

Report for Task 1: Review of Recent Literature

**Validating Modeling Parameters for Risk Assessment  
Of Metals in Fertilizers**

For

Pesticide Division  
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By

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## **Executive Summary**

This report is a summary of some of the recent literature on the environmental chemistry and toxicology of arsenic, cadmium, lead, mercury, and nickel. It also considers older work that especially well condenses research results that remain “state-of-the-art.” There is a separate section for each metal that contains an introduction; and sections for environmental chemistry, human epidemiology, mechanisms of toxicity, and ecotoxicology. The report provides perspective on past problems human uses of these metals produced. It considers mobility and pathways for transport of these metals in the open environment. It is in a format that allows expansion when new information pertinent to Oregon agricultural soils becomes available.

Comprehensive toxicological profiles for arsenic, cadmium, lead, mercury, and nickel are available from the Agency for Toxic Substance of Disease Registry (Atlanta, GA). These are online resources available at: <http://www.atsdr.cdc.gov>

# ARSENIC

## Introduction

The public readily recognizes arsenic as a poison. The name arsenic conjures up images of murder and arsenic trioxide is a well-known homicidal agent since antiquity (Oremland and Stolz, 2003). There are diverse sources of environmental arsenic contamination (Oremland and Stolz, 2003). Coal combustion, mining and smelting metal ores, and pressure-treating wood with copper chromated arsenate are significant sources. Past use of arsenic-based pesticides (up to 10,000 metric tons per year from 1930 to 1980) still contributes to arsenic concentrations in agricultural systems. Current uses of organic arsenicals to control intestinal parasites in swine and poultry generates up to 20 mg arsenic/kg manure. While these sources are of regulatory interest, “natural” arsenic contamination in water from deep wells is the most serious human health risk (Mushtague et al., 1999; Oremland and Stolz, 2003). In Bangladesh up to 30 million people consume water with high arsenic concentrations and thousands of new cases of human poisoning occur each year. Ironically, development of wells seem to accelerate subsurface changes that mobilize reduced arsenic from insoluble mineral forms to soluble and toxic arsenic (III). Enhancing activity of an anaerobic bacterial cycle that utilizes arsenic in organic matter oxidation may play a role in this. The following review focuses on arsenic environmental health and quality with emphasis on agricultural systems.

## Environmental Chemistry

The environmental chemistry of arsenic is extremely complex, largely because it exists in several oxidation states (-III,0,III,V). Various environmental conditions, especially pH and redox potential, determine predominant arsenic species (McComish and Ong, 1988). Arsenic readily forms anions in aqueous solution. Under conditions relevant to agricultural soils and water flowing through them, arsenious ( $\text{H}_3\text{AsO}_4$ ) and arsenic ( $\text{H}_3\text{AsO}_3$ ) acids and their salts are dominant species. Under mildly reducing conditions in water, pentavalent arsenious acid predominates only at low pH. The trivalent arsenic acid increases in concentrations as pH increases. In aerobic water between pH 2 and 11 arsenious acid predominates, arsenic acid is the dominant form below pH 2, an uncommon condition in agriculture soils and water flowing through them. In summary, within the pH range relevant to agricultural soil system, arsenious

acid is the dominant species under aerobic conditions, while arsenic acid dominates under anaerobic (reducing) conditions.

Arsenic anions readily form organic complexes in aqueous solution (McComish and Ong, 1988). Complexation of arsenic (III) and arsenic (V) by dissolved organic matter reduces sorption by solid phase organic matter and coprecipitation with other inorganics. Metal cations readily coprecipitate arsenic anions that are not in organic complexes. Arsenic is also strongly complexed by particulate hydrous ferric oxyhydroxides that are abundant in soils and sediments (Senn and Hemond, 2004). Arsenic readily forms sulfide complexes at circumneutral pH (Rader et al., 2004). At a sulfide-to-arsenic (III) ratio of two, virtually all arsenic (III) exists as dithioarsenite. Arsenic (V) readily reacts with reduced nitrogen, including amines (McComish and Ong, 1988).

Considering the complexity of arsenic speciation, and the array of organic and inorganic functional groups they interact with, extensive complexation in agricultural soils and waters flowing through them is predictable. Arsenic (III) binds more weakly than arsenic (V) to most soil minerals and is therefore more bioavailable and subject to leaching (Manning et al., 2003). While arsenic (III) as undissociated arsenious acid predominates under mild reducing conditions below pH 9.2, manganese oxides readily oxidize it to arsenic (V) on soil mineral surfaces. Oxidation of arsenic (III) to arsenic (V) also occurs rapidly in oxygen-saturated aqueous solutions from pH 3 to 10 (Motamedi et al., 2003). Conversion of mobile arsenious acid from an anaerobic soil or sediment to less mobile arsenic (V) is therefore likely upon oxygenation of previously anoxic soil, sediment, or water. Clearly, a multitude of potential reactions of arsenic influence sorption to soil and mobility in water flowing through it. Therefore, it is not surprising that total sorption capacity even in a single soil type can vary substantially. For example, sorption capacity for silty fine sand with little clay varies from 1-252  $\mu\text{g}$  total arsenic/g soil, and that for brown, clayey sand from 1-8  $\mu\text{g}$  total arsenic/g soil (McComish and Ong, 1988). Sorption capacity for fine sand is much less variable, 1-8  $\mu\text{g}$  total arsenic/g soil. Consistent with these sorption characteristics, mobility of arsenic in clay soils is low to moderate but much higher in loamy or sandy soils, 6-10 cm/day for loamy sand (McComish and Ong, 1988).

Plants typically contain one to ten percent of the arsenic concentration of soils in which they grow (Baes and Sharp, 1983). There is a direct relationship between the arsenic concentration in soil and that in cereals, vegetables and fruit grown on it (Cai and Ma, 2003). However, the relationship between soil and plant arsenic concentration is not always linear, it may be hyperbolic (Farago et al., 2003). The soil-to-plant arsenic concentration ratio often decreases at high soil arsenic indicating saturation of accumulation processes. Plants preferentially accumulate arsenic (V) over arsenic (III), and transport systems are similar to those for phosphorus (Cai and Ma, 2003; Farago et al., 2003). Roots typically contain higher arsenic concentrations than stems, leaves, or seeds, and food crops rarely exceed 1 µg total arsenic/g (Farago et al., 2003). Depending on the plant species and soil chemistry phytotoxicity occurs at threshold of 1-50 µg total arsenic/g soil. Some plants hyperaccumulate arsenic, which indicates these species accumulate the metal to concentrations that exceed that in their soil (Cai and Mai, 2003). Use of plants that hyperaccumulate arsenic is a candidate bioremediation strategy for soil contamination.

Soil microorganisms and those in sediments of aquatic systems form volatile species of arsenic under both aerobic and anaerobic conditions (Craig and Jenkins, 2004). Fungi aerobically produce trimethylarsine ( $\text{As}(\text{CH}_3)_3$ ) from inorganic arsenic. Anaerobic bacteria produce arsine ( $\text{AsH}_3$ ), mono-, di-, and trimethylarsine from inorganic arsenic. In both aerobic and anaerobic systems, trivalent arsenic species are substrates for methylation but reduction of inorganic pentavalent arsenic (V) to arsenic (III) occurs. Volatilization of arsenic from agricultural soils and sediments of aquatic systems is therefore a significant potential loss pathway.

