Case Studies in Mercury and Cadmium Toxicity

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Johns Hopkins University
Section A

- Basic Overview of Metal Toxicity
Periodic Classification of the Elements

<table>
<thead>
<tr>
<th>Period</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
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<tr>
<td>2</td>
<td>3 Li</td>
<td>4 Be</td>
<td>5 B</td>
<td>6 C</td>
<td>7 N</td>
<td>8 O</td>
<td>35 Br</td>
<td>36 Kr</td>
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<tr>
<td>3</td>
<td>11 Na</td>
<td>12 Mg</td>
<td>13 Al</td>
<td>14 Si</td>
<td>15 P</td>
<td>33 As</td>
<td>34 Se</td>
<td>35 Br</td>
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<tr>
<td>4</td>
<td>19 K</td>
<td>20 Ca</td>
<td>21 Sc</td>
<td>22 Ti</td>
<td>23 V</td>
<td>24 Cr</td>
<td>25 Mn</td>
<td>26 Fe</td>
</tr>
<tr>
<td>5</td>
<td>37 Rb</td>
<td>38 Sr</td>
<td>39 Y</td>
<td>40 Zr</td>
<td>41 Nb</td>
<td>42 Mo</td>
<td>43 Tc</td>
<td>44 Ru</td>
</tr>
<tr>
<td>6</td>
<td>55 Cs</td>
<td>56 Ba</td>
<td>57 La</td>
<td>58 Ce</td>
<td>59 Pr</td>
<td>60 Nd</td>
<td>61 Pm</td>
<td>62 Sm</td>
</tr>
<tr>
<td>7</td>
<td>87 Fr</td>
<td>88 Ra</td>
<td>104 Rf</td>
<td>105 Db</td>
<td>106 Sg</td>
<td>107 Bh</td>
<td>108 Hs</td>
<td>109 Mt</td>
</tr>
<tr>
<td>8</td>
<td>119 Uun</td>
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<td></td>
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</tr>
</tbody>
</table>

* Lanthanides

** Actinides
Essential Vs. Non-essential Metal Ions in Biology

Quality of health

Dose of metal

essential metals
(copper, iron, manganese)

nonessential metals
(mercury, cadmium)
Chelation Methods of Therapy for Metal Toxicity

![Chemical structure diagram showing ligand attachment to a metal center with a carboxylic acid group.]
Endogenous Protection Against Metal Toxicity

- Metallothionein
  - High cysteine content (30%)
  - High metal content (8-12 atoms/molecule)
  - Low molecular weight
  - Inducible at level of gene expression metals (Cd, Hg, Cu, Zn)
Endogenous Protection Against Metal Toxicity

- Function
  - Metal detoxification
  - Metal homeostasis
Factors that Affect Metal Toxicity

- Level and duration of exposure
- Chemical form of metal
- Metal-protein complexes
- Host factors
  - Lifestyle
  - Gender
  - Age
  - Immune status
Section B

Mercury In the Environment
Mercury

- Chemical forms: 3 oxidation states: Hg$^0$, Hg$^{+1}$, Hg$^{+2}$
- Elemental/metallic: Hg$^0$
- Inorganic salts:
  - Divalent (Hg$^{+2}$) or mercuric; HgCl$_2$
  - Monovalent (Hg$^{+1}$) or mercurous
- Organic:
  - Alkyl Hg: dimethyl or methyl Hg

Continued
Mercury

Sources
- Degassing of earth’s crust
- Fossil fuels
- Industrial release
- Diet - typically 2 µg/day (seafood)
- Dental amalgams
Daily Mercury Exposure

- Dental amalgams: 15–120 µg/day (15 µg/filling)
- Diet:
  - General population (seafood): 2 µg/day
  - Minamata Bay incident (fish): 50 µg/day
  - Iraq incident (bread): 500 µg/day
Mercury: Biomarkers

- Hair
- Blood
- Others
Concentration of Mercury in the Food Chain

Industrial release → Inorganic Hg

bacteria

inorganic Hg → organic Hg

plankton

[Hg] tissue
Is the mercury problem in the food chain reversible?

