Chemistry 2211a

Toxic Metals

- 1) General introduction “Toxic Metals”
- 2) Chelators
- 3) Examples of Pb, As, Cd, Hg

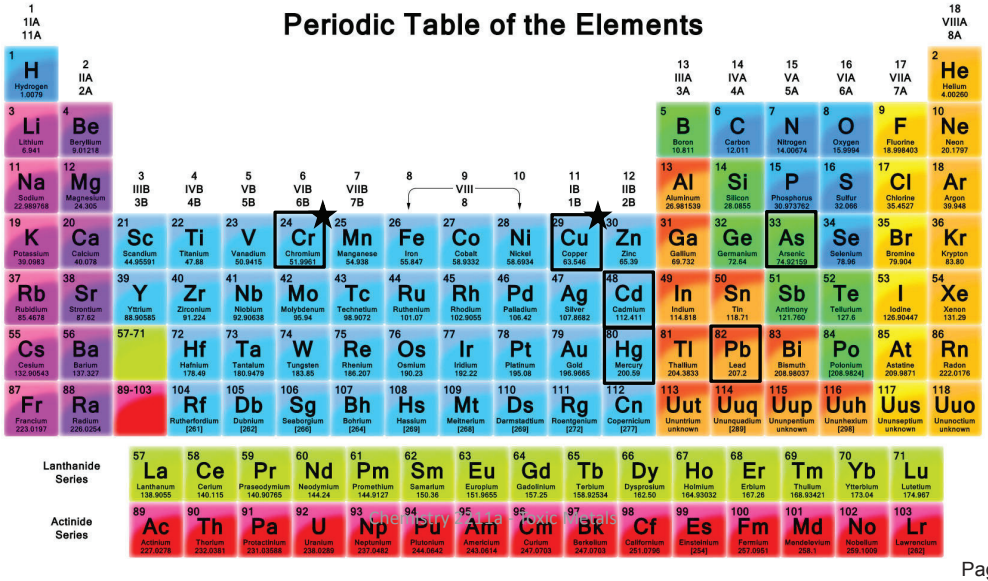
2016 Nov 27

Toxic Metals - Definition

- **Toxic** – ‘Poisonous’
- **Poison** – is a chemical/physical agent that produces adverse responses (molecular, biochemical or physiological effects) in biological organisms
- **Toxic Metals** – are metals that form poisonous compounds and may or may not have a biological role
  - *Definition may include essential metals that are dangerous at abnormally high doses*
  - *Metals that coordinated to certain ligands become more accessible to the physiological chemistry*

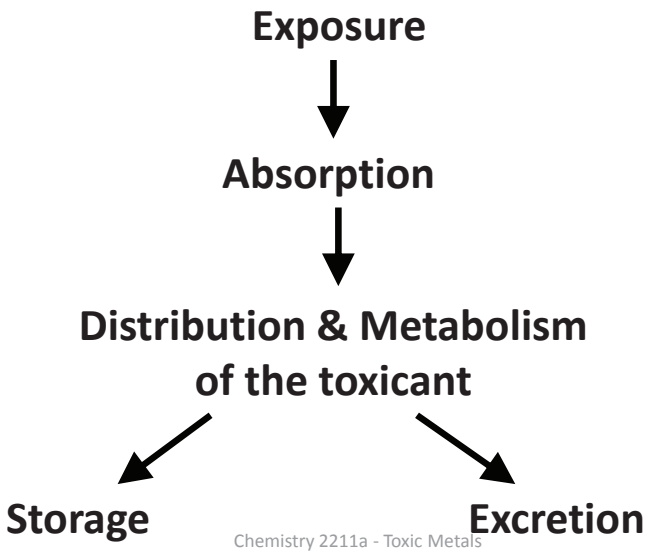
Common Toxic Metals

- Often are D-block metals
- Metals on the RHS of the Periodic Table
- Cu – high conc. toxic , Cr – oxidation state toxic



The Toxicological Process

Toxicokinetics: the quantitation of the time course of toxicants in the body



Mechanism of Action

METALS POISON BY A VARIETY OF DIFFERENT MECHANISMS

Molecular - combines with natural molecules and disrupts biological function

A common mode of action is to tie up sulfhydryl groups of catabolic enzymes[1].

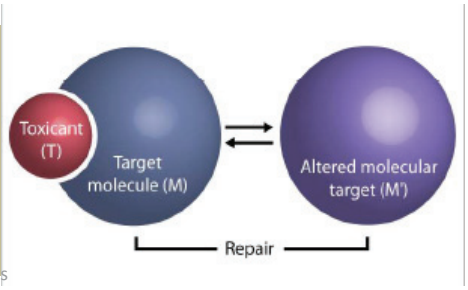
Biochemical - reduces metabolic activity

Affects a signalling pathway; Most of which interfere with enzymes involved in ATP production directly or indirectly

Physiological - Physical response

symptoms… death!

The toxic action of a metal is a consequence of the physical/chemical interaction of the active form of that metal with a molecular target within the living organism



How do these metals contact humans?

Cadmium

- commonly found in industrial workplaces, particularly ore is being processed or smelted.
- Several deaths from acute exposure have occurred among welders who have unsuspectingly welded on cadmium-containing alloys or with silver solders.

Arsenic

- Common sources of exposure include near or in hazardous waste sites; areas with high levels naturally occurring in soil, rocks, and water. As used to be used in rat poison and in preservatives applied to 'outside' green-wood used by the general population

Lead

- construction work, most smelter operations, radiator repair shops, and firing ranges. Pb also used to be in paint pigments and in the production of vinyl chloride but recently phased out for both of these uses.

Mercury

- Common sources of mercury exposure include mining, production, and transportation of mercury, as well as mining and refining of gold and silver ores.
- Hg used to be used in thermometers and paints, still used in fluorescent lights,
- High mercury exposure results in permanent nervous system and kidney damage.

Hexavalent Chromium

- Calcium chromate, chromium trioxide, lead chromate, strontium chromate, and zinc chromate are known human carcinogens.
- An increase in the incidence of lung cancer has been observed among workers in industries that produce chromate and manufacture pigments containing chromate.

ACUTE VS. CHRONIC TOXICITY

- *Acute* – a complete overload of the organism – a usually fatal concentration. A one time event → ☠.
- *Chronic* – exposure to low concentrations over a long time period. There may even be a acclimatization – a steady state – but alternatively, metabolic functions may slowly fail → ☠

- In both, the toxicity can be seen as: blockage of essential functional groups on enzymes; displacement of essential metals in enzymes; and/or modification of the conformation of key biomolecules.

Bioavailability

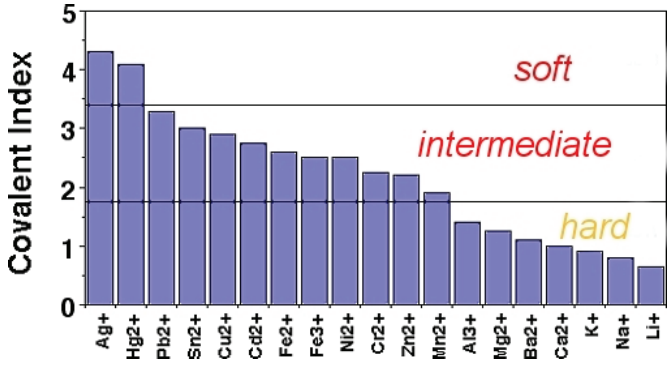
- Solubility and speciation
  - will determine whether a metal is bioavailable (particularly, the ligands the metal binds to) and
  - Whether there mechanisms in place in the organism to absorb the complex

- Acidic pH
  - will enhance solubility
- basic pH
  - results in hydroxides and carbonates that are insoluble.

- Availability also depends on whether the deposited metal is mobilized by a change in its form, common causes are:
  - Change in salt concentrations;
  - redox conditions;
  - presence of a chelator, eg EDTA

WHAT MAKES METALS TOXIC?

- The free ionic metal or complex of the metal is usually the toxic form



- **Soft metals are generally more toxic than very hard metals,**
  - being most effective at binding with SH- groups (cysteine, methionine)
  - and N- containing groups (histidine, lysine) which are commonly found in active centers of enzymes.
- **Soft (metal) – Int/Soft (ligands) form new metal-amino acid bonds that are not accounted for in the natural metabolic processes**
  - so may be permanent and block the protein or enzyme from subsequent chemistry. This makes the metal a metabolic poison. Particularly the case with Cd & Hg.

Toxicity Level - Summary

- **Chemical form of metal -** directly controls toxicity.
  - Important for Cr (3+ vs 6+); Hg (0 vs 2+ vs CH_3Hg^+); and As (3+ vs 5+).
- **Hard/Soft nature of the metal** – soft metals will bind readily to sulfur and are potentially more toxic because formation of covalent bonds to a large biological molecule might enhance the uptake and transport of the metal.
- **The mechanisms for controlling the metal inside the organism will affect the toxicity**.
  - toxicity can be changed by accumulation in "sinks" of bone (Pb), hair, and even target organs (kidneys for Cd)
- **Excretion** is also important because it requires transport in the organism

The most environmentally abundant toxic metals or metalloids (arsenic, cadmium, lead, and mercury) are each known to produce cell injury in the kidney. Each causes problems in the tubules, but by slightly different mechanisms.

Cadmium:

- Distributes first to liver
- Cd complex stored in liver or distributes to kidney
- Accumulates in lysosomes
- Damages proximal tubules -

Mercury:

- Binds to a variety of different enzymes
  - Sulfhydryl groups
- Interferes with cellular metabolism and function
- Nonspecific cell injury or death
- Accumulates in kidney
- Proximal tubule necrosis

Lead:

- Decreased mitochrondial respiration
- Acute or Chronic Damage to proximal tubular cells

CHELATORS –AN OVERVIEW

- Simply excreting the metals naturally may work if the metal has not done permanent damage– what does this require?...Time

- "Chelating agents" are substances that are extremely effective at removing heavy metals from the body.
  - These ligands generally have 2 or more S, O, or N atoms,
  - bind tightly to metals and keep them from reacting with proteins
  - Soft or intermediate ligands are more common because they bind more toxic metals and do not bind the essential, hard metals.

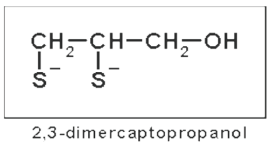
- Chelation is the formation of a metal ion complex – usually with a strong sigma donor atom - (oxygen, nitrogen and sulfur).

THE IDEAL CHELATING AGENT

1. the compound should be soluble in aqueous medium
2. should be stable in the circulation
3. if it is given orally, it should be absorbed by the GI tract and it should be cleared by the kidney
4. the compound should be active at physiological pH
5. the compounds should chelate only the specific metals
6. the chelator itself should not be toxic
7. the chelator-metal complex should be less toxic than the metal alone

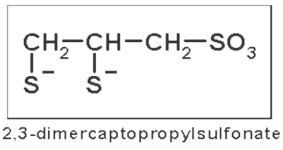
- CHELATORS -

KNOW AT LEAST ONE FOR EACH METAL
HERE: BAL, DMPS, DMSA, EDTA, D-PEN, NAPA, AND FE-DFO AND A NEW ENTRY



2,3-dimercaptopropanol

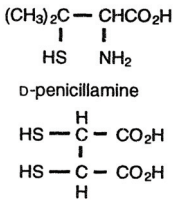
BAL



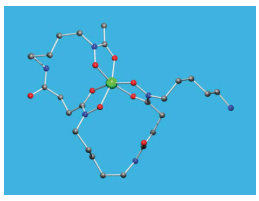
2,3-dimercaptopropylsulfonate

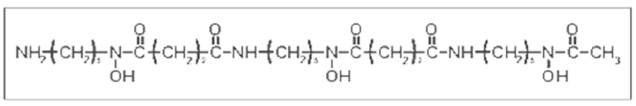
DMPS

D-PEN



D-penicillamine



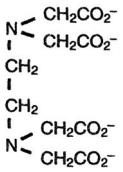


Desferrioxamine

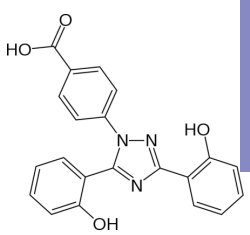
FE-DFO

2,3-dimercaptosuccinic acid

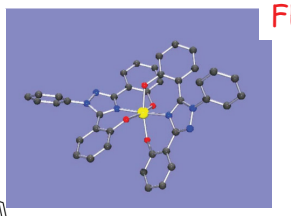
DMSA

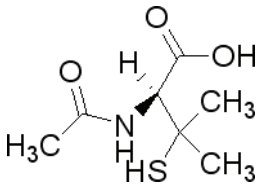


EDTA



DEFERASIROX



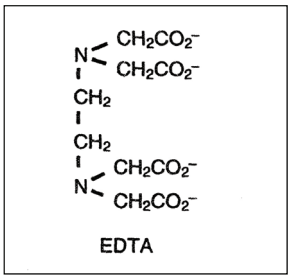


NAPA

WHICH CHELATOR TO USE WITH WHICH METAL? -

EDTA – ethylenediaminetetraacetic acid

- given IV as the calcium disodium salt.
- Used as disodium EDTA to bind calcium in blood to prevent clotting- used in blood collection and storage
- Used for Pb: only chelates circulating metal because EDTA cannot enter inside the cell membrane; frequently used in combination with BAL or penicillamine for treatment of lead poisoning, but now DMSA preferred
- Can also be used for Cd but DMSA preferred



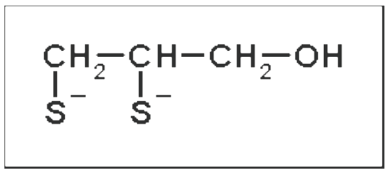
EDTA

- **Toxicity** - tubular destruction due to release of metal or the metal-EDTA complex in the kidney.