### **Human Epidemiology**

In terms of environmental exposures, arsenic contamination of drinking water is currently the dominant human health concern. Human poisonings, especially well-studied in Taiwan, reveal toxicities leading to cancer, vascular diseases, and diabetes mellitus (Chiou et al., 1995; Tseng, 2003; Tseng, 2004). Blackfoot disease results from damage to blood vessels of the skin. It is endemic in villages in Taiwan where water from artesian wells contain 0.70-0.93 mg arsenic/L. Before discontinuing consumption of this water, onset of blackfoot disease at the mean age of 52 (range of 2-87 years) prevailed (Tseng, 2003). Incidence of lung, bladder, and skin cancers increases in people consuming water high in arsenic, especially in those with

blackfoot disease (Chiou et al., 1995). Epidemiological studies reveal an association between arsenic in well water in Taiwan and Bangladesh, and type 2 diabetes mellitus (reviewed in Tseng, 2004). In addition to blackfoot disease, there are relationships between high arsenic concentration well water and other vascular diseases including ischemic heart disease, stroke, and hypertension (reviewed in Tseng, 2004). Serum lipid analyses from villages in Taiwan with people consuming high arsenic water from artesian wells indicate arsenic exposure alone explains high incidence of vascular disease (Tseng et al., 1997). Epidemiological work on occupational arsenic exposures confirm results from populations with drinking water exposures. Occupational inhalation arsenic exposures occur during smelting copper, gold and lead ores; and production of arsenical pesticides, pigments, dyes, art glass, semiconductors, and pharmaceuticals. Inhalation exposures to arsenic among copper smelters results in increasing lung cancer deaths and there is an association between use of arsenical drugs and pesticides and lung cancer (reviewed by Chiou et al., 1995). Aside from occupational exposures and consumption of high arsenic well water, there is little human epidemiological evidence for other exposure pathways of concern. With regard to food, seafood contains the highest total arsenic concentrations in the human diet (Lai et al., 2004). Most of the arsenic in seafood is in organic forms that are much less toxic than inorganic arsenic.

### **Mechanisms of Toxicity**

Tissues that accumulate arsenic to the highest extent in experimental animals (urinary, bladder, kidney, and skin) are especially prone to develop arsenic-associated tumors in humans (Hughes et al., 2003). Inorganic arsenic is a human carcinogen but producing this toxicity in experimental animals is difficult, perhaps due to species differences in metabolism (Goering et al., 1999). In mammals metabolism of inorganic arsenic involves methylation. If arsenic (V) is present, the liver reduces it to arsenic (III). Two subsequent methylations of arsenic (III), first to monomethylarsonate and second to dimethylarsinate (DMA) occur, detoxify the inorganic metalloid. DMA is the primary arsenic species in human urine (Goering et al., 1999; Lai et al., 2004). In humans the fraction of total urinary arsenic present as DMA decreases with increasing concentration and duration of arsenic exposure. Saturation of metabolism of inorganic arsenic to DMA appears an important event in onset of toxicity.

The role of arsenic toxicity in development of vascular diseases and cancers may share common mechanisms. Arsenic (III) induces oxidative stress (Bau et al., 2002; Kumagai and

Pi, 2004) and alters gene expression to stimulate cell proliferation (Beyersmann, 2002; Soucy et al., 2003). Treatment of various mammalian cell lines with arsenic (III) increases generation of reactive oxygen species that produce DNA double strand breaks, oxidative DNA adducts, and DNA-protein cross-links (Bau et al., 2002). Progression of oxidative stress to DNA damage differs between cell types, but error in repair of these lesions can lead to mutations and cancer. Arsenic (III) might also contribute to development of cancer through stimulation of cell proliferation (Soucy et al., 2003). Increases in melanoma metastasis to lung and tumor growth occurs in mice receiving arsenic (III). Enhancement of blood vessel growth (vascular cell proliferation) at least partially explains this result. There are also potential links between arsenic (III) stimulation of oxidative stress and cell proliferation in pathogenesis of vascular diseases (Bau et al., 2002). Increase in oxidative stress and reduction of nitric oxide synthesis may occur simultaneously (Kumagai and Pi, 2004). Inhibition of nitric oxide regulation of blood vessel relaxation is a plausible contributor to poor blood flow in blackfoot disease and ischemic cardiovascular disease after chronic arsenic (III) exposure. There is also evidence that inflammation of the cells lining blood vessels (endothelium) may play a key role in vascular arsenic toxicity (Simeonova et al., 2003). Induction of genes that code for inflammatory mediators appears important in this toxicity.

Consistent with human epidemiology, arsenic (III) damages vascular cells and disrupts regulatory systems for cell growth that can contribute to cancer development. Research to unravel the complex mechanisms of arsenic toxicity is perhaps more active than for any other metal or metalloid.

### **Ecotoxicology**

Copper smelting and coal combustion are the two largest anthropogenic sources of arsenic entering the global environment (Chilvers and Peterson, 1987; Dudka and Miller, 1999). Total global arsenic releases for copper smelting and coal combustion are about 87,000 and 41,000 tons/year, respectively of the residual arsenic. Air emissions constitute 13-15% of total releases, while solid wastes (ore slag and coal ash) contain the vast majority. Therefore, it is not surprising that arsenic contamination in ecosystems is most frequently a point source problem, often at a mining/smelting site.

Mean arsenic concentrations for different soil types range from 4-9 mg/kg. (Dudka and Miller, 1999). Soil arsenic concentrations at mine/smelting sites are often extremely high. For example, the soil concentration at a site in the United Kingdom is 4500 mg arsenic/kg soil (Langdon et al., 2003). Some organisms are capable of adaptation to high levels of soil arsenic contamination. The arsenic tolerant plant, *Agrostis tenuis*, grows on mine waste containing 26,500 mg arsenic/kg (Cai and Ma, 2003). Earthworms collected from contaminated sites demonstrate arsenic tolerance much greater than those from uncontaminated areas. Ten percent of earthworms from an uncontaminated site died at 50 mg arsenic/kg soil while 1,200 mg arsenic/kg soil killed the same percentage of earthworms from a contaminated site (Langdon et al., 2003). Tissue arsenic concentrations in tolerant plant and animal species from contaminated sites are much higher than for organisms from uncontaminated sites, but only about 10% of that the soils in which they live contain. While much of the tissue residue is organic arsenic, especially arsenobetaine, food chain transfer from tolerant to nontolerant species is a potential concern.

Arsenic exposure of aquatic species may involve their water, sediments, or the food web. Because mining and smelting of metal ores, and coal combustion produces arsenic-rich solid waste (reviewed above) high sediment and benthic invertebrate contamination are of concern. Feeding rainbow trout diets containing 33, 49 or 65 mg arsenic/kg for 24 weeks produces chronic inflammation of the gallbladder (Cockell et al., 1991). Growth reduction and anemia also occur with similar sensitivity. This species appears to tolerate 13 mg arsenate/kg diet. Lake whitefish appear somewhat more tolerant to dietary arsenic exposures (Pedlar et al., 2001). No significant growth reduction or anemia occurs after feeding 100 mg arsenate/kg diet for 64 days. There are inflammatory changes in the liver and gallbladder after that exposure and signs of mild inflammation in gallbladder after feeding 10 mg arsenate/kg diet. Waterborne exposures of rainbow trout for 121 days reveal a 55% growth reduction without evidence for anemia at 9.6 mg arsenite/L (Rankin and Dixon, 1994). In short term exposures, 18.5 mg arsenite/L water kills about 50% of the trout in 7 days. Since these results are for waterborne exposures near oxygen saturation significant conversion of arsenite to arsenate is likely, but measurements are not available.