If emissions were reduced:
   Timeline for reduction in organic mercury

       Lake - decades

       Watershed - centuries
Metallic Mercury
*Elemental, Hg*ₐ

- Absorption and accumulation
  - Exposure predominantly by inhalation
  - Lipid soluble
  - High fetal uptake
  - Crosses blood brain barrier
  - Concentrates in kidney
  - Slow G.I. Absorption
  - Half life = 35–90 days
Metallic Mercury
*Elemental, Hg₀*

- Targets of toxicity
  - Pulmonary effects
    - Corrosive bronchitis
    - Death
  - CNS effects
    - Changes in behavior
    - Loss of memory
    - Tremors
Inorganic Mercury

Mercuric or Mercurous Salts

- Absorption and accumulation
  - Exposure mostly through ingestion
  - G.I. absorption 10%
  - Concentrates in kidneys
  - Crosses fetal barrier
  - Half-life = 40 days

Continued
Inorganic Mercury

Mercuric or Mercurous Salts

- Targets of toxicity
  - Mercuric vs. mercurous (poorly soluble)
  - G.I damage
  - Renal effects
  - Generally not a CNS problem
Organic Mercury

Absorption and accumulation
- Exposure mostly by ingestion or inhalation (dimethyl Hg)
- Lipid soluble
- G.I. absorption 95%
- Concentrates in kidneys
- Crosses fetal barrier and is concentrated in fetal tissues

Continued 21
Organic Mercury

- High affinity for CNS
- Half-life = 70 days
- Targets of toxicity
  - Renal
  - PNS effects
  - CNS effects
Section C

Case Studies of Mercury Poisoning
Case Studies: *Minamata Bay, Japan*

Distribution of cases near Minamata, Japan

111 cases, including 41 deaths as of 8/1965
Factory Discharge

Four times a day, the factory would dump a large amount of mercuric chloride into the Minamata Bay.

Photo by JWOwens via Flickr.com. Creative Commons BY-NC.
Effect on Food Chain

- Damage to fishing industry as early as 1925
- Abnormal contents of methyl mercury was noted
- Factory to blame even though the discharged mercury was inorganic
- Bacterial biotransformation resulted in the creation of organic mercury, which are then accumulated in the food chain
Minamata Disease

- Minamata Disease was originally thought to be a contagious form of cerebral palsy
- Symptoms
  - Central and peripheral nervous system degeneration
  - Tingling & numbness of limbs
  - Impaired motor function
  - Impaired vision & speech
- Photos available at http://www.geocities.com/minoltaphotographyw/williameugenesthesmith.html
Mercury Content of Sludge at The Bottom of the Bay

Chronic Mercury Poisoning in Minamata Bay

1953: first neurological disturbance noted
1956: epidemic of “cerebral palsy” cats too
1958: possible involvement of mercury contamination
1965: 111 cases, including 41 deaths
1995: 2,200 cases admitted for care
Acetaldehyde Production Rate & Methylmercury in Umbilical Cords

Case Study: Iraq Acute Mercury Toxicity Incident

Fall 1971: Shipment of grain treated with alkyl fungicide to Iraq

Photo by Seema KK via flickr.com. Creative Commons BY-NC-SA.
Iraq Acute Mercury Toxicity Incident

- Fall 1971: first shipment of wheat and barley
- Winter 1971: 6200 cases, 500 deaths
- Source of exposure: homemade breads
Incidence of Hospital Admission per 1000 Rural Population According to Province

Case Studies in Mercury Toxicity: *Modern Day Concerns*

- Mercury in fish?
Consumption Guidelines

www.michigan.gov.mdch
New EPA/FDA advisory for consumption of fish

- **7/2002**: Re-evaluation of fish advisories for women and children: joint effort by EPA and FDA
- **12/2003**: report of findings
Solid white tuna has three times the Hg levels of light tuna
New EPA/FDA advisory for consumption of fish

- **7/2002**: Re-evaluation of fish advisories for women and children: joint effort by EPA and FDA
- **12/2003**: Report of findings
- **3/2004**: New advisory for women and children
1) Do not eat Shark, Swordfish, King Mackerel, or Tilefish

2) Eat no more than 12 ounces (two average meals) a week of fish and shellfish that are low in mercury (exception white tuna, only 6 ozs)

3) Check local advisories about the safety of fish.
Mercury in Maryland?

