

A Small Dose of Metals

Or

An Introduction to the Health Effects of Metals

Introduction

An excellent man, like precious metal, is in every way invariable; A villain, like the beams of a balance, is always varying, upwards and downwards.

John Locke

Metals occupy a large part of periodic table and are generally good conductors of electricity or heat. Metals forms cations and ionic bonds with non-metals which makes many of them essential for humans and indeed for all life, while making others very toxic. We began using metals to build and shape our society over 4000 years ago. The Greeks and Romans were some of the first document both the toxic and potential healing effects of metals. Arsenic was well known both as a poison and treatment for disease.

The use of metals in our industrialized society has significantly altered the natural distribution of metals in the environment. Our progress and folly is well documented in the Greenland ice. Lead in the Greenland ice began increasing about 800 BC, documenting its use and redistribution as civilizations flourished and declined. A dramatic increase occurred when lead was added to gasoline in the 1920s. Overall there has been a 200-fold increase in lead in the Greenland ice due to human use of lead.

Metals cannot be created or destroyed, but can change form, altering their biological availability and toxicity. Metallic mercury evaporates and is redistributed from the atmosphere across the globe. When the mercury is returned to land or water, bacteria form methyl mercury (Hg-CH₃), which is then taken up by increasingly larger organisms and ultimately ends up in fish, such as tuna, that humans and other animals consume.

The principles of toxicology, dose – response and individual sensitivity, are well illustrated by the metals. Historically, most of the interest and concern was with the obvious effects of metal toxicity such as colic from lead or symptoms of the “Mad Hatter” from mercury. The emphasis has changed to the more subtle and long-term effects and concern for potentially sensitive individuals. It is now well documented that children exposed to even low levels of lead will have a lowered IQ and other learning difficulties. This knowledge has resulted in significant changes in our use of metals.

In this chapter, the metals are divided into three sections: 1) nutritionally important metals or essential metals; 2) important toxic metals; and 3) medically useful metals. There is also a very brief section on chelating agents used to treat over-exposure to metals. Only selected metals are reviewed and the reviews are very brief, covering key points about their biological activity and toxic effects. The accompanying presentation material has one slide for each metal highlighting key facts. Three metals, arsenic, lead, and mercury are covered in more detail in separate chapters. These three metals are recognized as persistent environmental contaminants and are toxicologically important.

Nutritionally important metals

Introduction

Our very existence is dependent on a number of metals, the most common of which is iron. Some of the more important ones are described below. Because they are essential elements, the beneficial and adverse effects of these metals have been carefully studied and recommendations developed on daily intake. These recommendations are generally very broad and can vary depending on age – child or adult, young or old – or during pregnancy. The recommended daily intakes quoted below are for adults. These recommendations are actually oral exposure levels with intestinal absorption highly variable and dependent on the metal and other variables. A quick look at a typical cereal box will demonstrate the importance placed on these elements.

Since they are essential for life, the toxicity of these metals can result from either nutritional deficiency or excess exposure but the focus will be on excess exposure. However, nutritional iron deficiency is worth mentioning, as it is a problem in the United States as well as worldwide and lack of iron can contribute to lead toxicity. Depending on the route of exposure, metal toxicity can be very different. Metals like zinc and manganese can be very toxic when inhaled. As we have seen with many agents, there is a beneficial and a hazardous side depending on route of exposure and amount of exposure.

Summary Table - Nutritionally Important metals

Table 7.1 Summary of Nutritionally Important Metals

Metal	Function	Source	Toxicity (when in excess)	Recommended Daily Allowance
Chromium (Cr)	Associated with insulin	Food supply	Kidney damage, lung cancer (inhalation)	50 to 200 μg (Cr^{3+})
Copper (Cu)	Synthesis of hemoglobin	Food supply	Toxicity is very rare, deficiency – anemia; excess – liver and kidney	1.5-3.0 mg
Iron (Fe)	Hemoglobin	Food supply	Intestinal tract, liver damage	10 to 15 mg
Magnesium (Mg)	Associated with many enzymes	Food supply, grains and nuts	Deficiency – neuromuscular weakness, convulsions	280 to 350 mg
Manganese (Mn)	Associated with many enzymes	Food supply, Inhalation in welding	Parkinson's-like syndrome	2 to 5 mg
Selenium (Se)	Anticancer	Food supply	Heart	55 to 70 μg
Zinc (Zn)	Associated with many enzymes	Food supply	Deficiency - impaired growth	12 to 15 mg

Chromium (Cr)

Chromium is an abundant essential element that exists in oxidation states from Cr^{2+} to Cr^{6+} , of which Cr^{3+} is biologically important and Cr^{6+} industrially important. Cr^{3+} is associated with insulin and regulation of glucose. Recommended daily intake is 50 to 200 μg . Chromium (Cr^{6+}) has a range of industrial uses including as an alloy in stainless steel and in tanning leather, but it is also highly toxic. The most serious industrial exposure is by inhalation and is most prominent in chrome production and plating industries. Acute chromium exposure causes kidney damage and skin contact can cause contact dermatitis and when inhaled irritate the nasal lining. It should also be considered a lung carcinogen.

