Toxicity and Neurotoxicity of Metals
All elements are potentially toxic

Toxicity may be caused by:

- metal overload (causing inactivation of enzyme systems and inflammation in various organ systems)

- Immune reactions (cell reactions to foreign metal substances such as metal amalgams)
## Top 20 Hazardous Substances from the 2003 CERCLA*

### Priority List of Hazardous Substances

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*Agency for Toxic Substances and Disease Registry*
Environmental Toxins

Exposure through

- Environment (Industry i.e. dust, air)
- Intake (Pharmaceuticals, Food, Water)
The Detoxification of Metals depends on

- Patient Exposure
- Metal Availability and Binding Capacity of Chelating Agent
- Excretion Ability

Note: a chelating agent will bind more of a metal in a heavily exposed individual than in a lesser exposed person (mass principle)
Arsenic – As
Symptoms of Arsenic toxicity

- Skin lesions, *peripheral neuropathy*, and anemia are hallmarks of chronic arsenic ingestion.

- Arsenic is strongly associated with lung and skin cancer in humans, and may cause other internal cancers as well.
Except in the electronics industry, commercial use of arsenic is declining.

- electronics manufacturing (microwave devices, lasers, light-emitting diodes, photoelectric cells, and semiconductor devices), hardening metal alloys

Other Industrial use:
- purifying industrial gases (removal of sulfur),
- burning fossil fuels, burning wood treated with arsenic preservatives
- bronze plating
- clarifying glass and ceramics
- preserving animal hides,
Natural sources:
- Mining arsenic-containing mineral ores
- Groundwater (especially near geothermal activity).

Commercial products:
- Wood preservatives
- Insecticides
- Herbicides (weed killers and defoliants)
- Fungicides
- Cotton desiccants, cattle and sheep dips, paints and pigments, antifouling paints, leaded gasoline, and fire salts (multicolored flame).
Medicinal uses

- Until the 1940s, arsenicals (Salvarsan and Fowler's solution) were widely used in the treatment of various diseases such as syphilis and psoriasis.
- Arsenicals are still used as antiparasitic agents in veterinary medicine.
- In some countries, they are occasionally used to treat trypanosomiasis and amebiasis in humans.
- Arsenic is also found in some homeopathic and naturopathic preparations.
- Remedies such as *kushtay*, a tonic used in Asian cultures to cure various sexual disorders.
Arsenic — some lesser known sources

Food:

- wine (grapes sprayed with arsenic-containing pesticides)
- tobacco (plants sprayed with arsenic-containing pesticides)
- seafood (especially clams, certain cold water and bottom-feeding finfish)
  
  Seaweed and
  
  Kelp-containing health foods
Inhaling smoke = inhaling toxic metals

- Smokers inhale small amounts of arsenic, cadmium, lead, nickel, beryllium etc.
- Arsenic inhalation is result of pesticide residue on tobacco leaves.
As- Daily Intake

- average daily dietary intake of arsenic by adults in the United States is 11 to 14 milligrams per day.
- Meat, fish and poultry account for 80% of dietary arsenic intake.
- Algae and fish contain high concentrations of arsenic in the form of arsenobetaine and arsenocholine, sometimes referred to as "fish arsenic."
- ‘Fish arsenic’ has low toxicity to humans and is rapidly excreted in urine.
Chemistry of L (Lewisite)

Lewisite (L, 2Çchlorovinyldichloroarsine, 2-chlorovinylarsonous dichloride) has the chemical name (2Çchloroethenyl)arsonous dichloride, molecular formula C2H2AsCl3, and formula weight 207.32. Its Chemical Abstracts Service registry number is 541-25-3.

General Information

- Lewisite was discovered near the end of World War I by a team of Americans headed by Capt. W. Lee Lewis working at Catholic University in Washington DC.
- Production took place in the United States, Great Britain, France, Italy, the Soviet Union, and Japan in the immediate post war years.
- During World War II, the American, British, Soviet, German, and Japanese armies had considerable stocks of Lewisite available.
- **Following World War II, Lewisite was considered obsolete by the major powers because of the discovery that 2,3-dimercaptopropanol ("British anti-Lewisite," or BAL) was an inexpensive and effective antidote to Lewisite exposure.**
- It may have been used recently by the Iraqis in addition to mustard agent.
- Industrially-produced Lewisite has a strong penetrating geranium odor; the pure compound is odorless.
DMPS, DMPA, or DMSA will mobilize tissue arsenic.

