CE update [generalist]

The Toxicology of Mercury

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After reading this article, the reader should be able to understand the clinical manifestations and toxicological effects of mercury poisoning. Generalist exam 0204 questions and answer form are located after the "Your Lab Focus" section, p.635.

- Mercury exists in multiple oxidative states, as inorganic salts, and as organic complexes.
- Mercury ions produce toxic effects by protein precipitation, enzyme inhibition, and generalized corrosive action.
- Mercury poisoning is frequently misdiagnosed because of its insidious onset, coupled with nonspecific signs and symptoms.

The heavy metal mercury has been used for centuries both as a medicine and a poison and is currently used for many commercial purposes. Recently, attention has been refocused on this metal due to concern of environmental exposure. Some particular sources of exposure to mercury that have been publicized include ingestion of contaminated seafood, administration of vaccines to infants, use in dental amalgams, and inclusion in folk remedies and rituals. The chemistry, toxicokinetics, mechanism of action, sources of risk and exposure, regulatory actions, clinical manifestations of acute and chronic exposure, treatment, and laboratory testing for mercury will be reviewed and discussed. Salient features of both chronic and acute poisoning will be illustrated using case studies.

	Mercury	Mercuric (II) Chloride	Mercuric (II) Sulfide	Mercurous (I) Chloride
	Hg	Cl^- Hg^{2+} Cl^-	Hg=S	Cl—Hg—Hg—Cl
Synonym:	Hydrargyrum Liquid silver Metallic mercury	Bichloride of mercury Mercury chloride Mercury perchloride	Vermilion Mercury sulfide Red mercury sulfide	Calomel Mercury monochloride Mercury protochloride
Formula:	Hg	$HgCl_2$	HgS	Hg_2Cl_2
Valence:	0	+2	+2	+1
Molecular Weight:	200.59	271.50	232.66	472.09
Chemical State:	Elemental	Inorganic	Inorganic	Inorganic
Physical State:	Heavy Liquid	Solid	Solid	Solid
Toxicity:	High	High to Moderate	High to Moderate	Moderate to Low

	Mercurite Nitrate	Mercuric (II) Acetate*	Methylmercuric Chloride	Methyl Mercury
	O_3N—Hg—NO_3	O^- Hg^{2+} O O O^-	H_3C—Hg—Cl	Hg—CH_3
Synonym:	Mercury pernitrate	Mercury (2+) salt Mercury diacetate Diacetocymercury	Chloromethylmercury Monomethyl mercury chloride Methylmercury chloride	Monomethylmercury
Formula:	HgN_2O_6	$HgC_4H_6O_4$	CH_3HgCl	CH_3Hg
Valence:	+2	+2	+2	+2
Molecular Weight:	324.60	318.68	251.10	215.66
Chemical State:	Inorganic	Organic	Organic	Organic
Physical State:	Solid	Solid	Solid	Solid
Toxicity:	High to Moderate	Moderate	Moderate	High to Moderate

	Dimethylmercury	Thimerosal	Phenylmercuric acetate
	H_3C—Hg—CH_3	O C—ONa $SHgCH_2CH_3$	O O Hg
Synonym:	Mercury Methyl mercury	Thiomersalate Mercurothiolate Merthiolate	Phenylmercury acetate Acetoxphenylmercury Mercury (II) acetate
Formula:	C_2H_6Hg	$C_9H_9HgNaO_2S$	$C_8H_8HgO_2$
Valence:	+2	+1	+2
Molecular Weight:	230.66	404.82	336.74
Chemical State:	Organic	Organic	Organic
Physical State:	Liquid	Solid	Solid
Toxicity:	High	Moderate to Low	Moderate

*Although organic moieties are associated with the Hg atom, Hg^{2+} is released in aqueous solution due to the ionic nature of the mercury-carbon bonds.

References: 1) Agency for Toxic Substances and Disease Registry (ATSDR) ToxFAQs, September 1995 (http://www.atsdr.cdc.gov/toxprofiles). 2) Budavari S, O'Neil MJ, Smith A, et al, eds. The Merck Index 12th ed. Whitehousestation, NJ; 1996.

[F1] Structures, physical, and chemical properties of mercury compounds

Like arsenic, mercury has been used for various purposes, including medicinal. Prehistoric cave drawings were made using cinnabar, the red ore containing mercuric sulfide. The Romans mined cinnabar to extract mercury, and alchemists used mercury in their attempts to create gold from other metals. Today, mercury is produced as a by-product of gold and bauxite mining. Medicinal uses of mercury have included its use as a diuretic, antiseptic, skin ointment, laxative, and as a treatment of syphilis. Mercury has also been used as a poison. In an ironic illustration of the dose-related properties of mercury, the great sculptor Benvenuto Cellini, was apparently cured of a severe case of syphilis when poisoned by a sublethal dose of mercury.[1,2]

Mercury is 1 of 2 elements (bromine is the other) that are liquid at room temperature. Its elemental symbol is Hg, derived from the Greek word hydrargyrias, meaning "water silver." This is a fitting term, since elemental mercury does resemble liquid silver. The greatest source of mercury happens to be natural. Outgassing of granite rock accounts for more than 80% of the mercury found in the atmosphere and on the earth's surface.[3] Mercury is found in many industries, such as battery, thermometer, and barometer manufacturing. Some consumer products that contain mercury include automotive equipment with halide relay switches, fluorescent and high-intensity discharge lamps, and fungicides. Before 1990, paints contained mercury as an anti-mildew agent. In medicine, mercury is used in dental amalgams, as a preservative in vaccines, and in various antiseptic agents. It is also used ritualistically among Latino and African-Caribbean populations during the practice of spiritist faiths such as Santeria, Esperitismo, and voodoo.