Copper (Cu)

Copper is involved in hemoglobin synthesis and human toxicity is rare either from deficiency or excess. Recommended daily intake is 1.5-3.0 mg. It is widely used in a number of products including plumbing and electrical wire and is readily available in the food supply. Copper deficiency has been associated with anemia but is generally associated with broader nutritional problems. Grazing animals, for example cattle, can ingest too much copper, affecting the liver and kidney. Copper is much more toxic to aquatic life than to mammals and is an important environmental contaminant in water. In

humans, Wilson's disease, a genetic inability to metabolize copper can be treated with the chelator penicillamine.

Iron (Fe)

There is 3 to 5 grams of iron in the body and two-thirds of that is associated with the oxygen carrying hemoglobin of the red blood cells. Recommended daily intake is 10 to 15 mg, but this increases to 30 mg during pregnancy. Iron deficiency is the most common nutritional deficiency worldwide, affecting both children and adults. Iron deficiency results in anemia or a decrease in the oxygen-carrying capacity of the blood. The intestinal tract actively transports iron and if there is low iron in the diet other metal such as lead will be absorbed, resulting in increased lead toxicity. Before the introduction of childproof caps for medicine, children were often treated for the acute effects of iron toxicity after ingesting iron supplements, suffering vomiting, liver damage, shock, kidney failure and possibly death. Chronic excess exposure to iron can result in ulceration of the intestinal tract, which in turn results in bloody vomit and black feces.

Magnesium (Mg)

Magnesium, a nutritionally essential metal, is found in grains, seafood, nuts, meats and drinking water. Recommended daily intakes ranges from 280 to 350 mg per day for adult females and males, respectively. It is also used in a number of antacids and cathartics. Milk of magnesia or magnesium hydroxide is known as a universal antidote for poisoning. Magnesium is a cofactor in a number of essential enzymes and involved in several key metabolic reactions. Magnesium is primarily absorbed in the small intestine and is routinely excreted in the urine at about 12 mg/day. Magnesium blood levels are constant and consistently regulated by the body.

Magnesium deficiency, usually the result of decreased absorption or excessive excretion, results in neuromuscular weakness and ultimately convulsions. Dietary deficiency in cattle is known as the grass staggers. Magnesium toxicity from impaired excretion or excessive consumption of antacids results in nausea, vomiting, hypotension, and central nervous systems effects.

Manganese (Mn)

Manganese is an essential element involved in numerous enzymatic reactions, particularly those associated with the fatty acids. Intestinal tract absorption is poor (less than 5%) but it is readily available in the foods such as grains, fruits, nuts and tea. Recommended daily intake is 2 to 5 mg. There is increased interest in the toxicity of manganese because of its use in the gasoline additive, as MMT (methylcyclopentadienyl Mn tricarbonyl), which results in manganese salts being distributed into the environment from the tail pipes of cars. Manganese is also an important alloy in steel. Inhalation of

manganese dust during mining or steel production can cause respiratory disease. Manganese exposure can also result in a serious nervous system disease that resembles the movement disorders of Parkinson's disease, characterized by difficulty walking, irritability, and speech difficulties. There is ongoing research on the potential adverse effects from use as a fuel additive.

Selenium (Se)

Selenium is readily available in a variety of foods including shrimp, meat, dairy products and grains, with a recommended daily intake of 55 to 70 μg . Selenium occurs in a several forms, with Se^{6-} being biologically most important. Selenium is readily absorbed by the intestine and is widely distributed throughout the tissues of the body, with the highest levels in the liver and kidney. Selenium is active in a variety of cellular functions and interacts with vitamin E. Selenium appears to reduce the toxic effects of metals such as cadmium and mercury and to have anticarcinogenic activity. Selenium produces notable adverse effects both in deficiency and excess; thus recommended daily intake for adult is approximately 70 $\mu\text{g}/\text{day}$ but should not exceed 200 $\mu\text{g}/\text{day}$.

Excess selenium intake can occur in both animals and humans living in areas with elevated selenium in the soil. Most grass and grains do not accumulate selenium, but when an animal consumes plants that do accumulate selenium (some up to 10,000 mg/kg) they can develop a condition called the "blind staggers". Symptoms include depressed appetite, impaired vision and staggering in circles, and can ultimately lead to paralysis and death. Humans are susceptible to similar effects as well as additional neurological effects. Selenium deficiencies results in heart disorders, skeletal muscle effects and liver damage.