WHICH CHELATOR TO USE WITH WHICH METAL? -

BAL - 2,3-dimercatopropanol

- given IM in peanut oil
- Used for arsenic, mercury, antimony, lead, gold, zinc, bismuth. Half life is less than one hour.

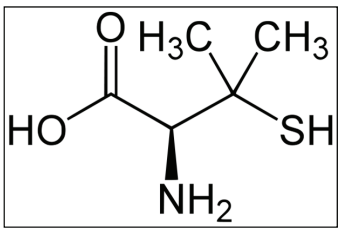


2,3-dimercaptopropanol

- **Toxicity:** - CNS convulsions in high dose; increased blood pressure; constriction of arterioles.; renal toxicity; nausea, vomiting and headache

D- PEN - d-isomer Penicillamine (Cuprimine®)

- given orally
- Used for Pb, Hg, As, and Cu (Wilson's disease where Cu^+ is elevated)

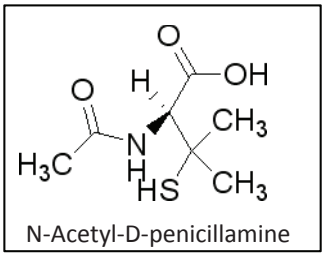


- **Toxicity** - Fever, skin rashes, leukopenia, nausea, vomiting

WHICH CHELATOR TO USE WITH WHICH METAL? -

NAPA (N-Acetyl-D-penicillamine)

-Hg, As



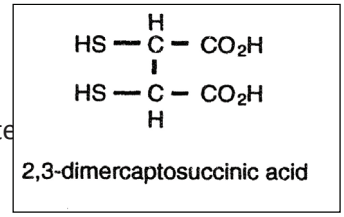
N-Acetyl-D-penicillamine

DMSA (Succimer)

•Can be given orally for As, Pb – Cd – minor side-effects – also chelates Zn(II).

•FDA approved for Hg but **DMPS** is preferred for serious syste intoxication

•Crosses the brain-blood barrier

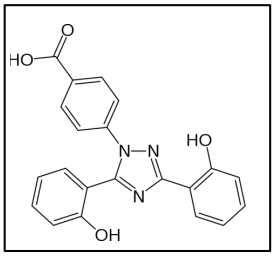


2,3-dimercaptosuccinic acid

DEFERASIROX

•for Fe overload – (prior 2005, used to be **DFO**)

•**Toxicity:** Leucopenia- decrease in the number of circulating white blood cells (leukocytes) in the blood.



Toxic metal transport

Once in the cell – transport to one of three routes – **excretion, storage or toxic damage**.

Via GSH?

See Arsenic section below. Possible excretion routes? See Fig 8.11

How do metals enter the cell?

1. **Passive diffusion** – simply move through a channel

2. **Active transport** – be moved through the membrane by a 'pump' located in the membrane\

3. **Facilitated transport** – a carrier molecule carries the metal through the membrane

4. **Extracellular ionophore diffusion** – specific molecule that encapsulates /chelates the metal and moves through the membrane with the metal

Bacterial mechanisms for disposal of Heavy Metals

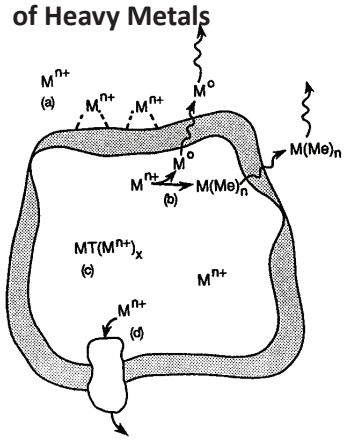
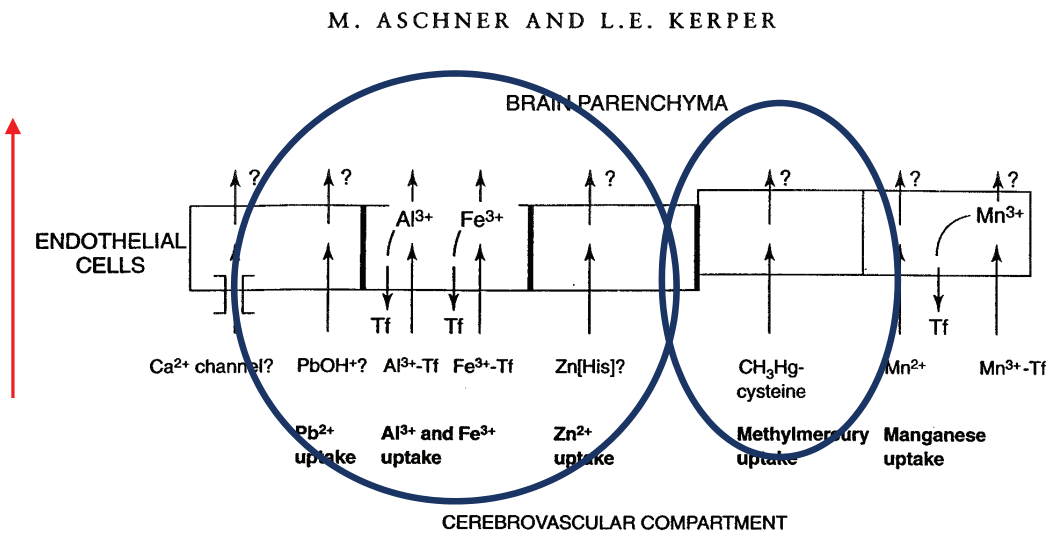


Figure 8.11 Bacterial mechanisms for disposal of heavy metals. (a) Binding to the outer membrane. (b) Chemical reduction and/or methylation to form volatile species. (c) Complexation by ligands or proteins (e.g., metallothionein, MT). (d) Export through an ion channel.

The flow of metals through the blood brain barrier Al^{3+} and Fe^{3+} use transferrin (Tf); Zn^{2+} a His complex; CH_3Hg^+ a complex with CYS – all carriers not channels

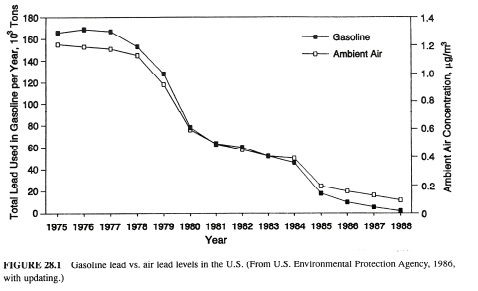
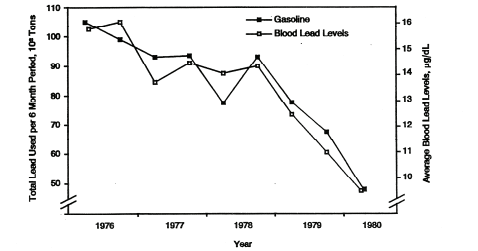


ure 10.1 Mechanisms of metal transport at the blood–brain barrier. For details on each specific metal, refer to text. ? denotes unknown mechanism.

"What is there that is not poison? All things are poison and nothing without poison. Solely, the dose determines that a thing is not a poison"
Paracelsus (1493-1541)

The Metals

Lead
Arsenic
Cadmium
Mercury

Toxicity of Metals– Pb Exposure and Health effects Pb- so useful, from sweetening wine to soldering pipes to beautiful glazes and Pb-glass and then there's plumbing.	Lead is a potent, systemic poison that serves no known useful function in the human body. Widely toxic because of the large number of sources for the general population and, in particular, children. Chronic overexposure to Pb may result in severe damage to heme synthesis Over the centuries, Pb was thought to be safe in low doses. But we know now that even extremely low levels of lead can cause health problems, especially in small children ages 6 months to 9 years.  FIGURE 28.1 Gasoline lead vs. air lead levels in the U.S. (From U.S. Environmental Protection Agency, 1986, with updating.)  FIGURE 28.2 Gasoline lead vs. blood lead levels in the U.S. (From Annest, J.L., *Lead vs. Health: Sources and Effects of Low Level Lead Exposure*, Rutter, M. and Russell Jones, R., Eds., John Wiley & Sons, New York, 1983.)
Lead is a heavy, soft metal<	It can be found naturally in all parts of the world. **Pb is released at ca. 4×10^5 tonnes/y natural sources and 3×10^6 tonnes/y due to man.** The softness of lead made it very adaptable and it was bent and shaped into many useful items. Lead has been used since antiquity – especially during the Roman Empire – as above.
Pb	Soft, malleable and ductile, resistant to corrosion. Heavy – hence for fishing weights, boat ballast. Mined in northwest Wales (UK) - mining dates back to at least Roman times and continued until well into the 20th century. 2007 metal production: 127,000 tonnes.

Pb2+ compounds	In old pipes, paints, pottery, and up until 1970's as Et_4Pb in gasoline across the world – banned in N America – but still in the developing countries. There were 2-3g/gallon of Et_4Pb in gasoline – which became a major problem due to the particulate fallout of PbO etc. on to soils and plants. Road-side dust was rich in PbO. Pb^{2+} accumulates in bones so animals concentrate Pb^{2+} from plants but not dangerously. Note drop in Pb in fig above – this has translated into a drop in blood lead levels in children – and in number of children with depressed IQ levels.
Pb is involved in the production of many items	EG pottery glazes, lead-acid batteries – all cars!, stabilizers for PVC plastics, pigments for inks, electrical and plumbing solders, and pipes Pb use for fishing weights and ammunition spread Pb (which rapidly dissolves in the stomachs of diving birds) across Canada (see graphic below). Stained glass connections. High lead glass (approx 15% by weigth Pb) used as decanters or even glasses will leach Pd rapidly into wine and acidic drinks leading to death. X-ray shields. As a weight – balancing car wheels – scuba diving.
Pb used to be used much more frequently	White paint, lead carbonate white was used by the Japanese geisha for face-whitening make-up, typesetting. Lead was used for plumbing in Ancient Rome and as a preservative for food and drink in Ancient Rome. Tetraethyl lead in gasoline.
Exposure to Lead **So that leads us to the next section --- how does Pb exhibit toxic effects?**	**Excessive exposure is usually from lead-based white paint in old houses (large amounts of lead-based paint persist in and around many older homes).** Although white lead-based paint is now not sold, yellow lead chromate paint is still available. And many toys are painted in lead-based paints if manufactured outside Europe and North America. (See Metals in the News web link on the INSTRUCT site for 2211a.) An estimated three million tons of lead remain in fifty seven million homes in the USA. Water passing through lead pipes and lead-soldered joints in newer copper water pipes (eg drinking fountains in primary schools in Ontario); road-side dust from the effects of leaded-gasoline (much of the lead from gasoline still contaminates the soil along busy roadways) and cooking or storing foods in low fired glazes. Pb is also taken up by the hair and nails. (Other uses: from batteries to lead aprons to protect from X-rays to .... the list is long.) In 1976 average BL in the USA was ca. 16 ug/dL plasma, in 1991 this fell below the critically low value of 3. However, blood lead values give an indication of only a small fraction of the total body burden Maximum dietary intake is 300 μg /day Plumbism is common in industrial workers from lead-based solder. Pb is stored in bones as well as in plasma. Lead poisoning was documented in ancient Rome, Greece, and China. Lead poisoning works on the cellular level by binding to the enzyme that inserts iron into the porphyrin ring → common symptom anemia.

THE POWER OF LEAD – THE FALL OF THE ROMAN EMPIRE

Lead (Pb) can attach tightly to proteins

Replaces metals such as zinc (Zn) or calcium (Ca), which are needed for normal metabolic function.

Lead accumulates in the soft tissues and bone[i].

Lead is particularly toxic when deposited in the brain. Lead crosses both the blood brain barrier (see earlier) and the placenta into the fetus. (Soft tissue/blood ½ life 20's days; in bone ½ life 20's years!)

In children Lead poisoning results in:

Developmental delays

Learning disabilities – even at low conc IQ is depressed

Behavior problems

In adults Lead poisoning results in:

Severe lead poisoning can damage the nervous system

Anemia – easy to understand why ... see below.

Lead poisoning is associated with male infertility

Lead is of considerable current concern[ii]

Lead poisoning is usually ranked as the most common environmental health hazard for children between the ages of six months and six years.

FILE

SCIENTIFIC SPECULATION BY JUENEMAN

INNOVATIVE NOTEBOOK

A lead-pipe cinch

FOR 2,000 YEARS and more, even while using lead as a metal of commerce, we have been aware of its toxic properties. The history of lead, not to mention its discovery, fades into antiquity. And yet, how well have we learned the lessons of history? Not very.

