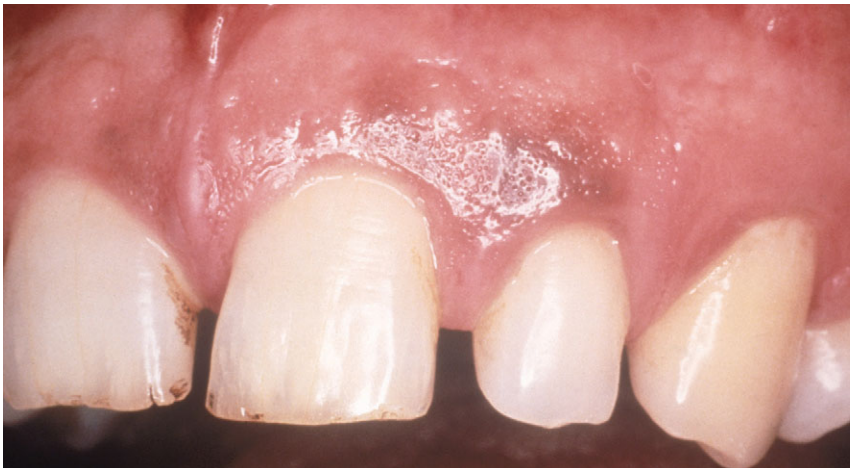
Recognizing and Managing Lead and Mercury Poisonings

After iron, which was covered in EM's May issue, lead and mercury are the two metals most likely to be implicated in heavy metal toxicity syndromes. The authors review the diagnostic considerations and update guidelines for detoxification.

What constitutes a heavy metal? It depends on who you ask. In industrial and environmental studies, heavy metals are generally defined as those elements that have high atomic weights—elements with a specific gravity of 5 or higher. A strict chemistry definition classifies everything between copper and bismuth on the periodic table as a heavy metal. Medical usage of the term, however, is much more liberal, encompassing lighter metals and metalloids that are excluded by other definitions. The list of medically recognized toxic metals and metalloids includes (but is not limited to) aluminum, arsenic, barium, bismuth, cadmium, cobalt, copper, chromium, gold, lead, manganese, mercury, selenium, silver, thallium, and zinc.[1]

Heavy metal or metalloid toxicity is relatively uncommon in urgent care centers, but for that very reason it is important to maintain familiarity with its signs, symptoms, and treatment. These poisonings can often result in significant morbidity and mortality if unrecognized and inappropriately treated. The physician also needs to be prepared for the postdiagnostic responsibility of identifying possible exposures to the same toxin within the patient's family, workplace, or community that may warrant testing, treatment, or both.



Chronic Effects of Lead Poisoning. Dark or bluish discoloration of the gum-tooth line, known as a "lead line," may be noted on exam and is the result of a chemical reaction between lead and dental plaque.

Christian Balmadrid, MD
Staff Physician
Durham Emergency Physicians
Durham Regional Hospital
Durham, North Carolina

Michael J. Bono, MD
Professor of Emergency Medicine
Eastern Virginia Medical School
Norfolk, Virginia

According to nationwide data collected by the American Association of Poison Control Centers, there were almost 13,000 exposures to heavy metals other than iron in 2005.[2] (Iron in its mineral form and as an ingredient in multivitamins accounted for nearly 35,000 cases in 2004[1]; for our recent discussion of iron toxicity diagnosis and management, see EMERGENCY MEDICINE, May 2009, page 36).

The aim of this article is to provide a brief refresher course on the epidemiology, biochemistry, and clinical aspects of toxic exposures to lead and mercury—after iron, the most likely causes of heavy metal toxicity. We would caution, though, that even the best-informed urgent care physician should consult a toxicologist or the regional poison control center whenever there is any suspicion of metal toxicity.