Zinc (Zn)

Zinc plays a number of important roles in the body and deficiency results in serious adverse effects. Recommended daily intake is 12 to 15 mg. Zinc is very abundant in the environment and readily available in many foods, including grains, nuts, legumes, meats, seafood, and dairy products. Numerous enzymes require zinc, as do proteins that regulate gene expression. Zinc plays a role in the immune system and is also important in the development and function of the nervous system.

Zinc deficiency during fetal or infant development can lead to impaired growth, increased illness, impaired healing, loss of hair, and central nervous system disorders. Some studies have linked adult zinc deficiency with neurological disorders such as Alzheimer's disease. Diseases associated with zinc deficiency are linked to liver disorders from alcoholism. A number of drugs, particularly chelating agents and some antibiotics, affect zinc's homeostasis. Exposure to zinc and other metals during welding can cause metal fume fever, characterized by chills, fever, weakness, and sweating.

Toxicologically important metals

Introduction

While some metals are nutritionally important, there is another group with no beneficial biological effects and in some cases serious toxic effects. Our complex relationship to metals is well illustrated by lead, which we have used for a variety of purposes since ancient times. In the last hundred years, lead was extensively used in paint and as a gasoline fuel additive. In the last 30 years, it was recognized that children exposed to even low levels of lead could suffer permanent brain damage and reduced intelligence. This worldwide use and distribution of lead has had significant effects on individuals as well as society as a whole. There is a somewhat similar story for mercury. The examples of lead and mercury clearly illustrate the fundamental principles of toxicology – dose / response and individual sensitivity.

Summary Table – Toxic Metals

Table 7.2 Summary of Toxic Metals

Metal	Toxic Effects	Source
Aluminum (Al)	Dialysis Dementia	During dialysis, food, drinking water,
Arsenic (As) (can exist in different forms)	Cancer (skin and lung) Neurotoxic (sensory effects) Liver and vascular	Drinking water, smelting of ore, used in pesticides, treated wood
Beryllium (Be)	Lung, hypersensitivity, delayed and progressive effects (berylliosis), contact dermatitis	Nuclear power plants, Alloy in metals, coal combustion,
Cadmium (Cd)	Lung, emphysema, kidney, calcium metabolism, possible lung carcinogen	Shellfish, cigarette smoke, taken up by plants, metal alloy - welding
Cobalt (Co)	Inhalation exposure “hard metal” pneumoconiosis	Alloy in metals – but also associated Vitamin B ₁₂
Lead (Pb)	Decreased learning and memory (children very sensitive)	Old paint, food, formerly used as a gasoline additive, auto batteries
Mercury Inorganic (Hg)	Tremor, excitability, memory lose, the “Mad Hatter”	Thermometers, switches, fluorescent lights, some “button” batteries
Mercury - Organic (Hg-CH ₃)	Tremor, developmental effects on nervous system	Fish
Nickel	Lung carcinogen, contact dermatitis	jewelry, cooking utensils, other objects containing nickel

Tin (Sn)	Inorganic – low, lung Organic – central nervous system	Inorganic - Food packaging, dust; Organic - rare
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Aluminum (Al)

Aluminum was first isolated in 1825 and is now recognized as the most abundant metal in the environment. Historically, this abundance has not translated into biological availability because it is highly reactive and remains bound to a range of elements. However, acid rain has increased the bioavailability of aluminum in the environment. Aluminum is used in a wide range of products from airplanes, to beer and soda cans, to cooking pans. Human exposure to aluminum is from drinking water, food, and some drugs. Daily intake ranges from 1 to 10 mg, but it is poorly absorbed in the intestine. Aluminum does not appear to have any essential biological function.

The neurotoxic effects of aluminum were first observed in people undergoing dialysis for treatment of kidney failure. This syndrome, called dialysis dementia, starts with speech disorders and progresses to dementia and convulsions. Symptoms corresponded with elevated aluminum levels commonly found in bone, brain and muscle following 3 to 7 years of treatment. Elevated levels of aluminum were also found in the brains of people suffering from Alzheimer's disease. Despite considerable research, it is not clear if the aluminum accumulation in the brain is a cause or Alzheimer's disease or a result of changes in the brain associated with the disease.

Arsenic (As)

Arsenic has a colorful history, having been used with great effect as a poison and also to treat variety of ailments, including cancer. Its properties were first studied over 2000 years ago and contributed to some of the first theories on toxicology. Despite its toxicity, arsenic was still found in cosmetics into the 20th century. Prior to the recognition of the toxic properties of arsenic, it was widely used as a pesticide in orchards, which resulted in soil contamination. The vast majority of treated wood in residential decks and other structures contains arsenic. Workplace exposure occurs in the smelting of ore, and arsenic is also widely used in the electronics manufacturing industry. Of considerable public concern, which has resulted in several large studies by the government, is the presence of arsenic in drinking water. Some municipal or well waters can contain elevated arsenic levels.