Exposures of fish and wildlife to arsenic (V) is more likely than for arsenic (III) since the former oxidation state prevails under aerobic conditions. The low water solubility of arsenic (V)

relative to arsenic (III) increases likelihood that trophic transfer in benthic food webs is more important than waterborne exposures. Presence of a large percentage of total arsenic as organic species in invertebrate tissues protects against toxicity in the food web (Lai et al., 2004; Langdon et al., 2003). Arsenic toxicity in ecosystems is more likely a point source than non-point source problem.

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## CADMIUM

### Introduction

There are two principle sources of environmental cadmium contamination: (1) mining and smelting of metal ore, especially zinc; and (2) industrial use and waste disposal (ATSDR, 1999; McComish and Ong, 1988). Industrial uses of cadmium include production of batteries (70% of total use), pigments, plastic stabilizers, photovoltaic devices, and alloys. It is also important in electroplating. Estimates of cadmium releases into the environment vary, but the general trend appears downward from the 1980s to 1990s (ATSDR 1999). One estimate for air releases, probably conservative, is 25,000 kg/year for the United States in 1996. The annual production of cadmium in the United States is about 2000 metric tons, and worldwide anthropogenic emissions for this metal exceed natural releases by about ten-fold (ATSDR, 1999).

High incidence of human cadmium poisoning occurred in the Fuchu area of Japan during and before World War II (Goyer et al., 2001). Improper disposal of industrial waste high in cadmium contaminated crops, especially rice, and fish. Bone deformities and kidney disease were attributed to this and were especially prevalent in postmenopausal women. Therefore, the tendency of cadmium to accumulate in the food web is a legitimate concern. The review that follows and recommendations for analysis of future research in agricultural systems emphasize transfer of cadmium from soils to plants.

### Environmental Chemistry

The environmental chemistry of cadmium is relatively simple since it exists only in the 0 or II oxidation states (McComish and Ong, 1988). In simple aqueous solution at and below pH 8.0 almost all of it exists as  $\text{Cd}^{2+}$ , with a few percent as  $\text{CdHCO}_3^+$ . At more alkaline pH  $\text{Cd}(\text{OH})_2$  formation increases to about ten percent at pH 8.5 and about one hundred percent at pH 9.0 and higher. Cadmium chlorides are dominant species in seawater. Cadmium exhibits low affinity for complexation with dissolved organic matter such as humic and fulvic acids (Turner, 1987). Under reducing (anoxic) conditions conversion of soluble cadmium to sulfide precipitates occurs if sufficient concentrations of the anion exist (Turner, 1987).

Average regional cadmium concentrations of uncontaminated agricultural soils in the United States range from 0.1 to 1.0 mg/kg (Holmgren et al., 1993; Page et al., 1987). The range for specific sites is much greater, however. Volcanic soils may contain up to 4.5 mg cadmium/kg (ATSDR, 1999). There is an approximately two-fold regional variation in soil cadmium concentration in the United States. Western, Northcentral, Northeast, and South soils average 0.33, 0.37, 0.17, and 0.15 mg cadmium/kg, respectively (Page et al., 1987). As with other metals, soil chemistry influences cadmium mobility and availability for uptake by plants and animals. Soil sorption of cadmium by clay minerals, carbonate minerals, oxides, and to a lesser extent organic matter reduces cadmium mobility (McComish and Ong, 1988). Therefore, soil cadmium sorption positively correlates with cation exchange capacity. Mobility of cadmium in soil diminishes markedly in the pH 6.0 to 8.0 range. A number of factors increase cadmium mobility in soil. Soil chloride concentrations as low as 35 mg/kg and acidity (pH 6.0 and lower) significantly increase cadmium mobility. Calcium and magnesium increase cadmium mobility in soil by competition for soil cation exchange capacity.

Plant accumulation of soil cadmium varies between species and with soil chemistry (ATSDR, 1999; Dudka and Miller, 1999; Page et al., 1987). Plants accumulate cadmium concentrations equivalent to or higher than the soil on which they grow. Baes and Sharp (1983) report a range of plant-to-soil concentration ratios of 1-10. Among food crops roots/tubers and leafy vegetables accumulate the highest cadmium concentrations. Averages for edible portions of potatoes, carrots, lettuce and spinach grown on uncontaminated soils are 0.14, 0.16, 0.44, and 0.80 mg cadmium/kg dry weight, respectively (Dudka and Miller, 1999). Grains and cereals accumulate less cadmium (0.01-0.04 mg cadmium/kg dry weight) but may contribute more to total dietary intake due to higher consumption rates for these crops (ATSDR, 1999). It is important to remember that soil chemistry greatly influences plant uptake of soil cadmium (DePieri et al., 1997). Soil cadmium concentration alone is not an adequate predictor of plant cadmium accumulation, since tightly sorbed cadmium is not available for plant uptake. Factors that increase cadmium mobility, such as soil chloride, increase plant uptake.

## **Human Epidemiology**

The human cadmium poisoning due to food web contamination in Japan during the 1940s was reviewed in The Introduction (Goyer et al., 2001). The ATSDR (1999) compiled a comprehensive review of human health effects of cadmium that includes data for occupational exposures. Worker inhalation of cadmium fumes and dusts produced a number of toxicities. Severe pulmonary edema and chemical pneumonias leading to death by respiratory failure were reported a few days after accidents leading to inhalation exposures. In such instances lung cadmium concentrations of 1.5 to 4.7  $\mu\text{g/g}$  were measured after death. Longer-term, lower concentration occupational exposures were associated with lung inflammation and emphysema. Kidney damage also occurred after long-term occupational cadmium exposures. This was sometimes associated with bone damage, consistent with the poisonings in Japan during the 1940s. Epidemiological evidence for immunotoxicity and increase in lung cancer incidence after occupational inhalation exposures were considered limited. Consumption of food or beverages that contained high cadmium concentrations produced severe irritation of the gastrointestinal tract with nausea, vomiting, cramps, and diarrhea. Such symptoms occurred in children that drank soft drinks containing 1 mg cadmium/L. Liver damage occurs after a fatal dose. Long-term, low concentration cadmium consumption produced anemia due to reduced iron uptake by the gastrointestinal tract. Painful bone disorders were mentioned above. This was associated with reduced renal conversion of vitamin D to the active form, and increased urinary calcium loss. Kidney damage was considered the major concern after environmental cadmium exposures via the diet. Epidemiological and clinical data were collected from residents from cadmium-polluted and nonpolluted areas in several studies from Japan, Belgium, and China during the 1980s. One study estimated that a cumulative lifetime consumption of 2,000 mg of cadmium (for a 53 kg person) produced kidney damage. This was equivalent to 2.1  $\mu\text{g}$  cadmium/mg/day.