LEAD: A LINGERING THREAT

Lead toxicity is considered a disease of industrialization, with the majority of poisonings worldwide resulting from exposure to lead-based paints and leaded gasoline. Fortunately, the use of those products in the United States was banned in the 1970s. However, it is estimated that more than 30 million homes still contain lead-based paints,[3] and an unknown number have lead pipes or alloys in their plumbing systems. Toxic levels of serum lead have been found in screening assessments of as many as 4 million children in a year in US households, and about 3 million industrial workers are at risk for lead exposure in such jobs as lead smelting, battery manufacturing, radiator repair, bridge and ship construction, welding, and glass production.[3] Other vehicles for lead exposure include lead-contaminated soils (especially in countries still using leaded gasoline), buckshot, fishing weights, moonshine whiskey, lead-glazed pottery, and some ethnic medications and folk remedies.[4,5]

>>FAST TRACK<<

Toxic levels of serum lead have been found in screening assessments of as many as 4 million children in a year in US households.

Lead has no biological role. It can be absorbed through the lungs, the gastrointestinal tract, or the skin. In adults, it is absorbed primarily through the respiratory system at a rate of about 40%, commonly during activities such as removing leaded paints from surfaces or certain smelting or burning processes. Gastrointestinal absorption is secondary, at a rate of 10% to 15%, but gastrointestinal absorption rates and efficiency can increase in pregnancy and malnourished states (particularly diets low in calcium, iron, phosphorus, or zinc). Conversely, in children the predominant route of absorption is through the gastrointestinal tract, at a rate of 50%. The organic lead found in gasoline can also be absorbed through the skin.[6]

In the bloodstream, 99% of lead is bound to erythrocytes, while the remaining 1% is in a free form, able to affect tissues such as kidney, brain, liver, and bone marrow. Lead is primarily excreted by the kidneys and has a half-life of 30 days in individuals with normal renal function.[7] However, lead can be stored in bone, where its half-life can extend to decades,[7] and may be released during times of bone turnover, as in hyperthyroidism,[8] menopause, pregnancy,[9] and breastfeeding.[10]

Pathophysiology. Lead primarily affects the hematopoietic, neurologic, and renal systems. In the hematopoietic system, lead inhibits heme biosynthesis, causing anemia. In the neurologic system, it induces demyelination and axonal degeneration that result in peripheral neuropathies and wrist and foot drop. It also increases brain capillary permeability and cerebral edema, resulting in acute lead encephalopathy. In children, chronic lead exposures have been found to correlate with neuropsychiatric disorders as manifested in decreased IQ scores, hyperactivity, overaggressive or criminal behavior, learning disabilities, and other signs.[3] Lead also causes nephropathy and renal impairment due to fibrosis of the proximal tubules.

Clinical features. Patients will typically present with either a known lead exposure, suspicious symptoms with a possible history of exposure, or a referral from a provider who found a toxic blood lead level (BLL) on a screening examination. Adults with chronic exposures may have only a mildly elevated BLL (less than 10 µg/dL)[3] and may be asymptomatic or have an insidious onset of vague symptoms such as myalgias, fatigue, irritability, insomnia, anorexia, impaired short-term memory, and difficulty concentrating. Prolonged exposure may cause renal disease that

continued from page 36

can progress to renal failure, hypertension (independent of lead's effects on the kidneys),[11] neurocognitive dysfunction,[12,13] white matter brain lesions, loss of brain volume,[14] distal sensory and motor neuropathies,[15] and cardiac conduction delays.[16]

Patients with acute exposure will present with higher BLLs, which will generally correlate with the severity of the presenting symptoms. Patients typically complain of gastrointestinal effects such as colicky abdominal pain ("lead colic"), constipation, nausea, vomiting, and anorexia. They may also present with central nervous system dysfunction ranging from mild headache or personality changes to full-blown encephalopathy with coma and convulsions. This can be rapidly fatal or result in permanent neurologic and behavioral changes. As previously noted, peripheral neuropathies presenting as wrist or ankle drop may also occur.[15]

