

# **Training Manual on Pediatric Environmental Health: Putting It Into Practice**



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# Metal Toxicity in Children

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Heavy metal poisoning is not uncommon in children and can seriously impair normal development. Lead accounts for most cases of pediatric heavy metal poisoning, and is addressed at length in a separate teaching module. This module will focus on other metals that can significantly harm a child's health: mercury, cadmium, arsenic, and iron. Although these are not the only metals that can poison children, they are the ones most likely to be encountered by pediatric health care practitioners. A clinical case study is included in the discussion of most metals. It is designed to serve as a descriptive example of the toxicity associated with the metal, and does not represent an actual case. The reader should consult the reference articles cited within this module for cases reported in the literature.

## Learning Objectives

After completing this module, students and residents will be able to:

- Describe the various forms of the metals discussed in this module (valence, organic forms) and identify those that are most toxic
- Identify sources (natural, industrial, etc.) and environmental reservoirs for each metal
- Describe the different routes of uptake into the body
- Describe the symptoms and signs of clinical toxicity
- Discuss pertinent treatment option

## General Principals of Metal Toxicity

### Introduction

Metals carry a positive charge and act as electron donors in chemical reactions. This makes them likely to form salt compounds such as mercuric ( $\text{Hg}^{2+}$ ) chloride ( $\text{HgCl}_2$ ) and mercurous ( $\text{Hg}^+$ ) chloride ( $\text{HgCl}$ ). In their elemental form, metals are usually solid at room temperature, with mercury being one notable exception. Metals can also combine with carbon to form organic compounds. Different forms can create very different degrees and types of toxicity. The degree of toxicity is largely a function of the valence state of the metal.

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Humans can accumulate metals through several routes of exposure:

- Gastrointestinal absorption is the most common route in children. This occurs through the normal hand-to-mouth activity of infants and toddlers (mouthing ob-

jects, playing outside, and not washing their hands before eating) as well as the active eating of objects (pica). Water contamination is another important source of ingested toxicants. Maternal milk is a possible source of neonatal metal exposure. Toxicants may also be brought into the home through dust on the clothes of a parent occupationally exposed to heavy metals. The child can then ingest this dust.

- Inhalation of airborne toxicants, typically emissions from industrial sources, tends to be a greater hazard to adults. When children live in close proximity to industrial sites, however, they may also be exposed to airborne toxicants. In addition, mercury, which is highly volatile, can produce vapors in a number of settings.
- Skin absorption is less common because of the highly polar properties of metal. Exceptions to this rule are the organometallic compounds, such as tetraethyl lead and methylmercury, that tend to have higher lipid solubility and are thus more easily absorbed through the skin. Poor transcutaneous absorption does not eliminate the possibility of toxicity. Nickel, for example, is known to cause contact dermatitis.
- Direct deposition into the tissues is another important, although less common, route of exposure. This includes direct injection of a metal such as technetium or gallium during a radiological procedure, and inappropriate dosing of metals such as chromium in mixtures of parenteral nutrition. Local toxicity from elemental mercury has occurred from a broken thermometer (Smith 1997) and self-administration in a suicide attempt (Lupton 1985).

Metals may cross the placenta and fetal uptake can be extremely high.

## Mercury

### Description

Mercury (Hg) exists in three forms: in the elemental form as a volatile metal, in the inorganic form as both a monovalent and divalent cation, and in the organic form.

### Sources of Mercury

**Elemental mercury** is generated naturally in the environment by degassing of the earth's crust and from volcanic emissions. Mining, chloralkali plants, and paper production are important industrial sources of elemental mercury (Goyer 1996). Atmospheric concentrations of mercury represent an important pathway in the global transportation of this metal: as the element diffuses into the atmosphere, it is returned as rainfall. Mercury can persist when deposited in lakes, where it is bioaccumulated in aquatic food chains. Acidification of lakes from acid rain increases the level of methylmercury in fish (Clarkson 1990).

**Organic mercury compounds** are the most toxic forms of mercury and result from the uptake of mercury into the food chain. Methylmercury compounds are the most toxic and widely known of the organic compounds, although other alkyl- and phenyl- compounds have been implicated in human poisonings, particularly through their use as fungicides (Eyl 1971, Agocs 1990, Snyder 1972). Methylation of mercuric ions can also occur, especially in fish (the major source of human exposure to organic forms of mercury) (Goyer 1996, Grandjean 1994). Some human populations where fish is the primary source of food—in Sweden, Peru,

Alaska, northern Canada, and the Faroe Islands—have very high blood concentrations of mercury, although no recent clinical outbreaks of poisoning have been reported (Grandjean 1994). Commercial and recreational fishing is restricted in many rivers and lakes in the United States and Canada; the sale of swordfish and shark is restricted due to the high mercury content in fish (Clarkson 1990).