The ancient Romans had a rather clever corps of engineers who found that lead made an easily workable and practical conduit for transporting potable water from their aqueducts and reservoirs. Moreover, lead had great staying power because it remained relatively free of corrosion. But, despite this, one of the more famous architects of the first century BC, Marcus Vitruvius Pollio, warned that lead was potentially toxic and recommended that terra-cotta pipes be used instead.

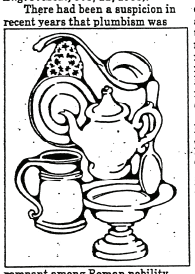
Of course, no one paid much attention to Vitruvius as lead was far too useful, especially for such items as pewter goblets, bowls, and serving dishes, as well as lead-lined copper vessels used for cooking and storage. The heavy pewter utensils, which were of an alloy of lead that could pass for antique silver, were somewhat resistant to being tipped by an inebriated guest or knocked over by gusts on a windy afternoon out on a Roman patio. The lead-lined copper pots took advantage of the thermal conductivity of the copper without introducing the metallic taste imparted by cooking in coppery vessels.

Actually, it seems to have been the preferred metal for lining copper to keep it from discoloring or corroding, but frequently the ores of metals with low melting points were blended and reduced together, giving alloys with a high lead content. Tin had been imported from the British Isles since about the fifth century BC, but because it was more expensive, it was alloyed with cheaper ores containing zinc, lead, and probably much more than a trace of arsenic and antimony.

So, for some two millennia, with the continued and extensive use of lead and lead alloys in the culinary arts and transport of potables, plumbism (lead poisoning) became a malady of Western civilization, but this only became quantitatively characterized early in the last century.

What had finally led up to this characterization was the recognition that gout and plumbism were coincident phenomena, a condition endemic during the period of Imperial Rome and again during the 18th to 19th century among the British aristocracy. Today gout is known as a typical result of subclinical lead poisoning (*New Eng. J. Med.*, 308, 11, 1983).

There had been a suspicion in recent years that plumbism was



rampant among Roman nobility because culinary recipes of the period called for unusual amounts of salt for savoring. Chronic lead poisoning dulls the sense of taste to where the palate is pleased only by very sweet or very sour condiments, else by heavy seasoning. Chronic plumbism also is manifested by colic and constipation, not to mention gout, and makes one go funny in the head, all of which we know affected more than a few Roman Emperors.

The Roman penchant for wine is legendary, much of which had been boiled down in lead-lined pots to enhance and concentrate the sugar content. It has been said that the epicurean general, Lucius Lucullus, ordered up some 4-million liters of vino for a triumphal feast. Meanwhile, closer to our own time, England imported more than 21-million liters of fortified port wine in 1825. All contained measurable, and hence potentially toxic, lead concentrations.

Organic acids, as acetic, attack lead, and wines which have been fermented too far, forming vinegar, are "sweetened" in the presence of lead. As a questionable benefit, lead acetate is a powerful fungicide and, in addition, this property may have been the reason why lead acetate has become known as "sugar of lead."

Podagra, or gout, has been the bane of those who dined well throughout the ages. In the fourth century BC, Hippocrates—the father of medicine—made the first clinical description of saturnine gout, and although he recognized that it had to do with rich food and wine, he did not connect it with lead vessels, but recommended regular cathartics to relieve the condition. Further, he noted that the best natural relief of gout was an attack of dysentery.

Curiously, nearly 2,100 years later, a chemist named N. Grew crystallized a salt in 1695 from the brine wells near Epsom, England. The substance was magnesium sulfate heptahydrate, and became known as Epsom salt. Within a short time its purgative properties achieved international renown, and it was widely used as a serial cathartic to rid the body's vital fluids of "bad humours." An unappreciated side benefit was the scavenging of soluble lead salts and precipitation as the sulfate, whereupon it could be eliminated more readily.

In the first century AD, Dioscorides, the Greek physician, and Pliny, the Roman naturalist, both mention the addition of "gypsum" (calcined calcium sulfate, or plaster of Paris) to wine, a practice which is still customary in the Mediterranean area. It improves color and clarity while acting as a preservative, although Pliny said that it corrected acidity—meanwhile removing the lead moiety. But Dioscorides objected to the practice because it was bad for the nerves—probably since the removal of water left a higher alcohol content.

However you look at it, the lessons of history would be a cinch if we just bothered to read them from time to time.

Frederic B. Juneman, FAIC

Exposure: inhalation, dermal absorption, or ingestion. Pb enters the bloodstream and attaches to proteins that carry it to different tissues and organs.	The gastrointestinal tract absorbs about 40% on ingested lead. Almost all organs are affected by Pb poisoning - with greatest damage being to sulfhydryl enzymes. Lead tends to accumulate in the body over time as the excretion rate is low (the 1/2 life from bone is 20-30 years – but it is in equilibrium with the blood). When lead enters the body, it replaces iron, calcium, and other minerals in the blood, which are extremely important during the stages of growth and development. Because young children require more minerals to grow and develop, they are thus more vulnerable to lead poisoning.
Symptoms of lead poisoning differ for children and adults. Pb is stored as complex with low molecular weight protein in erythrocytes, in the soft tissue, and loosely bound in bone – the major pool is tightly bound as insoluble and nontoxic Pb triphosphate in the skeleton – eventually becoming Pb-apatite (but is in equilibrium with the plasma bound Pb). Luckily, only minor amounts cross the blood-brain barrier.	High Pb leads to: iron deficiency and low Ca uptake because Pb and Ca compete for the same transport mechanism **Pb results in - anaemia due to interference in the Fe insertion reactions of heme synthesis (see next slide) and a shortened red blood cell life span.** Lead can damage the brain and nervous system -encephalitis (brain disorders) –there are several neurological disorders - in children attention disorders are common - neurologically in children - with effects of Pb poisoning quite clear at >80 ug/dl serum (4-5 uM).
Currently thought that blood Pb levels below the once-considered-safe 10-20 ug/dL in children can lead to behavioral problems	The US had a target of <5 µg/dL for children (& <2 in the future) but in 2001 there were still children with BPb or BLL > 25 µ g/dL The US Centers for Disease Control (CDC) now considers that any

(this may take place in the fetus as well).	blood lead is harmful to children. The Canadian picture is better probably because of the lower fraction of old homes[1] Normal excretion is very slow via the kidneys into the urine.
Measurement of exposure	The clearest indicator of Pb-exposure is the reduction in the activity of the delta- aminolevulinate dehydratase (ALHD or also called **Porphobilinogen Synthase**, E_2). In this reaction 2 molecules of ALA (δ-aminolevulinate) condense to form porphobilinogen (PBG) - on the pathway to formation of the heme – through a cyclization step followed by an iron insertion step.

Summary - Lead

1. Lead everywhere – mobilized by Man - even though not now in gasoline or paints – smelting spreads Pb – solders in water pipe connections – electrical connections – batteries – X-ray aprons. In the home: ammunition – hence bird kill – in plastics (blinds) – cosmetics - paint in the house (if older than 40 years), coloured paints on toys; bright glazes on pottery; heavy, crystal or leaded-glass decanters[2]. Water pipes in 40+ year old houses do have high Pb. Flush water fountains due to solder. Major intake: GI tract & lungs.
2. No known biological role – always Pb^{2+} - binds readily to biological sulfur – replaces Zn^{2+} & Ca^{2+} - readily absorbed and mobilized in the body – organoPb more toxic (Et_4Pb) – dealkylation by P_{450}. Pb: bioaccumulates, is

[1] www.hc-sc.gc.ca/ewh-semt/contaminants/lead-plomb/exposure-exposition_e.html
[2] Never ever store wine or juices in pottery or glass decanters for more than the time for a meal – many cases known of Pb poisoning from the Pb in the glass or glaze.

a carcinogen, causes birth defects, and reduces IQ. Pb laid down in bones, teeth and hair. RBC short term exposure indicator.

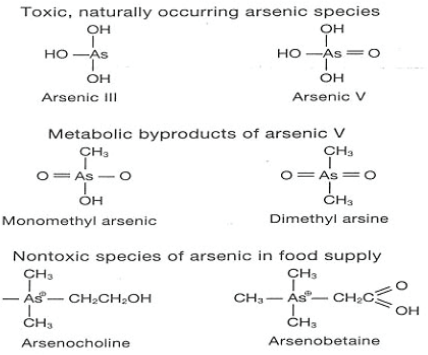
3. Most Pb intake from food and water – but for children – paint flakes, dust → 'pica' → Pb overload; inner cities paint & dust at a maximum.
4. Major neurological effects in children even below threshold of 10 µg/dL – even as low as 2-5 suspected as reducing IQ levels in children & behavioural problems[3]. Infants especially at risk → a wide range of problems, including anemia, kidney dysfunction, esp. neurological effects. Pregnant women → increased stillbirths. Adults → anemia, kidney dysfunction, peripheral neuropathy[4]. In large amounts -coma → ☠.
5. The average blood lead level of children in the US ages 6-16 years is now 1.9 µg/dL (c. 2001). Mainly due to bans on paints and gasoline. But, many recent events where Pb has been used in paints on toys (2007). Adult symptoms > ca. 40 µg/dL.
6. Pb inhibits heme synthesis. Leads to a rise in delta-aminolevulinic acid (ALA) in urine and PPIX in blood. = anemia.

[3] Safe' lead levels still reduce kids' IQs: new study finds Wednesday, November 21, 2007 | 12:10 PM ET CBC News " Lead levels in blood permitted by federal standards can still cause cognitive problems in children, a new U.S. study finds, prompting a call for stricter regulations. The authors found that the higher the lead concentration in the bloodstream, the lower the children's IQs. " www.cbc.ca/health/story/2007/11/21/lead-kids.html

[4] Nerve damage at the extremities → numbness; pins & needles.

Toxic Metals: Arsenic. Historical events: Massive poisoning of the peoples of Bangladesh & Bengal.

Humans are exposed to arsenic (As) from air, food and water.



1. Inorganic arsenic compounds are mainly used to preserve wood. Organoarsenic compounds are used as pesticides.
2. **But, arsenic has been known for thousands of years to be a toxic substance.** It is best known for its acute toxicity, for example when arsenic oxide or white arsenic (As_2O_3) is administered as a lethal poison. Chronic exposure to lower concentrations can likewise lead to dramatic situations, but in this case the poisoning develops very gradually. Pure metallic arsenic is not that poisonous, but its white salt is very poisonous. The lethal dose of arsenic oxide for an adult is about 120-200 mg. Arsenic causes toxicity by combining with sulfhydryl groups (SH-groups) present on several enzymes and thereby blocking their action. Pentavalent arsenic can imitate phosphorus and replace it in the backbone of DNA, resulting in conformational changes and strand breakage. Arsenic reductases in many organisms convert pentavalent arsenic to trivalent arsenic – increasing the toxicity.

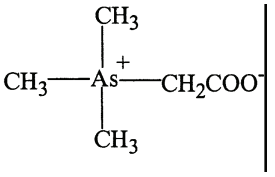
3061 **Fish and shellfish can accumulate non-toxic arsenic**. Particularly, cold water fin fish, crustaceans, and molluscs may contain large amounts of organo arsenic compounds – eg arsenobetaine - that have no known mammalian toxicity. In addition, certain edible marine foods, such a BUT Inorganic arsenic cmps and synthetic organoarsenoc cmpds ARE very toxic Asenic occurs in three main chemical forms in marine ecosystems: inorganic arsenic predominates in water and sediments; a group of closely related arsenicals known as arsenosugars occurs in marine algae; and arsenobetaine is the major arsenical in marine animals. **Inorganic arsenic is known to be toxic, whereas arsenobetaine (see 2 pages later) has been shown to be innocuous – that is, yes, completely harmless to mammals!** Ox. state of As is? Certain marine organisms, particularly bivalves such as clams, may contain over one hundred µg of dimethylarsonic acid in a typical serving, and may thus elevate urine As values even when the more restrictive speciation methods of analysis are used.

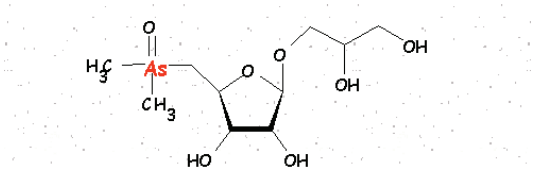
3. Arsenic exposure

- Eating food, drinking water, or breathing air containing arsenic.
- Breathing sawdust or burning smoke from wood treated with arsenic. (Cutting arsenic-treated wood requires dust masks, gloves, and protective clothing to decrease exposure to sawdust.)
- Living in areas with unusually high natural levels of arsenic in rock.
- In air from combustion of fossil fuels
- Pesticides and Herbicides – handling or making
- Cigarettes - contain very small amounts of As – not of concern compared with the Pb and Cd and the other carcinogens.
- Most non-occupational sources are from water, food, and use of Pressure Treated Wood.