Assessment. An occupational and environmental history to assess the risk and severity of lead exposure is essential. The most important laboratory test to obtain is a BLL. The Centers for Disease Control and Prevention has defined a BLL greater than 10 µg/dL to be toxic in children.[3] In acute exposures, BLL can be greater than 100 µg/dL. Other tests that may be helpful in the evaluation of lead poisoning include a complete blood count with peripheral smear (which may reveal the classically described basophilic stippling) and measures of blood urea nitrogen and creatinine (to assess renal function).[3]

Management. Patients who ingest a single lead foreign body, such as a fishing sinker, will usually pass it harmlessly through the gastrointestinal tract, with no treatment required.[17] A follow-up KUB radiograph may be warranted, however, to ensure that passage has occurred. If the lead foreign body has not passed in 2 weeks, surgical removal should be considered to prevent further lead toxicity.

>>FAST TRACK<<

When discharging patients after a lead exposure, it is important not to discharge them back to a contaminated environment.

Often, removal from exposure is the only therapy needed for mild lead poisoning. At the opposite extreme, significant lead poisoning can cause acute lead encephalopathy, which can be rapidly fatal. Treatment in these cases consists of standard measures to control cerebral edema, including intubation (to hyperventilate) and invasive intracranial pressure monitoring.[3] In moderate to severe toxicity, the goals of therapy are to prevent further exposure, minimize absorption, enhance elimination, and prevent or reverse cellular pathology. In acute ingestions, whole bowel irrigation can decrease the amount of lead absorbed through the gastrointestinal tract.[18]

To enhance elimination, chelating agents have been used, but controlled clinical trials have not been performed to assess their efficacy. The theory behind their use is that they will bind to lead to form nontoxic complexes that can undergo biliary and renal excretion. The chelating agents available include dimercaprol (also called British antilewisite or BAL), calcium disodium EDTA (ethylenediaminetetraacetic acid), DMSA (2,3-dimercaptosuccinic acid), and D-penicillamine. Which chelating agent to use is dictated by the patient's BLL and the severity of symptoms. The first two agents listed come in intramuscular or intravenous form and are used for severe toxicities that require admission, while the latter two agents are oral chelators and can be used for outpatient therapy.

Consensus guidelines have not been proposed for the treatment of lead poisoning, but the following have been recommended in some texts. Blood lead levels and the patient's symptomatology constitute the most useful guide to determining therapy.

If the BLL is between 45 and 69 µg/dL and the patient has no gastrointestinal or central nervous system symptoms, outpatient oral chelation therapy with DMSA is recommended.[19,20] Dosing is 10 mg/kg every 8 hours for 5 days, followed by 10 mg/kg every 12 hours for another 14 days. Second-line therapy is D-penicillamine, but it is not as effective and has an increased side effect profile.[3]

When discharging patients after a lead exposure, it is important not to discharge them back to a contaminated environment, particularly if they are undergoing chelation therapy, because its use in continued exposure may actually increase the absorption of lead.[3] Either the local health department or a physician specializing in occupational medicine may be helpful in making environmental site evaluations and identifying possible preventive measures.

continued on page 40

continued from page 38

If the BLL is greater than 70 µg/dL or there are protracted gastrointestinal symptoms or any signs of central nervous system toxicity, the patient should be admitted and undergo IV chelation therapy.[3] Dimercaprol is initially administered at 3 to 4 mg/kg deep IM injection every 4 hours for 2 days. After 2 days, dosing is spaced out to every 4 to 6 hours for another 2 days, and then every 4 to 12 hours for the last 7 days. A separate injection of calcium disodium EDTA is given with each dose of dimercaprol after the first one. Daily dosage is based on either 50 mg/kg or 1000 mg/m^2 of body surface area, given either IV or IM in two to four divided doses for up to 5 days.[3]