Chemically, arsenic is complex in that it can exist in a variety of forms including trivalent and pentavalent or as arsenic trioxide (computer chip manufacture) and arsenic acid. Arsenic is excreted in skin cells, sweat, hair and fingernails, which can be seen as white transverse bands. Acute exposure to arsenic results in gastrointestinal pain, sensory loss, cardiovascular failure and death. Chronic exposure or survival of acute exposure can

cause loss of peripheral sensory function and loss of central nervous system function. Chronic arsenic exposure can also cause cancer of the lung and skin.

Beryllium (Be)

Beryllium is an important metal component used in the nuclear power industry and combined with other metals. Its presence in coal and oil results in more than 1250 tons being released into the environment annually from fuel combustion at power plants. Exposure is primarily from inhalation, but skin contact can result in dermatitis. Cigarette smokers also inhale a little beryllium. Initially, beryllium distributes to the liver but ultimately is absorbed by bone.

Contact dermatitis and hypersensitivity to beryllium is the most common toxic reaction. Workplace inhalation of beryllium can be very serious. Acute exposure can result in an inflammatory reaction along the entire respiratory tract. Chronic beryllium disease (CBD) or berylliosis can result from chronic workplace exposure. This is a serious and progressive degenerative disease in which the lungs become increasingly fibrotic and dysfunctional. Long-term exposure can result in lung cancer, and beryllium is classified as a carcinogen by international regulatory agencies. Testing available for genetic susceptibility to CBD raises a number of ethical issues.

Cadmium (Cd)

Cadmium is a widely distributed metal used in manufacturing and is present in a number of consumer products. Dietary exposure to cadmium is possible from shellfish and plants grown on cadmium-contaminated soils. Absorption is increased when associated with low levels of iron or calcium in the diet. Some plants, such as tobacco, can concentrate cadmium from even low levels in the soil. The lung readily absorbs cadmium, thus cigarette smokers have elevated cadmium exposure. Cadmium is also used as a metal alloy, in paint, and in batteries (Ni-Cad, nickel-cadmium). Workplace exposure can occur in welding and battery manufacture.

Oral ingestion of cadmium results in less than 10% absorption, but inhalation exposure results in much higher absorption through the lungs. Cadmium accumulates in the liver and kidney, with the kidney being particularly important in binding cadmium and reducing its toxicity. Ingestion of high levels from acute exposure can result in abdominal pain, nausea and vomiting while inhalation exposure results in impaired breathing (pulmonary edema or accumulation of fluid in the lungs). Chronic exposure can result in obstructive lung disease, emphysema and kidney disease. Cadmium may also be related to increases in blood pressure (hypertension) and is a possible lung carcinogen. Cadmium affects calcium metabolism and can result in bone loss. This condition has been referred to as “Itai-Itai” disease, which means “Ouch-Ouch” in Japanese and reflects the bone pain associated with cadmium effects on calcium.

Cobalt (Co)

Cobalt in small amounts is an essential element associated with vitamin B12 but at high levels can be toxic. There are no daily-recommended intake levels for cobalt because intestinal bacteria use cobalt to produce cobalamin, which in turn is an essential component of vitamin B12. Industrially, cobalt is used in pigments, permanent magnets and as an alloy to harden metals as in tungsten carbide blades or drills.

High chronic oral consumption of cobalt has been used to treat anemia but can also cause goiter. High acute consumption of cobalt can cause vomiting, diarrhea and a sensation of warmth, and heart failure. The latter was noted during a period when cobalt was added to beer to improve foaming. When inhaled, for example in metal grinding for sharpening, cobalt can cause “hard metal” pneumoconiosis, a progressive disease of the lungs.

Lead (Pb)

Lead was as important in the Roman Empire as it was in the 20th century, and its use has been almost equally as disastrous. In the Roman Empire lead’s malleability and low melting point made it ideal for plumbing, not unlike its use in solder in plumbing centuries later that can be found in many households. The Romans also added lead to wine as a sweetener and preservative. In the 20th century lead was commonly added to paint, sometimes as much as 50%, which in fact created an excellent, long-lasting paint. But the sweetish taste of lead attracted children who readily consumed lead paint chips, a behavior referred to as pica. Due to its low melting point, lead was used as solder in tin cans containing food and in plumbing. In what some refer to as the greatest public health disaster of the 20th century, lead was added to gasoline to improve car engine durability. Lead was emitted from the tail pipes of cars, contaminating both local and distant areas. Children absorb up to 50% of lead that is orally ingested, as it substitutes for the much-needed calcium. In contrast, adults absorb only about 10% of orally ingested lead. Lead is still a serious concern in areas near smelters and in housing with lead-based paint. As the toxicity of lead at lower levels was recognized it was banned from paint and from gasoline.