The Basics: Chemistry and Toxicokinetics

As with other metals, mercury exists in multiple oxidative states, as inorganic salts, and as organic complexes [F1]. The oxidative states include elemental mercury (Hg^0), mercurous (Hg^{+1}), or mercuric (Hg^{+2}). Mercury in any form is toxic. The difference lies in how it is absorbed, how it is biotransformed to other mercury forms, the clinical signs and symptoms, and the response to treatment modalities. Mercury poisoning can result from vapor inhalation, ingestion, injection, or absorption through the skin.

Elemental mercury (Hg^0) is found as a liquid with a vapor pressure of 0.00185 mm at 25°C. This means that elemental mercury is extremely volatile. For example, if a dish of mercury is placed in the center of a room where the temperature is 25°C, one could expect to measure 20 mg of mercury (or 2.4 ppm) in the air (up to the distance of a radial meter) surrounding the mercury. The rate at which mercury volatilizes is directly related to temperature so that as the temperature increases so does the amount of mercury in the surrounding air. The American Conference of Governmental Industrial Hygienists (ACGIH) has established a threshold limit for mercury vapor of 0.05 mg/m^3 of air for continuous 40 hours/week exposure. Long-term chronic exposure to mercury vapor in excess of 0.05 mg/m^3 of air may result in cumulative poisoning. Exposure is most commonly through an occupational source including exposure in the home.

Safety issues within the laboratory arise when mercury is heated or atomized into small particles. A reason for avoiding the use of mercury-based thermometers to monitor heated ovens is because if the thermometer broke at the higher oven temperatures, the resulting exposure would be at a significantly higher dose than had the breakage occurred at room temperature or in a freezer. Other cases of exposure have occurred when mercury or mercury salts were disposed into metal drains that were later heated during repairs (ie, welding). Aerosolization into small particles occurs when mercury is subjected to a high air velocity system (ie, one tries to vacuum spilled mercury).

Since mercury easily vaporizes at room temperature, the route of absorption is often through the lungs. In humans, approximately 70% to 85% of a dose is absorbed in this manner whereas less than 3% of a dose will be absorbed dermally.[4] If elemental mercury is ingested orally, less than 0.1% is absorbed from the gastrointestinal (GI) tract and, therefore, when orally ingested is only mildly toxic.

Elemental mercury is highly lipid-soluble; a characteristic that facilitates its diffusion across the alveoli into the circulation, as well as its distribution throughout the lipophilic compartments of the body including passage across the blood brain barrier into the central nervous system (CNS) and across the placenta. In the circulation, elemental mercury binds to numerous tissues, proteins, and erythrocytes. In erythrocytes, catalase can oxidize elemental mercury to an inorganic metabolite. If elemental mercury penetrates the blood brain barrier, it is ionized and becomes trapped in the compartment where it is available to exert its neurotoxicity. Elemental mercury has the longest retention in the brain with detectable levels present for years following exposure.[5-7] The half-life of elemental mercury in adults is approximately 60 days (range: 35 to 90 days). Elemental mercury is also bioconverted to Hg^{+2} and CH_3Hg^{+1} in the gut by the action of microorganisms.[3]

Inorganic mercury salts are found in 2 oxidation states: mercurous and mercuric. Mercuric chloride (corrosive sublimate) was used as an antiseptic and though no longer used for this purpose, it is still used for many other applications including wood preservative, photographic intensifier, dry battery depolarizer, tanning agent for leather, catalyst in the manufacture of chemicals such as vinyl chloride and disinfectants, separating lead from gold, and others. Mercuric nitrate, commonly used in the felting industry, is considered to be the source of the neurological changes observed in felters in the 1800s that lead to the term "mad as a hatter." Inorganic mercury, found mostly in the mercuric salt form (eg, batteries), is both toxic and corrosive.

Common routes of exposure include the GI tract (following oral ingestion) and the skin. Studies using volunteers have shown that about 7% to 15% of an ingested dose of mercuric chloride is absorbed from the GI tract. Absorption is, in part, related to the water solubility of this compound. It has a non-uniform mode of distribution secondary to poor lipid solubility. The highest accumulation of inor-

ganic mercury is in the kidneys. Animal studies suggest that mercuric forms have a high affinity for metallothionein in renal cells. In contrast methylmercury has low affinity for metallothionein. Excretion of inorganic mercury, as with organic mercury, is mostly through feces. The charge of inorganic mercuric ions is somewhat protective, because charged particles do not cross membranes easily. Thus mercuric ions do not cross the blood-brain barrier or the placenta easily, but the slow elimination and the fact that exposure often takes place over a long period of time allows for significant CNS accumulation of mercuric ions and subsequent toxicity. The half-life of inorganic mercury is approximately 40 days. Chronic dermal exposure to inorganic mercury also may lead to toxicity.