The diet is the major route of cadmium exposure for the general public. In the United States the average person consumes about 30  $\mu\text{g}$  cadmium in their food each day with ten percent or lower absorption efficiency (ASTDR, 1999). Due to tobacco accumulation of cadmium from the soil and about 50% efficiency of absorption by the lung, smoking may more than double human cadmium accumulation. Horiguchi et al. (2004) studied cadmium absorption from the

diet in women of different ages. Subjects included women with diabetes and anemia as well as healthy controls. Age rather than either of these diseases was associated with cadmium absorption from the diet. Absorption decreased as a linear function of age. Women in the 20-39 year old age group absorbed forty-four percent of dietary cadmium while those in the 40-59 year old age group absorbed only one percent. This was only a single study but it indicated importance of age-specific toxicokinetics in risk assessment and future research.

### **Mechanisms of Toxicity**

Cadmium absorption and toxicity, at least in part, involves competition for calcium, iron, and zinc binding sites on proteins (Zalups and Ahmad, 2003). This is often thought of as ionic mimicry, since these are all divalent metals. Transport of divalent ions is one major kidney function. This certainly contributes to cadmium uptake and sensitivity to toxicity in this organ. Thiol (sulfur)-containing proteins are particularly prone to binding cadmium tightly. Binding is perhaps so tight that it disrupts protein operation and produces toxicity.

Current thinking is that kidney cadmium concentration reaches a critical level before toxicity occurs (ATSDR 1999). Elevation of urinary protein concentration (proteinuria) is a sensitive indicator of this damage. Experimental data from animal studies and epidemiological results suggest about 200  $\mu\text{g}$  cadmium/g renal cortex tissues damages renal tubules to the extent that proteinuria occurs. One human study suggests 50  $\mu\text{g}$  cadmium/g is a critical level.

Metallothioneins are specific metal binding proteins that protect cells from toxicity (Goyer and Clarkson, 2001). Metallothioneins are rich in thiols and each molecule can bind up to 7 cadmium ions. Cellular concentration of metallothionein increases up to several-fold after cadmium in a concentration-dependent manner. Cadmium binding to metallothioneins protects against toxicity. However, once metallothionein binding sites saturate, cadmium is available to bind other protein thiols leading to toxicity. Further, release of cadmium bound to metallothionein from other tissues, especially liver, is quite toxic to renal tubules. In summary, metallothioneins both protect against cadmium toxicity and contribute to long-term tissue accumulation. In humans the half-life of cadmium may be as long as 30 years, body burdens increase with age, and kidney damage occurs at a critical concentration. It is important to assure dietary levels of cadmium do not provide intakes that produce chronic toxicity.

## **Ecotoxicology**

Environmental cadmium contamination with negative ecological consequences is most likely from point source releases (ATSDR, 1999). Smelting nonferrous metal ores lends to air, water, and soil cadmium pollution. Spent electroplating solutions are another potential source of water pollution. One estimate for discharge from manufacturing and processing facilities to land is 300,000 kg cadmium/year. Land disposal of solid waste containing batteries, land application of sewage sludge, and phosphate fertilizers are other significant sources for cadmium entering soil.

Since plants accumulate cadmium from their soil the potential for food web transfer is significant for animals in terrestrial ecosystems. Land snails fed cadmium-contaminated lettuce (37, 269, 1646 or 3718  $\mu\text{g/g}$  dry wt) three days a week for 50 days accumulated the metal in a time-dependent manner except at the lowest dose (Chabicovsky et al., 2004). Midgut tissue of snails fed the lettuce containing 37  $\mu\text{g}$  cadmium/g dry wt contained about 224  $\mu\text{g}$  cadmium/g dry wt by 20 days and this tissue concentration was similar after 50 days (apparent steady state). Mortality in this group was not different from controls. Tissue cadmium and mortality increased over time in other groups. These data suggested tolerance was related to capacity to regulate cadmium accumulation and this capacity was saturable. Reproductive rate of earthworms decreased as soil cadmium concentration increased from 12-797  $\mu\text{g/g}$  (Spurgeon et al., 2003). Survival times of adults also decreased in a concentration-dependent manner. The highest soil cadmium concentration reduced survival time of adults from a maximum of 300 days in controls to about 175 days. There was little or no effect on survival at the lowest concentration. At least for the two species above, terrestrial invertebrates tolerated rather high cadmium concentrations. Bioaccumulation of cadmium in these species at apparently tolerated concentrations indicated food web transfer to their predators was a potential concern. Mallard duck embryos were highly sensitive to cadmium toxicity (Kertesz and Fancsi, 2003). Injection of 0.5 ng cadmium into eggs produced 68 percent mortality compared to 21 percent mortality in controls.

The cadmium sensitivities of an aquatic invertebrate (the cladoceran *Ceriodaphnia dubia*) and fish (fathead minnow) appeared similar (Brooks et al., 2004). Seven day waterborne exposures to 15  $\mu\text{g}$  cadmium/L produced no significant mortality in either species, while 143  $\mu\text{g}$  cadmium/L killed all the cladocerans and ninety-five percent of the fish. Exposures of mayfly nymphs to 19  $\mu\text{g}$  cadmium/g sediment (dry wt) produced no overt toxicity and yielded overlying water with 5.8  $\mu\text{g}$  cadmium/L (Gosselin and Hare, 2004). Behavior of these insects appeared normal, while bioaccumulation of 10-40  $\mu\text{g}$  cadmium/g dry wt occurred in two weeks. Similar to the situation with terrestrial invertebrates, there is significantly potential for food web transfer from aquatic invertebrates to their predators. Indeed, cadmium concentrations in sunfish and bass from storm water treatment ponds were 1.6 and 3.2  $\mu\text{g}$  cadmium/kg wet wt\*, respectively while those in controls ponds were about one-tenth this concentration (reviewed in ATSDR, 1999).

\*fish fillet is about 80% water, multiplying these numbers by five yields approximate dry wt concentrations of 8 and 16 mg cadmium/kg.

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# LEAD

## **Introduction**

Lead was recognized as a poison in the Ebers papyrus prepared circa 1500 B.C. (Gallo, 2001). Metalworkers and those smelting lead ores were victims of poisoning from antiquity through modern times. Use of lead or clay glazed with lead pigment vessels for storage of acidic beverages, especially wine, was a source of exposure for broader segments of human populations. In the more recent past lead-based indoor paints, lead in plumbing, lead soldered cans and leaded gasoline were major sources of environmental exposures for humans (ATSDR, 1999; Goyer and Clarkson, 2001). Children were at highest risk from lead-containing paint chips, and soil and dust contaminated with lead from gasoline exhaust due to hand-to-mouth transfer. Before 1980 about seventy-five percent of total lead exposure in two-year olds was estimated as derived from dust. Since leaded gasoline was phased out atmospheric lead emissions in the United States decreased by 65%. Elimination of the above uses of lead reduced daily average intake drastically from 1980 to 1990 (Table 1).

**Table 1. Daily Average Lead Intakes ( $\mu\text{g}$  lead/day) for selected human subgroups.**

Age	Sex	1980	1990
6-11 months	Male/Female	34	3.8
2 years	Male	45	4.3
25-30 years	Male	84	8.5

Results were taken from ATSDR, 1999.