MERCURY: KNOW THE GUISES

Mercury has been in medicinal use for more than 2000 years, continuing into the 19th century as a diuretic, antiseptic, and antisyphilitic agent.[21] However, it is also well recognized as a dangerous toxin. The most infamous cases of mercury toxicity occurred in Japan during the Minamata Bay tragedy, when from 1932 to 1968, ingestion of fish from mercury-contaminated waters caused at least 1000 deaths and significantly more morbidity in the population (in addition, birth defects manifested in the following generation).[22,23] Mercury was also commonly used in the manufacture of felt hats in the 19th century, when workers exposed to its vapors developed signs and symptoms of central nervous system toxicity that gave rise to the term "mad hatters."

There are three primary forms of mercury that cause toxicity: elemental (metallic), organic, and inorganic. The most common route of exposure to the elemental form is via inhalation of its volatilized vapor. Common sources of elemental mercury include spills from sphygmomanometers and thermometers. There have also been accounts of patients intentionally injecting themselves with elemental mercury either subcutaneously or intravenously.[3]

>>FAST TRACK<<

The most common exposure to the organic form of mercury is through ingestion of seafood from polluted areas.

The most common exposure to the organic form of mercury is through ingestion of seafood, particularly marine fish (shark, swordfish, tuna) and freshwater fish (pike, walleye, bass) from polluted areas.[24] Concentrations of mercury in these fish can reach 1 mg/kg or higher, resulting in blood mercury levels of up to 20 µg/L (normal levels are less than about 5 µg/L).[25]

Patients may also be exposed to mercury through mercury-containing amalgam dental fillings.[24] The amount of mercury released from dental fillings depends on the number of fillings and total amalgam surface area and is difficult to accurately assess. One study estimates an average exposure of 10 µg/day.[24] Subsequent studies have not revealed evidence linking dental fillings to mercury's known toxic effects on the central nervous system, and removal of these fillings has not been recommended.[26]

Pathophysiology. Like all metals, mercury imparts its toxic effects by disrupting cellular enzyme function. Additionally, mercury leads to nephrotoxicity both by direct caustic effects and by stimulating an immune reaction in the kidneys. Chronic exposure can cause atrophy of the cerebellum, postcentral gyri, and calcarine areas of the brain.[3]

Clinical features. The presenting symptoms of mercury toxicity are determined by the form, route, and acuity of the exposure. Elemental mercury, as noted before, is most often absorbed via inhalation of its aerosolized form, resulting in direct lung injury, chemical pneumonitis, and adult respiratory distress syndrome.[3] Inhaled elemental mercury also readily penetrates the blood-brain barrier, and large concentrations can rapidly provoke seizures and encephalopathy. With sufficient systemic absorption, acute nephrotoxicity may occur, presenting as proteinuria, nephrotic syndrome, and acute renal failure.[21] Chronic exposures can result in fine tremors, peripheral neuropathies, dysarthrias, parkinsonian symptoms, and a condition called erethism. Erethism is characterized by shyness, emotional lability, nervousness, insomnia, memory problems, and inability to concentrate; it was the syndrome of the "mad hatters."[21]

Subcutaneous injections can be systemically absorbed, and IV injections can be sequestered in the lungs, leading to acute toxicity. When ingested, elemental mercury will usually not produce any toxicity since it is not absorbed by the

gastrointestinal tract. It can be subsequently aspirated, however, causing pulmonary toxicity as it does via inhalation.[21]

Ingestion of inorganic mercury salts, on the other hand, does lead to a significant and potentially life-threatening gastrointestinal toxicity. Acute ingestions precipitate a corrosive gastroenteritis that presents as abdominal pain and hematemesis. Severe vomiting, third spacing, and gastrointestinal hemorrhage can cause massive fluid loss that rapidly leads to acute renal failure and tubular necrosis. Shock with cardiovascular collapse and death are the end result if fluid loss progresses. Other signs and symptoms of inorganic mercury ingestion include a grayish discoloration of the mucous membranes, and patients may also complain of metallic taste. Chronic exposures present similarly to chronic elemental mercury toxicity. Renal dysfunction, ranging from proteinuria to nephrotic syndrome, may also occur.[3,21]