Organic mercury can be found in 3 forms: aryl, short, and long chain alkyl compounds. The organic mercury compounds are of great interest today because they are often found in the food chain and have been used to inhibit bacterial growth in medications. Organic mercury is also found in fungicides and industrial run-off. As a result, exposure to these materials is likely. The toxicity of these compounds depends upon the ease with which the organic moiety can dissociate from the anion.

Organic mercurials are absorbed more completely from the GI tract than inorganic salts in part because they are more lipid-soluble and because they bind to sulfhydryl groups. More often, organic mercurials are absorbed from the GI tract by forming a complex with L-cysteine and crossing cell membranes on the large neutral amino acid carrier.[8] They are also corrosive, although less corrosive than inorganic forms. Once absorbed in tissues, the aryl and long chain alkyl compounds are converted to divalent cations that possess inorganic mercury toxic properties. The short chain alkyl mercurials are readily absorbed in the GI tract (90% to 95%) and remain stable in their initial forms. Alkyl organic mercury compounds have high lipid solubility and are distributed uniformly throughout the body, accumulating in the brain, kidney, liver, hair, and skin. Organic mercurials also cross the blood-brain barrier and placenta and penetrate erythrocytes, attributing to neurological symptoms, teratogenic effects, and high blood to plasma ratio, respectively.

Methylmercury has a high affinity for sulfhydryl groups, which explains its effect on enzyme dysfunction. One enzyme that is inhibited is choline acetyl transferase, which is involved in the final step of acetylcholine production. This inhibition may lead to acetylcholine deficiency, contributing to the signs and symptoms of motor dysfunction.

Excretion of alkyl mercury occurs mostly in the form of feces (90%), secondary to significant enterohepatic circulation. The biological half-life of methyl mercury is approximately 65 days.

Mechanism of Toxicity

Mercury ions produce toxic effects by protein precipitation, enzyme inhibition, and generalized corrosive action. Mercury not only binds to sulfhydryl groups but also to phosphoryl, carboxyl, amide, and amine groups. Proteins (including enzymes) with such groups readily available are susceptible to reaction with mercury. Once bound to mercury, most proteins are rendered inactive. Toxicity is in part related to the oxidative state and to the chemical form (organic versus inorganic).

As mentioned, elemental mercury vapor is highly lipid soluble which allows it to readily cross cellular membranes. It can also be oxidized to the mercuric state. Since mercuric salts form more soluble divalent compounds, these forms are more toxic than the mercurous salts that form monovalent mercury compounds. Thus, when ingested they will be more rapidly absorbed and produce greater toxicity. Only about 10% of an inorganic salt (regardless of the oxidative state) is absorbed compared to 90% absorption via the GI track of the organic forms. This means the inorganic forms are available within the GI track to exert corrosive effects on the gastrointestinal mucosa.

The organomercurial compounds are further classified according to chemical structure and relative toxicity. These groups are the long-chained arylmercury compounds and short-chained alkylmercury compounds. The group that poses the greater hazard is the short-chained alkyl compounds, such as methymercury. These are also most completely absorbed from the GI tract, distributed to the brain, liver, and kidney. Excretion is primarily in the feces. The aryl mercury compounds are excreted as mercuric ions.

Methylmercury

The dominant route of exposure to methylmercury is through the ingestion of fish. Most fish, both freshwater and saltwater, contain methylmercury. While the GI tract is the primary route of absorption, methylmercury can be absorbed through the skin and the lungs as well. Once absorbed into the circulation, methylmercury enters erythrocytes where more than 90% will be found bound to hemoglobin.[9] Lesser amounts will be bound to plasma proteins. About 10% of the burden of methylmercury is found in the brain where it slowly undergoes demethylation to an inorganic mercuric form. Methylmercury readily crosses the placenta to the fetus, where deposition within the developing fetal brain can occur. In the brain, methylmercury causes focal necrosis of neurons and destruction of glial cells and is toxic to the cerebral and cerebellar cortex. In 1953 and 1960, the toxicity of methylmercury was recognized worldwide following epidemics of mercury poisoning in the Japanese inhabitants of Minamata and Niigata Bays due to consumption of fish caught in the region. Waste containing mercuric chloride had been released into the bays and became concentrated in the fish after conversion to methylmercury by plankton.[10] The subsequent birth of infants suffering from degenerative neurological disorders, blindness, and deafness even though the mothers exhibited only mild symptoms demonstrates the increased susceptibility of the fetus to methylmercury exposure. Acute alkylmercury poisoning is often referred to as Minamata disease. The largest epidemic of methylmercury poisoning occurred in Iraq in 1971 to 1972 when more than 500 people died and more than 6,000 were hospitalized due to ingestion of bread made from seed grain treated with fungicide containing methylmercury.[11] A daily intake of more than 0.3 mg