4. Danger in the playground and on the deck

- A 4 m section of pressure-treated lumber contains about an ounce of arsenic, or enough to kill 250 people (calculated from application of 0.4 lb/cu ft of wood). Applied as: Chromated Copper Arsenate (CCA). [Now various combination of copper compounds are used]
- In less than two weeks, an average five-year-old playing on an arsenic-treated play set would exceed the lifetime cancer risk considered acceptable under US federal pesticide law. Some figures FYI:
- Total arsenic in PTW has been measured to be 0.2% i.e. 2,000 ppm or 2,000 mg kg-1 or 2 g kg-1
- To get a lethal dose: eat 3.8 g of wood – **main source of As from PTW is ingestion by licking hands.**
- If density is 0.5 g cm^{-3}. This is a 2-cm cube.[5]
- http://www.hc-sc.gc.ca/cps-spc/pest/pestprod/cca-acc_e.html

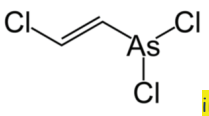


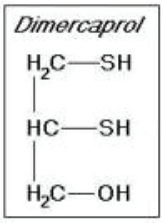


Arsenosugar B
3-[5'-deoxy-5'-(dimethylarsinoyl)-β-ribofuranosyloxy]
-2-hydroxypropylene glycol

[5] Katz and Salem, *J. Appl. Toxicol.*, 2005, **25**, 1-7.

5. **Lewisite,** dichloro(2-chlorovinyl)arsine, which is an arsenic derivative, was used in World War I as a chemical weapon – see earlier unit. It acted by forming blisters on exposed skin and damaging the lungs if the vapour was inhaled. Lewisite is administered as a gas. Its common name refers to the American chemist, Lewis, who developed it. The antidote for Lewisite is British Anti-Lewisite (BAL), which is injected in peanut oil (IM). See p 26 of the INORG unit.





6. **Drinking As-rich water** – for the Canadian perspective check out this web site[6]. – **see below**

7. Health effects of arsenic

a. Elevated inorganic As in drinking water is the major cause of chronic As toxicity.

b. **Chronic accumulation of arsenic**

i. Causes nausea and vomiting, decreased production of red and white blood cells, abnormal heart rhythm, damage to blood vessels, and a sensation of "pins and needles" in hands and feet; and anaemia, peripheral neuropathy, liver enlargement, chronic lung disease, and peripheral vascular disease.

ii. Causes hyperpigmentation, depigmentation, keratosis, and peripheral vascular diseases. Resulting in a darkening of the skin and the appearance of small "corns" or "warts" on the palms, soles, and torso these are hyperkeratotic skin lesions.

iii. **Skin manifestations are the most diagnostic**

c. As measurements from urine may not be a valid reflection of As ingestion from drinking water if there has been any consumption of seafood (including seaweed products) within the past three days

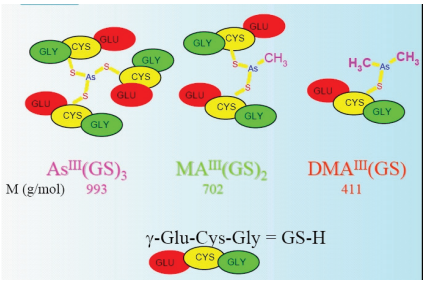
d. **Acute poisoning**

i. Inhalation of arsenic dusts may cause acute pulmonary oedema – fluid in the lungs.

ii. **Inorganic arsenic is a strong carcinogen.** Excessive and prolonged exposure to As is associated with an increased risk of skin, bladder, kidney, liver, lung and prostate cancers.

iii. Ingesting high levels of inorganic arsenic can result in death.

e. As(III) binds to 3 thiols – glutathione is a common metal transporter in cells As accumulates in soft tissue organs but clears rapidly <12 h.



[6] http://www.hc-sc.gc.ca/iyh-vsv/environ/arsenic_e.html

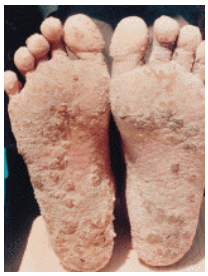
8. The Groundwater in India and Bangladesh is contaminated with As.

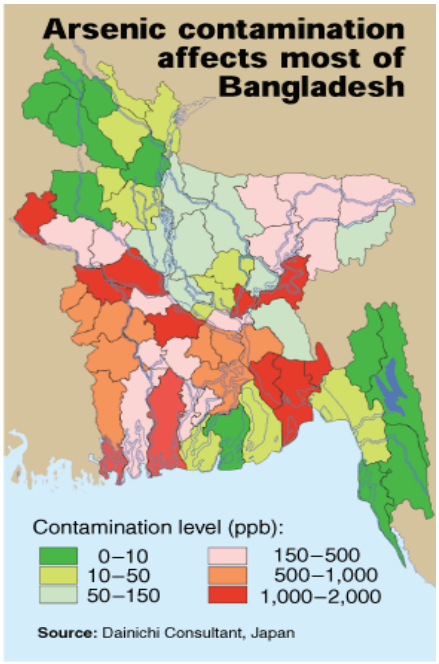
But so also is the groundwater in many other countries, including large regions of the USA – see map below.

A few notes: Major rivers deposit sediments into Bangladesh
Population of ~ 120 million (20.1% urban, 79.9% rural)

97% of the population use tube-well water during the 1970's, tube-wells were dug all over the country. A solution to contaminated surface water that was causing cholera and typhoid. Tube-wells became the main source for drinking/cooking water. Over 4 million wells were dug. In 1992, the British Geological Survey (BGS) analyzed about 150 wells to test the purity of the water.

Did not test for arsenic, but As was there…





9. The background[7]

i. In 1997, scientists from India re-tested the wells for arsenic and found the water to be contaminated

ii. The government had the safe wells painted green and the contaminated wells painted red until a solution was found. Many wells, when retested years later, were found to be marked the wrong color

b. Populations over 100 million – 30-50 million are drinking water from wells with >50 ppb As → illness and death. USA max is 10 ppb – most of Canada max is 10 ppb.

c. In one survey, out of 210 villages:

d. 83.% of hair samples were above the toxicity limit ; 94% of nail samples were above the toxicity limit. 62% of population at risk.

e. Number of Known Patients: ~ 7,000 – at risk: 50m!

f. Number of Tube-wells: ~ 4 million- affected: ~ 1.12 million

10. Source of As in tube-well water:

a. Naturally eroded from the Himalayas by the Ganges River over 20,000 years ago

b. Sediments migrate from the 4 main rivers in Bangladesh

c. Sediment deposition during the Quaternary Period, also known as the Younger Deltaic Deposition (25,000 to 80,000 years ago)

d. Geological processes: weathering, erosion, sedimentation

e. Agriculture use, irrigation, and fertilizers

f. Arsenopyrite and ferrous hydroxide are the source of the As(III).

Quoting from: United Nations Synthesis Report on Arsenic in Drinking Water
Chapter 4 : Diagnosis and treatment of chronic arsenic poisoning
By Dr. D.N. Guha Mazumder, Institute of Post Graduate Medical Education and Research, Calcutta, India

Chronic arsenic toxicity in man produces a range of clinical manifestations. However, skin manifestations are the most diagnostic and socially stigmatizing.

These are characterized by pigmentation of the body and limbs and keratosis of the palms and soles. Rain-drop like spotty pigmentation or depigmentation or diffuse melanosis affecting the whole body are the features of pigmentation. Diffuse thickening of palms and soles with or without nodular elevations **are diagnostic of keratosis.**

These features are manifested variably in different exposed populations, and may also be caused by As unrelated conditions **Hence evidence of chronic As exposure and detection of high levels of As in urine and/or in hair and nails in association with those symptoms need to be considered for the diagnosis of chronic As toxicity.**

Many of the clinical manifestations of chronic As toxicity are irreversible. Epidemiological studies have established As as an important agent which produces cancer of the skin, bladder and lung.

[7] Just as an example of information:
www.sos-arsenic.net/english/victims.html

No specific drug for altering the natural history of the disease has yet been available. Chronic exposure will lead to death.

How to tell if a person is poisoned by arsenic? The urine test is the most reliable test for arsenic exposure within the last few days. Tests on hair and fingernails can measure exposure to high levels or arsenic over the past 6-12 months.

Keratosis of palms and soles is diagnostic for long term exposure.

Is there any hope? Very recently as the result of Canadian research work – there has been a link proposed between low Se levels and As – As binds all free Se in humans. Se deficiency results in similar skin manifestations[8]

What about North America? USA … Yes, see the map at the end of the unit.

Toxicity of Metals– As: Release into drinking water

16. What causes elevated As in ground waters?

a. Acidic metal-bearing water draining from remote, abandoned mines has been identified by the EPA as a significant environmental/health hazard in the Western United States.

b. Many of these waters contain dissolved arsenic in the trivalent and pentavalent state.

c. Similar reports and concerns from Vietnam – read for interest:[9] "Groundwater Arsenic Contamination: Can It Happen In The Mekong Delta ? A Vietnamese Perspective by *Mai Thanh Truyet, Ph. D. & Pham Phan Long, P.E.*

Iron pyrite, FeS_2 Arsenopyrite: AsFeS.

- Arsenic is available in the sediment in non-toxic form
- During discharge – the AsFeS is exposed to air
- Non-toxic oxides of arsenic As^{5+} are reduced to the highly toxic forms = As^{3+}
- Release into the water as soluble salts – As dissolves in acidic solutions – the a[pparently pure water in the tube wells is now high in toxic As^{3+}.

Treatment of chronic Arsenic toxicity.

Chronic arsenicosis leads to irreversible damage in several vital organs and eventually cancer.

Despite the magnitude of this potentially fatal toxicity, there is no effective therapy for this disease; patients once affected may not recover even after remediation of the As contaminated water.

Possibly give Se to 'mop up' the As.

[8] www.cbc.ca/canada/saskatchewan/story/2006/11/29/synchrotron.html

[9] http://vastvietnam.org/truyet/tras.html

Summary of Arsenic toxicity and humans

Exposure Forms: As^{3+} and As^{5+} The 3+ is more toxic	Breathing – drinking – handling=surface contact	Breathing dust – pressure treated wood;– smoking cigarettes = small amount;	Drinking water – rocks high in As – ingestion – pesticides – herbicides Handling: walking on outside –'green' older-pressure treated wood structures
Occupational exposure	War-time – gas – Lewisite Pesticides Herbicides Handling pressure-treated wood	BAL invented for antidote	
Health effects	Many symptoms	Worst: skin pigmentation and warts, then …	Cancer - death
Cure?	No		
Major world-wide poisonings	Bangladesh and West Bengal Tube-well water	Cause: Water with As from arsenopyrites shale – As+Fe+ rocks dissolved by fertilizers possibly – certainly due to massive lowering of the water table and introduction of oxygen	Cure? Cannot reverse health effects – Response: Clean out the As with filters – eat Se in lentils

Toxic Metals: Cadmium

Key human toxicity history: Itai Itai disease in Japan

- Very common – same triad as zinc so often replaces Zn in enzymes – $4d^{10}$ forms 4-coordination complexes with sulfur – soft – binds also to water and HIS.
- Soft – in many products – also in soils – and smoke
- Induces metallothionein in all tissues – for example in the lungs of smokers – smoking a major source of Cd.
- Has a 20-30 yr ½ in the kidneys.
- Exposure results in bone osteomalacia and renal failure.
- Itai Itai disease.
- No cure

1. Inorganic chemistry

a. Cd is a soft, silvery-white metallic element that can easily be shaped. When heated, cadmium burns in air forming CdO.

b. Only exists as the 2+ oxidation state. Like Pb, the alkyl compounds are not naturally formed.

c. Always present during Zn smelting. Present in the ore.

2. Very many industrial and consumer product uses

a. NiCd batteries, metal plating, pigments (esp. bright ones), fireworks, metal coatings, glass, porcelains and plastics (pigments and plasticizers), soft alloys, solders and brazing rods – see a longer list in the "EXTRA_MATERIALS" file.

b. CdS and CdSe photocells and photovoltaic devices.

3. Cadmium Emissions occur from natural sources and man-made or anthropogenic sources to the three major compartments of the environment - air, water and soil; there may be considerable transfer between the three compartments after initial deposition.

a. Emissions to air are considered more mobile than those to water, which in turn are considered more mobile than those to soils.

i. Volcanic activity is a major natural source of cadmium release to the atmosphere, and estimates on the amount have been placed as high as 820 mt per year.

ii. Forest fires have also been reported as a natural source of cadmium air emissions, with estimates from 1 to 70 mt emitted each year.

iii. Mining (Cd-Zn-Cu co-occur); **smelting**

iv. Burning coal and household waste, and metal mining and refining processes.

b. To soils and waters: Spills and leaks from hazardous waste sites can also cause cadmium to enter soil or water. Cadmium attached to dust particles may travel a long way before coming down to earth as dust or in rain or snow.

i. The use of cadmium-containing fertilizers and sewage sludge is considered the primary reason for the increase in the cadmium content of soils over the last 20 to 30 years in Europe.

