Use & Misuse of Metal Chelation Therapy
February 29, 2012, 7:45am-5:00pm EST

Conference & Live Webinar
Roybal Campus, Global Communications Center, B19,
Auditorium A
Centers for Disease Control and Prevention, Atlanta, GA

The American College of Medical Toxicology
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Registry (ATSDR).

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The Role of Chelation During Pregnancy in the Lead Poisoned Patient
Mary Jean Brown, ScD, RN
Chief Healthy Homes/Lead Poisoning Prevention Branch
Centers for Disease Control and Prevention, Atlanta, GA

“The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry and should not be construed to represent any agency determination or policy.”

In the United States, blood lead levels at which chelation therapy would be considered is an extremely rare event.

The geometric mean blood lead level of US women 15-49 years old is less than 0.5 µg/dL.

Approximately 1% of US women of childbearing age have blood lead levels ≥ 5 µg/dL, and lead exposure is important for specific subpopulations including new immigrants and women with occupational exposure to lead.
Severe maternal lead intoxication, such as encephalopathy, will warrant chelation regardless of the stage of pregnancy.

Pregnant women with confirmed BLLs ≥45 µg/dL (repeated on at least two venous blood samples collected within 24 hours) may be considered for chelation therapy and should be managed in conjunction with experts in high-risk pregnancy and lead poisoning.

Immediate removal from the lead source is THE FIRST PRIORITY and, in some cases, may require hospitalization.

When chelation is being considered, it should be performed in an inpatient setting only with close monitoring of the patient and in consultation with a physician with expertise in the field of lead chelation therapy.

Data regarding the reproductive risk associated with chelation during pregnancy are sparse. Most case reports of infant outcomes report on the use of chelating agents after the first trimester.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Synonyms</th>
<th>Chemical Name</th>
<th>Number of Receptors/ Studies in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Disport</td>
<td>Calcium disodium versenate, versenate, substituted disodium calcium citrate (CaDisp)</td>
<td>Calcium-dimercapto succinic acid tetrasodium</td>
<td>6</td>
</tr>
<tr>
<td>Secluder®</td>
<td>Dravens® 3.0, 3.0 diethylenetriamine pentaacetic acid (DTPA)</td>
<td>N.N. 2,2-dimercaptobis (ethane-1,2-diamine)</td>
<td>1</td>
</tr>
<tr>
<td>WIN®</td>
<td>Diamimid dibenzilidithiocarbamate (DMDT)</td>
<td>2,3-dimercaptopropanol (DMP)</td>
<td>1</td>
</tr>
<tr>
<td>Ethylenediamine</td>
<td>Pen, Versenate, PLX, coprexisse (NP)</td>
<td>N-mercaptoethane-1,1-diols</td>
<td>0</td>
</tr>
</tbody>
</table>

*from U.S. Food and Drug Administration (2001)
The Weight of the Evidence: The Role of Chelation in the Treatment of Arsenic and Mercury Poisoning

Michael J. Kosnett, MD, MPH
Associate Clinical Professor
Division of Clinical Pharmacology & Toxicology
University of Colorado School of Medicine, and
Department of Environmental and Occupational Health
Colorado School of Public Health
Michael.Kosnett@ucdenver.edu

World War I, Poison Gas, and the “Dew of Death”

Dichloro (2-chlorovinyl) arsine

“Lewisite”

Father J.A. Nieuwland  Capt. Winford Lee Lewis

London, WWII
Lewisite
Skin LD50 24 mg/kg (rat)

\[ \text{Cl} \ - \ C \ = \ C \ - \text{As} \]

\[ \text{Cl} \]

\[ \text{C} - \text{SH} + \text{As} - R \rightarrow \text{C} - \text{S} - \text{As} - R \]

\[ \text{C} - \text{SH} \]

2, 3 - Dimercaptopropanol

Dimercaprol “British Anti-Lewisite”

\[ \text{BAL} \]

% Decline in \( O_2 \) uptake (skin + pyruvate) after Lewisite (0.03 mM), 1 hr

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>50 %</td>
</tr>
<tr>
<td>2-Mercaptoethanol (0.54 mmol)</td>
<td>55</td>
</tr>
<tr>
<td>BAL (0.27 mmol)</td>
<td>6</td>
</tr>
</tbody>
</table>

Survival (rats) after topical lewisite (≈ 35 mg/kg) (Treatment begun at 30 min post exposure)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>0/27</td>
</tr>
<tr>
<td>2-Mercaptoethanol</td>
<td>0/6</td>
</tr>
<tr>
<td>BAL (50 - 70 mg/kg inunction)</td>
<td>21/21</td>
</tr>
</tbody>
</table>

[Stocken & Thompson, Biochem J 40:535-548; 1946]
Human Arsenic Intoxications Treated with BAL: Comparison to Untreated Historical Controls

1. In syphilis patients with arsenical dermatitis, BAL appeared to reduce the average duration of dermatitis (21.5 days vs 62.5 days) [Carleton et al, Quart J Med 17:49-85; 1948]