Environmental and Occupational Exposure Limits of Mercury

T1

Defined Limit	Delegating Body/Document	Date Enacted	Threshold Exposure Limit
Permissible Air Exposure	OSHA		0.05 mg Hg/m³/8-h (organic) 0.1 mg Hg/m³/8-h (elemental)
	NIOSH		0.05 mg Hg/m³/10-h (elemental)
Ambient Air Criteria	NAAQS- Clean Air Act (EPA)	1970 (rev. 1990)	0.00006 mg Hg/m³ air
Threshold Limit	ACGIH		≤ 0.05 mg Hg/m³ of air/40-h
Ambient Water Quality Criteria	Clean Water Act (EPA)	1977 (rev. 2000)	144 ng/L (ppt)
Drinking Water Maximum	EPA		≤ 2 µg/L (ppb)
Total Body Burden			20-30 mg
Food Products (fish and seed grain)	FDA EPA (proposed recommendation)	1979 1996	≤ 1 mg/kg (ppm) CH_3Hg ≤ 0.01 mg/kg

Abbreviation: OSHA- Occupational Safety and Health Administration; NIOSH- National Institute for Occupational Safety and Health; NAAQS- National Ambient Air Quality Standards; EPA- Environmental Protection Agency; FDA- Food and Drug Administration; ACGIH- American Conference of Governmental Industrial Hygienists

References: 1) Agency for Toxic Substances and Disease Registry (ATSDR) ToxFAQs, September 1995 Available at: http://cerhr.niehs.nih.gov/genpub/topics/mercury2-ccae.html#Federal and State Government Regulatory Limits and http://www.atsdr.cdc.gov/toxprofiles. Accessed May 14, 2002.

2) Focus- Environmental Health Perspectives: Measuring mercury. Volume 104(8); August 1996. Available at: http://ehpnet1.niehs.nih.gov/docs/1996/104-8/focus.html. Accessed May 14, 2002.

methylmercury will produce chronic mercury poisoning in the average 70 kg adult. This level of consumption is consistent with steady-state mercury concentrations of 0.2 mg/L in blood, 60 mg/kg in hair, and an approximate total body burden of 25 mg.

Dimethylmercury

Dimethylmercury is the supertoxic form of mercury that has been fatal after accidental exposure. A volatile liquid organic mercuric compound, dimethylmercury is used as a reference material in nuclear magnetic resonance chemistry laboratories. In 1997 a chemistry professor at Dartmouth College died 298 days after several drops of dimethylmercury fell on her latex gloves. Clearly the gloves did not provide a protective barrier and absorption took place through the skin. Approximately 7 months after exposure, her blood mercury concentration was 1,000 µg/L.[12] Prior to death, dimethylmercury can cause devastating neurological damage such as loss of audiological (ie, speech recognition) systems.[13] Studies using mice suggest that dimethylmercury must be metabolized to methylmercury prior to entering the brain.[14]

Exposure and Risk

It has been estimated that 5,500 tons of mercury enter the global atmosphere annually from all sources including natural, anthropogenic (human activity), and oceanic emissions. Standards and guidelines for use and emissions of mercury have been implemented [T1]. Industrial demand for mercury declined by 75% from 1988 to 1996 due to elimination of mercury additives in paints and pesticides and reduction in batteries. Coal-fired utility boilers are the largest remaining identified source of mercury emissions in the United States.[15] World-wide, large quantities of liquid mercury are used to extract sedimentary gold from river bed soil by forming an amalgam which is then heated to evaporate the mercury, leaving pure gold. An estimated 130 or more tons of mercury are released per year in the Amazon basin.[16]

The 2000 Toxic Exposure Surveillance System[17] report of the American Association of Poison Control Centers documented 4,186 exposures to mercury in the United States. Of these, 980 were in children younger than 6 years with the majority of exposures in persons older than 19 years (*N*=1,843). Only 1, a gold miner, died due to an accidental exposure while attempting to extract gold with poor ventilation. World-wide exposure is much greater.

In most situations, the primary route of exposure to mercury for the general public is via the consumption of fish. The FDA advisory limit for methylmercury in commercial fish is 1 ppm (1 µg/g).[18] By comparison concentrations of 10 to 30 ppm were present in fish during the Minamata epidemic. The United States has placed restrictions on commercial fisheries prohibiting the sale of fish having a total mercury content of greater than 0.5 mg/kg. This limitation can be difficult to maintain in contaminated areas. Generally, marine levels of mercury range from undetectable to 5.0 mg/kg (average 0.2 to 0.5 mg/kg) but contaminated freshwaters have been as high as 40 mg/kg.[19] In 2001, the FDA issued an advisory to pregnant women and women of childbearing age who may become pregnant regarding the potential hazard of consuming fish that might have high levels of methylmercury. Among the fish included in the warning were shark, swordfish, king mackerel, and tilefish.[20] These fish tend to be highest in methylmercury content not only due to feeding on smaller fish, but also because they live longer and accumulate higher concentrations of mercury in their tissues. Once released into the ocean environment, mercury is sequestered by plankton and other microorganisms and converted to methylmercury. When fish consume these organisms, methylmercury accumulates in the fish without harm. Unfortunately, humans and other species that consume the fish are not as lucky.[21] The National Re-

search Council has estimated that 60,000 newborns are at risk annually of mercury-related developmental problems.[22] The Environmental Protection Agency (EPA) has established a reference dose (RfD) of 0.1 µg/kg body weight/day for methylmercury. The EPA defines a reference dose as an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD for methylmercury was originally established based on data from the Iraq epidemic and was re-evaluated using 3 epidemiological longitudinal developmental studies in the Seychelles Islands, the Faroe Islands, and New Zealand.[23-25] The National Academy of Sciences report to Congress in July 2000 determined that the EPA's RfD for methylmercury (0.1 µg/kg/day) is a scientifically justifiable level for the protection of public health, and that the Faroe Islands study is the most appropriate study for deriving this RfD.[26]