Organic mercury is also readily absorbed through the gastrointestinal tract. Exposure to organic mercury, however, generally does not lead to acute toxicity. Rather, delayed neurologic symptoms (ataxia, tremors, dysarthria, paresthesias of the hands, feet, and mouth), visual field constriction, hearing loss, spasticity, and hyperreflexia typically develop over weeks and months with chronic exposure.[3,21] The best-known form of organic mercury is methylmercury, which is the compound found in seafood and is often publicized for its teratogenic effects.[24,26] Once ingested and absorbed systemically, methylmercury can penetrate the central nervous system, to which its toxic effects are generally limited.[21]

Perhaps the largest health concern regarding mercury poisoning to emerge in recent medical literature is with the effects of methylmercury exposure in utero. Methylmercury readily crosses the placenta and will accumulate in higher concentrations in cord blood than in the maternal circulation. It can inhibit brain cell division and migration, resulting in micrognathia, microcephaly, developmental disorders, mental retardation, blindness, and symmetric motor deficits.[21]

Assessment. As with the other heavy metal poisonings, signs and symptoms are relatively nonspecific, so a thorough history and physical and high index of suspicion are often needed to arrive at the diagnosis of mercury poisoning. There are few practical tests available to confirm mercury poisoning.

The ideal laboratory value to obtain in a suspected mercury exposure is a 24-hour urine mercury level measured after a 5-day seafood-free diet. This test can detect both inorganic and elemental mercury compounds but cannot detect organic forms, which are excreted predominantly through bile. A normal urine mercury level is less than 20 µg/L, while a level greater than 100 to 150 µg/L suggests significant mercury exposure, in which chelation therapy is recommended.[3,21] However, there are no recommendations for urine mercury levels between 20 and 100 µg/L, partially due to the fact that urine assays detect both recent exposures and continued renal elimination of tissue burden.[3,21] Additionally, there is little correlation between mercury levels and actual toxicity. A spot urine mercury test is available, but there are few studies to confirm its validity compared to that of a 24-hour sample. Furthermore, some studies suggest the existence of diurnal variation in urinary mercury excretion, making a spot urine test likely even less useful.[27-29]

>>FAST TRACK<<

Methylmercury readily crosses the placenta and will accumulate in higher concentrations in cord blood than in the maternal circulation.

As noted earlier, organic mercury cannot be detected in urine assays. It does, however, concentrate in erythrocytes, so serum mercury levels can be obtained to confirm organic mercury exposure. A normal serum mercury level is less than 10 µg/L. Chelation therapy is recommended for values greater than 35 µg/L.[3,21]

Other tests that may be helpful in the initial evaluation include a urinalysis (looking for proteinuria) and a basic metabolic panel (looking for elevated creatinine). A complete blood count and a type-and-screen should be obtained because of the potential for gastrointestinal hemorrhage and perforation. Occasionally, plain film radiographs may identify ingested, aspirated, or injected mercury.[21]

Management. Initial management of acute mercury toxicity should include aggressive pulmonary support in cases of aspiration and aggressive cardiovascular support in cases of in-

gestion where gastrointestinal symptoms are prominent. The patient should also be quickly decontaminated. In organic and inorganic mercury ingestion, a nasogastric or orogastric tube should be placed, and gastric lavage should be performed with solutions containing mercury-binding sulfhydryl groups such as egg whites or milk. Activated charcoal binds very little mercury and thus is not generally recommended. Whole bowel irrigation with polyethylene glycol should be considered in large ingestions, and the response to treatment can be followed with serial abdominal radiographs.[21]

