and is thought to be the result of direct accumulation of mercury in distal tubules, which impairs protein synthesis and results in renal dysfunction. Initially, the first signs are degenerative changes to the epithelial cells of the proximal tubules, which are accompanied by tubular regeneration. With further injury, the lesions progress to general tubular necrosis,

fibrosis, atrophy and glomerular changes. The other mechanism is direct damage to the basal membrane of the glomeruli, thought to be the result of an auto immune reaction. This mechanism appears to affect only certain strains of rabbits, rats and mice. Further information is provided in the Immunotoxicity section.

Genetic Toxicity

Genetic effects of mercury compounds have been extensively reviewed and summarized by ATSDR (1997) and U.S. EPA (1997). In brief, mercury compounds have little mutagenic activity in most bacterial assay systems. Mercuric chloride failed to produce a mutagenic response in *Salmonella* tester strains. One of these experiments showed that mercuric chloride failed to show AT to GC base pair substitution. Other assays showed no induction of SOS repair. However, in one case, HgCl₂ was associated with marginal growth inhibition in recombinant repair deficient *Bacillus subtilis* at a concentration of 1.4 mg Hg/L. In contrast, the response with methyl mercuric chloride was significantly greater at 0.14 mg Hg/L (Kanematsu et al., 1980).

Mercury has been demonstrated to inhibit the formation of the mitotic or meiotic spindle in eukaryotic cells, similar to the effect of colchicine (Vershaeve et al., 1985). The inhibition of the mitotic spindle formation is thought to be caused by binding of inorganic mercury to sulfhydryl groups in the proteins of the spindle fibers, although the interaction of mercury with other proteins and enzymes such as RNA polymerase I may also be involved (Vershaeve et al., 1985). Other reported effects of mercury compounds in mammalian systems include breakage of DNA, induction of point mutations, dominant lethal mutations, sister chromatid exchanges, chromosomal aberrations, inhibition of the activity of nucleolus organizing regions, and decreases in DNA synthesis (U.S. EPA, 1994; ATSDR, 1998).

Mercuric chloride specifically was found to increase chromosomal aberrations in cultured human lymphocytes and in Chinese hamster ovary cells (U.S. EPA, 1994; ATSDR, 1998). However, other studies reported no such increase with mercuric chloride in the same systems. Mercuric chloride was mutagenic in L5178Y mouse lymphoma cells, inducing 1.4 to 3.5 times (with S9) the control frequency of mutations. Decreases were noted in the molecular weight of DNA from intact cells and from nucleoids (isolated nuclear preparations). These decreases were attributed to single strand DNA breaks, rather than double strand. DNA to DNA crosslinks, but not DNA to protein crosslinks were found, suggesting that the Hg²⁺ ion binds to DNA replacing hydrogen in the complementary binding of thymidine to adenine (Cantoni et al., 1984).

In whole animal assays, male rats given daily doses of mercuric chloride of 0.25 or 2.5 µg/kg-day for 12 months exhibited about a four fold increase in the frequency of dominant lethal mutations, but no increase at a dose of 0.025 µg/kg (Zasukhina et al., 1983). No evidence of dominant lethal effects was noted in male mice treated with 1.35 mg/kg of mercuric chloride in a single intraperitoneal dose (Lee and Dixon, 1975; Lee et al., 1983). The incidence of structural, but not numerical, chromosomal aberrations was slightly increased in bone marrow cells of female Syrian (golden) hamsters injected subcutaneously with inorganic mercury (Watanabe et al., 1982).

In comparison with other potent mutagens including other metals, it appears that mercuric chloride is not particularly potent as a mutagen, nor does it significantly induce chromosomal aberrations. The *in vitro* and *in vivo* information occasionally gives a conflicting profile. Nevertheless, it does appear that mercuric chloride can cause DNA damage.

Developmental and Reproductive Toxicity

Mercuric chloride administered by one ip injection at a concentration of 1 mg/kg caused decreased fertility in male mice, attributed to inhibition of DNA synthesis in spermatogonial cells and possible inhibition of various essential enzymes (Lee and Dixon, 1975).

Animals receiving mercuric acetate by injection (0, 4, 8, 20, 35, or 50 mg) had increased fetal resorptions and increased in abnormal, retarded and edematous fetuses (Gale, 1974). Kavlock et al. (1983) injected pregnant Sprague-Dawley rats (6-25 per group) subcutaneously with 0, 1, 2, 3 or 4 mg mercuric chloride per kg on either day 7, 9, 11, or 12 of gestation. On day 21, rats were sacrificed. No increase in malformations was observed in fetuses from mercuric chloride-treated dams. Exposure on day 7 resulted in a significant decrease in fetal weights and increases in the number of supernumerary ribs at 3 mg/kg-day.

Increased maternal toxicity was observed at doses of 2 mg Hg/kg and higher, as evidenced by higher kidney weights, but could not be correlated with fetal effects.

Kajiwara and Inouye (1992; 1986) injected Kuj:ddY mice with mercuric chloride at concentrations from 0 to 2.5 mg Hg/kg. They observed a decrease in number of implantations and number of living fetuses from dosed animals.

Gale (1974) administered 0, 4, 8, 25, 35, 50, 75 or 100 mg mercuric acetate/kg bw (0, 2.5, 5, 16, 22, 32, 47, or 63 mg Hg/kg bw) to pregnant golden hamsters (10/dose; 3 controls used) by gavage in distilled water on day 8 of gestation. The pregnant animals were sacrificed on gestation day 12 or 14. A statistically significant increase in the percentage of abnormal fetuses (small fetuses) was observed in the 8 mg mercuric acetate dose group. Statistically significant increases in the percentages of resorbed fetuses was observed at 35 mg and higher mercuric acetate dose groups and in the percentages of small, retarded and edematous fetuses at 50, 75 and 100 mg mercuric acetate per kg. Almost all fetuses were resorbed at 100 mg of mercuric acetate/kg. No treatment-related effects were observed in fetuses at the 4 mg mercuric acetate per kg dose.

Rizzo and Furst (1972) administered 2 mg Hg as mercuric oxide to pregnant Long-Evans rats (5 per group) by gavage in peanut oil on gestation day 5, 12, or 19. On gestation day 20 or 21, rats were sacrificed. Rats administered Hg on gestation day 5 had a higher percentage of fetuses with growth retardation and inhibition of eye formation.

In abstracts, Pritchard et al., (1982a, b) and McAnulty et al (1982) report on the effects of orally administered mercuric chloride. No decrease in litter size or viability was reported for 4, 8, 16 or 24 mg HgCl₂/kg-day given from day 15 until day 25, but subsequent weight gain of offspring was reduced in treated groups. No malformations were reported in treated animals, except at dose of 16 and 24 mg HgCl₂/kg-day; there were a few animals with delayed ossification and a range of major malformations. No effects upon fertility, conception, or survival of offspring *in utero* were found in female rats exposed to 12 mg HgCl₂/kg-day.