In Japan in 1953-1960 and in 1964, methylmercury chloride was discharged from two different plastics manufacturing plants into Minamata Bay. Accumulation was extremely high in fish (50 ppm) and in shellfish (85 ppm). A total of 241 people were poisoned from ingesting contaminated fish, and 52 of them died (Eyl 1971).

Outbreaks of mercury poisoning in Northern Iraq and Pakistan were linked to flour and seed treated with organic mercury fungicides (Eyl 1971, Grandjean 1994). A family in New Mexico was poisoned from eating hogs that had been fed grain treated with a methylmercury fungicide (Snyder 1972).

Until 1990, organic mercury compounds were added to latex paint as a fungicide, a source that poisoned a 4-year old boy in Michigan when the interior of his home was painted (Agocs 1990). Although use of mercury in paint is now banned, many supplies and painted surfaces will persist in the environment. (The clinical manifestations of the above cases are described below.)

Elemental mercury is used in thermometers and thermostats. Other forms of mercury have also been a component of numerous topical medications. Some are no longer in use; others such as Mercurochrome and Merthiolate are still available.

Elemental mercury spills should always be scooped up and never vacuumed, as the heat of a vacuum volatilizes the mercury (Zelman 1991). Mercury vapors will also be released if elemental mercury is spilled into a floor vent of a heating system.

Mercury is also used in some Caribbean-based religious practices, in which many New York City Latinos, in particular, participate. “Azogue,” as mercury is called, is believed to provide luck in love, good health, and protection against evil. A capsule containing 9-10 grams of elemental mercury is carried by a family member in a sealed pouch, or the contents may be sprinkled throughout the house. When sprinkled, mercury poses a significantly higher hazard to a crawling infant, as mercury vapors are concentrated at floor level (Zayas 1996).

## **Toxico-Kinetics**

### **Absorption**

Elemental mercury readily volatilizes to mercury vapor at room temperature and inhalation is the most frequent cause of exposure to this form of the metal. When ingested in its liquid state, elemental mercury is poorly absorbed through the gastrointestinal tract. There is some absorption through the skin in both the vapor and liquid states.

Like elemental mercury, inorganic and organic forms of mercury are readily absorbed through inhalation. The organic methylmercury is highly absorbed

in the gastrointestinal tract(90-100%), and there is significant absorption of inorganic mercury in the digestive tract (approximately 7%-15%) (Goyer 1996).

All forms of mercury cross the placenta and fetal uptake of elemental mercury and methylmercury can be extremely high. Mercury concentrations in the fetus are often double those found in the mother after exposure to methylmercury, which poses a particular threat to the developing fetal central nervous system. Maternal milk is a possible source of neonatal mercury exposure; mercury concentrations in breast milk are approximately 5% of those found in maternal blood (Goyer 1996, Grandjean 1994).

### **Target Organs**

Brain tissue is the major target organ for methylmercury, mercury vapor, and mercury salts. The kidney is the other major target organ, especially for inorganic mercury.

### **Metabolism**

Mercury can convert in situ to various forms. Elemental and organic mercury, for example, tend to transform into the inorganic form. This metabolic process is especially important when organic mercury or inhaled mercury vapor has been absorbed into the central nervous system. Once there, it can transform into the inorganic form, which then cannot cross the blood-brain barrier to exit the brain (Goyer 1996, Zelman 1991).

### **Elimination**

Mercury is primarily eliminated through the urine. The metal is also secreted into the bile; however, some undergoes enterohepatic circulation (Zelman 1991, Goyer 1996). Mercury vapor can also be exhaled. The biologic half-life of this element averages around 60 days, although it is slightly longer (70-90 days) for methylmercury and shorter (about 40 days) for inorganic mercury (Goyer 1996).

## **Clinical Manifestations of Mercury Toxicity**

Symptoms of mercury poisoning vary and depend on the form of mercury and whether the exposure has been acute or chronic. A high index of suspicion is necessary to identify cases of mercury poisoning when the patient or family member does not identify an obvious exposure. One should consider mercury poisoning whenever signs of acrodynia, or unexplained peripheral neuropathy or encephalopathy are present.

### **Methylmercury**

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Methylmercury is the most important source of environmental exposure. It is a neurotoxin and effects include paresthesia, difficulty concentrating, ataxia, dysphagia, muscle weakness, fatigue, vision and hearing loss, tremors, atetoid movements, paralysis, seizure, coma, and death. Exposure during pregnancy is known to have potentially devastating consequences, including cerebral palsy in the newborn (Eyl 1971, Snyder 1972).