The Greek Dioscorides recognized the health effects of lead in the 2nd century BC when he stated, “Lead makes the mind give way”. In the 1700s Benjamin Franklin noted that lead exposure caused the “dry gripes”, or stomach upset. Painters that used lead-based paint suffered from “wrist drop” caused by the effects of lead on the peripheral nervous system. At the turn of the 20th century it was recognized that children seemed to be particularly sensitive to high levels of lead that resulted in a swelling of the brain, kidney disease, effects on hemoglobin and possible death. In the 1970s, studies demonstrated that even low levels of lead exposure harmed the developing nervous system. It is now well accepted that lead is a very potent neurotoxicant. Australia banned the use of lead in

paint in the 1920s but this step was not taken until 50 years later in the United States. On the average the biggest drop in the blood lead levels of children occurred following the phase-out of lead in gasoline in 1980s. The U.S. Centers for Disease Prevention and Control (CDC) has established a blood lead level of 10 $\mu\text{g}/\text{dl}$ or greater as an action level. There is no safety factor associated with this number and there are sufficient data to indicate that the nervous system of children is damaged at blood lead levels of 10 $\mu\text{g}/\text{dl}$ and that the blood action level should be lowered (see chapter on Lead).

The BLL for children was changed in 2012, affectively making it 5.0 $\mu\text{g}/\text{dl}$ While acknowledging that there is no safe level of lead exposure. “CDC now uses a blood lead reference value of 5 micrograms per deciliter to identify children with blood lead levels that are much higher than most children’s levels. This new level is based on the U.S. population of children ages 1-5 years who are in the highest 2.5% of children when tested for lead in their blood.

This reference value is based on the 97.5th percentile of the National Health and Nutrition Examination Survey (NHANES)’s blood lead distribution in children. The current reference value is based on NHANES data from 2007-2008 and 2009-2010.”

Mercury – Inorganic (Hg)

Inorganic mercury is a silvery colored liquid at room temperature. Many people have had the opportunity to “play” with mercury, coating pennies and pushing it around on a flat surface. Now we know that the mercury was evaporating and that there are serious health consequences to the inhalation of mercury vapor. Due to its reactive properties and ability to combine with other metals, inorganic mercury was used at nuclear weapons facilities and in gold mining. In the gold mining process, the ore would be mixed with the mercury and the metallic mixture heated to evaporate the mercury leaving the gold behind. This process results in a significant release of mercury into the atmosphere. The atmospheric circulation of mercury has made it an important worldwide contaminant. When returned to the earth or water, inorganic mercury is converted into an organic mercury compound (see below). Although there are growing efforts to phase the use of mercury out of consumer products, it has been widely distributed in thermometers, switches (thermostats and car trunk lid switches), fluorescent light bulbs and scientific instruments such as used in measuring blood pressure. Many of us have mercury in our mouths as a dental amalgam with silver. Dental fillings contain approximately 50% mercury. This use of mercury has resulted in crematoriums being an important source of atmospheric release. Dental offices are also an important source of mercury entering the waste stream and then into the environment. Mercury has also been used to treat a variety of diseases including syphilis. Coal contains mercury, and combustion of coal at power plant is a significant source of atmospheric mercury. While human activity has greatly contributed to the release of mercury, some release occurs naturally from soil containing mercury and from volcanic activity.

The toxic effects of mercury vapor have been well documented and even recorded in the literature as the “Mad Hatter” in Louis Carol’s Alice in Wonderland. Mercury was used to cure the felt used in hats, and workers developed the characteristic signs of mercury vapor toxicity. Acute exposure to high concentrations of mercury vapor causes respiratory distress that can be fatal. The symptoms of chronic exposure to mercury vapor include personality changes such as excitability, depression, memory loss, fine motor tremor that can become progressively worse, gingivitis, and hallucination. There is some mercury inhalation exposure from dental amalgams but for most people there are no health related effects. Metallic mercury is very poorly absorbed from the intestine, thus it is less hazardous to swallow the mercury from a thermometer than to inhale it (see chapter on Mercury).

Mercury – Organic (Primarily Hg-CH₃)

There are several different types of organic mercury, but by far the most important in terms of health effects is methyl mercury. When atmospheric mercury is deposited on the ground or in the water it is converted to methyl mercury by bacteria. Mercury compounds are very toxic and converting the inorganic mercury to methyl mercury is the bacteria’s way to reduce the toxicity the mercury. Small animals then consume the bacteria, along with the methyl mercury and bigger animals in turn consume the smaller animals, thus increasing the concentrations of methyl mercury. Methyl mercury accumulates in the larger carnivorous animals, most important of which are fish such as tuna, pike and shark. Mercury accumulates in the muscle of the fish, which makes it all but impossible to avoid consumption of the methyl mercury. Methyl mercury is readily absorbed from the intestine, and it crosses the blood brain barrier and the placenta.