Immunotoxicity

Evidence for mercuric-mercury induced glomerular nephritis was noted above under renal toxicity. It was discovered that the Brown-Norway strain of rats are particularly sensitive to inorganic mercury with early signs of impaired immune response at doses lower than that which would cause renal tubular necrosis. Brown Norway rats when injected with low intravenous

doses of mercuric chloride show a variety of autoimmune abnormalities, including lymphoreticular proliferation as indicated by spleen and lymph node enlargement, increased production of nonspecific IgE, and development of circulating antibodies to the glomerular basement membrane (EPA, 1994). The autoimmune response is not seen in other strains of rats, suggesting a genetic component. However, the Lewis rat can exhibit immunosuppression upon exposure to mercury (WHO, 1991).

Druet et al. (1978) exposed Brown Norway rats (6-20/group) to mercuric chloride by subcutaneous injection of 0, 0.1, 0.25, 0.5, 1, or 2.0 mg /kg for 3 times/weeks, for 8 weeks. Another group of rats (unknown number or sex) received 0.05 mg/kg for 12 weeks. Proteinuria occurred at doses above 0.1 mg/kg (which can be designated as a LOAEL of 0.226 mg Hg/kg-day). Binding of some antibodies to the glomerular basement membrane was noted in the group exposed to 0.05 mg Hg/kg. However, effects at the 0.05 mg Hg/kg dose level could not be defined as to their adversity (U.S. EPA, 1997a).

Bernaudin et al. (1981) force-fed 5 Brown Norway rats/group 0 or 3 mg/kg/week mercuric chloride. No abnormalities of kidney were noted, but IgG deposition (as detected by immunofluorescence) was evident in all treated rats and proteinuria was noted in 3/5 dosed rats. An adjusted LOAEL of 0.315 mg/kg-day was defined (U.S. EPA, 1997a).

Andres and Brentjens (1984) gave 5 Brown Norway rats, 3 mg/kg of mercuric chloride by gavage 2 times/week for 60 days. In addition, two Lewis rats got the same dosing regimen as the Brown Norway rats. Two treated Brown Norway rats died after 30 days. The kidneys of all treated and untreated rats appeared normal histologically and there was no increase in proteinuria. However, the treated Brown Norway rats had IgG deposition in the glomeruli. An adjusted LOAEL of 0.633 mg Hg/kg-day was derived (U.S. EPA, 1997a).

The autoimmune response is characterized by production of autoantibodies to renal and extrarenal basement membranes. These antibodies are found deposited along the glomerular basement membrane in a linear pattern. The rats then develop proteinuria, which progresses to nephrotic syndrome. The disease is transient and animals may recover (U.S. EPA, 1994).

Other types of immune response are possible with inorganic mercury including decreases in hemolytic components and induction of antinuclear antibodies (U.S. EPA, 1994).

Neurotoxicity

Limited information is available on the neurotoxic effects of inorganic mercury. In rats exposed orally to 0.74 mg /kg-day mercuric chloride for 11 weeks, there was weakening of hindlegs, crossing reflex of limbs, ataxia, degenerative changes in neurons of dorsal root ganglia and Purkinje and granule cells of cerebellum (U.S. EPA, 1997a). A dose of 2.2 mg/kg-day of mercuric chloride in feed for 3 months was associated with inactivity and abnormal gait (U.S. EPA, 1997a). Mice administered mercuric chloride in drinking water ad lib for 17 months (doses ranging from 0.74-to 2.2 mg HgCl₂) had no signs of neurotoxicity, or effects on optic or peripheral nerve structure. However, the study suffers from lack of suitable statistical analysis and large uncertainty over exact dosage (Ganser and Kirschner, 1985).

Chronic Toxicity/ Carcinogenicity

Several studies have been conducted evaluating the carcinogenicity and chronic toxicity of mercury and its compounds. In a two year rat feeding study, mercuric acetate was administered

via the diet at concentrations of 0, 0.5, 2.5, 10, 40, and 160 ppm (0, 0.02, 0.2, 0.4, 1.7, and 6.9 mg Hg/kg-day) (Fitzhugh et al., 1950). With 20-24 animals per group and only half of the animals being examined histologically with limited statistical analysis, this study has rather limited sensitivity to detect toxicity. An increase in kidney weights and renal tubular lesions were observed at 40 and 160 ppm, but no elevated tumor incidence was reported.

Schroeder and Mitchener (1975) evaluated the carcinogenicity of mercuric chloride in white Swiss mice. Groups of 54 mice/sex were exposed until death to mercuric chloride in drinking water at 5 ppm Hg (0.95 mg Hg/kg-day). After death, mice were evaluated, but complete histology was not performed. No differences were seen between treated and controls with regard to the incidence of tumors or survival.

NTP (1993) (Dieter et al., 1992) conducted 6-month studies in Fischer 344 rats and B6C3F₁ mice using mercuric chloride. The rats (10/sex/group) were given 0, 0.312, 0.625, 1, 2.5, or 5 mg/kg HgCl₂ (0, 0.23, 0.462, 0.739, 1.847, and 3.694 mg Hg/kg-day) 5 days/week by gavage. Body weight gains were decreased in males at the high dose and in females at doses of 0.462 mg Hg/kg and above. Absolute and relative kidney weights were increased in both sexes at doses of 0.462 mg Hg/kg and above. The incidence of minimal nephropathy, as characterized by foci of tubular regeneration, thickened tubular basement membrane and scattered dilated tubules containing hyaline casts, was 80% in the male controls and 100% in the male dosed groups. Minimal to mild severity of nephropathy was observed in the two highest dose groups. In females, significant nephropathy was only present in the highest dose group. No effect on survival was noted. Based on decreases in body weight gains, and increases in absolute and relative kidney weights, the 0.23 mg Hg/kg-day dose can be determined as the NOAEL.