### Mercuric Salts

Ingested mercuric salts tend to be extremely corrosive and cause ulceration, bleeding, GI tract necrosis, and bloody diarrhea. Renal failure due to proximal tubule necrosis usually occurs within 24 hours if the patient survives the initial gastrointestinal injury (Goyer 1996, Goldwater 1972). Additional renal toxicity (from mercuric salts and mercury vapor) includes proteinuria due to glomerular damage. (Clarkson 1990).

### Mercurous Salts

Mercurous salts are less corrosive and have often been used in various medicinal preparations. Mercurous salts and phenylmercuric fungicides are known to cause acrodynia, symptoms of which include erythema of the palms and soles, irritability, edema, hyperkeratosis, vasodilatation, fever, and splenomegaly (Clarkson 1990, Agocs, 1990). The patient may also experience tachycardia, hypertension, and, in the adult, ataxia, visual field defects, dysarthria, and paresthesias.

### Mercury Vapor

Inhaled mercury vapor produces a corrosive bronchitis and interstitial pneumonitis. In addition, some central nervous system (CNS) effects, such as excitability, tunnel vision, and tremor, may occur. Chronic vapor exposure primarily affects the CNS. Symptoms may range from depression, weight loss, and muscle weakness to severe muscle wasting with decreased deep tendon reflexes (Zelman 1991). Other symptoms have included tremors of fine motor muscles with eventual progression to generalized tremors or spasms in other muscle groups, personality and behavioral changes, memory loss, and delirium. Thyroid dysfunction and thyroid enlargement have also been reported. Many of the signs described above were first recognized from workers in the felt hat industry (Goyer 1996, Goldwater 1972).

### **Case Study**

A six-month-old male is brought in for a well-child visit. The mother is concerned that he does not seem to be developing like her other children and that he often exhibits strange movements. The child is breast-feeding well, but has not taken readily to a spoon for soft foods. The child will smile and react to the mother's face, but is unable to roll over or sit up without support. The mother describes the pregnancy as having been normal, with adequate weight gain and no infections. The child was initially dusky in color at birth, but his color seemed to quickly improve and he went home after the second day. The family has kept its appointments for well-child care. On the last visit at four months, the child was noted to have a weak cry and was unable to lift his head when in the prone position.

Today the boy's developmental exam is that of a one-month-old child. He has the ability to follow objects to the midline and to lift his head in the prone position. Generalized hypotonia is present and he is unable to maintain good truncal con-

trol or to roll from front to back. While in the office, he exhibits one of the movements that the mother had mentioned, which proved to be a myoclonic seizure.

Upon further history, it was noted that the child's older sister is in special education, often seems tired, and has a wobbly gait. The family lives in a southern coastal fishing town and the father operates a shrimp boat, which supplies the family's primary food group.

Discussion of this case should address the possibility of mercury poisoning due to the children's consumption of methylmercury-contaminated shrimp. Discussion should also address the children's potential prenatal and neonatal exposure to mercury, perhaps through ingestion of maternal breast milk.

### **Treatment of Mercury Toxicity**

Chelation therapy is the usual method of treatment for mercury poisoning. Dimercaprol (also known as British Anti-lewisite – BAL) is widely used for acute inorganic mercury poisoning (Zelman 1991, Clarkson 1990). This is contraindicated in methylmercury poisoning because it increases the concentration of this substance in the brain. D-penicillamine can be used as an alternative (Zelman, 1991) as can a newer derivative of BAL, dimercaptosuccinic acid (DMSA) (Clarkson 1990). Supportive treatment is also necessary, especially in cases of acute elemental mercury inhalation.

## **Cadmium**

### **Description**

Cadmium (Cd) was discovered relatively recently (1817) and has been used in industry only during the last 50 years. It is now widely employed in electroplating and galvanizing, as well as in the production of nickel-cadmium batteries and in some color pigments used in paint and plastics. Most of the clinical effects of cadmium poisoning are chronic and result from the build-up of the toxicant in tissues over time.

### **Sources**

Cadmium is a by-product of zinc and lead mining and smelting, which are important sources of environmental pollution. Common reservoirs include shellfish such as mussels, oysters, shrimp, and scallops. Exposure to cadmium can occur in industries that involve welding, or the smelting and/or cutting of metal (Barnhart 1984). Cadmium is also found in soil due to fallout from the air, and the use of cadmium-containing irrigation water and some fertilizers, including commercial sludge. Indeed, there has been a slow, steady rise in cadmium concentration in vegetables over the years as a result of agricultural sources of this metal (Goyer 1996). Finally, cigarettes contain up to 1-2 ug of cadmium. This is an important source of human exposure, not only to smokers but also to children and others exposed to second-hand smoke (Frery 1993, Lauwerys 1994, Shaham 1996).