- BAL, however, increases the arsenic content of the brain of rabbits injected with sodium arsenite. These results raise the question as to the appropriateness of BAL as the treatment for systemic arsenic poisoning.

- Either DMSA or DMPS will protect rabbits against the lethal systemic effects of subcutaneously administered Lewisite.

- The sodium arsenite inhibition of the pyruvate dehydrogenase (PDH) complex can be prevented and reversed in vitro or in vivo by DMPS, DMSA, DMPA, or BAL.

- DMPS is most potent and BAL appears to be the least potent.

PMID: 6327446 [PubMed - indexed for MEDLINE]
Aluminum – Al

- considered relatively non-toxic;
- healthy individuals can tolerate oral doses as high as 7 grams per day without experiencing harmful effects.
- Longterm exposure contributes to chronic overload
- evidence now shows that aluminum accumulation adversely affects the nervous system in humans and animals.
Aluminum pathway

- 98% of oral Aluminum is excreted through (the healthy) gastrointestinal tract
- Some is absorbed into plasma and bound primarily to transferrin (leaky gut syndrome enhances absorption)
- Some of plasma Al is deposited in bone and nerve (brain) tissue
- Excretion: almost exclusively in urine

Kaplan LA, Pesce AJ. Clinical Chemistry, Theory, analysis, and correlation, Mosby Co. 1989
Clinical Signs and Symptoms of Aluminum intoxication

- Neurological Disorders

  Symptoms:
  progressive, fatal neurological syndrome, manifested by speech disturbance (hesitancy, stuttering), followed by disorientation. Later followed by myoclonic movement, seizure, dementia and death

- Long-term complications include bone disease, including Vit.D resistance, osteomalacia and microcytic, hypochromic anemia

Werbach MR, Nutriolische Medizin, Hädecke1999
Kaplan LA, Pesce AJ. Clinical Chemistry, Theory, analysis, and correlation, Mosby Co. 1989
Aluminum Distribution in Body Tissues

![Bar Chart showing aluminum distribution in different body tissues.](chart.png)
Aluminum-binding of chelating agents

- Pre Urine N=228
- DMSA N=249
- EDTA+DMSA N=104
- DMPS N=52
- DMPS+ZnDTPA+DMSA N=51

mcg/g Creatinine

E.Blaurock-Busch
TMI Trace Minerals International
Cadmium-Cd
Most toxic to virtually every bodily system
Cadmium - Cd

- Exposure to cadmium happens mostly in the workplace where cadmium products are made.
- The general population is exposed from breathing cigarette smoke or eating cadmium contaminated foods.
- Cadmium damages the lungs, can cause kidney disease, and may irritate the digestive tract.
Cadmium Pathway

- No special mechanism for gut absorption.
- It is estimated that 1-5% of ingested cadmium are absorbed.
- Inhaled or injected cadmium is bound chiefly to low-molecular-weight protein metallothiones and rapidly transported to liver, kidney, and other tissue.
- Main accumulation in kidney and liver.
Cadmium uptake

- In areas of Japan and China where rice is grown on soils contaminated by mining wastes, people have suffered adverse health effects from cadmium intake.

- People in other countries who consumed similar amounts of cadmium in foods grown on more highly contaminated soils did not experience adverse effects from cadmium intake; those foods contained adequate zinc, iron, and calcium to retard cadmium absorption into the body.
Cadmium Metabolism & Excretion

- Due to firm binding in tissues, cadmium has a long biological half-life, estimated at 20 to 30 years

- Half-life in blood: est. 2.5 mo

- Excretion: slow and primarily in urine
Symptoms of Cadmium intoxication

- Weakness
- Anorexia
- Loss of taste & smell
- Alopecia
- Dry skin (quick aging as seen in smokers)
- Liver problems
- Anemia due to disturbed iron metabolism
- Osteoporosis

- Kidney dysfunction
- Nephrocalcinosis due to disturbed renal calcium clearance
- High blood pressure
- Pulmonary irritation
- Lung Emphysema

Werbach MR, Nutriolische Medizin, Hädecke1999
Cadmium and Early Development

- Cadmium does not readily go from a pregnant woman's body into the developing child, but some portion can cross the placenta. (Smokers beware!)
- Cd can be found in breast milk.
- Babies of animals exposed to high levels of cadmium during pregnancy had changes in behavior and learning ability.
- Cadmium may affect birth weight and the skeleton.
Lead – Pb
Biochemical basis for Pb toxicity