NTP (1993) used the two highest doses of the 6-month study as the doses for their two-year study of administering mercuric chloride by gavage to Fischer 344 rats and B6C3F₁ mice. Groups of 60 rats/sex were administered 0, 2.5 or 5 mg/kg of HgCl₂ (0, 1.847 and 3.694 mg Hg/kg-day) in deionized water for 103 to 104 weeks. Diminished survival was noted only in dosed male rats, with 17% at 2.5 mg/kg, 8% at 5 mg/kg and 55% of controls alive at the conclusion of the experiment. During the second year of the study, body weight gains of males at 2.5 and 5 mg/kg dose were 91 and 85% of the controls, respectively and body weight gains of female rats at 2.5 and 5 mg/kg dose were 90 and 86% of the controls, respectively. At the end of the study, nephropathy had occurred in all male and female rats, including controls, but the number of males with the grade of severity "marked" was much greater at 2.5 and 5 mg/kg dose than for the females. After the 15-month interim termination point, the forestomach of male rats in both treated groups developed basal cell hyperplasia, which became more extensive upon the final termination. Focal papillary hyperplasia and squamous cell papillomas of the forestomach (0/50 for controls, 3/50 for low dose, 12/50 for high dose) were observed in the dosed males rats at 2 years. These papillomas were not known to progress to malignancy. Thus, NTP reported "some" evidence rather than "clear" evidence of carcinogenic activity in male rats. Squamous cell papillomas of the forestomach were also observed in females (0/50, 0/49, 2/50), but the incidence was considered not significant. A marginally significant increased incidence of thyroid follicular cell carcinomas was observed in male rats (1/50, 2/50 and 6/50, for control, low dose and high dose, respectively). However the combined incidence of thyroid follicular cell adenomas and carcinomas was not increased significantly (2/50, 6/50, 6/50 for control, low-dose, and high dose, respectively). NTP (1993) indicated that the relevance of the elevated thyroid follicular tumors must be questioned since there was no concomitant increase in hyperplasia and adenomas.

Mice were gavaged with 0, 1, 2.5, 5, 10, or 20 mg/kg-day HgCl₂ (0, 0.738, 1.847, 3.693, 7.388, or 14.777 mg Hg/kg-day) 5 days/wk for 6 months (NTP, 1993). Effects were noted only in males and these were decrease in body weight at the highest dose and increased relative kidney weights at the two highest doses. Increased kidney weight correlated with an increase incidence of cytoplasmic vacuolation of renal tubule epithelium in males exposed to 3.693 mg Hg/kg-day and higher.

In the NTP (1993) mouse study, groups of 60 mice of each sex were given 0, 5 or 10 mg/kg HgCl₂ (0, 3.696, 7.388 mg Hg/kg-day) by gavage for two years. The male mice survival was not affected by the administration of mercuric chloride, but the survival of high-dose females was slightly lower than controls. Body weight gain was not affected. Mice exhibited significant increase in the incidence of nephropathy, 80-90% more than controls. Both males and females exhibited significant increase in severity scores for nephropathy with increasing dose. Renal tubule adenomas or adenocarcinomas in males dosed by gavage occurred in 3/49 high dose males, while the historical incidence was 0/205. Still, tumor incidence was not statistically significant over controls, but a statistically significant trend (p=0.032) for increased incidence with increasing dose was noted.

Although both studies provide suggestive evidence for carcinogenicity of mercuric chloride, the seriousness of the renal lesions and the decreased survival, particularly in male rats, led NTP to conclude that the potential for nephrotoxicity from HgCl₂ poses a far greater hazard than the potential for carcinogenicity (U.S. EPA, 1994; NTP, 1993).

Toxicological Effects in Humans

Acute Toxicity

Mercury salts pose a greater acute health hazard via ingestion than metallic mercury. Typically, fatalities range from the ingestion of 1 to 4 g of mercury chloride although some have occurred with as little as 0.5 g. Signs of acute intoxication occur in two phases. Phase I is characterized by burning pain in the chest, discoloration of the oral mucous membranes, severe gastrointestinal pain, vomiting, bloody diarrhea, metallic taste, salivation, tachycardia, weak pulse, tachypnea, pallor, prostration, and possibly shock, circulatory collapse and death. If the patient survives to the third day, Phase II signs appear and these are: mercurial stomatitis- characterized by glossitis and ulcerative gingivitis, loosening of the teeth, jaw necrosis, proximal tubular necrosis resulting in transient polyuria, albuminuria, cylindruria, hematuria, anuria and renal acidosis. Other effects may include dysentery, tenesmus, colonic ulceration, capillary damage, liver necrosis, occasionally tremors and peripheral neuropathies or other neurological effects. Death may occur from minutes to weeks after exposure (Gosselin et al., 1984; Troen et al., 1951).

Subchronic Toxicity

Mercurous chloride was used in the treatment of worms as well as colic in children (U.S. EPA, 1994). Some children developed a syndrome called acrodynia or "pink disease." This condition was characterized by generalized body rash, pink coloring of the extremities, listlessness and irritability, excessive perspiration and thirst, depressed appetite, and severe pain (Warkany and Hubbard, 1953).

Renal toxicity is a common effect seen in shorter-term to longer-term exposures to inorganic mercury. In occupational studies, workers in several industries were reported to have increased proteinuria, increased urinary excretion and plasma content of β -galactosidase, increases in albuminuria; all associated with glomerular dysfunction. However, there are other studies which provide either limited evidence or no evidence at all of the association of mercury exposure with signs of renal toxicity (WHO, 1991; Kazantzis et al., 1962; ATSDR, 1997). These results may indicate that there are sensitive human subpopulations to mercury-induced renal toxicity.

Decreased renal output and renal failure were reported in a man receiving daily applications for two months of Chinese medicine containing mostly mercurous chloride (Kang-Yum and Oransky, 1992). Young African women using skin lightening creams containing ammoniated mercuric chloride showed nephrotic syndrome (Barr et al; 1972). This syndrome consisted of elevated urinary protein, edema and decreased serum albumin, alpha-1-globulin, beta-globulin, and gamma-globulin. Remission was reported upon discontinuation of the creams.

Genetic Toxicity

Two occupational studies attempted to identify genotoxic effects in workers inhaling inorganic mercury. In the first study (Popescu et al., 1979), 18 workers were exposed to a mixture of mercuric chloride, methyl mercuric chloride and ethyl mercuric chloride had significant increases in the frequency of acentric fragments (chromosome breaks). Unfortunately, the study was not controlled for the effects of gender, smoking habits or sample size. The second study evaluated 19 mercury fulminate-manufacturing workers (Anwar and Gabal, 1991). Increases in the incidence of chromosomal aberrations and micronuclei in peripheral lymphocytes were reported when exposed workers were compared with age-matched controls. However, there was no correlation with mercury levels or with duration of exposure, and the study authors concluded that mercury may not have been involved with these effects.

Developmental and Reproductive Toxicity

Sikorski et al. (1987) studied reproductive failure in Polish female dental personnel. Increased rates of spontaneous abortions, still births or congenital malformations (23% vs. 11% in controls) were noted. However, there are notable study deficiencies and these results have been disputed (Larsson, 1995).

In one case, spontaneous abortion was observed 18 hours after a women ingested one tablet of mercuric chloride (U.S. EPA, 1997A). It is unclear whether this was the result of the direct effect of mercury.