Elemental mercury is generally harmless when ingested, requiring no gastric lavage. In cases of inhalational exposures, however, patients should be suctioned and placed in a position favoring postural drainage. There is no role for steroids or empiric antibiotics. Injected mercury will require surgical debridement to prevent systemic absorption.[3,21]

As noted earlier, laboratory tests that confirm mercury toxicity are generally not readily available in acute care settings. Therefore, if mercury poisoning is suspected, empiric chelation therapy should be initiated soon after the decontamination process has begun. All the chelating agents available contain sulfhydryl groups that bind mercury. In patients with normal renal function, the first-line chelating agent for all forms of mercury is DMSA, administered at 10 mg/kg orally three times per day for the first 5 days, then twice daily for 14 days. Treatment should be continued until laboratory measurements have confirmed that mercury levels have dropped below a specific value. In elemental and inorganic mercury poisonings, 24-hour urine mercury levels should be less than 20 µg/L. In organic mercury poisonings, blood mercury levels should be less than 20 µg/L. If repeat courses of DMSA therapy are required to obtain these levels, treatment courses should be separated by a 2-week "drug holiday."[3,21]

>>FAST TRACK<<

If mercury poisoning is suspected, empiric chelation therapy should be initiated soon after the decontamination process has begun.

In patients with renal dysfunction needing treatment for elemental or inorganic mercury poisoning, dimercaprol should be used. It should be avoided, however, in organic mercury toxicity, as there is some concern that it will redistribute the toxin and actually increase the level of mercury in the central nervous system.[3,21] The dose is 5 mg/kg initially followed by 2.5 mg/kg once or twice daily for 10 days.

D-penicillamine is a third-line agent, less effective because it contains only one sulfhydryl group, compared to two in DMSA and dimercaprol. Typical adult dosing is 250 mg four times a day orally for 1 to 2 weeks; for children, 20 to 30 mg/kg/day in four divided doses is given. D-penicillamine is contraindicated in renal failure, as it is exclusively excreted by the kidneys.[21]

Asymptomatic patients can be treated as outpatients with follow-up urine or blood testing to confirm the clearance of mercury. Patients exhibiting any signs of potentially life-threatening toxicity, such as encephalopathy, shock, acute renal failure, or acute pneumonitis, or requiring intramuscular dimercaprol therapy (versus oral DMSA) will need to be admitted. Patients who have self-injected mercury will also need to be hospitalized and will require surgical consultation for debridement of the affected soft tissue.[3,21] □

REFERENCES

1. Watson WA, Litovitz TL, Rodgers GC Jr. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*. 2005;23(5):589-666.
2. Bronstein AC, Spyker DA, Cantilena LR, et al. 2007 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25th Annual Report. *Clin Toxicol (Phila)*. 2008;46(10):927-1057.
3. Velez LI, Delaney KA. Heavy metals. In: Marx JA, ed. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 6th ed. Philadelphia, PA: Mosby Elsevier; 2006:2418-2427.
4. Agency for Toxic Substances and Disease Registry. Toxicological profile for lead. www.atsdr.cdc.gov/toxprofiles/tp13.html#bookmark05. Updated 2007. Accessed September 11, 2009.
5. World Health Organization. Lead. In: Air Quality Guidelines for Europe. 2nd ed. http://www.euro.who.int/document/aiq/6_7lead.pdf. Published 2001. Accessed September 11, 2009.
6. Fischbein A, Hu H. Occupational and environmental exposure to lead. In: Rom WN, Markowitz SB, eds. *Environmental and Occupational Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:954-990.
7. Rabinowitz MB. Toxicokinetics of bone lead. *Environ Health Perspect*. 1991;91:33-37.
8. Goldman RH, White R, Kales SN, Hu H. Lead poisoning from mobilization of bone stores during thyrotoxicosis. *Am J Ind Med*. 1994;25(3):417-424.
9. Riess ML, Halm JK. Lead poisoning in an adult: lead mobilization by pregnancy? *J Gen Intern Med*. 2007;22(8):1212-1215.
10. Gulson BL, Mahaffey KR, Jameson CW, et al. Mobilization of lead from the skeleton during the postnatal period is larger than