A reoccurring controversial potential source of mercury exposure is the continued use of dental amalgam fillings containing slightly less than 50% mercury. Studies have documented the release of very small amounts of mercury from the amalgam during the chewing of food but the only verified clinical effects are rare hypersensitivity reactions.[27] In 1993, the United States Department of Health and Human Services concluded that "there is scant evidence that the health of the vast majority of people with amalgam is compromised or that removing fillings has a beneficial effect on health."[28] A later report of the American Dental Association Council on Scientific Affairs in 1998 concluded "there currently appears to be no justification for discontinuing the use of dental amalgam."[29]

Another controversial potential risk is the use of vaccines with the mercury-containing preservative thimerosal, CH_3CH_2-Hg-S-C_6H_4-COONa [F1]. Manufacturers are required to use preservatives in the multidose vials of vaccines often preferred over single-dose vials for financial reasons. The FDA performed a risk assessment which included calculations of maximal potential exposure to mercury from vaccines and determined that for the smallest infants the cumulative exposure of infants to mercury from thimerosal during the first 6 months of life may exceed the EPA's RfD of 0.1 µg/kg/day.[15,30] The effects of the thimerosal metabolite, ethyl mercury, are not well studied but the investigators performing the risk assessment assumed that they were similar to those of methylmercury based on limited animal studies. On July 7, 1999, the American Academy of Pediatrics (AAP) and the United States Public Health Service (USPHS) issued a joint statement[31] calling for the reduction or elimination of thimerosal in vaccines for children. They also recommended that physicians delay the first dose of hepatitis B vaccine for infants with hepatitis B surface antigen negative mothers until the child is 2 to 6 months old. In addition to hepatitis B vaccine, the diphtheria-tetanus-whole cell pertussis (DTP) and *Haemophilus influenzae* (HIB) vaccines were also of concern.[32] Although, the reduction in the lifelong exposure to any mercury compound is prudent, several groups have failed to find a correlation between thimersol-containing vaccines and pediatric neurological developments (ie, autism).[33,34] Thimerosal-free vaccines are now available for almost all infant immunizations. A current list of the mercury content in vaccines is available on the Institute for Vaccine Safety web site (http://www.vaccinesafety.edu).

In addition to vaccines, mercury has been used in numerous other prescription and homeopathic drug products. As part of the FDA Modernization Act of 1997, the FDA is required to compile a list of drugs and foods that contain intentionally introduced mercury compounds and provide analysis of the mercury compounds in the list. In November 1999, the Center for Drug Evaluation and Research of the FDA issued a report based on the agency's files, information supplied by manufacturers of any food or drug products containing mercury, and other sources. This report estimated that 1,000 to 1,100 homeopathic drug products contain mercury as an active ingredient and that the amount of mercury used annually as an active and inactive ingredient in all products is 75 to 80 kg.[35]

The use of mercury in some cosmetic products has resulted in at least 4 cases of mercury poisoning. Three of these cases were due to a Mexican acne prevention cream[36] and 1 resulted from the use of a Chinese skin-lightening cream.[37] When 38 brands of cosmetic cream (from 8 different countries) available in Hong Kong were analyzed for mercury content, 8 had levels greater than the 1 µg/g limit recommended by the FDA.[37]

Another source of mercury exposure that clinicians and laboratory professionals should be aware of is the use of elemental mercury in the ritualistic practices of Latino and African-Caribbean populations. Elemental mercury, sometimes called azogue, is usually obtained in folk pharmacies known as Botanicas and is believed to protect from harm and serve to bring good health, wealth, successful relationships, and happiness. The mercury may be carried in a sealed pouch (49% of the time in 1 survey), sprinkled in the home (29%), or burned in candles, boiled in a pot, or ingested.[38]

Clinical Signs and Symptoms

Mercury poisoning is frequently misdiagnosed because of the insidious onset coupled with nonspecific signs and symptoms [T2].

The clinical presentation of an individual exposed to mercury depends upon the dose, the length of, and form of exposure. Acute toxicity is more commonly associated with the inhalation of elemental mercury or ingestion of inorganic mercury. Chronic toxicity is more common from exposure to organic mercury. Irrespective of the chemical form of mercury present, the kidneys and the CNS are the 2 primary target organs of toxicity. All mercury compounds concentrate in the kidney to some extent.