Immunotoxicity

The immune response to mercury in humans appears to be idiosyncratic as not all exposed persons affected show the same response as either increased or decreased immune activity. In some studies of chlor-alkali workers, there were no reported increases in serum antibody or autoantibody titers. In a study of mercury refinery workers, increases in these titers were noted (ATSDR, 1997; U.S. EPA, 1997A).

Contact dermatitis caused by varying exposures to inorganic mercury has been reported. Patch tests show cross-reactivity with many forms of mercury, both inorganic and organic. Skin prick tests have demonstrated that mercury salts can induce hypersensitivity responses. Furthermore, some claims have been made regarding hypersensitivity associated with the presence of dental amalgam restorations (ATSDR, 1997).

Neurotoxicity

Neurotoxicity is common to all forms of mercury intoxication. Acute, intermediate and chronic exposures elicit similar toxicologic effects. However, with acute exposures these effects generally follow some time later than other symptoms.

Studies in chlor-alkali workers (exposed to a number of inorganic mercury salts) and other chemical workers report neurological deficits. Tremors appeared at urinary mercury concentrations of 0.5 mg/L (ATSDR, 1997). Nerve conduction velocities were decreased in chemical industry workers exposed to a variety of inorganic mercury compounds. These decreases were proportional to urinary and blood mercury concentrations (Singer et al., 1987).

Chronic Toxicity

No information was located on human chronic exposure to mercury salts.

Carcinogenicity

No studies were located that evaluated the incidence of human cancer from inorganic mercury exposure.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

As stated in the introduction, this evaluation is concerned with the health effects posed by the presence of inorganic mercury in drinking water. The most appropriate representative of the class of inorganic mercury compounds is mercuric chloride, being the most toxic and well studied of all. From the foregoing discussion, it should be apparent that the most sensitive effect of inorganic mercury exposure is renal toxicity. Other toxicities noted with inorganic mercury exposure include effects on the gastrointestinal tract and developmental toxicity.

Two risk assessment approaches have been used by the Agency for Toxic Substance and Disease Registry (ATSDR) and United States Environmental Protection Agency (U.S. EPA) to address the risk of ingestion of inorganic mercury.

The ATSDR derives Minimum Risk Levels (MRLs) for acute duration exposure (14 days or less) and intermediate term exposure (15- 364 days) for inorganic mercury. The intermediate value is based on the subchronic portion of the NTP (1993) study (also described in Dieter et al., 1992), where rats were exposed to mercuric chloride 5 days/wk for 6 months by gavage. In this study, a NOAEL of 0.23 mg Hg/kg-day is identified based on absence of renal effects (increased absolute

and relative kidney weights at the 0.462 mg/kg-day dose level). The derived MRL is 0.002 mg Hg/kg-day based on the NOAEL of 0.16 mg Hg/kg-day (adjusted to 7 day exposure period) and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

No MRL for chronic exposure was derived because the study identifying the lowest LOAEL from the chronic exposure study (NTP, 1993) reported a substantial decrease in survival rate and kidney toxicity for male rats at the lowest dose.

The U.S. EPA (1997; 1995; 1994) approach for determining an MCL for mercury in drinking water is based on the results of a workshop conducted in 1987 (U.S. EPA, 1988). The workshop concluded that the most sensitive adverse effect of exposure to mercuric mercury was that of induced autoimmune glomerular nephritis. They concluded that studies evaluating this effect in the most sensitive strain identified, the Brown Norway rat, would be a good surrogate for human safety evaluations to represent the most sensitive human population. As a result of this decision, no additional safety factor would be used to account for human variability, because it was assumed that the most sensitive human would be as sensitive as this rat strain. Druet et al. (1978), Bernaudin et al. (1981), and Andres and Brentjens (1984) conducted three studies evaluating this autoimmune glomerular nephritis. In the Bernaudin et al. (1981) and Andres and Brentjens (1984) studies, mercuric chloride was administered orally either in feeding or by gavage for 60 days. In Druet et al. (1978), mercuric chloride was given subcutaneously for 12 weeks. No NOAEL could be identified in any of these studies and limited numbers of animals were used. Individual Drinking Water Equivalent Levels (DWELS) were calculated to determine a concentration in water (although no mode of exposure included the drinking water route) and they were 7.0 µg/L (Druet et al., 1978), 11 µg/L (Bernaudin et al., 1981) and 22 µg/L (Andres and Brentjens, 1984). Since no study was adequate in itself for sole use as a determinant of a safe level, all DWELS were compared and the consensus choice for the final DWEL was 10 µg/L.

The approach undertaken here is an adaptation of the ATSDR (1997) approach, in that it develops health protective values from the results of the subchronic and chronic studies conducted by the NTP (1993). Although ATSDR would not derive a chronic MRL from the chronic NTP (1993) study, because of concerns over frank toxicity, OEHHA believes that the results from the chronic study can be used. In the chronic NTP (1993) study, rats exposed to a dose 1.847 mg Hg/kg-day (to yield 1.319 mg Hg/kg when adjusted from a five to seven-day dosing period) showed lower survival rates than controls and had more severe kidney toxicity. This dose can be designated as a LOAEL, and the severe signs of toxicity can be accommodated in the risk computation by using a higher level of uncertainty in the public health protective concentration estimation.

Mercury and mercury compounds are listed as reproductive toxicants under the Safe Drinking Water and Toxic Enforcement Act of 1986 (22CCR 12000).

Carcinogenic Effects

Genotoxicity and mutagenicity studies conducted indicate that inorganic mercury compounds are either non-genotoxic or weakly genotoxic. There is some indication from *in vivo* and *in vitro* studies that mercury causes chromosomal aberrations and clastogenicity. However in two occupational studies, the results were inconclusive. Generally, mercury was negative in point

mutation assays. U.S. EPA concludes that at least mercury is not a potent mutagen (U.S. EPA, 1994). Nevertheless, it appears that mercury is capable of damaging DNA.

Based on the results from two animal studies, orally administered inorganic mercury resulted in no associated increase in tumors. Fitzhugh et al. (1950) exposed rats to mercuric acetate (which behaves more like inorganic rather than organic mercury). Only renal effects were found at the higher doses. The Fitzhugh et al. (1950) study cannot prove conclusively that mercuric acetate was not associated with an increase in tumors. Tumors may have been missed because of incomplete histological analysis of animal tissues. No effects on cancer incidence were indicated in a long-term study conducted in mice (Schroeder and Mitchener, 1975). However, this study is deficient in that only one dose was used and the maximum tolerated dose may not have been achieved. Mice appear to be more resistant to the effects of mercury than rats (NTP, 1993).