Prior to 6d BAL rx 14 d after start of BAL rx

2. In children admitted to Charity Hospital for arsenic poisoning [Woody & Komentani, Pediatr 1:372-378; 1948]

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Deaths</th>
<th>LOS(d)</th>
<th>% Symptomatic @Admit</th>
<th>% Symptomatic @12h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without BAL</td>
<td>111</td>
<td>3</td>
<td>4.2</td>
<td>46.2%</td>
<td>29.3%</td>
</tr>
<tr>
<td>With BAL</td>
<td>42</td>
<td>0</td>
<td>1.6</td>
<td>47.6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

BAL has high incidence of side effects

At high therapeutic doses (4 - 5mg/kg i.m. in peanut oil) as many as 2 / 3 of patients experience side effects which commonly include:

- Nausea and Vomiting
- Restlessness
- Hypertension
- Lacrimation and Salivation
- Fever
- Pain at injection site
2,3 dimercaptopropane sulfonic acid, Na salt
DMPS, unithiol
LD50 i.p. (m) 1371 mg/kg

2,3 dimercaptosuccinic acid, Na salt
DMSA, succimer
LD50 i.p. (m) 2500 mg/kg

DMPS is more potent than DMSA as an arsenic antidote

Reversal of arsenite inhibition of renal PDH enzyme activity in vivo

Aposhian et al. Fund Appl Toxicol 4:S58-S70; 1984
Efficacy of chelation is enhanced by prompt administration following metal exposure

Delayed chelation is diminished chelation

Time - Dependent Efficacy of Chelation in Experimental Arsenic Poisoning

1. In Lewisite poisoned rabbits (Eagle et al., 1946):
   One injection BAL 5 min post exposure: 100% survival
   Multiple injections begun 6h post exp. 0% *

2. In arsenite poisoned mice (0.14 mmol/kg sc)
   (Tadlock & Aposhian, 1980):
   0.25 mmol/kg DMSA
   at 60 min 79% survival
   at 120 min 55% survival

Randomized Placebo-Controlled Trial of 2,3-Dimercapto-1-propanesulfonate (DMPS) in Therapy of Chronic Arsenicosis Due to Drinking Arsenic-Contaminated Water (Guha Mazumder et al., Clin Toxicol 39:665-674, 2001)

• 21 adults with chronic arsenic exposure (avg = 20 y) and hyperpigmentation/hyperkeratosis
• Removed from As exposure < 3 mo; avg Urine As = 46 µg/L
• Single-blind randomization to 4 one-week courses of DMPS 100 mg qid (n=10) or placebo (n=10) over a 7 week period (in-hospital)

Primary outcome variable: Change in "clinical score" of multiple signs and symptoms assessed pre- and post-treatment
Skin biopsy pre- and post-treatment also assessed by blinded pathologist
<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline clinical score</th>
<th>Final clinical score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPS</td>
<td>8.90 ± 2.84</td>
<td>3.27 ± 1.73</td>
<td>0.0002</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.50 ± 1.96</td>
<td>5.40 ± 2.12</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Authors' conclusion: DMPS “caused significant improvement in the clinical score of patients suffering from chronic arsenic toxicity”

Many limitations render findings inconclusive, including:

- More than half of clinical improvement resulted from non-blinded assessment of subjective parameters, including “lung disease” (cough, dyspnea, and rales/ronchi), and “weakness”
- Groups differed by gender: DMPS (9M, 2F); Placebo (5M, 5F)
- Subjects received nonrandomized “symptomatic treatment” (e.g. bronchodilators)
- Nonblinded clinical observer reported improvement in skin findings not confirmed by blinded skin biopsy assessment

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**DRUG AND CHEMICAL TOXICOLOGY, 22(1), 129-142 (1999)**

**EMERGENCY RESPONSE/CASE EXAMPLES SESSION**

**MERCURY**

*Top of the Hit Parade for Eight Years*

Richard A. Nickle
Environmental Health Scientist
Agency for Toxic Substances and Disease Registry

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Acute Human Poisoning by Mercuric Chloride: Decreased Mortality with BAL Compared to Historical Controls

Langlois WJ, Luetzsch JA.
Ann Intern Med

- Patients treated by HgCl2 after methylation of mercury salt treated within 4 hours
- By old conventional methods
- Intramuscular injections of BAL
Chelators - Acute Hg intoxication

HgCl₂ 109 mg/kg p.o. to rats. Single dose chelator given 15 minutes later.