Acute exposure caused by inhaled elemental mercury can lead to pulmonary symptoms. Initial signs and symptoms, such as fever, chills, shortness of breath, metallic taste, and pleuritic chest pain, may be confused with metal fume fever. Other possible symptoms could include stomatitis, lethargy, confusion, and vomiting. Complete recovery is possible, but pulmonary complications of inhaled toxic-

Clinical Symptoms of Acute and Chronic Mercury Poisoning*

T2

Target System	Acute	Chronic
Cardiovascular	Hypertension, heart palpitations, hypovolemic shock, collapse	Hypertension, tachycardia
Pulmonary	Shortness of breath, pneumonitis, edema, emphysema, pneumatocele, pleuritic chest pain, cough, interstitial fibrosis, RDS	
GI Tract	Nausea, vomiting, severe abdominal pain, diarrhea, bloody stool	Constipation, diarrhea, generalized distress
Central Nervous System	Tremors, irritability, lethargy, confusion, psychomotor and EEG anomalies, convulsions, decreased reflexes, nerve conduction, and hearing	Tremor, insomnia, shyness, memory loss, depression, anorexia, headache, ataxia, dysarthria, unsteady gait, visual and vasomotor disturbances, peripheral neuropathy, paresthesias
Skin and Keratinized Tissues	Mucosal inflammation (stomatitis) and grayish membranes, buccal pain, burning and bleeding, contact dermatitis, erythematous and pruritic skin rash, alopecia	Gingivitis, acrodynia (Pink Disease), presence of thin blue lines on gums, alopecia
Hepatic	Elevated serum enzymes	
Renal	Oliguria, anuria, hematuria, proteinuria, failure	Polyuria, polydipsia, albuminuria
Reproductive/Fetal	Spontaneous abortion	Spontaneous abortion, fetal brain damage (retardation, incoordination, blindness, speech problems, deafness, seizures, paralysis)
Musculoskeletal	Lumbar pain	Muscle weakness, loss of muscle tone, tremor, paralysis
Other	Fever, chills, metallic taste, foul breath, loosening of teeth	Weight loss, perspiration, blushing, salivation, photophobia

Abbreviation: RDS- respiratory distress syndrome; GI- gastrointestinal; EEG- electrocardiogram

**Table is a comprehensive list of acute and chronic symptoms for all mercury compounds. The specific mercury form (elemental, inorganic, and organic) will define exact presentation of symptoms. Generally, acute toxicity is associated with inhalation of elemental mercury or ingestion of inorganic mercury, while chronic effects are associated with organic mercury.*

ity may include interstitial emphysema, pneumatocele, pneumothorax, pneumomediastinum, and interstitial fibrosis. Fatal acute respiratory distress syndrome has been reported following elemental mercury inhalation.

Acute exposure to inorganic mercury or mercuric salt will most likely occur through an oral route. The corrosive properties of these compounds account for most of the acute signs and symptoms of toxicity. The acute presentation can include ashen-gray mucous membranes secondary to precipitation of mercuric salts, hematochezia (bloody stool), vomiting, severe abdominal pain, and hypovolemic shock. Systemic effects usually begin several hours post-ingestion and may last several days. These effects include metallic taste, mucosal inflammation, gingival irritation, foul breath, loosening of teeth, and renal tubular necrosis leading to oliguria or anuria.

Chronic exposure usually results from prolonged occupational exposure to elemental mercury that is converted into the inorganic form, topical application of mercurial salves, or the chronic use of diuretics or cathartics containing mercury. Chronic and high-dose acute mercury exposure produces a variety of renal, neurological, psychological, and cutaneous symptoms. The exposed individual may experience rather vague and non-specific symptoms, including anorexia, weight loss, fatigue, and muscular weakness that could be indicative of a number of diseases.

Elemental mercury vapor and short-chain alkylmercury compounds readily enter the CNS where they bind to, and thus inactivate, proteins and enzymes involved in synaptic and neuromuscular transmission. Blocking of these signals lead to characteristic degenerative changes. Early on the patient may have fine tremors in the extremities (the fingers and hands) that over time progress to the entire limb. The classic triad found in chronic toxicity is tremors, gingivitis, and erethism (ie, a constellation of neuropsychiatric findings that includes insomnia, shyness, memory loss, emotional instability, depression, anorexia, vasomotor disturbance, uncontrolled perspiration, and blushing). Additional clinical features may include headache, visual disturbance (eg, tunnel vision), peripheral neuropathy, salivation, insomnia, and ataxia.

Symptoms of exposure to organic mercury compounds are similar to those found following exposure with elemental mercury: ataxia, tremors, unsteady gait, and illegible handwriting. Slurred speech may also occur as muscle tone of the facial muscles is lost.

Acrodynia, known as Pink Disease and considered to be a mercury allergy, presents with erythema of the palms and soles, edema of the hands and feet, desquamating rash, hair loss, pruritus, di-

aphoresis, tachycardia, hypertension, photophobia, irritability, anorexia, insomnia, poor muscle tone, and constipation or diarrhea. Acrodynia typically presents in only a small percentage of those exposed to inorganic mercury and is an indicator of widespread disease. It was more prevalent when mercury-containing teething powders were used or when diapers were washed with detergents or fungicides containing mercury.