- Only 8-12% of orally ingested lead is absorbed by small intestines
- Reacts easily with sulfhydryl groups in enzymes, thereby inactivating them
- Hematological manifestations are mainly due to inactivating Delta-aminolevulinic acid (ALA-) dehydratase and ALA synthetase
Symptoms of Lead Intoxication

- Anemias
- Blue-black lead line near gingival margin of teeth
- Weakness
- Headaches
- Energy loss
- Bone & muscle pain
- Abdominal pain & digestive disorders
- Anorexia

- Large range of neurological disorders
- Loss of concentration (affects ability to learn)
- Irritability
- Depression
- Anxiety and fear neurosis
- Restlessness & sleep disorders
- Tremor
Physiological Distribution of Lead in Human Tissue

Source: Thomas L., Labor & Diagnose, Med. Verlag Marburg
Mercury – Hg

Toxin #3
Biochemical basis for Hg toxicity and detoxification potential

Mercury, like Cd and Pb, easily reacts with sulfhydryl groups. Therefore….

- Hg easily inactivates sulfhydryl groups in enzymes
- Hg easily reacts and binds with sulfhydryl groups of chelating agents such as DMPS or DMSA
- DMSA (Meso-2,3-dimercaptosuccinic acid) is a sulfhydryl-containing, water-soluble, non-toxic, orally-administered metal chelator which has been in use as an antidote to heavy metal toxicity since the 1950s. More recent clinical use and research substantiates this compound's efficacy and safety, and establishes it as the premier metal chelation compound, based on oral dosing, urinary excretion, and its safety characteristics compared to other chelating substances. (Altern Med Rev 1998;3(3):199-207)
Symptoms of Mercury Intoxication

- Gastrointestinal disorders
- Renal dysfunction
- Hypertension
- Chronic poisoning results in atrophy and degeneration of the sensory cerebral cortex, hearing and visual impairment

- Wide range of neurological disorders
- Memory loss
- Depression
- Insomnia
- Psychosis
- Metallic taste

Werbach MR, Nutriolische Medizin, Hädecke1999
Mercury Distribution in Body Tissues

Source: Thomas L. Labor & Diagnose, Med.Verlag pg 430
Hg in Brain Tissue

- AA and Neutronactivation Analysis of brain tissue (gray vs white matter from 83 adult cadavers) demonstrated a positive correlation between occlusal surfaces of dental amalgam and mercury level of brain.

Eggleston DW, Nylander M. Univ.So.Calif., School of Dentistry, LA and Karolinska Institute, Stockholm, Sweden

Mercury Values pre and post DMSA

# Multiple Sclerosis Patients
mcg/g Creatinine
Hg post
Hg pre
Chronic Thallium Intoxication (Tl)

- Chronic intoxication is easily overlooked. Blood levels are generally <500mcg/l, often under <100mcg/l.

- Consider thallium toxicity when treating a patient with a neuropathy, diffuse and acute hair loss, loss of lateral eyebrows; gastrointestinal spasms.

- Thallium intoxications is still reported in countries where Tl is still used as a rodenticide.

- Recent cases of thallium poisoning associated with malicious criminal activity have been reported in the US.
Progression of acute Tl Toxicity

- Thallium blood levels rise 2-3hrs after oral intake and can rise to >500mcg/l
- First symptoms: vomiting
- Followed by 2-4 days symptom-free
- Followed by severe gastrointestinal spasms and constipation
- Followed by acute polyneuropathies of lower extremities and/or encephalytic symptoms, tachycardia, hypertension,
- 2-3 weeks after exposure: severe hair loss (high intake can be visually seen (better microscopically) as melanin pigments in hair root)
Thallium Distribution in Body Tissue

Source: Thomas L., Labor & Diagnose, Med.Verlag Marburg, pg 430
The Carcinogenic Metals

- which include both arsenic and nickel, may cause cancer either alone or by enhancing the effects of other agents through some additive or synergistic actions.
- Therefore, it is important to study metal-metal interactions in carcinogenesis and this arsenic-induced cross-tolerance to nickel

- **Acute Cytotoxicity of Nickel in Control and CAsE Cells**
  Romach et al reported that chronic arsenite exposure for 18 weeks or more induced malignant transformation in TRL 1215 cells and that self tolerance to arsenic and cross-tolerance to nickel occurs concurrently with transformation (Romach *et al.*, 2000.; Zhao *et al.*, 1997.)
Nickel – Ni
Nickel compounds: well-established human carcinogens (Costa and Klein, 1999; Salnikow et al., 1999).