## Toxico-Kinetics

### Absorption

Approximately 2-7% of ingested cadmium is absorbed through the gastrointestinal tract, and its absorption is enhanced when the diet is deficient in calcium, iron, or protein (Lauwerys 1994). Absorption through the respiratory tract is more efficient, ranging from 15% to as much as 50% of an inhaled dose (Lauwerys 1994, Goyer 1996). Both these routes are potential sources of exposure in children.

### Metabolism

Cadmium binds to red blood cells, plasma albumin, and metallothionein, which is synthesized in the liver and also by the placenta. Metallothionein may serve as a barrier to protect the fetus (Goyer 1996); however, in cases of excessive maternal exposure, it appears that some cadmium will cross the placenta (Frery 1993).

Cadmium is initially detoxified in the liver through the formation of a metallothionein-cadmium complex, which is slowly released from that organ. Although initially non-toxic, the cadmium-metallothionein complex can be nephrotoxic as it accumulates in the kidneys (Goyer 1996, Dorian 1995).

The average blood level of cadmium in adults without excessive or occupational exposure is about 1 µg/dL or less, as is the amount excreted in the urine in the adult population. Blood and/or urinary cadmium excretions exceeding 5 µg/dL generally indicate excessive exposure (Barnhart 1984). Human breast milk concentrations of cadmium are usually very low.

## **Clinical Manifestations of Cadmium Toxicity**

There is only one reported pediatric case of acute toxicity directly linked to cadmium. In that instance, a two-year-old child who had died from acute cerebral edema was found to have elevated cadmium in the neuroglial cells, as well as cadmium deposition in the renal tubules and glomeruli (Provias 1994).

Skeletal toxicity represents an important component of cadmium exposure. During World War II, individuals from a single village in Japan were afflicted with a metabolic bone disease that is now being called itai-itai (ouch-ouch) disease. This consists of severe, generalized bone pain, multiple bone fractures, osteomalacia with bone mass reduction, and physical disability (Noda 1990, Anonymous 1971). The area in Japan is located downstream from a river that was the primary discharge for a mine. The surrounding water and irrigated rice were found to have high levels of zinc, lead, and cadmium. As zinc and lead have never been associated with such toxicity in the past, cadmium was attributed as the most likely cause of the symptoms (Anonymous 1971), and mounting pathologic evidence supports cadmium as the cause (Noda 1990).

As to specific effects in children, preliminary work suggests that cadmium is associated with poor fetal growth and subsequent low birth weight.

Symptoms of acute toxicity generally resolve without long-term effect. Ingestion of high concentrations of cadmium may produce transient nausea, vomiting, and abdominal pain. Inhalation of contaminated fumes may produce an acute chemical pneumonitis and pulmonary edema, which appears to resemble metal fume fever. However, the symptoms usually have a longer, more serious course. (Such severity of illness generally requires a prolonged exposure in poorly ventilated space.) (Barnhart 1984).

The symptoms of chronic toxicity, in which the lungs and kidneys are the major target organs, are more serious than transient acute effects. In the lungs, chronic toxicity typically produces chronic obstructive pulmonary disease, with a decreased vital capacity and increased residual volume (Hendrick 1996). The kidneys may develop chronic renal tubular disease. Primary findings in kidney disease include proteinuria, aminoaciduria, glucosuria, and decreased tubular reabsorption of phosphate. In long-term follow-up studies, it appears that the proteinuria is irreversible and that serum creatinine will increase over time (Roels 1989).

Cadmium is considered a category I carcinogen based on several studies that found a relationship between exposure to cadmium and the development of lung tumors (IARC 1994).

#### **Treatment of Cadmium Toxicity**

The only effective method of treatment for cadmium toxicity is the elimination or prevention of exposure. The induction of metallothionein with dietary zinc, cobalt, or selenium may be protective; however, there have been no clinical trials of this treatment.

## **Arsenic**

### **Description**

Arsenic (As) is the most common cause of acute heavy metal poisoning in humans, although iron ingestion probably accounts for more such cases in children. Although the incidence of arsenic poisoning is declining, it is important for the clinician to be familiar with its effects.

Arsenic has both metal and non-metal physical and chemical properties. It exists in the elemental form, trivalent (-3 or +3) form as arsenite, and pentavalent forms, and combines covalently with nonmetals (oxygen and sulfur) and metals (lead, calcium, copper). It also can combine with hydrogen to form arsine—an extremely poisonous gas with unique toxicities.