Organic mercury poisoning usually results from ingestion of contaminated food, particularly fish. The long chain and aryl forms of organic mercury have similar characteristics of inorganic mercury toxicity. Organic mercury targets specific sites in the brain, including the cerebral cortex (especially visual cortex), motor and sensory centers (precentral and postcentral cortex), auditory center (temporal cortex), and cerebellum. The onset of symptoms usually is delayed (days to weeks) after exposure. Organic mercury targets enzymes, and the depletion of these enzymes must occur before the onset of symptoms. Symptoms related to toxicity are typically neurological, such as visual disturbance (eg, scotomata, visual field constriction), ataxia, paresthesias (early signs), hearing loss, dysarthria, mental deterioration, muscle tremor, movement disorders, and, with severe exposure, paralysis and death.

All forms of mercury are toxic to the fetus, but methylmercury most readily passes through the placenta. Even with an asymptomatic patient, maternal exposure can lead to spontaneous abortion or retardation.

Laboratory Studies

Exposure to mercury and mercury compounds can be determined using blood, urine, or hair samples. The quantity of mercury in blood and urine correlates with toxicity. Samples should be collected in trace-metal-free containers.

Urine mercury levels are typically less than 10 to 20 µg/24 hours. Excretion of mercury in urine is a good indicator of inorganic and elemental mercury exposure but is unreliable for organic mercury (methylmercury) because elimination occurs mostly in the feces. No absolute correlation exists between the urine mercury levels and the onset of symptoms; however, neurologic signs may be present at levels higher than 100 µg/L.[27] Urine concentrations of mercury greater than 800 µg/L are usually associated with death. Mercury levels in the urine also can be used to gauge the efficacy of chelation therapy. Guidelines from several occupational health groups and the WHO consider urinary excretion of mercury > 50 µg/L suggestive of significant exposure.

Hair has high sulfhydryl content. Mercury forms covalent bonds with sulfur and, therefore, can be found in abundance in hair samples. However, the rate of false-positive results is high with hair analysis secondary to environmental exposure. Hair analysis should not be used alone to confirm mercury toxicity or exposure. Generally, mercury concentrations in the hair do not exceed 10 mg/kg. Following moderate and severe intoxications with methylmercury, hair concentrations were 200 to 800 mg/kg and approximately 2,400 mg/kg, respectively.[19] In 1994, the World Health Organization recommended monitoring of hair levels of methylmercury in women of childbearing age in populations consuming ≥100 g/day.[39] Maternal hair mercury concentrations ≥10 ppm indicate an increased risk of neurological deficits in offspring.

Because methylmercury concentrates in erythrocytes elevated blood levels are seen in acute toxicity but correlation in chronic methylmercury toxicity is variable. The methylmercury blood-to-plasma ratio has been touted as a means to differentiate methylmercury and arylmercury exposure.[40] Arylmercury exposure is characterized by a lower blood-to-plasma ratio than observed with methylmercury exposure. Whole blood mercury levels are usually <10 µg/L (ppb) in unexposed individuals (exceptions may be individuals with a high dietary intake of fish).

Inorganic mercury redistributes to other body tissue; thus, its levels in the blood only are accurate after an acute ingestion. In general, blood levels of mercury are helpful for recent exposures and for determining if the toxicity is secondary to organic or inorganic mercury, but they are not useful for a guide to therapy.

Additional testing should include a complete blood count and serum chemistries to assess renal function and possible anemia secondary to GI hemorrhage.

Treatment

Choice of treatment depends upon the form of mercury involved. For example, elimination of the source of exposure may be sufficient following exposure to a relatively low dose of mercury vapor.

As with any toxin, it is critical to obtain as much information as possible regarding the source, time, type, and mode of mercury exposure. Supportive care begins with the ABCs (airway, breathe, circulation), especially when managing the inhalation of elemental mercury and the ingestion of caustic inorganic mercury, both of which may cause the onset of airway obstruction and failure. If the patient was exposed to mercury via the skin, decontamination may involve copious irrigation of the exposed area. Aggressive hydration may be required for acute inorganic mercury ingestion because of its caustic properties, and for the same reason, one should not induce vomiting. Gastric lavage is recommended for organic ingestion, especially if the compound is observed on the abdominal radiographs. Gastric lavage with protein-containing solutions (eg, milk, egg whites, salt-poor albumin) or 5% sodium formaldehyde sulfoxylate solution may bind gastric mercury and limit its absorption. Activated charcoal is indicated for GI decontamination because it binds inorganic and organic mercury compounds to some extent.

Thiol-containing chelating agents such as dimercaprol (BAL), 2,3-dimercaptosuccinic acid (DMSA, succimer), 2,3-dimercapto-1-propane sulfonic acid (DMPS), sodium 4,5-dihydroxybenzene-1,3-disulfonate (Tiron), and penicillamine which compete with endogenous sulfhydryl groups have been used for treating mercury poisoning. In general, chelation therapy is more effective for elemental mercury than for methylmercury elimination. Newer agents such as DMSA and DMPS that can be given orally are replacing the agents such as BAL that are given by deep intramuscular injection.[41] A prom-

Data for Case Study 2 T3

Patient	Mercury (µg/L) Urine (24 hour)	Blood	Effect of exposure
45 days	35	117	No sequela
13 months	120	160	Death
3 years	161	-	No sequela
7 years	177	-	No sequela
10 years	485	-	No sequela
14 years	107	-	No sequela
38 years (mother)	163	322	Death
58 years (father)	112	275	Chronic

ising new chelating agent is N-acetylcysteine.[42] Typically chelation therapy requires repeating cycles lasting for days because of the large volume of distribution, long half-life, and progressive release of mercury from tissues.