- Mercury level in rain - Maryland highest among mid-southern Atlantic
Maryland Fish Consumption Guidelines

- Recommended maximum meals each year for Maryland water

http://www.mde.state.md.us/CitizensInfoCenter/FishandShellfish/home/index.asp
Maryland Guidelines For Women and Children Who Eat Fish

Do Not Eat More Than the Meals Per Month From Each Category Below

For Advice About Maryland Areas and Species Not Listed Below, Contact MDE

**CATEGORY 1**
- Fish Caught by Friends and Family from All Freshwater Areas in Maryland
- Fish from Stores & Restaurants (U.S. FDA)

<table>
<thead>
<tr>
<th>MEALS PER MONTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATEGORY 1</td>
</tr>
<tr>
<td>Freshwater panfish (Crappie, Sunfish, White and Yellow Perch)</td>
</tr>
<tr>
<td>Freshwater gamefish (Bass and Walleye)</td>
</tr>
</tbody>
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<tr>
<th>CATEGORY 1</th>
<th>MEALS PER MONTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish Caught by Friends and Family from All Freshwater Areas in Maryland AND Fish from Stores &amp; Restaurants (U.S. FDA)</td>
<td></td>
</tr>
<tr>
<td>Freshwater panfish (Crappie, Sunfish, White and Yellow Perch)</td>
<td>8 OR</td>
</tr>
<tr>
<td>Freshwater gamefish (Bass and Walleye)</td>
<td>4 OR</td>
</tr>
<tr>
<td>Canned LIGHT Tuna and certain store-bought fish (see back for list)</td>
<td>8 OR</td>
</tr>
<tr>
<td>Canned ALBACORE (white) Tuna</td>
<td>4</td>
</tr>
<tr>
<td>Shark, Swordfish, King Mackerel, Tilefish</td>
<td>AVOID</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CATEGORY 2</th>
<th>MEALS PER MONTH</th>
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<tbody>
<tr>
<td>Fish Caught by Friends and Family from Tidal Areas in Maryland</td>
<td></td>
</tr>
<tr>
<td>All Eastern Shore rivers south of Kent Island</td>
<td></td>
</tr>
<tr>
<td>White Perch</td>
<td>8 OR</td>
</tr>
<tr>
<td>Catfish</td>
<td>4 OR</td>
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<tr>
<td>All Western Shore rivers</td>
<td></td>
</tr>
<tr>
<td>White Perch</td>
<td>1 OR</td>
</tr>
<tr>
<td>All Western Shore rivers south of Baltimore Harbor</td>
<td></td>
</tr>
<tr>
<td>Catfish under 18&quot;</td>
<td>1 OR</td>
</tr>
<tr>
<td>Chesapeake Bay and tributaries</td>
<td></td>
</tr>
<tr>
<td>Striped Bass &lt;28&quot; May 16 - Dec.</td>
<td>1 OR</td>
</tr>
<tr>
<td>Patapsco River and Baltimore Harbor</td>
<td></td>
</tr>
<tr>
<td>Crabmeat without the mustard</td>
<td>8 OR 2 for children</td>
</tr>
<tr>
<td>Mustard from Crabs</td>
<td>AVOID</td>
</tr>
<tr>
<td>White Perch, Carp, Catfish, Eel</td>
<td>AVOID</td>
</tr>
</tbody>
</table>

http://www.mde.state.md.us/CitizensInfoCenter/FishandShellfish/home/index.asp
Now at your local grocer
Is the mercury problem in the food chain reversible?