### **Sources**

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Arsenic has historically been used in many different pesticides and herbicides. Most preparations are no longer available in the United States, but many homes and farms harbor residual supplies that pose a health risk. These compounds are still widely used in other countries, and are available through several international distributors and brokers.

Arsenic is released into the environment from a number of sources, including the smelting of copper, zinc, and lead, and the manufacture of chemicals and glass. Occupational sources of exposure to arsenic are significant and occur mainly in smelting and pesticide industries. Arsine gas is usually produced in the manufacture of arsenical pesticides, but can also be released in the process of refining non-ferrous metals, when the metal comes in contact with a strong acid solution.

Arsenic is found in various water supplies worldwide and represents an important source of environmental pollution. High levels have been reported in Minnesota, California, Chile, and West Bengal, India. (Whorton 1988, Feinglass 1973, Moore 1997, Das 1995, Mandal 1998). The contamination in India affects an area with a population of 34 million people. An estimated 1.5 million of these people have consumed contaminated water and more than 175,000 have skin lesions that are manifestations of arsenic toxicity (Das 1995, Mandal 1998). Additional human exposure comes from seafood, particularly shellfish, cod, and haddock. After ingestion, arsenic is typically cleared from the urine within 2 days. (Ellenhorn 1997).

### **Toxico-Kinetics**

#### **Absorption**

Ingestion is the usual route of arsenic poisoning in children. In general, pentavalent and trivalent arsenical compounds, especially the salts, are well absorbed through the gastrointestinal tract. Trivalent arsenicals, such as white arsenic and Paris green, have a greater lipid solubility and therefore greater skin penetration (Malachowski 1990).

#### **Target Organs**

Toxicity occurs in the central nervous, hematologic, renal, gastrointestinal, and dermatologic systems after gut absorption.

#### **Metabolism**

Arsenic is metabolized to monomethyl and dimethyl forms, which is thought to be part of the detoxification process. Methylation of inorganic arsenic is rapid and the compounds are easily excreted through the urine. It is when exposure to inorganic arsenic exceeds the rate of metabolism that toxicity occurs (Goyer 1996).

### **Clinical Manifestations of Toxicity**

Arsine gas is extremely toxic: inhalation of a dose as low as 25 ppm over 30 minutes usually results in lethal hemolysis (Fowler 1974). In order of toxicity, arsine ranks first, followed by the trivalent form (arsenite) and the pentavalent form.

Patients who have experienced an acute exposure to arsenic usually develop vomiting, severe abdominal pain, and diarrhea (sometimes with blood in the stool) as early as one hour after ingestion. Other symptoms include anorexia, fever, hepatomegaly, mucosal irritation, and arrhythmia. The latter can begin as subtle electrocardiographic changes, such as a prolonged Q-T interval, and progress to

ventricular tachyarrhythmias, leading to eventual cardiovascular collapse—a common cause of death in such poisonings (Campbell 1989, Ellenhorn 1997, Malachowski 1990).

Chronic (and at times acute) exposure can lead to progressive peripheral and central nervous system toxicity, producing sensory changes, paresthesia, and muscle tenderness. One symptom is typically described as a burning pain in the feet. Chronic exposure can also involve demyelination of axons. Neuropathy progression is usually gradual, occurring over the course of several years.

Liver injury may also result from long-term exposure. The initial symptom is jaundice, which may progress to cirrhosis and ascites (Malachowski 1990, Ellenhorn 1997).

Several prominent dermatologic features of sub-acute and chronic arsenic exposure may give the clinician clues to the underlying diagnosis. Hyperpigmentation can occur, especially in non sun-exposed areas such as the areolar region and the groin. Hyperkeratosis may be present on the palms and soles. Squamous cell carcinoma is a potential complication in some cases. In addition, a pathognomonic sign known as Mees' lines may occur, consisting of horizontal white bands of arsenic deposits across the bed of the fingernails. Mees' lines usually appear 4-6 weeks after exposure (Malachowski 1990, Das 1995).

### **Case Study**

A three-year-old male is rushed to the emergency room with acute onset of vomiting, abdominal pain, and bloody diarrhea over a four-hour period. He has had five episodes of emesis and has passed four stools. The child was previously well and had eaten the same foods as the rest of his family the previous day. On examination, he is found to be diaphoretic, tachycardic, and mildly dehydrated. His pharynx is red, with some vesicles along the posterior wall. His abdomen is diffusely tender and his liver is slightly enlarged. The rest of his exam is normal. He is initially worked up for infectious causes of diarrhea and is placed on fluids. However, his pain worsens and he starts running a low-grade temperature. A diagnosis of appendicitis is considered about the time his heart monitor alarm goes off as a result of ventricular tachycardia.