Hemodialysis is used in severe cases of toxicity when renal function has declined. The ability of regular hemodialysis to filter out mercury is limited because of mercury's mode of distribution among erythrocytes and plasma. However, hemodialysis, with L-cysteine compound as a chelator, has been successful.

Neostigmine may help motor function in methylmercury toxicity. This toxicity often leads to acetylcholine deficiency. Polythiol is a nonabsorbable resin that can facilitate the removal of methylmercury (short chain alkyl organic mercury), which is then excreted in the bile after enterohepatic circulation.

Special Concerns: Significant oral ingestion of elemental mercury may lead to significant environmental contamination as the mercury is passed, essentially unabsorbed, through the GI tract and expelled in the feces.

Case Studies: Two case studies from the literature are presented to familiarize the reader with the signs, symptoms, and laboratory findings of mercury poisoning in acute and chronic situations.

Case 1. Chronic Mercury Toxicity[43]

A 34-year-old male foundry worker was found to have multiple small opacities of probable metallic origin subsequent to a routine chest x-ray. Further radiographs revealed multiple sites of opacity throughout the body. A biopsy of the particles was significant for the presence of mercury. The distribution of particles was suspicious for intravenous injection of mercury; however, the subject declined to provide information on the timing, dose, or explanation for injection.

Toxicology testing was significant for elevated urinary mercury of 930 µg/L (reference range <20 µg/L). A routine physical examination was normal. Renal function tests revealed a slight proteinuria that was not otherwise defined. Specialized tests for signs of mercury toxicity including lung function, evoked potentials, vision, electroneurography, and psychological assessment were also normal.

At follow-up 11 years later, the patient's symptoms were vague and included memory disturbances and occasional hand tremors. X-rays and CT scans were significant for the continued presence of multiple metallic opacities in the lungs, liver, kidneys, and subcutaneous tissue. Spirometry, somatosensories, motor evoked potentials, conduction velocities, and psychological testing were all within normal ranges. Further lung function testing revealed diffusing capacity for carbon monoxide and PO_2 to be 55% and 86% of predicted values, respectively. Electroneuromyography was significant for mild axonopathy. Renal function tests were within normal limits. Toxicology testing was significant for elevated urine mercury of 113.1 µmol/mol creatinine (reference range: <2.8 µmol/mol creatinine).[43]

Case 2 Acute Mercury Poisoning[44]

A 13-month-old boy and his 45-day-old sibling were admitted to a children's hospital with symptoms of respiratory distress. Chest x-rays revealed bronchial thickening. Respiratory failure requiring mechanical ventilation developed within 36 hours of admission. An initial working diagnosis of pneumonia of unknown origin was replaced with possible mercury vapor poisoning after further investigation revealed that the parents were extracting gold ore with liquid mercury in their kitchen approximately 6 hours before the onset of symptoms in the 2 children. Within 96 hours of exposure, both parents had been admitted to the hospital due to respiratory distress with the mother requiring mechanical ventilation. Four other children (ages 3 to 14) present in the home (in rooms adjacent to the kitchen) during the mercury exposure were also admitted to the hospital prophylactically despite having only mild symptoms of sore throat, headache, and nonproductive cough.

Mercury poisoning was affirmed by elevated blood and/or urine mercury concentrations [T3]. Chelation therapy (DMSA) was initiated on the 6 children and the mother. The father refused treatment and was released. The infant and 4 of her siblings continued to improve and were eventually discharged. Both the 13-month-old and the mother had respiratory difficulties that gradually increased, and despite aggressive treatment both patients died from respiratory failure 25 and 12 days post exposure, respectively. Autopsy revealed severely compromised lungs in both patients, with advanced chemical pneumonitis and cellular infiltrate of alveolar structures in the 13-month-old and chemical destruction of epithelium and thickening of alveolar septa in the mother.

The local public health authorities were notified when the source of the mercury exposure was revealed so that decontamination of the residence could be initiated. Air samples for mercury vapor

in the home were highest in the kitchen where the ore was being processed and measured 0.193 mg/m^3. In contrast, the ambient air standard for mercury vapor is 0.00006 mg/m^3. On follow-up, the surviving children had no evidence of developmental delay or chronic sequela of mercury toxicity while the father experiences chronic problems including periods of mental confusion, memory loss, insomnia, and persistent non-productive cough.[44]

Discussion and Summary

These cases illustrate some of the differences in toxicity occurring when mercury exposure is acute versus chronic. The route of introduction in the first case is injection of elemental mercury that serves as a source of chronic exposure. In the case of acute exposure, the mercury is inhaled causing pulmonary damage in addition to neuromuscular effects. Mercury has been used for centuries for medicinal, religious, and industrial purposes and has severe toxic effects. Mercury is a volatile liquid, and the primary current concerns include environmental exposure from mercury released into the atmosphere and from ingestion of seafood in which the mercury has been concentrated. Other controversial potential routes of exposure are dental amalgams and infant vaccines.

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