The workplace remains a significant source of lead exposures for adults. Lead smelting and refining, battery manufacturing, printing, lead soldering, welding or cutting steel, and radiator repair are potential high exposure occupations (ATSDR, 1999). Transfer of lead dust from the workplace to the home remains a potential source of exposure for children.

## Environmental Chemistry

Lead exists in the 0, II, and IV oxidation states, but lead (IV) only occurs under extremely oxidizing conditions outside an environmentally relevant range of pH and redox potential (McComish and Ong, 1988). Elemental lead (0) is only chemically or toxicologically important if conversion to Pb (II) occurs under acidic conditions. The divalent metal cation ( $\text{Pb}^{2+}$ ) is the principle species in aqueous solution below pH 6. Between pH 6 and 7  $\text{PbOH}^+$  becomes the predominant species, and essentially all soluble lead is in this form between pH 8 and 9.5 (McComish and Ong, 1988). Hardness and sulfate also influence lead speciation in water. Below pH 5.4 availability of sulfate for formation of  $\text{PbSO}_4$  limits solubility (ATSDR, 1999). At low hardness soluble lead is predominantly  $\text{Pb}^{2+}$  but complexation with chloride, carbonate, and hydroxyl ions increases with hardness (Turner, 1987). Above pH 5.4 and appreciable hardness formation of lead carbonates ( $\text{PbCO}_3$  and  $\text{Pb}_2(\text{OH})_2\text{CO}_3$ ) leads to precipitation that limits soluble lead concentration (ATSDR, 1999). Above pH 5.4 total soluble lead is about 30  $\mu\text{g/L}$  in hard water and about 500  $\mu\text{g/L}$  in soft water. Chloride complexes are much less stable and less likely produce precipitates (Turner, 1987). Lead also forms soluble complexes with humic and fluvic acids, the strength of these interactions are stronger than for cadmium but weaker than those for mercury (Turner, 1987).

Lead sorption to soils involves formation of insoluble precipitates with the anions above and phosphate; binding to organic matter, clay minerals, and iron and manganese oxides (McComish and Ong, 1988). Soil sorption of lead increases with pH, consistent with other metals. The stability of various lead complexes in soil leads to very low mobility except under acidic conditions. This low mobility corresponds with generally low uptake of lead by plants. Plant-to-soil concentration ratios for lead are often 0.01-0.10 (Baes and Sharp, 1983). Non-the-less lead content of barley and potatoes is about four-fold higher in lead contaminated (5450 mg/kg) than control (6.8 mg/kg) soil (Dudka and Miller, 1999). This control soil concentration is comparable to the average lead concentration in Oregon soils of 8.6 mg/kg (Holmgren et al., 1993). Plant uptake of lead does not increase as a linear function of soil concentration but plateaus (Dudka and Miller, 1999). Average lead concentrations in crops from uncontaminated United States growing areas are (in  $\mu\text{g/g}$  wet weight): lettuce (0.013), potato (0.009), wheat (0.037), sweet corn (0.022), and tomato (0.002) (ATSDR, 1999).

Overall, ingestion of soil or dust containing with high lead concentration represents a much more significant route for a toxic human exposure than food web transfer (Dudka and Miller, 1999).

### **Human Epidemiology**

Human lead poisonings most frequently occurred after environmental exposures of the fetus, neonates, and of children; and occupational exposures of adults (ATSDR, 1999; Goyer and Clarkson, 2001). Due the past uses of lead paint and leaded gasoline urban populations were at especially at risk for environmental exposures. Overt neurotoxic effects of lead can produce encephalopathy. This begins with lethargy, irritability, loss of appetite, vomiting, and dizziness; progressing to ataxia, reduced level of consciousness, coma and death. Blood lead of 80  $\mu\text{g}/\text{dl}$  and higher can produce this toxicity in children. Children that consume chip of lead-based paint (pica) can develop this severe form of poisoning. There are serious concerns over more subtle neurological deficits in children at much lower blood lead levels. Hearing threshold deficits were associated with 20  $\mu\text{g}/\text{dl}$  and IQ scores declined with increase in blood lead in the range of 5-35  $\mu\text{g}/\text{dl}$ . Peripheral neuropathy (foot drop and wrist drop) was a classic sign of lead poisoning after occupational poisoning. This was frequent in house painters that used lead-based paint. Heavy exposure of battery workers produced lead encephalopathy in adults. Kidney damage was another adverse health effect of occupational lead exposure. In summary, environmental lead exposures due to lead-based paint deterioration and lead gasoline exhaust deposition produced health risks to children, especially in urban areas, in the past.

Lead-contaminated dust from hazardous waste sites and lead smelting facilities remain sources for human exposures (ATSDR, 1999; Lorenzana et al., 2003). Intervention studies indicate decreasing the dust ingestion pathway can reduce pediatric blood lead by up to fifty-eight percent (Lorenzana et al., 2003). Protection of the fetus from lead toxicity by reducing maternal exposures is also important. Lead interferes with development of the nervous system and interactions with calcium transport are potentially important (Goyer and Clarkson, 2001). Lead inhibits uptake of calcium by transport cells in the human placenta by thirty percent (Laford et al., 2004).

## **Mechanisms of Toxicity**

Neurotoxicity in children is the most sensitive response to lead exposure. This is partly due to greater retention of lead after ingestion in children than adults, about thirty and five percent respectively (Goyer and Clarkson, 2001). Competition for higher calcium transport capacity in the intestine of children probably explains this. Sensitivity of the developing nervous system to lead is another factor. The blood brain barrier and choroid plexus accumulative lead facilitating delivery to developing neurons (Zheng et al., 2003). Impairment of cell-cell connections and alteration of cell migration in the developing brain are subtle mechanisms of lead toxicity (Goyer and Clarkson, 2001). Damage to the microvasculature of the brain occurs at higher lead concentrations and is characteristic of overt encephalopathy in children and adults (Zheng et al., 2003).

Kidney damage was a common problem in adults after occupational lead exposures but improved industrial hygiene greatly reduced this hazard (Goyer and Clarkson, 2001). Toxicity was related to decreased energy-dependent transport in renal proximal tubules. This was explained by damage to mitochondria. Tubular dysfunction progressed to atrophy of tubules, interstitial fibrosis, and loss of renal filtration capacity in chronic lead nephropathy. Lead-induced anemia due to increased mechanical fragility of red blood cell was associated with occupational exposures higher than those that produce nephropathy.

Lead produces toxicities in other tissues and organ systems including skeletal, vascular, reproductive, gastrointestinal, and immune (Goyer and Clarkson 2001). Because of concerns over sensitivity of fetal and neonatal humans to lead-induced immunotoxicity there is significant new experimental work in this area (Chen et al., 2004; Hudson et al., 2003). Blood levels of 10-15  $\mu\text{g}$  lead/dl can produce cognitive and behavioral deficits in children and the low end of this range are associated with juvenile immunotoxicity (reviewed in Chen et al., 2004). Animal experiments indicate a low protein maternal diet increases sensitivity of offspring to lead immunotoxicity (Chen et al., 2004). Other studies suggest genetic predisposition is a factor in lead increasing susceptibility to autoimmune disease (Hudson et al., 2003).