The NTP (1993) study of rats and mice is a better study in terms of protocol. However, the major deficiency of the chronic study is that the applied doses are too high, since the male rat lethality was significant; hence, the applied doses exceeded the maximum tolerated dose. The increases in hyperplasia and squamous papillomas of the forestomach in male rats were considered to be "some evidence" of carcinogenic activity. The thyroid follicular carcinomas "may have been" dose-related in the male rats. The increase in forestomach papillomas in female rats and the positive trend toward renal adenomas and carcinomas in male mice were considered "equivocal" findings by NTP (1993). There was "no evidence" for carcinogenic activity of mercuric chloride to female mice. The NTP (1993) considered the forestomach tumors to be of limited relevance to humans, since there is no evidence that these contact site tumors progress to malignancy. The thyroid carcinomas appeared to be elevated in a dose-related way, but without the concomitant increase in adenomas and hyperplasia, their relevance is suspect.

Based on limited animal data and the absence of human data, mercuric chloride was designated as Group C, possible human carcinogen by the U.S. EPA (1997; 1994)(IRIS, 1997). IARC (1993) has stated that there is limited evidence for carcinogenicity of mercuric chloride in experimental animals and not classifiable as to their carcinogenicity to humans (Group 3).

The potential carcinogenicity of inorganic mercury compounds is judged to be rather weak, as compared with the potential for renal toxicity. Therefore, a cancer risk calculation will not be undertaken.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, as well as for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures. In this case, inorganic mercury is not volatile or permeable enough to consider other routes of exposure besides ingestion of drinking water.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for inorganic mercury in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{\text{NOAEL/LOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{L/day}}$$

where,

NOAEL/LOAEL	=	No-observed-adverse-effect-level or lowest-observed-adverse-effect-level
BW	=	Adult body weight (a default of 70 kg for male or 60 kg for female)
RSC	=	Relative source contribution (a default of 20% to 80%)
UF	=	Uncertainty factors (typical defaults of a 10 to account for inter-species extrapolation, a 10 for uncertainty from the subchronic nature of the principal study and a 10 for potentially sensitive human subpopulations)
L/day	=	Adult daily water consumption rate (a default of 2 L/day)

In the NTP (1993) two-year study, male rats were administered or 1.847 and 3.693 mg Hg/kg-day in water by gavage. Significant numbers of increased deaths occurred at both doses, thus the lower dose can be designated as a LOAEL.

Therefore,

$$C = \frac{1.319 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{10,000 \times 2\text{L}}$$

$$C = 0.000924 \text{ mg/L} = 0.923 \text{ } \mu\text{g/L}$$

where:

LOAEL	=	adjusted LOAEL of 1.32 mg/kg-day (resulting from 2.5 mg/kg HgCl ₂ converted to 1.85 Hg/mg-day and then adjusted for five to seven days of exposure)
BW	=	70 kg
UF	=	10,000 (10 for interspecies, 10 for intraspecies, 10 for LOAEL to NOAEL, 10 as a modifying factor for frank toxicity)

$$\begin{aligned} \text{L/day} &= 2 \text{ L/day} \\ \text{RSC} &= 0.20 \end{aligned}$$

In the NTP (1993) six month study, rats were administered 0, 0.23, 0.462, 0.739, 1.847 or 3.694 mg Hg/kg-day by gavage. The decreases in body weight gains and increases in absolute and relative kidney weights at doses of 0.46 mg Hg/kg-day and above were sufficient to designate the dose of 0.462 mg Hg/kg-day as LOAEL. Therefore, the dose of 0.23 mg Hg/kg-day would be NOAEL.

Therefore,

$$C = \frac{0.16 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{1,000 \times 2 \text{ L}}$$

$$C = 0.0012 \text{ mg Hg/L} = 1.2 \text{ } \mu\text{g/L}$$

Where,

$$\text{NOAEL} = 0.16 \text{ mg Hg /kg-day (0.23 mg Hg/kg converted from five to seven days of exposure)}$$

$$\text{BW} = 70 \text{ kg}$$

$$\text{UF} = 1,000 \text{ (10 for interspecies, 10 for intraspecies, 10 for subchronic to chronic estimation)}$$

$$\text{L/day} = 2 \text{ L/day}$$

Essentially, the two calculated health-based concentrations are fairly close but the chronic value reflects higher levels of uncertainty, since an additional uncertainty factor was used to accommodate frank toxicity. The value derived from the subchronic study is more appropriate as the recommended PHG. Therefore, the PHG is 0.0012 mg/L, or 1.2 $\mu\text{g/L}$.

This value differs by factor of two from U.S. EPA's MCL of 0.002 mg/L, which was based on a consensus DWEL of 0.01 mg Hg/L.

RISK CHARACTERIZATION

The primary sources of uncertainty in the development of this PHG are also the general issues of uncertainty in any risk assessment, particularly inter- and intraspecies extrapolation and relative source contribution (RSC). It was assumed that animals would be less sensitive as compared to humans to the effects of inorganic mercury. With no information on chronic intoxication of humans with inorganic mercury, this would be a conservative assumption. Likewise, it would be prudent and conservative to assume that there would be individuals more sensitive to the effects

of inorganic mercury than the general population. Indeed, there is evidence that strains of rats show particular sensitivity to the renal effects of mercury, which would support this assumption.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using uncertainty factors (UFs), body weights and water consumption rates (L/day) and the RSC, respectively. The RSC range is 20% to 80% (0.2 to 0.8) depending on the scientific evidence. In this case, an RSC is assumed to be 20% based on the understanding that most of the mercury body burden is contributed from other avenues of exposure. As was stated above, large amounts of organic mercury are available through ingestion of fish and mercury is released into the blood from dental amalgam restorations. Both metallic and organic mercury is converted to inorganic mercury in the body. Besides these sources, inorganic mercury found in food contributes to the mercury body burden. To take into account these non-drinking water sources of inorganic mercury; an RSC of 20% is used.

Other areas of uncertainty related to inorganic mercury PHG development are related to inadequate toxicological information. Ideally, for assessing the human health risks of chronic exposure to a chemical in water, chronic bioassays need to be performed which adequately demonstrate progressive nature of toxicity due to the agent. Unfortunately, this has not been the case with the best chronic mercury study performed to date (NTP, 1993). There was no NOAEL identifiable from the study and the lowest dose produced significant mortality. A LOAEL to NOAEL uncertainty factor was used in the risk assessment, but this factor is used under the assumption that the actual NOAEL is reasonably close to the LOAEL (usually for minor to moderate degrees of toxicity) (Dourson et al., 1996). Because the LOAEL is actually frank toxicity (lethality), one factor of 10 may not be sufficient to approximate the NOAEL, therefore an additional modifying factor of 10 is used. Nonetheless, the PHG is based on a computation of a dose from the 6 month exposure study (NTP, 1993) conducted in rats which indicates a NOAEL.