4. Human exposure:

Smelting in China – major problems:

» **12/22/2005 13:13 CHINA**

http://www.asianews.it/index.php?art=4940&l=en
Cadmium spill in the Beijiang River leaves millions of people without water

Yingde (AsiaNews/SCMP) – A state of emergency has been declared in the city of Yingde, in Guangdong. Residents are without drinking water because the Beijiang River has ten times the allowed concentration of cadmium after a state-owned smelting plant released cadmium waste into the river in Shaoguan Country six days ago. …

Bulletin of Environmental Contamination and Toxicology (2007) Metals Contamination in Soils and Vegetables in Metal Smelter Contaminated Sites in Huangshi, China
http://www.springerlink.com/content/7190444j341540g3/fulltext.html

This study investigated the source and magnitude of metal contamination in soils and vegetables collected in the vicinity of the Daye smelter, China. Results showed that soils and vegetables were heavily contaminated by cadmium (Cd) and lead (Pb). The average levels of Cd and Pb in vegetables were 0.21 and 3.28 mg/kg fresh weight, respectively…. The analytical results indicated that the total concentrations of metals were elevated in surface layers for all samples relative to the underlying subsoils. Furthermore, Cd contents in all soil samples were 8 to 20 times higher than the limit level; Cu and Pb concentrations slightly exceeded the limit values in some samples from the nearer sample sites to the smelter, while the other samples did not exceed the threshold value;

Smelter waste poisons farmers Shanghai Daily

By Yang Lifei | 2008-10-16 | NEWSPAPER EDITION

THE legal representatives of four smelting plants in Hubei Province have been detained after more than 1,000 farmers were diagnosed with skin ailments due to pollution from the factories.
More than 1,000 farmers in Jianli County have suffered severe rashes and other skin ailments since March, when local industrialists and their counterparts from nearby Hunan Province opened plants to smelt the highly profitable alloy vanadium, Changjiang Times reported.

There are 10 vanadium smelting plants in Jianli, six of which have been closed again since September. The other four plants had defied the government ban until yesterday, when they were shut down, the report said.
The smelting plants discharged waste containing toxic cadmium and arsenic into waterways which led to the pollution of both water and farms.
The contaminated water also spread to several villages and polluted tens of thousands of hectares of fields.
Lin said the wastewater discharged by one of the plants near the Jiangxintai Village contained vanadium 209 times above the national standard.

a. **Cadmium in Agricultural Soils** is relatively immobile under normal conditions, but could become more mobile under certain conditions such as increased soil acidity

i. Cadmium levels may be enhanced by the use of phosphate fertilizers, manure or sewage sludge. In general, soils which have been contaminated with cadmium from industrial operations cannot be used for agricultural purposes.

ii. Fertilizers often contain cadmium, which when transferred to soils used for growing vegetables they incorporate the Cd into S-containing peptides.

iii. Because cadmium is also a naturally occurring component of all soils, all food stuffs will contain some cadmium and, therefore, all humans are exposed to natural levels of cadmium. Leafy vegetables and potatos accumulate higher levels of cadmium than do fruits and cereals – but rice can be particularly high in Cd.

iv. Meat and fish normally contain lower cadmium contents, from 5 to 40 ppb – but …

v. Animal offal such as kidneys and liver can exhibit extraordinarily high cadmium values, up to 1,000 ppb, as these are the organs in animals where cadmium concentrates.

b. **Cadmium in Water** – leads to chronic exposure – slow degeneration of the kidneys and bone tissues – also issues with food grown in the contaminated waters.

i. **In the past, there have been examples of marked cadmium contamination in areas where food has been grown.** This was particularly so for rice crops in Japan in the 1950s and 1960s where cadmium concentrations from 200 to 2,000 ppb were found.

ii. Consumption of a diet rich in shellfish can double the intake of dietary cadmium without producing significant impacts upon blood cadmium.

Ingestion of cadmium in food is the major source of cadmium for non-smokers.

5. **Cadmium in Tobacco Smoke** Tobacco leaves naturally accumulate and concentrate relatively high levels of cadmium, and, therefore, smoking tobacco is an important source of air cadmium exposure for smokers. Smokers generally exhibit significantly higher cadmium body burdens than non-smokers.

Food and cigarette smoke are the largest potential sources of cadmium exposure for members of the general population.

6. **Occupational exposure to cadmium is mainly by inhalation.**

a. Cadmium emits a characteristic brown fume (CdO) upon heating, which is relatively non-irritating and thus does not alarm the exposed individual.

b. Breathing air with very high levels of cadmium severely damages the lungs and can cause death.

c. Breathing lower levels for years leads to a build-up of cadmium in the kidneys that can cause kidney disease. Other effects that may occur after breathing cadmium for a long time are lung damage and fragile bones – due to depletion of Ca^{2+}.

7. **Biology**

a. **Cadmium has no known essential role.**

b. Absorption from the GI tract is followed by binding to GSH or albumin- transport to liver then to the kidneys for 20 years or so before being excreted.

8. **Liver is the first binding site –** to metallothionein – then the kidneys are the initial site of damage and the critical target organ for the general population as well as for occupationally exposed populations.

a. General damaging effects of Cd are replacement of Zn in enzymes, eg carbonic anhydrase, Zn-Cu-superoxide dismutase (SOD).

b. **Cd does not cross the BBB so the CNS exhibits little damage following Cd acute poisoning.**

The most serious cases of environmental pollution by cadmium occurred in Japan after World War II. In 1946

a. Dr. Noboru Hagino noted a syndrome ("itai-itai" or "ouch-ouch" disease) that occurred in Toyama Prefecture that began with renal dysfunction and eventually resulted in painful bone changes.

b. The source of the problem was ultimately identified as cadmium in the wastes of the Kamioka mine of the Mitsui Mining and Smelting Company.

c. The cadmium was transported to rice paddies irrigated from the Jintsu River.

d. The daily cadmium intake in the endemic area was approximately 600 ug.

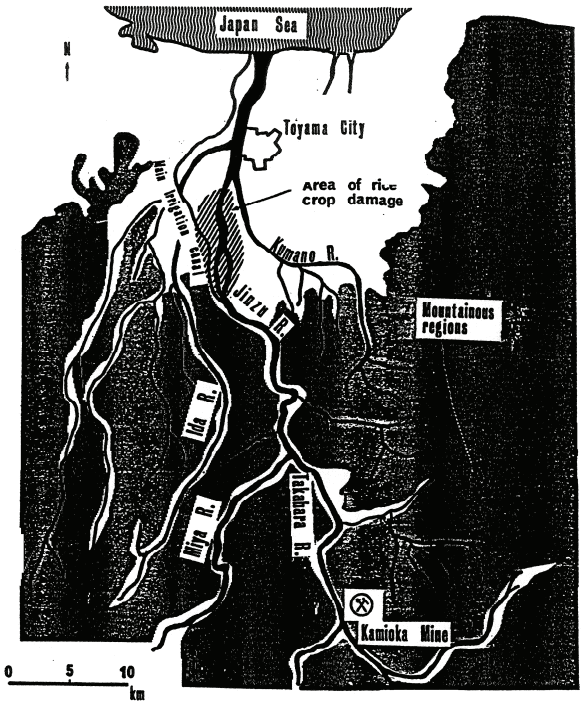


FIG. 1. Localities of the Kamioka Mine and the area of rice crop damaged.

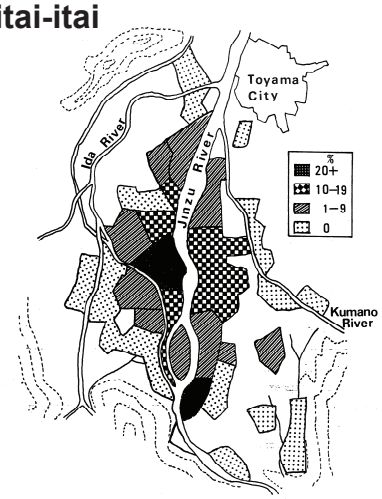


FIG. 12. Distribution of itai-itai patients (percentage of women over 50 years of age) (from Ishizaki and Fukushima [48] or Yamagata and Shigematsu [30]).

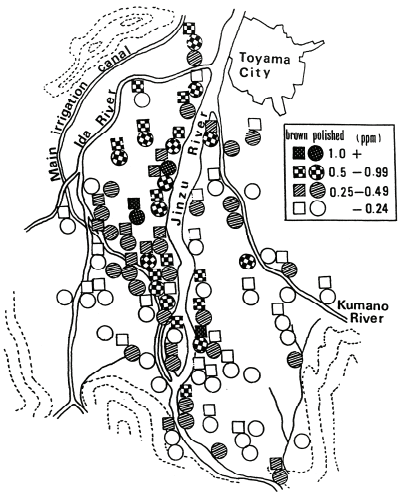


FIG. 13. Distribution of Cd in ordinary (nonglutinous) rice (from Fukushi et al. [49] or Fukushima [50]).

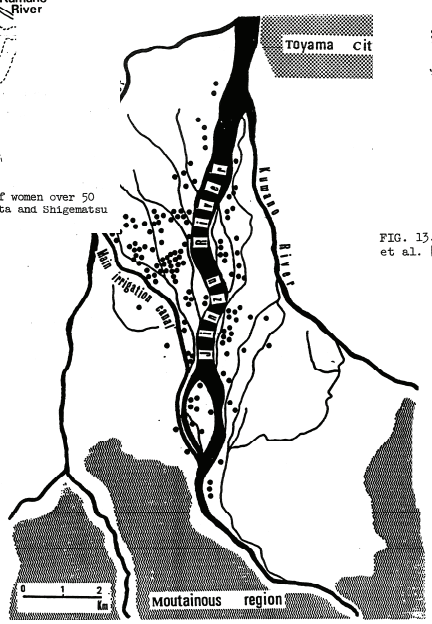


FIG. 4. The locality where the patients were found (dead patients included).

Summary of cadmium toxicity and humans			
Exposure Forms: just $Cd^{2+}$and fumes CdO	Breathing – drinking – eating offal - handling=surface contact	Breathing dust – smoking cigarettes – major exposure route – plus offal of large animals	Drinking water – from contaminated run-off; food grown on Cd-containing fertilizer – esp rice and leafy vegetables Liver & kdneys very high in Cd
Occupational exposure	Many products involve Cd Smelting – releases large amounts of Cd into water	Breathing fumes (CdO) from welding	
Biochemistry known?	Replaces Zn in many enzymes	Interferes with Ca deposition in bone formation	Binds first in the liver – then the kidneys – 20+ years. Does not cross BBB Binds to metallothionein
Health effects	Many symptoms – medical – kidney failure after 10-20 years leading to death.	Worst: demineralization of bones – osteomalcia - bones become very fragile - break	Cancer - death
Cure?	No	BAL used to reduce body burden – not as effective as needed – not an antidote – Cd remains bound in the liver and bones	Overall Preferred is DMSA - BAL is more efficient but mortality is high due to renal failure; also ethylenediamine-tetraacetic acid (EDTAH4)
Major world-wide poisonings	Itai Itai in Japan	Cause: Water with Cd from a Zn smelter waste that contaminated water used for rice and drinking.	Cure? Cannot reverse health effects – Response: Must remove Cd – actually – high Cd in many sources of rice in Asia

Toxic Metals: Mercury - significant poisonings

Some of the more recent exposures include Minamata Bay in Japan (1960), mercury contaminated fish in Canada, methylmercury-treated grain in Iraq (1960 and 1970), Northern Ontario in the 1970's and, in the U.S. (1996), a beauty cream product from Mexico called "Crèma de Belleza-Manning."

1. Properties of Mercury?

a. Mercury is the only metal that is a liquid at room temperature and also a gas. Known to the Greeks and Romans. Produced from the ore cinnabar (HgS), either by roasting:

b. $HgS(s) + O_2(g) \rightarrow SO_2(g) + Hg$ or by oxidation with lime (CaO):

c. $4HgS(s) + 4CaO(s) \rightarrow 4Hg + 3CaS(s) + CaSO_4(s)$.

d. World production of mercury is about 9,000 tonnes/year and this is mostly used in the chloralkali industry.

e. Inorganic chemistry - Hg

f. Mercury exists as: elemental Hg0 and $[Hg\text{-}Hg]^{2+}$, Hg^{2+}, and alkyl organic compounds, mono and di. The most common organic form is CH_3Hg^+ which toxic to the CNS - a neurotoxin.

g. Mercury is found in both organic and inorganic forms. The inorganic form can be further divided into elemental mercury and mercuric salts. Organic mercury can be found in long and short alkyl and aryl compounds.

2. Environmental aspects – Hg

a. 15 x 104 tons/year natural mobility

b. Volcanic action- degassing- dissolution of minerals into rivers

c. 18 x 104 tons/year

1. mining fossil fuel combustion - industrial & agricultural uses

d. Tuna fish can store Hg^{2+} but as $MeHg^+$ - 0.5 - 1 ppm in most fish - both old (in museums) and recent.

e. This high level is due to the large throughput of water

f. The biggest problem is the Hg^{2+} + B12 → CH_3Hg^+ taking place in anaerobic sediments. Methylmercury is rapidly absorbed by fish either directly from water passing over the gills or ingested. Since fish eliminate mercury at a very slow rate, concentrations gradually accumulate. For coastal populations the problem is that shell fish concentrate Hg^{2+} very much

g. Clams 10^5 x greater conc than in sea water

3. Biological effects of Mercury

a. Mercury in any form is toxic.