The devastating health effects were first documented in Minamata, Japan in the late 1950s, chiefly among fishermen and their families. A subsequent mercury-poisoning incident took place in Iraq when people consumed seed grain coated with organic mercury fungicides. Both of these incidents, as well as others, affected thousands of people and clearly demonstrated the most significant adverse developmental effects of mercury exposure. Early-stage effects include tingling and numbness around the mouth and lips and may extend to the fingers and toes. Continued exposure can result in difficulty walking, fatigue, inability to concentrate, loss of vision, tremor and eventually death. The developing fetus and young children are particularly sensitive the effects of methyl mercury exposure. The serious health effects of mercury combined with its widespread distribution have resulted in numerous health advisories and restriction on fish consumption. Typically children and women of childbearing age are advised to limit their consumption of species of fish known to accumulate mercury. The U.S. Food and Drug Administration limits the amount of mercury in canned tuna to 1 ppm. (see chapter on Mercury)

Nickel (Ni)

Nickel is widely used as a metal alloy component in stainless steel, where it increases hardness and corrosion resistance. Nickel is used in nickel-metal hydride batteries found in some electronics and electric vehicles. It is generally present in the environment and appears to be an essential element for some plant life and bacteria. It is available in low concentrations in the food supply. The most serious workplace exposure is from inhalation. Exposure to the general population is from jewelry, cooking utensils and other metals containing nickel.

For the general population the primary health concern is an allergic response from skin contact. In the workplace, inhalation of nickel compounds can cause respiratory tract cancer, particularly lung and nasal cancers. Nickel is one of the few proven human carcinogens. Contact dermatitis is also a common workplace hazard.

Tin (Sn)

Tin is another ancient metal that continues to have a variety of uses. The inorganic form is used in food packaging, solder, brass, and in alloys with other metals. The organic forms of tin, triethyltin and trimethyltin, are used as fungicides, bactericides and generally as antifouling agents for boats.

Inorganic tin is poorly absorbed in the intestine and toxicity is rare. Prolonged inhalation of tin dust can cause lung disease. Organic tins are readily absorbed by the intestine and are far more toxic. Exposure to organic tins can cause swelling of the brain and cell death in the nervous system.

Medical important metals

Introduction

The medical use of metals has declined with the advent of more-targeted drug therapies, but historically metals were used to treat a wide range of human diseases from diarrhea to syphilis and malaria. Currently, they are used to treat a limited number of diseases such as ovarian cancer and arthritis, but even this use is in decline. The exception to this is fluorine, which, while technically a halogen, is covered in this section because of its widespread use as in municipal water supplies to reduce dental caries. The therapeutic use of metals is generally limited by their toxicity. Metals illustrate well balancing the benefits of treatment against toxic side effects.

Summary Table - Medically Important Metals (and Fluoride)

Table 7.3 Summary of Medically Important Metals

Metal	Function	Source	Toxicity (when in excess)

Bismuth (Bi)	Antacid (ulcers)	Medial, consumer products	Kidney damage
Fluoride (F)	Strengths teeth enamel	Naturally occurring, added to drinking water	Mottled tooth enamel, increased bone density, more?
Gallium (Ga)	Soft tissue visualization in x-rays	Mining, medical injection	Kidney damage
Gold (Au)	Treat rheumatoid arthritis	Mining, medical	Dermatitis, kidney damage
Lithium (Li)	Treat psychiatric disorders	Food supply	Tremor, seizures, heart, nausea
Platinum (Pt)	Anti-cancer agent (cisplatin), catalytic converters	Anti-cancer drug, mining	Kidney, hearing, nervous system

Bismuth (Bi)

Bismuth, discovered in 1753, has a long history of medical uses including treatment of diseases ranging from syphilis and malaria to diarrhea. More recently, the antibacterial properties of bismuth-containing antacids have been used to treat peptic ulcers. In general the medical use of bismuth has declined with the advent of new drug therapies.

Acute toxicity of high-level exposure to bismuth is kidney damage. Chronic low-level exposure to bismuth can result in weakness, joint pain, fever, mental confusion and difficulty walking. Symptoms usually resolve when exposure is stopped but can lead to death with ongoing exposure.

Fluoride (F)

Fluoride is widely distributed in soils and is present naturally in drinking water. Fluoride is the salt, such as sodium fluoride, of the element fluorine. It is readily absorbed by the intestine and incorporates into bone or tooth enamel. Fluoride is commonly added to municipal drinking water across the United States based on strong data that it reduces dental decay. The current recommend level of fluoride in the drinking water is 1 ppm. This practice is supported by the U.S. Centers for Disease Control (CDC). In addition to drinking water, fluoride is also present in a range of consumer products, often at much higher levels, including toothpaste (1,000-1,500 parts per million or ppm), mouthwashes and fluoride supplements. It also occurs in foods prepared with fluoridated water. The majority of the beneficial effects of dental fluoride are related to its topical application rather from ingestion.