during pregnancy. *J Lab Clin Med.* 1998;131(4):324-329.
11. Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. Lead exposure and cardiovascular disease—a systematic review. *Environ Health Perspect.* 2007;115(3):472-482.
12. Weisskopf MG, Wright RO, Schwartz J, et al. Cumulative lead exposure and prospective change in cognition among elderly men: the VA Normative Aging Study. *Am J Epidemiol.* 2004;160(12):1184-1193.
13. Shih RA, Glass TA, Bandeen-Roche K, et al. Environmental lead exposure and cognitive function in community-dwelling older adults. *Neurology.* 2006;67(9):1556-1562.
14. Stewart WF, Schwartz BS, Davatzikos C, et al. Past adult lead exposure is linked to neurodegeneration measured by brain MRI. *Neurology.* 2006;66(10):1476-1484.
15. Thomson RM, Parry GJ. Neuropathies associated with excessive exposure to lead. *Muscle Nerve.* 2006;33(6):732-741.
16. Cheng Y, Schwartz J, Vokonas PS, et al. Electrocardiographic conduction disturbances in association with low-level lead exposure (the Normative Aging Study). *Am J Cardiol.* 1998;82(5):594-599.
17. Durback LF, Wedin GP, Seidler DE. Management of lead foreign body ingestion. *J Toxicol Clin Toxicol.* 1989;27(3):173-182.
18. Roberge RJ, Martin TG. Whole bowel irrigation in an acute oral lead intoxication. *Am J Emerg Med.* 1992;10(6):577-583.
19. Centers for Disease Control and Prevention. Managing elevated blood lead levels among young children: recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention. http://www.cdc.gov/nceh/lead/casemanagement/caseManage_main.htm. Accessed September 14, 2009.
20. American Academy of Pediatrics Committee on Drugs. Treatment guidelines for lead exposure in children. *Pediatrics.* 1995;96(1 pt 1):155-160.
21. Chiang WK. Mercury. In: Ford MD, Delaney KA, Ling LJ, Erickson T, eds. *Clinical Toxicology.* Philadelphia, PA: WB Saunders; 2001:737-743.
22. Ministry of the Environment. Government of Japan. Minamata disease the history and measures. http://www.env.go.jp/en/chemi/hs/minamata2002/index.html. Accessed September 14, 2009.
23. National Institute for Minamata Disease. Ministry of the Environment. Government of Japan. Mercury and Health. http://www.nimd.go.jp/english/index.html. Accessed September 14, 2009.
24. World Health Organization. Environmental Health Criteria 118: Inorganic mercury. http://whqlibdoc.who.int/ipcs/IPCS_EHC_118.pdf. Accessed September 14, 2009.
25. World Health Organization. Biological Monitoring of Metals. http://whqlibdoc.who.int/hq/1994/WHO_EHG_94.2.pdf.Accessed September 14, 2009.
26. Clarkson TW, Magos L, Myers GJ. The toxicology of mercury—current exposures and clinical manifestations. *N Engl J Med.* 2003;349(18):1731-1737.
27. Woods JS, Martin MD, Leroux BG. Validity of spot urine samples as a surrogate measure of 24-hour porphyrin excretion rates. Evaluation of diurnal variations in porphyrin, mercury, and creatinine concentrations among subjects with very low occupational mercury exposure. *J Occup Environ Med.* 1998;40(12):1090-1101.
28. Martin MD, McCann T, Naleway C, et al. The validity of spot urine samples for low-level occupational mercury exposure assessment and relationship to porphyrin and creatinine excretion rates. *J Pharmacol Exp Ther.* 1996;277(1):239-244.
29. Wallis G, Barber T. Variability in urinary mercury excretion. *J Occup Med.* 1982;24(8):590-595.