The 6 month study is considered a subchronic study for the purposes of risk assessment because of the severity of the cumulative effects of mercury. The two highest doses in the 6 month study were selected for the 2 year study, because of the mild degree of toxicity noted after 6 months. However, it was clear that these doses were severely toxic after two years. Therefore, effects seen upon 6 months of exposure to inorganic mercury can not be indicative of a lifetime of exposure (two years). To accommodate less than lifetime exposure when using a NOAEL from a subchronic study, an additional uncertainty factor of 10 is used. Overall, the six-month exposure study is selected because, there is slightly less uncertainty in the derivation of the PHG.

Two other approaches used to derive chronic toxicity values for inorganic mercury compounds are available. The U.S. EPA approach is dependent upon the unique sensitivity of a specific strain of rat to renal toxicity induced by mercuric chloride. There are two major sources of uncertainty in this approach. First, it is difficult to address whether using this strain will adequately address the most sensitive human population. Second, the response is dependent upon dose estimation from studies which are so limited individually that they need to be combined for a determination. Finally, a committee decision on the final DWEL, rather than a more precise extrapolation, was used. In the ATSDR approach, a subchronic study is used to define a NOAEL for "intermediate duration" exposures. No lifetime values are derived, because the chronic study had substantial lethality at the lower dose. No attempt was made (perhaps due to policy) to use an additional uncertainty factor of 10 to accommodate the subchronic to chronic results in the subchronic study. They also choose not to use an additional factor of 10 to

accommodate frank toxicity in the chronic study. As a result, no chronic (lifetime) extrapolation of a safe dose is derived.

The approach used for derivation of the PHG for inorganic mercury in water is an adaptation of the ATSDR approach, using the subchronic NTP (1993) study rather than immunological studies conducted with the Brown Norway rat. The NTP study ranks as the best conducted and evaluated studies using inorganic mercury. The chronic NTP (1993) study would have been better if the doses used in the chronic study were not too high, as substantial lethality occurred to warrant using an additional uncertainty factor for frank toxicity. However, when compared with the subchronic study, the health protective value from the chronic study is fairly close to 1.2 ppb, the selected PHG. The uncertainty factors used to derive the basis for this PHG are rather large (total of 1000). Although the U.S. EPA approach appears to use fewer orders of magnitude in uncertainty factors, this does not mean that inherently, there is less uncertainty in the MCL estimation than with the PHG. A major assumption is that the Brown Norway rat's immunological sensitivity would be as sensitive as the most sensitive human population; there is no way of knowing this. Furthermore, these studies are short-term and age-related changes in sensitivity are not known. OEHHA feels there is as much certainty using a more "conventional" rat population exposed for a longer period of time and accounting for interspecies differences with the use of an uncertainty factor as there is with using a more sensitive rat strain.

The Peer Review Workshop consensus MCL was 0.001 mg Hg/L based on the DWEL of 0.010 mg Hg /L and RSC of 10 percent. The WHO value (1993) is also 0.001 mg/L (1 ppb) for all forms of mercury in water.

OTHER GUIDANCE VALUES AND REGULATORY STANDARDS

Federal and state drinking water regulations for mercury in drinking water have been based on the hazards of inorganic mercury. The federal Maximum Contaminant Level Goal (MCLG) and MCL is 0.002 mg/L for drinking water (U.S. EPA, 1997a). This MCL is derived from the DWEL of 0.01 mg Hg/L selected by the Peer Review Workshop convened by the U.S. EPA on October 26-27, 1987 and based on the autoimmune response in a sensitive strain of rat. In its review of the literature in 1994 covering the intervening years, U.S. EPA concluded that no revision of the MCL was needed at that time (U.S. EPA, 1994).

A Maximum Contaminant Level (MCL) of 0.002 mg/L was established by the California Department of Health Services (DHS) in 1995 (22 CCR 64431). This value is identical to that of the U.S. EPA MCL because it adopted the U.S.EPA MCL as the California one.

WHO has developed a guideline 0.001 mg/L for all forms of mercury in drinking water (WHO, 1993).

REFERENCES

- 22 CCR 12000 (1997). Code of California Regulations. Title 22, Chp 3, Safe Drinking Water and Toxic Enforcement Act of 1986.
- 22 CCR 64431 (1998). Code of California Regulations. Title 22, Chp 15, Art 4. Primary Standards -Inorganic Chemicals. Sec 64431. Maximum Contaminant Levels- Inorganic Chemicals. Table 64431-A.
- Aberg B, Ekman L, Falk R, Greitz U, Persson G, Snihs J-O (1969) Metabolism of methyl mercury (^{203}Hg) compounds in man . Arch Environ Health 19:478-484.
- Andersson AW (1979). Mercury in soils. In: Nriagu JO, ed. The biogeochemistry of mercury in the environment. New York, NY: Elsevier/North Holland Biomedical Press, pp. 79-112.
- Andres P, Brentjens JR (1984). IgA-IgG disease in the intestine of Brown Norway rats ingesting mercuric chloride. Clin Immunol Immunopathol 30:488-494.
- Anwar WA, Gabal MS (1991). Cytogenic study in workers occupationally exposed to mercury fulminate. Mutagenesis 6(3): 189-192.
- ATSDR (1997). Toxicological Profile for Mercury. Draft for Public Comment (Update).. Prepared by Research Triangle Institute under Contract No. 205-93-0606. Prepared for : U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. August 1997.
- Barr RD, Rees PH, Cordy PE, Kungu A, Woodger BA, Cameron HM (1972). Nephrotic syndrome in adult Africans in Nairobi. Brit Med J 2:131-134.
- Berlin M. (1986). Mercury. In: Handbook on the Toxicology of Metals, 2nd ed., Friberg GR, Norber VB, Vouk VB, ed. New York : Elsevier Press
- Bernaudin JF, Druet E, Druet P, Masse R (1981). Inhalation or ingestion of organic or inorganic mercurials produces auto-immune disease in rats. Clin Immunol Immunopathol 20:129-135.
- Cantoni O, Christie NT, Swann A, Drath DB, Costa M (1984). Mechanism of HgCl_2 cytotoxicity in cultured mammalian cells. Mol Pharmacol 26:360-368.
- Carmignani M, Boscolo P, Artese L, Del Rosso G, Porcelli G, Felaco M, Volpe AR, Giulliano G (1992). Renal mechanisms in the cardiovascular effects of chronic exposure to inorganic mercury in rats. Brit J Ind Med 49:226-232.
- Carmignani M, Boscolo P, Presiosi P (1989). Renal ultrastructural alterations and cardiovascular functional changes in rats exposed to mercuric chloride. Arch Toxicol (Suppl 13):353-356.
- Carmignani, M, Finelli VN, Boscolo P (1983). Mechanisms in cardiovascular regulation following chronic exposure of male rats to inorganic mercury. Toxicol Appl Pharmacol 69:442-450.