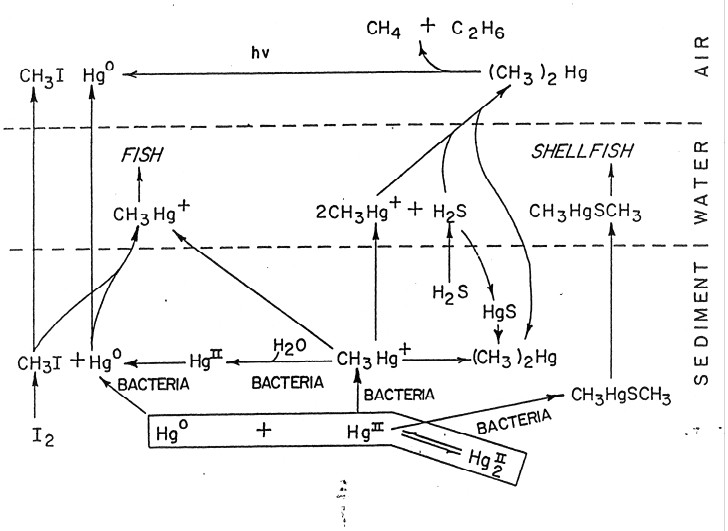


Figure 3. The mercury cycle.

b. The difference lies in how it is absorbed, the clinical signs and symptoms, and the response to treatment modalities.

c. Mercury poisoning can result from vapor inhalation, ingestion, injection, or absorption through the skin.

d. Hg^0 vaporizes at room temperature and is readily absorbed through inhalation. It is lipid soluble, which allows for easy passage through the alveoli into the bloodstream and red blood cells. Once inhaled, it is mostly converted to the Hg^{2+} form by catalase in the erythrocytes. This Hg^{2+} has poor lipid solubility, limited permeability to the blood brain barrier, and is excreted in the feces.

e. Unfortunately, a small fraction of Hg^{2+} crosses the BBB from the blood where it

reacts with catalase as well but now forming in the brain – binds to S in cysteine.

f. Hg^0 is not absorbed efficiently by the GI tract and, therefore, liquid Hg spilled due to broken thermometers, for example, is only mildly toxic.

4. Exposure to Mercury

i. For centuries, mercury was an essential part of many different medicines, such as diuretics, antibacterial agents, antiseptics, and laxatives. More recently, these drugs have been substituted and drug-induced signs of mercury toxicity are rare. Mercury toxicity in environmental pollution is a major concern because of increased usage of fossil fuels and agricultural products, both of which contain mercury.

ii. Mercury poisoning usually is misdiagnosed due to the insidious onset, nonspecific signs and symptoms, and lack of knowledge within the medical profession.

iii. Mercury is found in many industries, such as battery, thermometer, and barometer manufacturing. Mercury can be found in fungicides used in the agricultural industry. Before 1990, paints contained mercury as an antimildew agent. In medicine, mercury is used in dental amalgams and various antiseptic agents

iv. **In the chloralkali industry, the major process is electrolysis of aqueous NaCl solution to produce NaOH and chlorine.** Mercury cells were in wide use because they are more economic; they are being replaced now by less polluting techniques. The NaOH, the spent NaCl solutions and other plant effluents from this process carry traces of mercury which are discharged into lakes and rivers. In 1970, chloralklai plants lost about 600 tonnes/year. This was the source of much of the Hg in the north of Canada.

5. But in Canada?[10]

a. In Canada, the largest anthropogenic source of mercury until the 1980s was the chloralkali industry. Although mercury is still employed in this industry to manufacture chlorine and sodium hydroxide, emissions have now declined due to antipollution measures, conversion to non-mercury processes and plant closures. In the 1970s,

[10] www.ec.gc.ca/MERCURY/SM/EN/sm-cr.cfm

Canada reported 15 chlor-alkali plants in operation; however, only one Canadian facility remains in operation in New Brunswick.

Between 1990 and 1995, Canadian anthropogenic mercury emissions dropped from approximately 32 to 11 tonnes primarily as a result of process improvements in the base metal mining industry. In 1995, this industry was the largest source of mercury into the atmosphere, contributing approximately 40% of total emissions. From 1995 to 2000, Canadian anthropogenic mercury emissions dropped to a total of just over 8 tonnes. Two sectors, electricity generation and metal smelting, were equally the largest sources of mercury into the atmosphere, each accounting for 25% of Canadian emissions.

6. Compact fluorescent lamps are frequently used in place of traditional incandescent lights.

a. Compact fluorescent lamps have all the same characteristics as linear fluorescent tubes, except they have been designed to replace incandescent bulbs, which are common in residential, commercial, industrial, and accent lighting applications. Mercury content: Mercury content is generally between 1 and 25 milligrams.

7. Thermostats

a. Mercury-containing thermostats may be used in heating and cooling systems in residential, medical, commercial and industrial settings.

b. Thermostats comprise a tilt switch with a mercury ampoule used to activate or deactivate the heating or cooling device.

8. Dental Amalgam

a. Dental amalgam is prepared by mixing approximately equal parts of liquid mercury and alloy powder, which typically consists of silver, tin, copper, and zinc. Mercury Content: Silver coloured dental amalgams generally contain about 50% mercury.

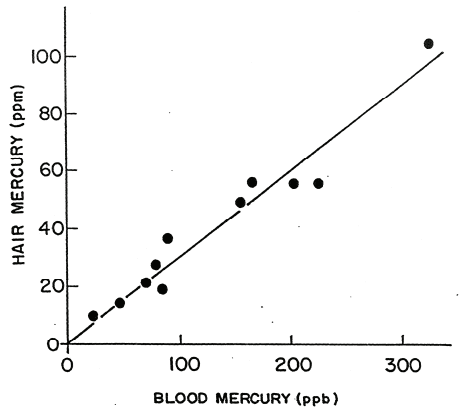


Fig. 9-5. The relationship between the concentration of total mercury in blood and in the 1-cm segment of a hair sample immediately adjacent to the scalp (from Clarkson 1976). The line was drawn by least squares linear regression analysis of the hair concentration (y, ppm) on the blood concentration (x, ppb) following the derived relationship y = 0.49 + 0.30x. The square of the regression coefficient is r^2 = 0.95. The standard error in the slope of the line is 0.02.

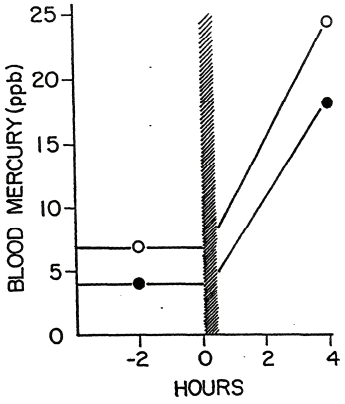


Fig. 9-6. The concentration of total mercury in blood samples before and after the consumption of one meal of fish (from Clarkson 1976). Each subject was an adult white female who consumed the cooked muscle tissue of a northern pike caught on the English River system.

● consumed approximately 0.5 lb at 2.6 µg Hg/g uncooked tissue

○ consumed approximately 0.75 lb at 2.9 µg Hg/g uncooked tissue

Top predators, such as walleye and pike, usually have the highest mercury levels. Smaller, younger fish and fish that are not top predators, such as panfish and yellow perch, are lower in contaminants. You can reduce your contaminant intake by choosing these fish to eat.

If you do wish to keep a legal-sized muskellunge for consumption, it will likely have elevated mercury levels, and should not be consumed by women of child-bearing age and children under 15. Trophy-sized muskellunge usually have very high mercury levels and should not be consumed by anyone"

Hg - Environmental exposure

Canada has a very big problem with the Hg content of fish.

"Examining Fish Consumption Advisories Related to Mercury Contamination in Canada." Prepared by MaryEllen Wood and Luke Trip, Environment Canada (2001), - reproduced with. acknowledgement to Dr Wood.

Her report concerned advisories issued warning of mercury bioaccumulating in the fish tissue. This is a risk for people who consume fish on a regular basis because elevated levels of mercury in fish tissue have serious implications on human health, especially for the development of unborn and young children. In 1970 Ontario, Canada, banned all fishing in the St. Clair River, Lake St. Clair, and the Detroit River. No clear data are available on numbers affected but there no known dead. Levels of mercury in fish flesh from Lake St. Clair, in 1935, were 0.07 - 0.01 ppm; but in 1970, some were 7.0 ppm, although the average was 0.5 ppm. Canadian max is 0.5 ppm.

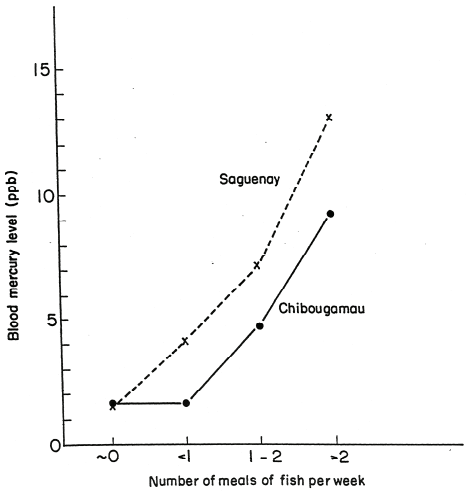


Fig. 9-2. Blood mercury levels in white Quebecois as a function of fish intake (adapted from Weber *et al.* 1978).

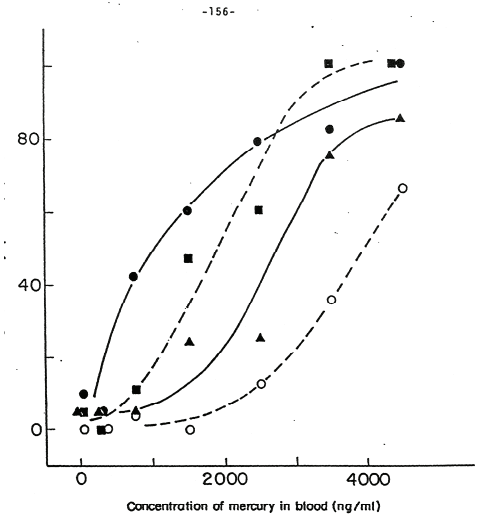
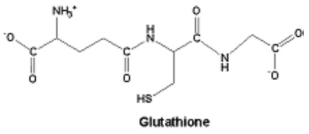
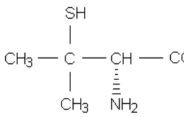
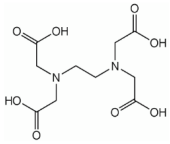


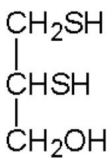
Fig. 9-7. Relation between the concentration of mercury in the blood and the incidence of symptoms (data from Bakir *et al.* 1973, Table 4). ● - paresthesia; ▲ - dysarthria; ■ - ataxia; ○ - hearing defects.

Some ligands that chelate Hg – BAL, glutathione, D-penicillamine, not EDTA,









9. Occupational exposure

a. **Mercury and hatters – details not tested**

The felt hat industry has been traced to the mid-17th century in France, and it was probably introduced into England some time around 1830. A story passed down in the hat industry gives this account of how mercury came to be used in the process: In Turkey camel hair was used for felt material, and it was discovered that the felting process was speeded up if the fibers were moistened with camel urine. It is said that in France workmen used their own urine, but one particular workman seemed consistently to produce a superior felt. This person was being treated with a mercury compound for syphilis, and an association was made between mercury treatment of the fibers and an improved felt. Eventually the use of solutions of mercuric nitrate was widespread in the felt industry, and mercury poisoning became endemic. Danbury, Connecticut, an important

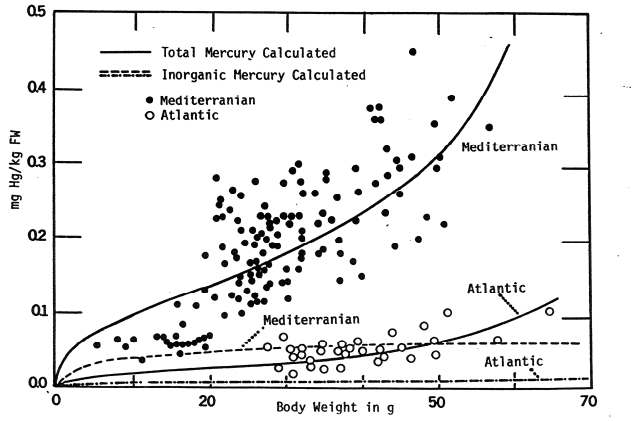


Figure 2. Concentrations of inorganic mercury and total mercury in ~~Thunnus~~ ~~thynnus~~ from the Mediterranean and the Atlantic versus body weight.