## **Ecotoxicology**

As with other metals, processing of lead ore, especially smelting, and disposal of lead-rich wastes are major point sources of ecosystem contamination (ATSDR, 1999). Contamination in Coeur d'Alene River Basin sediments reaches 3.5 g lead/kg due to past mining (Mateo and Hoffman, 2001). Lead also enters the environment from recreational uses. Lead shot and fishing weights in areas where waterfowl feed is especially problematic (Mateo and Hoffman, 2001). Ingestion of lead pellets by waterfowl dabbling on submersed vegetation results in lead ionization under acidic conditions of the stomach. Ingestion of lead-contaminated sediment from mining areas also poisons waterfowl in a similar manner. Toxicity is similar to that resulting from ingesting lead salts (Mateo et al., 2003). Lead toxicity in waterfowl is quite similar to that in humans, the nervous system exhibits the most severe clinical signs. Signs of lead poisoning in mallard ducks include reduction of leg withdrawal reflex, reduction in muscle tone, depression, and weakness (Mateo et al., 2003).

Due to low lead water solubility animals tolerate rather high concentrations in soils or sediments. Reproduction in springtails, soil-dwelling insects, decreases about ten percent around 1 g lead/kg dry soil (Bongers et al., 2004). The absolute concentration varies with prior leaching of soil and use of chloride or nitrate lead salts. Prior leaching probably removes the relatively low amounts of the most bioavailable lead species. This illustrates the importance of soil complexation reducing bioavailability of most lead in soils. Sediment is the principal site of lead accumulation in aquatic ecosystems. Work with aquatic vascular plants and crayfish demonstrates modest potential for food web transfer (Knowlton et al., 1983). Translocation of lead from sediment through the roots to foliage is not apparent. Lead in the roots remains localized there. Most accumulation by crayfish is sorption of lead to the exoskeleton after leaching from the sediment. More than half this lead is loosely bound and readily washes away. There is no evidence for toxicity in these crayfish after fifty days of exposure to 1 g lead/kg dry sediment. It seems consumption of lead with soil or sediment is the major hazardous in ecosystems, except in acidified environments where significant mobilization of lead can occur.

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## MERCURY

### Introduction

Two large-scale human mercury poisonings, one in Japan in the 1950s and another in Iraq in the early 1970s, illustrated the risks of careless releases of this metal (ATSDR, 1999; Newman and Unger, 2003). Over 1000 people accumulated toxic body burdens of methylmercury via aquatic food web transfer after industrial releases of mercury into Minamata Bay, Japan. Consumption of bread prepared from seed grain treated with a methylmercury fungicide poisoned 6,530 people in Iraq, 459 of them died. Less dramatic, but perhaps more widespread, concerns over lower level exposures after aquatic food web transfer of methylmercury intensified over recent years (ATSDR, 1999; Harris et al., 2003). Subtle neurotoxicity or immunotoxicity after maternal transfer to the fetus were subjects of numerous epidemiological studies (reviewed below).

Natural releases of mercury into the global environment probably exceed current anthropogenic releases (ATSDR, 1999; Grigal, 2002). The atmosphere is an extremely important pathway in global mercury cycling and accurately estimating inputs and outputs to land and water is a great challenge. Natural weathering of mercury in igneous rock may release 800 metric tons per year to surface water. Global off-gassing from the lithosphere and hydrosphere is in the 2700-6000 metric ton per year range. Recent estimates suggest the low end of the range reflects current conditions with approximately equal contributions of the total coming from natural sources, industrial sources, and recycling of past anthropomorphic emissions. There is a strong trend for reduction of mercury in solid waste. A decline in municipal waste releases from 665 metric tons in 1985 to 131 metric tons in 2000 for the United States reflects avoidance of use of mercury in many products, especially batteries. While it is clear that industrial sources contributed substantially less mercury to the global cycle now than in the past, current air concentrations are four-to-five-fold higher than before the industrial revolution. Rates for global recycling of this anthropogenic mercury remains a major research question.

## **Environmental Chemistry**

The environmental chemistry of mercury is quite complex, especially when one considers atmospheric cycling. Mercury exists in the 0, I, and II valence states (ATSDR, 1999; McComish and Ong, 1987). The two main forms that occur in the environment are elemental mercury (0) and divalent mercury (II). As with other metals, formation of complex ions and complexation reactions are important determinants of mercury mobility in soil and aquatic systems. Mercury forms complex ions with chloride and hydroxyl ions in fresh water. The  $\text{HgOH}^+$  predominates at low pH (2.2-3.8), while  $\text{Hg}(\text{OH})_2$  predominates in the environmentally relevant pH range in fresh water. Complexation of mercury (II) with humic acid is of major importance in fresh water. High affinity of chloride for mercury results in predominance of these complexions at salinity above five parts per thousand. Mercury strongly sorbs to humic materials and sesquioxides in soil above pH 4.0 (ATSDR, 1999). Soils with high iron or aluminum content can bind up to 15 g mercury/kg soil. Sulfide and iron sulfide co-precipitates are highly insoluble complexes important for mercury immobilization in soils and sediments of aquatic systems (McComish and Ong, 1988). Chloride complexes are of lesser importance in most soils and fresh water systems.

Biological methylation of mercury is an extremely important factor in transport, fate, and especially toxicology of this metal (ATSDR, 1999; Newman and Unger, 2003). Methylation is most rapid in anaerobic aquatic or wetland systems and involves bacterial, especially sulfate-reducing activity. Low pH and high dissolved organic matter also favor methylation of mercury. Methylmercury is fat soluble and accumulates in food webs. More than 95 percent of the total mercury body burden in fish is methylmercury. Methylmercury is volatile and readily off-gasses from water. Less than three percent of total dissolved gaseous mercury in water occurs as methylmercury, more than 97 percent is elemental mercury.

Movement of gaseous mercury between the atmosphere, lithosphere, and hydrosphere is an exceptionally important factor in global fate and transport of this metal (ATSDR, 1999; Grigal, 2002). Over 95 percent of the mercury in the atmosphere is the gaseous elemental form, less than five percent is in particles. Conversion of divalent mercury (II) to elemental mercury (0) is an important factor in this pathway. Microbes enzymatically reduce  $\text{Hg}^{2+}$  to volatile  $\text{Hg}^0$  in a

two electron transfer reaction. Microbial capacity for this reaction increases at toxic mercury concentrations reflecting an adaptation that removes the metal from their environment. This reaction is most likely to occur in aerobic environments. Direct photolysis and indirect photolysis after activation of other reactants also reduce  $\text{Hg}^{2+}$  to  $\text{Hg}^0$ . Another abiotic conversion pathway for  $\text{Hg}^{2+}$  to  $\text{Hg}^0$  exists in strongly reducing environments of landscapes near stream channels and microtopographic depressions. Photodegradation of methylmercury to  $\text{Hg}^{2+}$  and  $\text{Hg}^0$  occurs in the photoactive zone of aquatic ecosystems. Bacteria also oxidize methylmercury to  $\text{Hg}^{2+}$  in aquatic systems that can undergo subsequent conversion to  $\text{Hg}^0$ . The aggregate of these reactions contributes to mercury available for efflux into the atmosphere. Volatilization of  $\text{Hg}^0$  from the soil requires diffusion or mass transport to the soil surface and across the soil-air boundary. Probably due to increase in vapor pressure with temperature, the highest rates of  $\text{Hg}^0$  volatilization are in summer. Any factor that decreases soil sorption capacity for  $\text{Hg}^0$  (e.g., low clay or organic matter, high pH) increases volatilization.