Excess exposure to fluoride results in stained or mottled teeth, referred to as dental fluorosis. This is common in areas where fluoride water levels are above 4 ppm. Chronic elevated fluoride exposure can also result in increased bone density. Unresolved is what level of fluoride exposure results in harmful health effects to children. Children's small size means that, pound-for-pound of body weight, they receive a greater dose of fluoride than adults. The CDC estimates that up to 33% of children may have dental fluorosis because of the excessive intake of fluoride either through drinking water or through other fluoride-containing products. This concern resulted in the CDC recommendation to limit fluoride exposure in children under eight years of age and to use fluoride-free water when preparing infant milk formula.

The EPA has a maximum contaminant level goal for fluoride in drinking water of four ppm. In 2006, the National Research Council of the National Academies issued a report that examined the appropriateness of EPA's 4 ppm maximum contaminant level goal for fluoride in drinking water in light of new evidence of the hazards of low level fluoride exposure. The NRC was not directed to conduct a risk assessment of the effects of low-level fluoride exposure nor to analyze other sources of exposure to fluoride. Referring to human and animal studies related to neurobehavioral effects, the NAS reports states "the consistency of the results appears significant enough to warrant additional research on the effects of fluoride on intelligence." The NRC suggested that 2 ppm might be a more appropriate maximum contaminant level. The primary question remains as to whether exposures to fluoride via multiple routes of exposure, from drinking water, food and dental-care products, may result in a high enough cumulative exposure to contribute to developmental effects.

Gallium (Ga)

Gallium, like mercury, is a liquid at room temperature but unlike mercury is much less hazardous. Its most interesting use is that when ingested it becomes a visualization tool of soft tissues and bone lesions during an x-ray. Industrial applications include use in high temperature thermometers, metal alloys and as a substitute for mercury in arc lamps.

Gallium's low toxicity and liquid state at room temperature make it an excellent diagnostic tool. Gallium has a half-life in the body of 4 to 5 days. Higher levels of exposure can cause kidney damage as well as nausea, vomiting and anemia.

Gold (Au)

Gold's aesthetic and electrical properties make it highly desirable and widely used in a number of industrial applications. Medically, gold and gold complexes are used to treat rheumatoid arthritis, but due to its toxicity this use is declining as better treatments become available. Gold has a long half-life in the body.

As with many metals, gold can damage the kidney. Lesions of the mouth and skin are seen following gold therapy to treat arthritis.

Lithium (Li)

Lithium was first used to treat manic-depressive illness in 1949 but was not used in the United States until 1970 due to concerns for its toxicity. When used as a therapeutic agent, lithium blood levels must be kept within a very narrow range (i.e. a narrow therapeutic index). Lithium appears to be non-essential but is readily absorbed by the intestine and is found in plants and meat. Normal daily intake is about 2 mg. Lithium is used in some manufacturing processes, as a lubricant, as an alloy, and most recently in batteries.

Outside its therapeutic range, lithium has a wide range of undesirable effects. Nervous system related effects include tremor, difficulty walking, seizures, slurred speech, mental confusion, as well as others. In addition there can be cardiovascular effects, nausea, vomiting and kidney damage.

Platinum (Pt)

Platinum is a relatively rare earth metal usually found with related metals osmium and iridium. While it has a number of industrial applications, its common consumer application is in catalytic converters. This application has actually increased platinum concentrations in roadside dust. The ability of platinum and its derivatives to kill cells or inhibit cell division was discovered in 1965. Platinum-based drugs, such as cisplatin, are used to treat ovarian and testicular cancer, and cancers of the head and neck, as well as others. Unfortunately, the toxic side effects of these agents often limit their usefulness.

In the industrial setting, the platinum metal is relatively harmless but a few people may be susceptible to developing an allergic skin response (contact dermatitis) and possibly a respiratory response. When used as an anti-cancer agent it is typically administered intravenously. It kills cells or inhibits cell division by interfering with DNA synthesis. The most common toxic side effect is kidney damage, but hearing loss, muscular weakness and peripheral nerve damage are also possible. Platinum is a good example of the benefits and hazards of using a highly toxic drug to treat the uncontrolled cell division of cancer.

Chelating agents

The most obvious treatment of poisoning from excessive metal exposure is to remove the metal from the body, thus the development of chelating agents. While treatment may be necessary, it is far more desirable to prevent exposure. In fact the best treatment for low-level exposure is often to identify the source of exposure and eliminate contact with the

metal. An excellent example of this principle is lead, where the most important action is to reduce or eliminate exposure.

While the word chelate comes from the Greek word for “claw,” the development of chelating agents is not that old. The first chelating agent, BAL (British Anti Lewisite), was developed during World War II as a potential treatment for arsenic-based war gases. The ideal chelating agent would readily bind only with the target metal, forming a non-toxic complex that would be easily excreted from the body. Unfortunately, this is easier said than done. BAL, for example, binds with a range of metals but actually enhances the toxicity of cadmium.