A more extensive medical and environmental history reveals that the child lives on a farm and often plays in a barn and storage shed. He has had two similar episodes of illness in the past three months, though neither was as severe as this one and both were treated at home with fluids and bed rest. The family is questioned about whether old pesticides might be present on the farm and his grandfather recalls he does have some Paris green on hand from 20 years back. Examination of the fingernails confirms the suspicion of arsenic ingestion.

### **Treatment of Arsenic Toxicity**

The primary form of treatment for acute arsenic toxicity is dimercaprol, also known as British Anti-lewisite (BAL). The injections are painful, however and there are

reports that this treatment increased arsenic levels in brain tissue in rabbits exposed to arsenite. The dosage is 2.5-3.0 mg/kg/dose according to the following schedule: Day 1 and 2 q. 6 h., Day 3 q. 12 h., and Day 4 and above q. 24 h.

Two oral chelating agents are effective in treating arsenic poisoning. DMSA (Succimer) and DMPS are similar, oral derivatives of BAL. Succimer has been used for treatment of arsenic intoxication but it is not currently labeled for this purpose (Mückter 1997). DMPS is available only outside the United States. The usual DMSA dosage (as described for lead chelation) is 10 mg/kg/dose given q. 8 h. for the first 5 days, and q. 12 h. for 14 more days.

The primary treatment for arsine intoxication is supportive care, with abundant fluids to dilute urine and increase excretion of arsenic and hemolysis products. Exchange transfusion and sometimes hemodialysis may be necessary to maintain fluid composition in the event of renal failure, but these interventions do not remove arsine from the blood (Fowler 1974).

## Iron

### Description

Iron (Fe) is an essential element necessary for good health, but ingestion of dietary iron supplements may also be a cause of acute poisoning death among children. Most overdoses are attributed to the coated ferrous sulfate tablets (red in color) that resemble candy. Although other forms of iron toxicity exist, such as chronic iron overload, this module will limit discussion to accidental overdose, which is by far the most common method of iron poisoning seen in pediatric practice. It is essential for pediatric practitioners to recognize the symptoms of iron overdose so that acute poisoning can be effectively treated and delayed-onset toxicity prevented.

### Sources

Iron preparations are widely available in forms that include the enteric-coated ferrous sulfate tablet and multivitamins with iron. Pediatric preparations are also available in liquid form. The number of fatalities from iron overdose in children has significantly decreased since the introduction of child-resistant bottle caps in the 1970s. Adult iron supplements have the highest concentration of elemental iron of any vitamin preparations. Between 1984-1993 there were 34 iron-overdose fatalities reported in children under 6 years of age: 25 resulted from ingestion of adult supplements, and 9 from ingestion of adult multivitamins with iron. No fatalities from this same time period occurred from pediatric vitamin preparations despite 96,826 reported cases of iron exposure from this source in children under age 6 (McGuigan 1996). The most recent poison control data show that in the United States in 1997, there were 29,260 exposures to iron; 22,929 (78%) occurred among children less than 6 years of age. There were 2 deaths during this period, both from non-multivitamin formulations. Of the 24,716 total exposures to multi-vitamins with iron (all age groups), only 170 had moderate to major morbidity (Litovitz 1997).

## **Toxico-Kinetics**

The disposition of iron within the body is extremely complex. This module will address only the toxic effects produced by iron overdose.

### **Absorption**

Gastrointestinal absorption accounts for virtually all of iron's toxic effects. Iron is rapidly absorbed from the gastrointestinal tract, primarily the duodenum. The corrosive nature of iron on the gastrointestinal mucosa is thought to increase further this absorption (Howland 1996).

### **Metabolism**

Once in the blood, iron is bound to transferrin and taken to various storage sites including the liver, where ferritin (an iron storage protein) is synthesized.

### **Target Organs**

In cases of iron overdose, the storage system, which includes hemosiderin as well as ferritin, is overwhelmed and free iron creates toxic effects in tissues such as the liver, cardiovascular system and kidney (Goyer 1996).

### **Elimination**

Iron is rapidly removed from the blood compartment and its distribution to tissues and elimination is complete in about 24 hours (Howland 1996).

## **Clinical Manifestations of Toxicity**

The symptoms of iron toxicity appear in stages that are generally dose-responsive. Stage I (acute) symptoms of vomiting, diarrhea, and abdominal pain usually develop in children 1 to 6 hours after ingestion. The emesis may be bloody due to the ulcerative effects iron has on the gastrointestinal mucosa. The stool may also be melanotic. Stage II, the latent stage, is characterized by an apparent recovery from symptoms. Within 12 to 36 hours of ingestion, however, the patient's condition may rapidly deteriorate (Stage III) with liver and kidney failure, metabolic acidosis, coagulopathy, and cardiovascular collapse. If the patient recovers, there may be residual hepatic cirrhosis and gastrointestinal strictures (Morse 1997, McGuigan 1996, Cheney 1995).