Atmospheric deposition of mercury on the landscape also occurs and this is a pathway of concern for contamination of remote ecosystems (Grigal, 2002). More than 95 percent of mercury in the atmosphere is elemental. Sorption of this to leaves of terrestrial plants and subsequent oxidation to mercury (II) is an important route for entry into terrestrial ecosystems. Most mercury in precipitation is mercury (II) due to high water solubility in water. Less than one percent of total atmospheric mercury is methylmercury, probably due to photolysis of this species after off-gassing from surface waters and wetlands. Accurate modeling of inputs and outputs of mercury through the atmospheric pathway will require much more research due to the diversity of interacting factors that determine fluxes.

### **Human Epidemiology**

The Introduction described two major incidences of human poisonings with organic forms of mercury. Numerous examples of occupational and accidental exposures to elemental mercury were reviewed by ATSDR (1999). Inhalation of mercury (0) vapors produced neurotoxicity evidenced by tremors, emotional liability, cognitive deficits, among other problems. Mercury vapors also damage the lung. Inorganic mercury salts were highly nephrotoxic after ingestion as part of Chinese medicine (ATSDR, 1999). Some evidence for immune system cell

dysfunction occurred in workers from a mercury producing plant without increased incidence of infections (ATSDR, 1999). While these reports were important for improved industrial hygiene, broader public health concerns centered around environmental exposures in children (Counter and Buchanan, 2004). The sensitivity of the developing nervous system among other physiological systems prompted this. Mercury poisoning in children was most commonly associated with consumption of methylmercury-contaminated fish. Maternal transfer of methylmercury to the fetus was considered a greater risk than direct consumption by children. There were two large epidemiological studies using neurophysiological and cognitive tests in children from populations that consumed diets that included whale meat (1.6  $\mu\text{g}$  methylmercury/g) or averaged twelve fish meals a week (0.05 to 0.25 ppm methylmercury). The former study reported detected significant neurodevelopmental deficits while there were none in the latter. The reasons for this inconsistency remain the subject of investigation. Epidemiological studies of human populations with relatively high environmental methylmercury exposures were often confounded by other factors. Contaminated fish and shellfish were frequently identified as major sources of human methylmercury exposure. However, biomagnification of multiple persistent and fat soluble contaminants in aquatic food chains was more often the rule than the exception. A recent study compared an urban population (Quebec) with a subsistence maritime fishing population from a remote area of eastern Canada (Belles-Isles et al., 2002). Umbilical cord blood was collected shortly after babies were delivered for measurements of contaminant concentrations and immune system status. Numbers of one type of white blood cell (naïve helper T-cell subset CD4+CD45RA+) and immunoglobulin M were lower in the maritime compared to the urban population. Other measures of immune system status were similar in both groups. The methylmercury concentration in plasma from cord blood averaged twice as high in maritime compared to urban subjects (9.1 and 4.5 nmol/L, respectively). The presence of polychlorinated biphenyl concentrations about three-fold higher in cord plasma from maritime than urban subjects confounded interpretation of these results. Since both methylmercury and polychlorinated biphenyl concentrations were elevated measures of immune suppression were not specifically associated with either.

Cases of elemental and inorganic mercury poisoning in children were associated with misuse of liquid mercury or medicines and cosmetics that contained mercury salts (ATSDR 1999; Counter and Buchanan, 2004).

### **Mechanisms of Toxicity**

Toxic actions of elemental mercury, inorganic mercury salts, and organic mercury compounds differ significantly (ATSDR, 1999). The kidney rapidly accumulates inorganic mercury (II) via active transport systems in the proximal tubules. Interactions with intracellular sulfhydryl groups, oxidative stress, and mitochondrial dysfunction progress to proximal tubular necrosis (Schellmann, 2001). Inorganic mercury (II) contributes to development of autoimmune disease in susceptible strains of mice and rats and possibly in humans (reviewed in McCabe et al., 2003). The mechanism appears to involve interference with the normal programmed cell death of autoreactive lymphocytes. Kidney damage from inhalation of elemental mercury (0) vapors occurs after oxidation to  $\text{Hg}^{2+}$  and is of secondary importance to neurotoxicity and lung damage. Corrosive damage to the airways and pneumonitis occur after inhalation of high mercury vapor concentrations (Goyer and Clarkson, 2001). Central nervous system toxicity can also occur after heavy exposures but neurotoxicity is characteristic of long-term exposures to lower concentrations. Excitability, tremors, and gingivitis are hallmarks of this type of poisoning. Methylmercury is primarily neurotoxic. Numbness around the mouth and extremities, ataxia, weakness, tremor, hearing and vision loss are signs and symptoms of this toxicity (Goyer and Clarkson, 2001). In adults brain damage occurs in specific areas within the cerebellum and visual cortex of the cerebrum (Zheng et al., 2003). Exposures of the fetus produce ubiquitous damage probably due to disruption of neural differentiation. This explains regulatory emphasis and to limit exposures for women of childbearing age.

### **Ecotoxicology**

Mercury contamination of ecosystems is extremely complex since both point and non-point sources are significant. There are sites where elemental mercury from past industrial uses persist in soils at g/kg concentrations (ATSDR, 1999). Sediments of lakes, streams and rivers contains high  $\mu\text{g}/\text{kg}$  concentrations in many locations due to past activities including mining, and chlor-alkali plant operations. In addition to these localized point-source problems

atmospheric transport and deposition of mercury is now a global issue. Given the blending of emissions in the atmosphere and global elevation of gaseous mercury concentration, this is now a non-point source problem.

Contamination of soils with mercury concentrations that present a toxic hazard to natural populations of plants and animals is most likely a point-source issue. Elemental and inorganic mercury are dominant species in these environments. There is potential for food web transfer of mercury in terrestrial ecosystem. Earthworms accumulate mercury in amounts dependent on soil concentration and duration of exposure (ATSDR, 1999). Plant-to-soil concentration ratios for mercury are in the 0.01-0.10 range (Baes and Sharp, 1983). Virtually no mercury from soil that enters roots transfers to shoots or leave of plants (ATSDR, 1999; Frescholtz et al., 2003). Leaves of plants do accumulate atmospheric mercury that enters soils with leaf fall.

Food web transfer of methylmercury in aquatic ecosystems represents the most widespread contamination problem. Most of the mercury entering aquatic systems derives from the landscape rather than direct atmospheric deposition (Grigal, 2002). A complex set of reactions determine dynamics of mercury speciation in aquatic ecosystem (Campbell et al., 2003). Precipitation of inorganic mercury in deep sediments removes it from active cycling. At the surface of hypoxic sediments  $\text{Hg}^{2+}$  reduction produces methylmercury that enters solution and is available for transport to oxygenated layers. Phytoplankton are the main initial point for methylmercury entry into food webs. Transfer to invertebrates and fish follows. Dissolved methylmercury reaching the top layers (photoactive zone) can off-gas or undergo photodegradation to  $\text{Hg}^{2+}$  and  $\text{Hg}^0$ . The efficiency of food web transfer of methylmercury is remarkable. Current public health recommendation suggest limiting consumption of food containing more than  $0.3 \mu\text{g/g}$  (Counter and Buchanan, 2004). Muscle concentrations in some fish species reach over one  $\mu\text{g/g}$  (ATSDR, 1999; Counter and Buchanan, 2004). Fish eating whales have muscle concentrations even higher. Contamination of wetlands and surface waters by point-source pollution yields severe food web contamination. Young of wading birds around Carson River, Nevada fed invertebrates from mining-contaminated wetlands receive overtly toxic methylmercury concentrations (Henny et al., 2002).