A consistent undesirable property of all chelating agents is that they also complex with essential metals and increases their excretion from the body. The two most common essential metals adversely affected by chelating agents are calcium and zinc. Excessive lead exposure can be treated with the chelating agent calcium-EDTA, not its related sodium salt because this would greatly increase excretion of calcium, potentially having toxic side effects. Blood lead levels are reduced when the lead displaces the calcium to bind with EDTA and is then excreted in the urine. This results in a movement of lead from the soft tissues such as muscle into the blood, which can result in a spike in blood lead levels that may elevate brain lead levels and cause subsequent neurological effects. The lead stored in bone is not affected and will remain until some event mobilizes calcium distribution from the bone. A recent study showed that lead chelation dropped blood lead levels, but did not protect against cognitive deficits (Rogan et al., 2001).

In summary, while chelating agents can be an effective treatment in some circumstances, they must be approached cautiously. The most important action is to identify the source of exposure and reduce or eliminate it. It is also very important to consider what essential metals may be bound and excreted by the agent. The body tightly regulates most essential metals, and disruption of these levels can have serious undesirable (toxic) effects.

More Information and References

Slide Presentation

- A Small Dose of Metals presentation material and references online: www.asmalldoseoftoxicology.org .
Web site contains presentation material related to the health effects of the various metals.

European, Asian, and International Agencies

- England – Department of Health - Maternal and child nutrition. Online: <<https://www.nice.org.uk/Guidance/PH11>> (accessed: 02 October 2020). The Department of Health provides information on nutritional requirements for children and mothers.
- World Health Organization. Online.: < <https://www.who.int/health-topics/nutrition>> (accessed: 02 October 2020). Who information on nutrition, also search the health topics section for a specific metal.

North American Agencies

- Health Canada – Food and Nutrition. Online: <<https://www.canada.ca/en/health-canada/services/food-nutrition.html>> (accessed: 02 October 2020). Health Canada provides information on nutritional issues.
- U.S. Agency for Toxic Substance Disease Registry (ATSDR). Online: <<http://www.atsdr.cdc.gov/>> (accessed: 02 October 2020). See fact sheets and case studies in many metals and other agents.
- Centers for Disease Control and Prevention (CDC Maternal, Infant & Toddler Nutrition, Physical Activity & Healthy Growth. Online: <https://www.cdc.gov/nccdphp/dnpao/resources/maternal-infant-toddler-resources.html> (accessed: 02 October 2020).

Non-Government Organizations

- Dartmouth Toxic Metals Research Program. Online. <<https://sites.dartmouth.edu/toxmetal/>> (accessed: 02 October 2020). The site has general information on toxic metals.

References

Timothy Ciesielski , Jennifer Weuve , David C. Bellinger , Joel Schwartz , Bruce Lanphear , and Robert O. Wright. (2012) Cadmium Exposure and Neurodevelopmental Outcomes in U.S. Children. Environmental Health Perspectives. Vol. 120, No. 5. <https://doi.org/10.1289/ehp.1104152>

Adefris Adal, MD, MS; Chief Editor: Asim Tarabar, MD Heavy Metal Toxicity: Background, Pathophysiology, Epidemiology. Medscape Refence, A good overview.

Online: Heavy Metal Toxicity/ Background, Pathophysiology, Epidemiology .pdf.
(accessed: 02 October 2020).

Citation: Nuss P, Eckelman MJ (2014) Life Cycle Assessment of Metals: A Scientific Synthesis. PLoS ONE 9(7): e101298. doi:10.1371/journal.pone.0101298

Alexander C. Ufelle and Aaron Barchowsky. Toxic Effects of Metals. In Casarett & Doull's Toxicology. The Basic Science of Poisons. 9th edition. Ed. Curtis D. Klaasen. McGraw Hill, New York, 2020. pp 1107-1162.

Michael C. Byrns and Trevor M. Penning (2018). Environmental Toxicology: Carcinogens and Heavy Metals. Chapter in Laurence Brunton, Bjorn Knollmann, Randa Hilal-Dandan. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th edition. McGraw-Hill, New York, 2018, pp. 1297-1316.

Rogan, W.J., Dietrich, K.N., Ware, J.H., Dockery, D.W., Salganik, M., Radcliffe, J., Jones, R.L., Ragan, N.B., Chisolm, J.J., Jr. & Rhoads, G.G. (2001). The Effect of Chelation Therapy with Succimer on Neuropsychological Development in Children Exposed to Lead. N Engl J Med, 344, 1421-1426.

National Research Council. Fluoride in Drinking Water: A Scientific Review of EPA's Standards. In: National Research Council of the National Academies. Available at http://books.nap.edu/openbook.php?record_id=11571&page=R1; 2006.