If the amount of ingested iron is extremely high, there may be enough gastric ulceration to cause massive blood and fluid losses. In this case, the child may bypass the latent stage and immediately develop hypovolemic shock and progress to multi-organ system involvement (McGuigan 1996). On the other hand, if a relatively low amount of iron has been ingested, toxicity may only be manifested by the acute (Stage I) presentation. What appears to be the latent phase can often be the resolution of all toxicity in mild cases. In children whose GI symptoms resolve within 6 hours of presentation in the emergency department, inpatient observation is still prudent because of the potential for unpredictable and abrupt onset of shock.

Children who manifest systemic toxicity will develop a coagulopathy characterized by a prolonged prothrombin time (PT) and partial thromboplastin time (PTT) (Morse 1997, McGuigan 1996, Cheney 1995). Early on, this is due to excess ferric iron and is amenable to chelation therapy as discussed below. Later, the coagulopathy is caused by direct hepatotoxicity and reduced levels of clotting factors. Other manifestations of hepatic toxicity include elevated serum transaminases, lactate dehydrogenase (LDH), and bilirubin. Elevated iron levels cause myocardial damage and decreases in contractility, cardiac output, mean arterial pressure, and heart rate. Tissue hypoxia occurs, leading to anaerobic metabolism and metabolic acidosis. Renal failure may also occur (McGuigan 1996). Patients' mental status may range from lethargy to coma (Morse 1997).

### Case Study

A 3-year-old male is brought to the emergency room with vomiting and diarrhea. The child is crying and says his stomach hurts. All symptoms began early in the afternoon and have been going on for about 5 hours. The first appearance of blood in the emesis prompted the family to bring the child to the ER. On exam the child is alert but very fussy and appears to be mildly ill. Vital signs are normal. The mucous membranes are slightly tacky and minimal tearing is present. The rest of the exam is within normal limits. The stool is not tested for occult blood. After several hours in the ER, he seems to feel better, his symptoms are all resolving, and he has finished 12 ounces of electrolyte solution. Because the blood in the emesis occurred only once after several hours of emesis, it was felt to be from a small tear due to the excessive vomiting. He is discharged with a diagnosis of acute gastroenteritis and parents are instructed to continue fluid administration and follow up with their primary physician in the next day or two.

The next morning, the child is found to be difficult to arouse, pale, and limp and is transported by EMS to the ER. He has blood trickling out of his nose. His respirations are shallow, his blood pressure is 70/30, and he is tachycardic. Intraosseous access is obtained and blood oozes through needle punctures from failed attempts to obtain an IV. He is unresponsive to stimulation. Of note on his initial metabolic profile is a bicarbonate level of 6,  $K^+$  of 5.8, and a BUN/creatinine of 40/2.8. This time an environmental history is obtained and it is noted that the mother is taking an iron supplement. After a quick call home, the mother reports an empty medicine container that held an unknown number of ferrous sulfate tablets and some tablets that were scattered on the floor of the child's upstairs playroom. The mother recalls that yesterday the boy came down from his playroom saying his stomach was hurting, which led to the ER visit yesterday; they had not returned to the room since.

Due to his level of consciousness and the rapid progression of shock, the child is intubated and ventilated. No tablets are seen on an abdominal X-Ray. His iron level at approximately 20 hours post-ingestion is 800 mg/dL. Deferoxamine is started at 15 mg/kg/hr for about 24 hours. He is also treated with fluids, oxygen, sodium bicarbonate, dopamine, nitroprusside, and fresh-frozen plasma. The child gradually improves over the next 2 to 3 days.

### **Treatment of Iron Toxicity**

Supportive care with special attention to fluid balance and cardiovascular stabilization is of paramount importance. GI decontamination is recommended as early as possible if the estimated ingested dose exceeds 20 mg/kg or the patient is symptomatic (Morse 1997). (Iron levels should be obtained to further guide therapy, but the estimated dose allows one to determine the initial course of action.) Charcoal is not recommended because it does not adsorb iron. Induction of emesis may be helpful if the patient seeks help within the first hour after ingestion. Gastric lavage may remove some tablet fragments. However, there are several reports where emesis and/or lavage failed to remove large masses of ferrous sulfate tablets where they embedded into the mucosa or formed a bezoar (Tenenbein 1985, Peterson 1980, Landsman 1987). Adequate supportive care is often all that is necessary in patients with relatively low serum iron concentrations (less than 350 µg/dL).