*Proc Natl Acad Sci U S A.* 2007 Sep 27; [Epub ahead of print]

**Whole-ecosystem study shows rapid fish-mercury response to changes in mercury deposition.**


University of Wisconsin, 660 North Park Street, Madison, WI
Freshwater Institute, Fisheries and Oceans Canada, 501 University Crescent, Winnipeg, MB, Canada
Experimental Lakes Area (ELA)  
Northwestern Ontario

- 58 small lakes & watersheds
- Whole lake manipulation studies
- “Lake 658” - site of 3 year mercury study

Photo by Mark Elliott via flickr.com. Creative Commons BY-NC
Lake 658 - Low ambient Hg

- Different isotopes of inorganic mercury added to watershed and lake over 3 years. Levels added approximate contamination of polluted areas.

- Monitored total Hg and organic Hg isotopes.

- RESULTS: watershed Hg remained in local vegetation, did not enter runoff, was not converted to organic Hg.

- Lake Hg: rapidly entered food chain.
Effects of mercury added to lake 658

Inorganic Hg isotope

bacteria

inorganic Hg → organic Hg

3 DAYS

plankton

1 month

2 months

[Hg] tissue

2 months
Is the mercury problem in the food chain reversible?

Timeline for reduction in organic mercury if emissions were reduced:

Lake – decades

Watershed - centuries
Case Study: laboratory accident

Dimethyl mercury
Laboratory Accidents

- Chemist Karen E. Wetterhahn was accidentally poisoned in her own lab.
- A drop of mercury spilled on her glove.
- She immediately cleaned up the spill, but she began experiencing symptoms 3 months later.
- Finally, she was diagnosed with mercury poisoning and treated with chelation and transfusion.
- Treatment was unsuccessful, and Dr. Wetterhahn eventually died from the incident.
Section D

Cadmium in the Environment and Cadmium Toxicity
Cadmium

- Chemical form: +2 state
- Sources
  - Mining
  - Food and water
    - Average intake 10–40 ug/day
  - Fertilizers
  - Tobacco—body burden doubled in smokers
Absorbed by respiratory—30%
By G.I. tract—8% (higher with poor diet)
Accumulates in cells and tissues—50%
body burden in liver and kidney
Continues to concentrate in kidney until age 50–60
Half-life = 20–30 yrs in kidney, 6–10 years in liver
Only a fraction of absorbed Cd is excreted
Cadmium

Targets of Toxicity

- Lung—smokers
- Kidney—role of metallothionein
Role of Metallothionein

In Renal Cd Accumulation

G.I. Tract

Cd → Cd

Cd-MT synthesis and accumulation

Kidney

Cd-MT synthesis

Liver
Role of Metallothionein

*In Renal Cd Toxicity*
Cadmium

Targets of Toxicity

- Lung—smokers
- Kidney—role of metallothionein
- Bone—secondary to kidney effects
  - Increased urinary loss of calcium
  - Cd effects on vitamin D
Cadmium

Biomarkers

- Urine Cd
- Urine glucose
- Proteinuria—β2–microglobulin
- Urine Cd–metallothionein
Section E

Case Study of Cadmium Poisoning
Itai-Itai Disease in Toyama Prefecture

Tsuchiya, 1978
Nriagu, 1981
Case Study
Itai-Itai Disease

- Itai-Itai disease (Japan)
  - The Kamioka zinc mine

- Cd contamination of water and rice along Jinzu river basin
  - Average daily intake = 500 – 800 µg

- Effects on female inhabitants of Jinzu river basin
Effects of Itai Itai Disease

- Bone
  - Soft and fragile
  - Excessive production of osteon

- Kidney
  - Very thin renal cortex
## Itai-Itai Disease

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
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<td>45–49</td>
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<tr>
<td>50–54</td>
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<td>55–59</td>
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<td>60–64</td>
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<td>65–69</td>
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<td>70–74</td>
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<td>80–84</td>
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<td>85–89</td>
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</tr>
<tr>
<td>Total</td>
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<td>115</td>
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Source: Nakagawa, 1990. Arch Env Health