- The precise molecular mechanism of nickel carcinogenesis is undefined.
- Nickel is a redox active metal and indirect damage due to generation of reactive oxygen species (ROS) is probably important in nickel toxicity and carcinogenesis (Kasprzak, 1991).
- Nickel-mediated lipid peroxidation may be also involved in carcinogenesis. For example, it has been reported that products of nickel-induced lipid peroxidation can damage DNA in vitro (Ueda et al., 1985).
- Hydroxyl radicals are involved in nickel-mediated lipid peroxidation, a finding that may have implications in the carcinogenicity of nickel compounds (Athar et al., 1987).
- Nickel impairs cellular defense mechanisms against peroxidation by depleting free-radical scavengers including glutathione (GSH), or by inhibiting catalase, superoxide dismutase, glutathione peroxidase, glutathione S-transferase, or other enzymes that protect against free-radical injury (Donskoy et al., 1986; Sunderman, 1989). Thus, nickel exposure disrupts cellular redox status as part of its adverse effects.
Variability due to environmental exposure?

Exposure to nickel occurs through breathing air or smoking tobacco containing nickel, eating food containing nickel (the major source of exposure for most people), drinking water which contains nickel, handling coins and touching other metals containing nickel.

- A small amount of nickel *may be* essential for humans, although a lack of nickel has not been found to affect the health of humans.
- Fumes from heated nickel can cause a pneumonia-like illness, with cough and shortness of breath. Higher exposures can cause a build-up of fluid in the lungs (pulmonary edema), a medical emergency, with severe shortness of breath.
- People who are not sensitive to nickel must ingest very large amounts to show adverse health effects. Workers who accidentally drank water containing very high levels of nickel (100,000 times more than in normal drinking water) had stomachaches and effects to their blood and kidneys.
- Exposure to Nickel can cause a sore or hole in the "bone" dividing the inner nose (septum).
- Cancers of the lung, nasal sinus, and throat have resulted when workers breathed dust containing high levels of nickel compounds while working in nickel refineries or nickel processing plants. There may be no safe level of exposure to carcinogens.
- Nickel may damage the developing fetus.
Nickel and Allergies

- The most common adverse health effect of nickel in humans is an allergic reaction.
- People can become sensitive to nickel when jewelry or other things containing this metal come into direct contact with the skin. Once a person is sensitized to nickel, further contact with it will produce a reaction. Symptoms include burning, itching, redness and bumps or other rashes. A rash may spread to other areas and last for weeks after exposure stops, but usually improves in about a week.
- Less frequently, some people who are sensitive to nickel have asthma attacks following exposure to nickel.
- Eye or skin contact may cause irritation.
- Lung effects, including chronic bronchitis and reduced lung function, have been observed in workers who inhaled large amounts of nickel.
- High exposure can cause cough, shortness of breath and fluid in the lungs, which is sometimes delayed for 1 to 2 days after exposure.
- Single high or repeated lower exposures may damage the lungs, with scarring of lung tissues, and may cause damage to heart muscle, liver and/or kidney.
Gold – Silver- Palladium

Palladium (Pd)
The German Health Ministry has been warning dentists since 1993 not to use palladium-copper alloys any longer.

...especially people who have nickel allergies react to palladium. Adding dental metals like palladium heightens the risk of illness in some people.

In Switzerland Palladium dental alloys have been banned.
Early Symptoms of Pd Toxicity:

- increased salivation
- pain in teeth and jaw
- tongue burning
- cold feeling in mouth
- metal taste
- peeling of mucous membrane around teeth
- fungus like coating in throat and sore throat
- painful, swollen lymph nodes in the neck
Palladium toxicity

- obstruction of important enzymatic systems like creatin-linase, aldolase, alcalite phosphatase, carbon-anhydrase, trypsin, chymotropsin

- disturbance of collagen synthesis like bone and cartilage

- obstruction of thymidin in the DNA

- accumulation in different organs
Thank you!

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