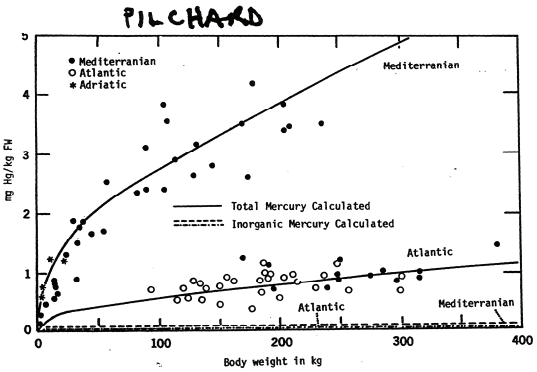


*Figure 1. Concentrations of inorganic mercury and total mercury versus body weight in **Thunnus thynnus** from the Mediterranean and the Atlantic.*

center of America's hat-making industry until men's hats went out of fashion in the 1960s, developed its own reputation for madness. Regionally, the "Danbury shakes" were a commonly recognized series of ailments.

b. Throughout the 20th-century, mercury has been useful in a number of everyday items — alkaline batteries, fluorescent light bulbs, electrical switches, scientific and medical devices and the ubiquitous thermometer. Thermometers contain the less toxic elemental form of mercury and have almost never been a safety issue in peoples' homes. However, in the 1970s and '80s, workers at the Staco thermometer plant in Poultney, Vermont, began to notice a common series of health problems—headaches, bleeding or sore gums, upset digestive systems, and coordination problems. Upon investigation, mercury was detected in the air of workers' homes, on their clothing and furniture, and most tragically, in the bodies of many workers and their children. This was the first time in which the children of mercury-handling workers were proven to have been affected. The plant closed in 1984.

10. Biology - role in biological molecules - Hg

11. Metallic mercury – Hg^0

a. Unique for a metal to exhibit a liquid state - the vapour pressure is high making Hg very volatile at room temperatures, which results in significant release of Hg vapor - this is especially a problem in enclosed spaces - including our mouths. **Vapour entering the lungs is converted into oxidized forms by catalase and transported into the plasma.** Much more Hg accumulates in the brain following Hg^0 exposure through the lungs than following intravenous injections of Hg^{2+}. The whole body ½ life of inhaled mercury is about 60 days. Many symptoms results from intoxication with mercury vapour - including major neurological changes, gastrointestinal disturbances, and tremors.

12. Inorganic mercury

a. Salts are not absorbed efficiently into the gastrointestinal tract so that only an estimated 10% of $HgCl_2$ is absorbed. In the plasma Hg(II) is primarily bound to HSA (albumin). Skin absorption occurs and results in dermatitis.

b. The key problem is the extremely high binding constants for S. Glutathione – above - is thought to be the primary carrier both in plasma and in membrane transport. In critical poisoning the kidneys and GI tract are most affected. Renal failure eventually occurs. The kidneys are the primary target for inorganic mercury.

c. Chronic exposure to mercuric salts (ie low levels over a long period of time) result in the 'Mad Hatter' syndrome - neurological effects.

d. Acute exposure results in damage to the intestines and the kidneys leading to renal failure.

13. Organic mercury

The short chain alkyl mercury (methyl and ethyl) are extremely toxic to humans.

These compounds are efficiently absorbed through the GI tract. Most is bound to red blood cells - methyl mercury readily and rapidly crosses the blood brain barrier (BBB), slowly accumulating in the brain. (4 hr after ingestion and 5 min after intravenous injection reaching brain tissue.)

Although CH_3HgCl is lipid soluble - CH_3Hg^+ is bound almost completely to RSH groups in proteins and small peptides (GSH) in blood and other tissues, not free.

1) Absorption efficiency in the gastrointestinal tract for $HgCl_2$ is 20% max but $MeHg^+$ 100%

2) Eventually the Hg^{2+} is transported to the kidneys leading the renal failure.

3) The neurotoxicity is considered to occur following a series of interactions.

ROLE OF GLUTATHIONE IN THE METABOLISM, TRANSPORT A TOXICITY OF METALS

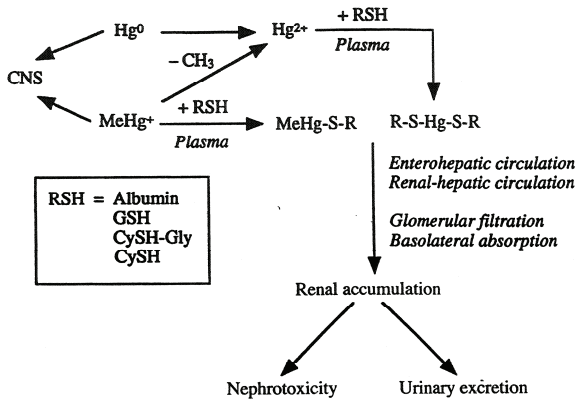


Figure 13.4 Role of sulfhydryl-containing compounds in the tissue distribution of the v forms of mercury. Elemental mercury (Hg^0) can either be accumulated in the central n system (CNS) or it can be oxidized to inorganic divalent mercury (Hg^{2+}). Hg^{2+} is bour sulfhydryl-containing ligand (R) in plasma and is translocated eventually to the kidneys. Sir methylmercury ($MeHg^+$) can accumulate in the CNS, it can be demethylated to form Hg can be transported to tissues such as the kidneys bound to a sulfhydryl-containing Abbreviations: GSH, reduced glutathione; CySH–Gly, L-cysteinylglycine; CySH, L-cystei

It appears that there is a threshold level below which there is no renal damage found. Above this level, renal damage is rapid and severe.

Thiols (RSH) are the key ligands

14. Minamata Disease - MD

a. MD was first reported in 1956 in the region around Minamata Bay in Japan although probably began in 1953. The first patients were 2 young girls with serious cerebral disorders of an 'unknown' origin. The symptoms were numbness of the fingers, lips and tongue, clumsiness of the hands and strange gait. Then, deafness and constriction of the visual field, and death. Soon after, 30 similar patients were discovered in the neighbourhood of Minamata City (with 40,000 population) that faced the Minamata Bay. In addition, cats were found to exhibit the same condition after eating dead fish from the bay.

b. MD was caused by eating fish and shellfish caught in Minamata Bay. The local fisherman were very poor and were the main patient body. These families ate large amount so of fish and sea foods.

15. Up to 1960, 111 cases of MD had been reported. 41 deaths had occurred. **MeHg readily crosses the placenta dramatically affecting the unborn leading to mental retardation, growth disorders, etc. from damage to the CNS.**

CAT DANCING

by Jack Perdue

The river ran clean and clear. It had its beginnings in a sparkling lake, and tumbled between forest-clad shores on its long journey to the sea.

As time passed, settlers from Europe found it, built their communities on its shores and began shaping the wilderness to their will. Its cold northern waters became famous for fighting game fish; northern pike, walleye and the mighty muskellunge.

One day a pulp mill was built on the upper reaches of the river. It was to provide much-needed products for the growing country, and for export. And it was to provide jobs. In fact, it was to eventually provide 1,500 jobs in a town where all other industries employed less than 150 people among them. The town depended heavily on the pulp mill for its survival.

Pulp mills need great quantities of water for their operations, and this river ran fast and clear. Over the years the daily dumpings of wood fibre, together with the cleaning water that washed away the chemicals used in the pulp-making process, seemed to have little effect on the quality of the water and the downstream watershed. The river was not truly polluted at that time, although some of the game-fish species and other aquatic life began to diminish. Nearly 50 years in the future, the river would indeed become dangerously polluted, but long before that happened, it simply and quietly died. For wood fibre destroys the oxygen in a water system, and this once deep-running river was to develop a bottom layer of wood fibre up to 40 feet thick!

One of the heavy metals used extensively in the pulp-making process is mercury. For many years it was believed that organic mercury would simply sink into the sediment on the river bottom and remain there in a chemically inert form.

And then came the cat dancing.

Minamata disease, also known as 'cat dancing disease' because it was first detected through the peculiar behavior of infected cats, was originally diagnosed in Japan where 90 people died at Minamata in 1975 as the result of mercury poisoning caused by eating fish infected by the effluent from a local industry.

Mercury poisoning is nothing new. It dates back to the 15th century and even earlier, the victims at that time usually being workers in the mercury mines.

In recent times, organic mercury compounds have been used as seed dressings. The consumption of this dressed seed led to a number of severe outbreaks of mercury poisoning: in Guatemala in 1966, Pakistan in 1969 and Iraq in 1971, '72 when several thousand people died and as many became seriously ill.

An extensive monitoring program was begun in Canada as early as 1969 to detect the presence of mercury in higher-than normal quantities in bodies of water. It must be remembered, however, that Canada has nearly one-third of the world's fresh, unsilted water in the form of hundreds of thousands of lakes and rivers. The task was all but insurmountable.

It was to be expected, however, that areas in Canada would eventually be found where mercury levels were dangerously high, and they were.

They included our river, once clean and clear. And the Indians who lived along its banks and hired out as guides to visiting sport fishermen and ate the fish in the river as their staple food were the first residents of Ontario to show signs of Minamata disease.

As you might imagine, this caused a great deal of publicity, and government studies were immediately undertaken. The main result was the discovery that anaerobic bacteria in river-bottom sediment were attacking the inorganic mercury there and converting it into methyl mercury. And methyl mercury is organic and can be concentrated in the fatty tissues of fish and birds — and man.

The effects of mercury poisoning are highly unpleasant. Mercury, together with other heavy metals used in industry, attacks the human liver, the essential part of man's immunity system. Studies also suggest a definite connection between mercury and cancer.

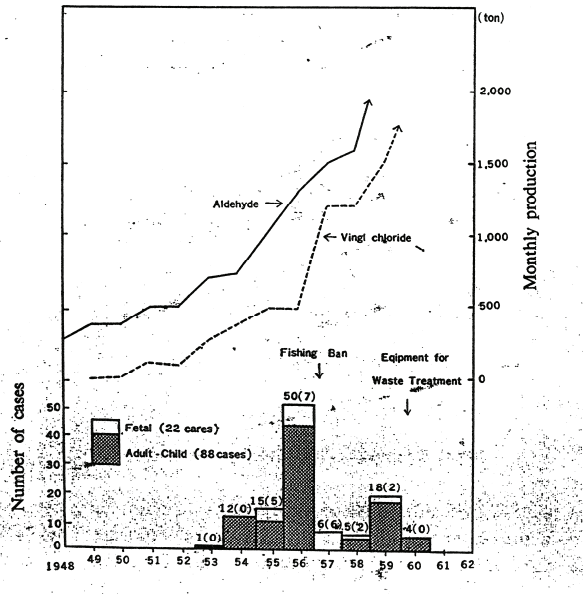
a. The estimates over several decades were that thousands of people were affected.

b. Initially identified as an intoxicant disease but not associated with Hg, rather Mn, Se or Tl from the marine life. Because of large amount of Mn and known neurolgical effects of Mn, Mn was initially strongly identified with the brain disorders, except that cats fed Mn did not exhibit the strange behaviours observed. In 1959, mercury was identified as the probable cause. And, then organic mercury was identified following observations of identical symptoms after oral ingestion by lab cats, again in 1959.

c. The Hg from mud and sediment in the Minamata Bay region with concentration of 2100 ppm wet weight was found at the drainage site for the Minamata factory of Shin Nihon Chisso Co.

d. In 1960, organic mercury was isolated from fish in the bay - and was shown to be $CH_3HgS.CH_3$ Methyl methylmercuric sulfide. CH_3HgCl was then isolated from the mud containing the mercury efflux of the vinyl acetate factory. .

Fig. 4 Number of patients of Minamata disease and the production of chemicals at the factory



e. The vinyl factory was identified as the source. $HgCl_2$ was used as a catalyst for vinyl chloride synthesis and $HgSO_4$ for acetaldehyde. This factory began use of mercury in 1932, producing vinyl first in 1941. The Minamata factory became the largest producer of vinyl in Japan, dumping more mercury than at any other site, directly into the Minamata River. Estimates of 500-1000 g mercury were lost for each ton of acetaldehyde made. 200 tons of mercury were used over a 5 year period ending in 1953. In 1961, waste disposal was installed and the mercury content of the effluent dropped. Treatments with EDTA and BAL were attempted. Both roughly doubled the urine concentration of Hg but did not appear to relieve symptoms. Later MD was found in other areas of Japan (Niigata) following the pollution of the Agano River - called MD-2. Directly related to eating contaminated fish. Hg levels in hair were elevated. About 200,000 people have been exposed, with 2200 officially designated MD patients

Cabinet approves Minamata disease plan

CONTINUED FROM PAGE 1

in Minamata in 1956.

However, a group of about 100 unrecognized Minamata victims who have filed damage suits with the Osaka District Court are still demanding the government accept official responsibility.

The government's statement Friday, which only expressed "regret," is unlikely to be enough for these litigants.

Under the final settlement plan, Chisso will pay ¥2.6 million to individual victims of the disease in Kumamoto and a total of ¥4.94 billion to five victims' groups to cover litigation and other costs.

In the Niigata case, the victims' group has reached an agreement with Showa Denko K.K. — the company that discharged the polluted water there — in which the company will pay ¥2.6 million to individual victims and ¥440 million to the group. Showa Denko will also pay ¥250 million to Niigata Prefecture to help revitalize the local economy.