Patients with serum levels greater than 500 µg/dL should be chelated with deferoxamine. This cutoff should be considered only as a guide to therapy and not as a rigid rule, since in one recent study, 3 of 6 patients with cardiovascular instability had levels below 500 µg/dL and one patient had a level of 513 µg/dL and was asymptomatic (Chyka 1996). Deferoxamine binds absorbed iron very well and is easily excreted in the urine. Intravenous administration is preferred because intramuscular injection is more painful and less efficient in clearing iron. The standard dose is 15 mg/kg/hour as a continuous infusion. Moderate to severe toxicity should be treated for 8 to 24 hours, although the exact dosing schedule is still not well established (Morse 1997, Tenenbein 1996). One report of a severe overdose with an iron level exceeding 16,000 µg/dL used a dose of 25 mg/kg/hour for a 12-hour infusion, with a 12-hour rest prior to restarting the deferoxamine, in order to prevent pulmonary toxicity from the deferoxamine (Cheney 1995). Blood pressure and serum pH should be monitored 2 to 3 hours after stopping the deferoxamine to be sure that toxicity does not recur.

## **Learning Methods**

This material can be effectively presented in a lecture format, using a clinical case (the one included, or one of your own) to introduce each metal. An alternative is to use small group discussions or a "Jeopardy!"-style game format in which questions from this and other toxicology-related modules are featured.

## **Visual Aids**

128 The table included at the end of this module summarizes the sources, clinical effects, and recommended treatment for four metals of concern: arsenic, cadmium, iron, and mercury. This table can be reproduced and distributed to students and/or residents.

## **Evaluation Methods**

Knowledge of this material is best assessed by pre- and post-tests.

<b>Metal</b>	<b>Sources</b>	<b>Clinical</b>	<b>Treatment</b>
<b>Arsenic</b>	<p>Pesticide use in the past, and present in some countries</p> <p>Industrial sources: copper, lead, and zinc smelting, chemical and glass manufacturing</p> <p>Arsine gas released in the manufacture of pesticides and metal refinement</p>	<p>Acute: severe GI disturbances, dysrhythmia, cardiovascular collapse, mental status changes, seizures</p> <p>Chronic: Peripheral neuropathy, skin changes, liver injury, malignancy</p>	<p>Dimercaprol (BAL)</p> <p>DMSA (Succimer, Chemet)</p> <p>DMPS (Not available in USA)</p>
<b>Cadmium</b>	<p>By-product of lead and zinc mining</p> <p>Shellfish such as shrimp, scallops, oysters</p> <p>Soil, ground and irrigation water, fertilizers, etc, resulting in rising concentrations in vegetables</p> <p>Nickel-cadmium batteries</p> <p>Cigarette smoke</p>	<p>Acute: nausea, vomiting, abdominal pain, chemical pneumonitis</p> <p>Chronic: Chronic obstructive lung disease, chronic renal tubular disease and ultimately failure, calcium loss</p> <p>Carcinogen: Lung tumors</p>	<p>Prevention of exposure is only tested treatment</p>
<b>Iron</b>	<p>Enteric-coated ferrous sulfate tablets</p> <p>Multivitamin preparations with iron</p>	<p>Stage I: Acute GI disturbance 1-6 hours after ingestion. Emesis may be bloody due to gastric ulceration</p> <p>Stage II: Apparent recovery</p> <p>Stage III: Rapid deterioration with cardiovascular collapse, liver and kidney failure</p> <p>May be severe enough to bypass latent phase, or may be mild enough not to develop state III</p>	<p>Deferoxamine</p>
<b>Mercury</b>	<p>Natural degassing of Earth's crust</p> <p>Volcanic emissions</p> <p>Mining</p> <p>Burning of coal and natural gas</p> <p>Other industries: chloralkali plants, paper</p> <p>Thermometers, thermostats</p> <p>Medicines: Mercurochrome and merthiolate</p>	<p>Neurological: Paresthesia, ataxia, muscle weakness, fatigue, vision and hearing loss, cerebral palsy, tremors, seizure, coma</p> <p>Nephrotic syndrome</p> <p>GI tract necrosis and bloody diarrhea, ulceration from mercuric salts</p> <p>Acrodynia, hypertension, ataxia paresthesia, visual defects from mercurous salts</p>	<p>Dimercaprol (BAL) for inorganic poisoning (<b>Contraindicated</b> in methylmercury poisoning)</p> <p>d-Penicillamine, DMSA are oral alternatives</p> <p>Correct environmental abatement is of utmost importance</p>

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