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# NICKEL

## **Introduction**

The ATSDR (2003) recently reviewed uses, potential for human exposure and toxicity of nickel. Occupational exposures to fumes and particles rich in nickel were verified as human health risks (see Epidemiology below). Risks to the general population through nickel exposures by air, water, and food were not identified.

About 30,000 metric tons of nickel enters the atmosphere from global natural sources each year (mostly windblown dust and volcanic emissions). Anthropogenic sources may exceed this by about 1.4-fold. Burning of oil (62%), nickel refining (14%), municipal incineration (12%), production of steel and other nickel alloys (5%), and coal combustion (2%) are sources of these emissions. In the United States about 96 percent of nickel releases are to land, with two percent to air, less than one percent to water, and the remainder to underground injection. Disposal of ash, slag, and nickel-containing products (i.e., batteries) are solid waste streams for nickel. One 2003 estimate for annual nickel releases to land for facilities in the United States that produce, process or use it is 30,439 metric tons.

## **Environmental Chemistry**

Nickel exists in the 0, I, II, or III oxidation states but only nickel (II) is significant form under environmental conditions (McComish and Ong, 1988). Most free nickel in fresh water between pH 3 and 9 is the hexahydrate of  $\text{Ni}^{2+}$ , above pH 9.5  $\text{Ni}(\text{OH})_2$  dominates (ATSDR, 2003; McComish and Ong, 1988). Nickel complexes with both inorganic and organic ligands in aquatic systems. Nickel sulfate is an important complex below pH 8.0. Between pH 8 and 10  $\text{NiOH}^+$  and  $\text{NiHCO}_3^+$  can be important. Humic acid binds nickel with sufficient affinity to dissociate nickel carbonate precipitate. Typical soil nickel concentrations vary with local geology but 4-80  $\mu\text{g/g}$  is a reasonable range for background levels (ATSDR, 2003; Holmgren, 1993). Nickel sorbs to soil by specific adsorption, ion exchange and co-precipitation. Nickel ferrite is the solid species most likely to precipitate in soils (ATSDR, 2003). Insoluble nickel sulfide, hydroxides, and to a lesser extent, carbonate are also important (McComish and Ong, 1988). Iron and manganese oxides, clay minerals, and organic matter are important sorbents

for nickel. High soil pH and cation exchange capacity reduce nickel mobility, as with other metals (ATSDR, 2003). Calcium and magnesium increase nickel mobility in soil by competition for binding sites. In a general sense, nickel is more mobile in soils than lead or cadmium.

The average plant-to-soil concentration ratio for nickel ranges from 0.1 to 1.0 (Baes and Sharp, 1983). However, some plants hyperaccumulate nickel. Alfalfa for example can accumulate 22 to 26 times higher nickel concentrations than the soil between pH 4.5 and 7.1 (ATSDR, 2003). Nickel also exhibits phytotoxicity, with the toxicity of increasing at higher soil acidity (Weng et al., 2003). Most nickel plants accumulate remains in the root and there is significant transport to shoots and leaves relative to many other metals including arsenic, lead, and mercury (ATSDR, 2003; Weng et al., 2003). Despite tendency of nickel to accumulate, especially in some plant species, overall potential for biomagnification in food webs is not significant.

### **Epidemiology**

Nickel is a human carcinogen (ATSDR, 2003; Goyer and Clarkson, 2001). Inhalation exposures to fumes and dusts in the nickel-refining industry produces lung and nasal cancers. A doubling of lung cancer rate in Finnish nickel refinery workers is one example. Dermal exposure to nickel produces contact dermatitis in four to nine percent of human subjects. Dermal exposure to nickel is of secondary importance to inhalation occupational exposures in the general public. Jewelry and coins made of nickel alloys are common sources of exposures. Nickel in food is the primary route of exposure to nickel in the general human population. Daily average exposures are in the 100 to 300  $\mu\text{g}$  range. Drinking water typically provides much lower amounts of nickel. There is no evidence nickel produces adverse health effects in humans at concentrations present in the general environment or food web.

### **Mechanisms of Toxicity**

Inhalation of nickel fumes and dusts in occupational settings were consistently associated with lung and nasal cancers (ATSDR, 2003). Understanding the disease process was pursued to improve the basis for setting exposure limits. Two hypotheses were advanced for explaining results of these investigations. The first proposed nickel-induced cancer was primarily

explained by alterations in gene expression patterns, not mutation due to DNA damage (Zhang et al., 2003; Zaho et al., 2004). Silencing of genes that repress transformation to cancer by nickel-induced inhibition of histone acetylation and enhancement of histone methylation was a favored mechanism. Other work suggested nickel produced DNA damage, specifically strand breaks related to oxidative stress (Chen et al., 2003). Thus, direct nickel genotoxicity with mutations that contribute to progression towards cancer remained a mechanism of potential importance. The high nickel concentrations used in investigation of these mechanisms of nickel-induced cancer with heavy occupational exposures.

### **Ecotoxicology**

Point sources such as refineries, producers of stainless steel or other nickel alloys, oil-fired or to a lesser extent coal-fired power plants, and refuse incinerators are most likely to contaminate ecosystems with nickel (ATSDR, 2003). Further, solid waste disposal rather than atmospheric emissions is a more likely pathway for contamination levels of concern. Waste water from manufacture inorganic chemicals, iron and steel, batteries, metal finishing, and porcelain enameling may contain high nickel concentrations and require treatment.

Soluble nickel is rather toxic to some aquatic animals, especially invertebrates. A no observable effect concentration in a cladoceran (*Ceriodaphnia dubia*) is the 3.8-15.3  $\mu\text{g}$  nickel/L range (Keithly et al., 2004). The precise values vary with pH and hardness of water. A freshwater amphipod (*Hyalella azteca*) is more nickel tolerant than the cladoceran (Keithly et al., 2004). The no observable effect level in the amphipod is 29  $\mu\text{g}$  nickel/L. Lethal concentrations at about 100 mg hardness/L are 148 and 3,045  $\mu\text{g}$  nickel/L for the cladoceran and amphipod, respectively. Fish are generally more tolerant to nickel than the invertebrates above (Keithly et al., 2004). Chronic values for rainbow trout and fathead minnows are in the 40-50  $\mu\text{g}/\text{L}$  range.

Aside from hyperaccumulation in some plant species there is little potential for food web transfer of nickel in terrestrial or aquatic ecosystems (ATSDR, 2003). There is no evidence for bioaccumulation of nickel in voles or rabbits feeding on plants from a site with high soil nickel.

The nickel concentration of lake trout does not increase with age. In fact nickel concentrations in organisms tend to decrease at higher trophic levels.

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