- Clarkson TW (1989). Mercury. *A J Am Coll Toxicol* 8:1291-1295.
- Dieter MP, Boorman GA, Jameson CW, Eustis SL Uraih LC (1992). Developments of renal toxicity in F344 rats gavaged with mercuric chloride for two weeks, or 2,4,6,15, and 24 months. *J Toxicol Environ Health* 36:319-340.
- Dourson ML, Feltier SP Robinson D (1996). Evolution of Science-Based Uncertainty Factors in Noncancer Risk Assessment. *Regulatory Toxicol and Pharmacol* 24:108-120.
- Druet P, Druet E, Potdvin F, Sapin C (1978). Immune type glomerular nephritis induced by HgCl₂ in the Brown Norway rat. *Ann Immunol (Paris)* 129c:777-792.
- Dunn JD, Clarkson TW, Magos L (1981). Interaction of ethanol and inorganic mercury: generation of mercury vapor *in vivo*. *J Pharmacol Exp Ther* 216:19-23.
- Fitzhugh OG, Nelson AA, Laug EP Kunze FM (1950). Chronic oral toxicities of mercuric-phenyl and mercuric salts. *Arch Ind Hyg Occup Med* 2:433-442.
- Gale, TF (1974). Embryopathic effects of different routes of administration of mercuric acetate in the hamster. *Environ Res* 8:207-213.
- Ganser AI, Kirschner DA (1985). The interaction of mercurials with myelin: Comparison of *in vitro* and *in vivo* effects. *Neurotoxicology* 6:63-78.
- Gosselin RE, Smith RP, Hodge HC, Braddock JE (1984). Mercury. In : *Clinical toxicology of commercial products*. 5th ed. Baltimore, MD: William & Wilkins. pp. III-262 - III-275.
- Gunderson EL (1988). FDA total diet study, April 1982-April 1984, dietary intakes of pesticides, selected elements and other chemicals. *J Assoc Off Anal Chem* 71(6):1200-1209.
- Halbach S, Clarkson T (1978). Enzymatic oxidation of mercury vapor. *A Rev Respir Dis* 47(1):175-178.
- Hapke HJ (1991). Metals accumulation in the food chain and load of feed and food. In: Merian E, ed. *Metals and their compounds in the environment*. Fed. Rep Ger: VSH. Weinheim, 469-479.
- HSDB (1997). Hazardous Substances Data Bank (HSDB). Bethesda, Maryland: National Library of Medicine (NLM), National Toxicology Program (NTP).
- Hursh JB, Clarkson TW, Cherian MG Vostal JJ, Mallie PV. (1976). Clearance of mercury (Hg 197, Hg-203,) vapor inhaled by human subjects. *Arch Environ Health* 31:302-309.
- IARC (1993). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 58. Lyon, France: International Agency for Research on Cancer. World Health Organization. pp. 239-346
- IRIS (1997). Mercuric Chloride. Integrated Risk Information Service, last revised on 4/01/97. Washington, D.C.: U.S. Environmental Protection Agency (U.S. EPA).
- Jasinski SM (1993). Mercury. In: *Mineral commodity summaries, 1993*. Washington, D.C.: US Depart of Interior, Bureau of Mines. pp 110-111.
- Jonker D, Woutersen RA, van Bladeren PJ, Til HP, Feron VJ (1993). Subacute (4 wk) oral toxicity of a combination of four nephrotoxins in rats: comparison with the toxicity of the individual compounds. *Food Chemical Toxicol* 31(2):125-136.
- Kajiwaraya Y, Inouye M (1986). Effects of methyl mercury and mercuric chloride on preimplantation mouse embryos *in vivo*. *Teratology* 33:231-237.

- Kajiwara, Y, Inouye M (1992). Inhibition of implantation caused by methylmercury and mercuric chloride mouse embryos *in vivo*. Bull Environ Contam Toxicol 49:541-546.
- Kanematsu N, Hara M, Kada T (1980). REC assay and mutagenicity studies on metal compounds. Mutat Res 77:109-116.
- Kang-Yum E, Oransky SH (1992). Chinese patient medicine as a potential source of mercury poisoning. Vet Hum Toxicol 34(3):235-238.
- Kavlock RJ, Logsdon T, Gray JA (1993). Fetal development in the rat following disruption of the maternal renal function during pregnancy. Teratology 48:247-258.
- Kazantzis G, Schiller KFR, Asscher AW, Drew RG (1962). Albuminuria as the nephrotic syndrome following exposure to mercury and its compounds. Q J Med 31(24):403-418.
- Kostial K, Kello D, Jugo S, Rabar I, Maljkovic T (1978). Influence of age on metal metabolism and toxicity. Environ Health Perspect 25:81-86.
- Larsson KS (1995). The dissemination of false data through inadequate citation. J Int Med 238:445-450.
- Lee IP, Dixon RL (1975). Effects of mercury on spermatogenesis studied by velocity sedimentation cell separation and serial mating. J Pharmacol Exp Ther 194:171-181.
- Lee YH, Shaikh ZA, Tohyama C (1983). Urinary metallothionein and tissue metal levels of rats injected with cadmium, mercury, lead, copper or zinc. Toxicology 27:337-345.
- McAnulty PA, Tesch JM, Pritchard AL, Wilby OK, Tesh SA (1982). Effects of mercury on foetal development. Teratology 25:26A.
- Nielsen JB, Andersen HR, Andersen O (1991). Mercuric chloride-induced kidney damage in mice: Time course and effect of dose. J Toxicol Environ Health 34 (4): 469-483.
- Nielsen JB. (1992). Toxicokinetics of mercuric chloride exposure in mice. J Toxicol Environ Health 37:85-122.
- Nielsen-Kudsk F (1973). Biological oxidation of elemental mercury. In: Mercury, mercurials and mercaptans, M.W. Miller and T.W. Clarkson, Ed., Springfield, Il: Charles C Thomas. p. 355.
- NTP (1993). Toxicology and carcinogenesis studies of mercuric chloride (CAS no. 7487-94) in F344/N rats and B6C3F₁ mice (gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, National Institutes of Health; NIH publication no. 91-3139. (National Toxicology Program technical report no. 408). NTIS number: PB94-10649/XAB.
- Piotrowski JK, Trojanowska B, Wisniewska-Knypl JM, Baloanowska W (1974). Mercury binding in the kidney and liver of rats repeatedly exposed to mercuric chloride: induction of metallothionein by mercury and cadmium. Toxicol Appl Pharmacol 27:11-19.
- Piotrowski JK, Szymanska JA, Skrzypinska-Gawrysiak M, Kotelo J, Sporny S (1992). Intestinal Absorption of Inorganic Mercury in Rat. Pharmacol & Toxicol 70:53-55.
- Popescu HI, Negru L, Lancranjan I (1979). Chromosome aberrations induced by occupational exposure to mercury. Arch Environ Health 34:461-463.