The Cabinet agreed that medical panels designated by the prefectural governments of Kumamoto, Kagoshima and Niigata will resume accepting applications from patients in January to determine their qualifications based on medical certificates prepared by both public and private hospitals.

As a result, about 8,000 people who have not been officially recognized as Minamata disease victims are expected to be eligible.

More than 13,000 people have applied for recognition as Minamata victims to be eligible for compensation from Chisso, but the government has so far recognized only about 3,000 of them.

The Cabinet has agreed that Kumamoto Prefecture and the central government will both supply funds to financially support Chisso and revitalize the local economy.

The government will extend about ¥25 billion from the general account to the fund, while Kumamoto Prefecture will extend about ¥5 billion through a bond issue.

The fund will be used to provide ¥26 billion to Chisso and ¥4 billion for the development of the regional economy in Minamata and Ashikita, including the construction of a welfare center.

If Chisso is unable to repay the loans from the prefecture, the national government will take every possible measure to make good on them. That pledge was made in deference to a demand by the Kumamoto Prefectural Government.

Tadamori Oshima, director general of the Environment Agency, told a news conference that the agency's role now is to implement various measures approved at Cabinet meetings.

Koichi Kato, secretary general of the Liberal Democratic Party, said that the entire party supports Friday's solution to the long-running issue.

"If politicians had allowed the problem to lag on for another 10 or 20 years, it would not have been a pretty sight," he said. "It was time for us to exert leadership over administrative authorities."

He pointed out that no members of the party had opposed the plan.

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16. The legal recognition of fault and a payment scheme to the living MD victims was settled on 29 October, 1995. The government officially recognized 2,265 victims - 1,435 already dead

17. Summary: The methylmercury was absorbed by eating fish and shellfish from contaminated water Levels of mercury in fish flesh in Minimata Bay in 1952 were 5 - 10 ppm (In Canada <0.5 ppm is the limit). The 1965 instance in Niigata, Japan was a similar case to Minimata Bay; 330 persons are known to have been affected, of which 13 died..

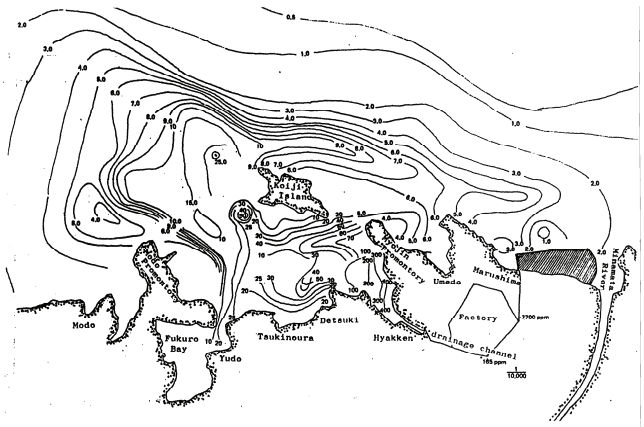

FIG. 3. Recent mercury content of sludge at the bottom of Minamata Bay. Figures = ppm Hg (dry weight) (Environmental Agency 1973).

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Minamata and the search for justice

Paradise in the Sea of Sorrow: Our Minamata Disease
by Michiko Ishimure, translated from Japanese by Livia Monnet
Yamaguchi Publishing House, pp 365, 5000 yen/$35

Michael Cross

A LONG time ago and a long way away, a factory dumped sludge containing organic mercury into the sea. The mercury found its way into fish. Some people who ate the fish died in nasty ways. Others gave birth to children with almost unimaginably awful deformities. The town where this happened, Minamata, became the name of a disease and a worldwide symbol of industrial pollution.

If this explanation is simplistic, it is because there is little point in saying more about Minamata now that the classic written account of the tragedy is available in English. *Paradise in the Sea of Sorrow* appeared in Japanese in 1969, the first part of a trilogy. It spans the first 15 years of the disease, from its appearance in the early 1950s to the Japanese government's official statement that mercury pollution was to blame.

Don't expect a systematic or even chronological history. *Paradise* is the work of a passionate activist, written at the height of the struggle to win recognition of the disaster from the Japanese establishment and even people in Minamata itself.

The key word in the title is "our"—these are the participants' voices. And as so often happens when "victims" have the chance to tell their own story, the lasting impression is of human dignity. These are people who were too proud to register for compensation, who were shy about meeting delegations from Tokyo and who were diffident about making a political issue over "our little pollution incident".

They faced the prospect of an agonising premature death with anger and humour, stoicism and frustration, wisdom and stupidity. In short, as human beings. Mercifully, Ishimure leaves to our imagination most of the physical horrors. The little

Eugene Smith's photographs showed the pain of Minimata disease

© Eugene Smith/Magnum

details she slips in become almost unbearable: a teenage boy weighs no more than a wood Bhudda; a fisherwoman ragin the routine indignities of bein a hospital bed.

The book's format, mixing subject ideally. The result, rendered into beautiful and economical English, lives up to the publisher's claim of "a new literary form".

Even the abrupt and anticlimatic conclusion tells a story. For, almost incredibly, the story is still not over. Nearly 35 years after the first lawsuit, arguments over responsibility and compensation for Minamata are still ploughing through the Japanese courts. The government is resisting calls for a "quick settlement" because of the principle involved. The official responsible for explaining this stance hanged himself the week before I read this book.

I do not know how easy it will be to find *Paradise in the Sea of Sorrow* outside Japan. Perhaps a canny distributor will see possibilities for three trendy niche markets, Japanism, environ-

Michael Cross is a science writer based in Japan.

Minamata sufferers win official 'regret,' redress

The government endorsed a final plan at a Cabinet meeting Friday that grants compensation to people who have not been officially designated as victims of Minamata disease but who suffer from the disease nonetheless.

Prime Minister Tomiichi Murayama released a statement expressing "regret," generally recognized as a step necessary to terminate the four-decade-long confrontation between the state and the victims.

Minamata disease has been prevalent since the 1950s and afflicts people who consumed fish and other marine life taken from Minamata Bay, Kumamoto Prefecture, after Chisso Corp. dumped mercury into the bay over several years.

The mercury attacks the nervous system, causing such problems as numbness of the extremities, sight defects, loss of hearing, ataxia and mental disablement, among other symptoms.

The plan calls for Chisso Corp. to pay compensation to the unofficial victims, who are ineligible to receive money under the existing compensation plan. It also includes loans from the national government and Kumamoto Prefectural Government to Chisso to help the financially stretched chemical company pay the redress.

Murayama is the first prime minister to admit government responsibility in the Minamata affair.

"Looking back at the history of Minamata disease, the government should honestly reflect on the fact that it took too long to determine the cause of the disease and take appropriate measures against the companies responsible for causing it, including the recurrence of Minamata disease in Niigata," Murayama said in the statement.

Murayama said he is saddened when he ponders the feelings of those who were forced to undergo years of unbearable suffering.

The National Alliance of Victims of Minamata Disease and Lawyers, the largest organization involved in the case, said it welcomes Murayama's statement, as it details the government's failure to prevent the spread of the disease. But the organization added that it will continue to work so that every victim is entitled to receive money.

With Murayama's statement and a package of measures to help Chisso pay billions of yen to thousands of victims, the disputes in Kumamoto and Niigata prefectures should now finally be settled, 39 years after the disease was officially recognized

CONTINUED ON PAGE 2

MINAMATA, Kumamoto Pref. — Kiyoto Sasaki (second from right), chairman of the Minamata Disease Patients Federation, and Teruo Kawamoto, a Minamata Municipal Assembly member and long-time activist for the patients, read on Friday a copy of the prime minister's comment on the disease.

grams or 1.7 Kilogram
the label specified.
London Free Press 3/Sep/82

Japanese doctors to check mercury at Indian reserves

OTTAWA (CP) — A group of Japanese doctors wants to return to the Northern Ontario reserves at Whitedog and Grassy Narrows to continue their study of the effects of mercury contamination on the Indian population.

A message was to be sent to Japan on Thursday formally inviting the Japanese contingent, headed by Dr. Kenichi Miyamoto of Osaka, said Bruce Crofts of Toronto, negotiator for the Whitedog reserve.

Miyamoto was one of the doctors who visited the two isolated reserves north of Kenora in 1975 and 1976 to study the frightening parallels between the mercury poisoning in the English-Wabigoon River system and at Minamata, a chemical company town in southern Japan.

In both cases, residents have dangerously high mercury levels from eating fish contaminated with mercury.

While there have been cases of hideous deformities and death in Japan, there haven't been any clinically proven cases of so-called Minamata disease at the two reserves.

Both reserves have been devastated financially and socially since the discovery of the mercury pollution in the early 1970s wiped out their commercial fishing industry.

Indians still eat the contaminated fish, despite warnings that they are risking their health.

Mercury levels found in the hair of some Whitedog residents tested this spring ranged from nine to 20 parts per million. Federal officials consider 30 parts per million high risk.

Crofts said he hopes the doctors can visit the reserves in October, when mercury levels will be at their peak after a summer of fishing.

Chiefs at both the reserves say they welcome the return visit, he said.

The reserves are still trying to negotiate compensation settlements with Reed Ltd. and Great Lakes Forest Products Ltd., the Dryden paper mill which contaminated the river during the 1960s.

In March, Whitedog agreed to about $2.3 million in compensation from the federal government. Grassy Narrows has yet to reach a federal settlement.

Summary of mercury toxicity and humans			
Exposure forms - Hg^0;Hg^{2+}; RHgX Non-occupational exposure to Hg – fish, shellfish; paints; fungicides; dental amalgams Hg^0 from broken thermometers, switches,	Breathing – Hg^0 - - eating fish - sea food chloralkali industry released 1000's tonnes $HgCl_2$ into water used for fishing Eating Canadian fresh water fish – still an issue	Breathing Hg from coal-power electric stations - Hg vapour– smoking cigarettes – major exposure route eating fish (all tissue – but high in muscle) – worst – sword fish - tuna -	Major difference between Hg^0, Hg^{2+}, and CH_3Hg^+ exposure Note – old sources: amalgam, paints, fungicides, thermostats, light switches, batteries. New sources: compact fluorescence lamps;
Occupational exposure	Major sources of occupational exposure to Hg – mining, refining precious metals (gold and silver ore using liquid Hg in Brazil),	And chloralkali plants in paper production, mercury contact switches; Hg in fungicides and paints	Mad hatters Gold miners
Biochemistry known?	Binds to sulfur in cysteine as well as a number of other proteins interrupting a large number of essential metabolic pathways	CH_3Hg^+ crosses the BBB Alkyl-Hg most toxic – liquid Hg^0 least toxic	Hg2+ methylated in sediments by anaerobic bacteria – via Vit B12
Health effects Organic and Hg vapour accumulate in the brain, heart and kidneys.	Many symptoms – medical – depend very much on type of Hg (0, 2+, or alkyl)	Worst: neurological – rapid coma and death	Cancer - death
Cure? Recovery? Yes, possible if not too much exposure	Cure? None really. Some success with Hg2+ if early with DMSA. Cannot reverse health effects – Response: Must remove Hg source. No success	FDA approved- 2,3-dimercaptosuccinic acid (DMSA, Succimer) – taken orally -	For serious systemic intoxication DMPS (dimercaptopropanesulphonic acid) is the treatment of choice. Also used –or N-acetyl-penicillamine (NAPA) - and

and if not alkylmercury.	with chelators for CH3Hg+ poisoning.		2,3-dimercaptopropanol (BAL, Dimercaprol) good but bad side effects
Major world-wide poisonings	Minamata, Japan Niigata, Japan Northern Ontario Mexico Iraq Gold miners in Brazil – on-going ..	Cause: Hg contaminated fish from Hg wastes in water; treated grain eaten; a cream.	
A note from a web site An essential web site to check out if you eat fish..	Many consumers are not aware, for example, that a 115 pound women consuming just two cans of albacore tuna in a week puts her 310% above what the EPA and FDA considers safe; a child weighing 45 pounds eating just one can of albacore tuna per week would get a dose 420% higher than the EPA/FDA's safe limit of .1 microgram/kilogram-day of mercury exposure. The same person consuming swordfish would have mercury level of more than three times that high. http://www.commondreams.org/news2004/0310-02.htm Source: **http://www.gotmercury.org/** **Eating seafood high in mercury is hazardous to your health, especially for women and children.** The "Got Mercury?" calculator below helps you make healthier seafood choices. Just enter your weight, the seafood type, the amount of seafood you will eat during a week, and click the calculator button. These calculations are based on EPA and FDA data (updated January 2006).		

[i] See Gov of Canada web site for possible health effects www.hc-sc.gc.ca/ewh-semt/contaminants/lead-plomb/asked_questions-questions_posees_e.html

[ii] In 2007: (a) Lead in toys: What to look for Last Updated Aug. 14, 2007 CBC News www.cbc.ca/news/background/consumertips/lead.html, and (b) Calif. sues 20 companies for exposing consumers to lead. Last Updated: Tuesday, November 20, 2007 | 10:17 AM ET CBC News www.cbc.ca/consumer/story/2007/11/20/california-lawsuit.html