- Pritchard AL, Collier MJ, McAnulty PA, Tesh JM (1982a). The effects of peri- and post-natal exposure to inorganic mercury on growth, development and behaviour of rats. *Teratology* 26:20A.
- Pritchard AL, Collier MJ, McAnulty PA, Tesh JM (1982b). The effects of inorganic mercury on fertility and survival in utero in the rats. *Teratology* 26:20A.
- Rahola T, Hattula T, Korolainen A, Miettinen JK (1973). Elimination of free and protein-bound ionic mercury in man. *Ann Clin Res* 5:214-219.
- Regnell O, Tunlid A (1991). Laboratory study of chemical speciation of mercury in lake sediment and water under aerobic and anaerobic conditions. *Appl Environ Microbiol* 57(3): 789-795.
- Rizzo AM, Furst A (1972). Mercury teratogenesis in the rat. *Proc West Pharmacol Soc* 15:52-54.
- Rowland I, Davies M, Evans J (1980). Tissue content of mercury in rats given methylmercury chloride orally: Influence of intestinal flora. *Arch Environ Health* 35:155-160.
- Schroeder HA, Mitchener M (1975). Life-term effects of mercury, methyl mercury, and nine other trace metals on mice. *J Nutr* 105:452-458.
- Schwartz JG, Snider TE, Montiel MM (1992). Toxicity of a family from vacuumed mercury. *Am J Emerg Med* 10(3):258-261.
- Sikorski R, Juskiewicz t, Paszkowski T, Szprengier-Juszkeiwicz T (1987). Women in dental surgeries: Reproductive hazards in occupational exposure to metallic mercury. *Int Arch Occup Environ Health* 59:551-557.
- Sin YM, Lim YF, Wong MK (1983). Uptake and distribution of mercury in mice from ingesting soluble and insoluble mercury compounds. *Bull Environ Contam Toxicol* 31(5): 605-612.
- Singer R, Valciuska J, Rosenman A (1987). Peripheral neurotoxicity in workers exposed to inorganic mercury compounds. *Arch Environ Health* 42(4):181-184.
- Storm DL (1994). Chemical Monitoring of California's Public Drinking Water Sources: Public Exposures and Health Impacts. In: Wang, RGM, ed. *Water Contamination and Health*. New York, NY: Marcel Dekker, Inc. pp.67-124.
- Suda I, Hirayama K (1992). Degradation of methyl and ethyl mercury not inorganic mercury by hydroxyl radical produced from rat liver microsomes. *Arch Toxicol* 66(1):34-39
- Suzuki T, Hongo T, Matsuo N (1992). An acute mercuric mercury poisoning: chemical speciation of hair mercury shows a peak of inorganic mercury value. *Hum Exp Toxicol* 11(1):53-57.
- Troen P, Kaufman S, Katz KH (1951). Mercuric Bichloride Poisoning. *New England J Med* 244:459-463.
- U.S. EPA (1980). Ambient water quality criteria for mercury. Washington, D.C.: U.S. Environmental Protection Agency. Office of Water Regulations and Standards. Document no. EPA 440/5-80-058.

U.S. EPA (1988). U.S. Environmental Protection Agency Peer Review Workshop on Mercury Issues. Summary Report February 5, 1988. Washington, D.C.: Prepared by Heidi Shultz, Eastern Research Group, Inc., Arlington, Massachusetts.

U.S. EPA (1994). Summary Review of Health Effects Associated with Mercuric Chloride: Health Issue Assessment. U.S. Environmental Protection Agency . Office of Research and Development. EPA/600/R-92/199. June 1994.

U.S. EPA (1992). 40 CFR Parts 141 and 142, National Primary Drinking Water Regulations (NPDWR); Synthetic Organic Chemicals and Inorganic Chemicals, Final Rule. Federal Register, Vol. 57, No. 138, pp. 31776-31849. Friday, July 17. Washington, D.C.: U.S. EPA.

U.S. EPA (1990). 40 CFR Parts 141, 142 and 143, National Primary and Secondary Drinking Water Regulations; Synthetic Organic Chemicals and Inorganic Chemicals, Proposed Rule. Federal Register, Vol. 55, No. 143, pp. 30370-30448. Wednesday, July 25. Washington, D.C.: U.S. EPA.

U.S. EPA (1997a) Mercury Study Report to Congress. Volume V: Health Effects of Mercury and Mercury Compounds. U.S. Environmental Protection Agency, Office of Air Quality Planning & Standards and Office of Research and Development. EPA-452/R-97-007. NTIS number: PB98-124779

U.S. EPA (1997b). Mercury Study Report to Congress. Volume III: Fate and Transport of Mercury in the Environment. U.S. Environmental Protection Agency, Office of Air Quality Planning & Standards and Office of Research and Development. EPA-452/R-97-005. NTIS number: PB98-124753.

Vershaeve L, Kirsch-Volders M, Hens L, Susanne C, (1985). Comparative in vitro cytogenetic studies in mercury-exposed human lymphocytes. *Mutat Res* 157:221-226.

Von Berg R (1995). Toxicology Update: Inorganic Mercury. *J Appl Toxicol* 15(6):483-493.

Warkany J, Hubbard DM (1953). Acrodynia and Mercury. *J of Pediatrics* 42:365-386.

Watanabe T, Shimada T, Endo A, (1982). Effects of mercury compounds on ovulation and meiotic and mitotic chromosomes in female golden hamsters. *Teratology* 25:381-384.

Weigert P (1991). Metal loads of food of vegetable origin including mushrooms, In: Merian E, ed. *Metals and their compounds in the environment*. Weinheim, Fed Rep Ger :VCH p 449-468.

WHO (1993). Guidelines for drinking water. Second Edition. Volume 1: Recommendations. Geneva, Switzerland: World Health Organization..

WHO (1990). Methyl mercury. Vol 101. Geneva, Switzerland: World Health Organization.

WHO (1991). Inorganic Mercury Vol 118. Geneva, Switzerland: World Health Organization.

Winship KA (1985). Toxicity of mercury and its inorganic salts. *Adverse Drug React. Acute Poisoning Review* 4(3):129-160,

Yess NJ (1993). U.S. Food and Drug Administration survey of methyl mercury in canned tuna. *J AOAC Int* 76:(1)36-38.

Zasukhina GD, Vasilyeva IM, Sdirkova NI, Krasovsky GN, Vasyukovich LY, Kenesariiev UI, Butenko PG (1983). Mutagenic effect of thallium and mercury salts on rodent cells with different repair activities. *Mutat Res* 124:163-173.