<table>
<thead>
<tr>
<th>Chelator</th>
<th>dose</th>
<th>Mortality*</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>9 / 10</td>
<td>90 %</td>
</tr>
<tr>
<td>BAL (i.p.)</td>
<td>400 µM (50 mg/kg)</td>
<td>5 / 10</td>
<td>50 %</td>
</tr>
<tr>
<td>DMSA (p.o.)</td>
<td>1600 µM (291 mg/kg)</td>
<td>4 / 10</td>
<td>40 %</td>
</tr>
<tr>
<td>DMPS (p.o.)</td>
<td>1600 µM (336 mg/kg)</td>
<td>0 / 10</td>
<td>0 %</td>
</tr>
</tbody>
</table>

*by day 14


Immediate DMPS prevents oliguric renal failure from i.v. HgCl₂ in rats

HgCl₂ 1.4 mg/kg (5 µmol). DMPS 54 mg/kg (250 µmol) i.v.

<table>
<thead>
<tr>
<th>Urine Volume (ml)</th>
<th>No DMPS</th>
<th>Immediate DMPS</th>
<th>DMPS after 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>14.5</td>
<td>10.0</td>
<td>14.5</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.7</td>
<td>6.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Day 3</td>
<td>4.0</td>
<td>15.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Histopathology</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
</tr>
</tbody>
</table>


DMPS exceeds DMSA in reduction of renal Hg content after i.v. HgCl₂

[Planas-Bohne, Toxicology 19:275-278; 1981]

HgCl₂ (0.67 mg/kg) i.v. to rats. After 24 h, chelators begun at 100 µmol/kg i.p. 4x/wk x 4 wk

Kidney Hg content (% of administered dose)

<table>
<thead>
<tr>
<th>(n = 6 per group)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11.57 ± 0.04</td>
</tr>
<tr>
<td>DMSA</td>
<td>5.73 ± 1.02</td>
</tr>
<tr>
<td>DMPS</td>
<td>0.71 ± 0.71</td>
</tr>
</tbody>
</table>
Antidotal benefit from DMPS is lost if treatment is delayed

HgCl₂ 1 mg/kg i.v. to rats. DMPS (150 µmol/kg) (32 mg/kg) p.o. given qd x 5 beginning 6 or 24 hours later:

<table>
<thead>
<tr>
<th>Group</th>
<th>Mortality*</th>
<th>Percent</th>
<th>Survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8 / 18</td>
<td>44 %</td>
<td>19 days</td>
</tr>
<tr>
<td>DMPS @ 6h</td>
<td>1 / 18</td>
<td>6 %</td>
<td>29</td>
</tr>
<tr>
<td>DMPS @ 24h</td>
<td>6 / 18</td>
<td>33 %</td>
<td>22</td>
</tr>
</tbody>
</table>

* by 30 d


Reported Adverse Effects: DMPS, DMSA

- Allergic reactions, exanthems (1-10%)
- Mild gastrointestinal complaints (e.g. nausea) (1-10%)
- Isolated, reversible, slight increase in LFT's, decrease in wbc
- Increase in urinary Cu, Zn w/o Δ serum levels

Mobilization does not always equal excretion

*Net redistribution of metal deposits, even when accompanied by increased excretion, may have undesirable consequences.*
Dimercaprol (BAL) redistributes arsenic to the brain

Aposhian et al, ibid 1984

Dimercaprol (BAL) redistributes Hg^{2+} to the brain

Berlin M, Rylander R. J Pharm Exp Ther
146:236-240; 1964

DMPS increases urine mercury excretion in acute Hg vapor intoxication [Cichini GM et al. Intensivmed Notf Med 26:303-306; 1989]

• 19 caisson workers drilling a subway tunnel developed acute symptomatic Hg° vapor intoxication after a mean of 27h (range = 8 - 40h) exposure.
• Subjects randomized to DMPS (100 mg or 200 mg tid) or D-Pen 150 mg tid
Following subacute exposure to Hg vapor, DMPS and DMSA reduce Hg concentration in kidneys but not the brain

Rats (n = 8 per group) underwent 14 days inhalation to Hgº (244 µg/m³)
Seven days later, treated for 5 days with 1 mmol/kg/day po DMSA or DMPS, then sacrificed 24 hours later.

<table>
<thead>
<tr>
<th>Group</th>
<th>Hg concentration (µg/100g body wt)</th>
<th>Kidney</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgº only</td>
<td>2.78 ± 0.60</td>
<td>0.088 ± 0.017</td>
<td></td>
</tr>
<tr>
<td>DMSA</td>
<td>0.46 ± 0.20</td>
<td>0.076 ± 0.008</td>
<td></td>
</tr>
<tr>
<td>DMPS</td>
<td>0.10 ± 0.02</td>
<td>0.098 ± 0.030</td>
<td></td>
</tr>
<tr>
<td>Control (n=4)</td>
<td>0.17 ± 0.15</td>
<td>0.0022 ± 0.0005</td>
<td></td>
</tr>
</tbody>
</table>

Buchet JP, Lauwerys RR. Toxicology 54:323-333; 1989

Summary

1. Chelation with DMSA, DMPS, or BAL has therapeutic benefit in acute intoxication by inorganic arsenic or inorganic mercury salts if administered promptly (within minutes to hours)
2. DMPS and DMSA have a higher therapeutic index than BAL, and unlike BAL do not redistribute As or Hg to the brain
3. Although chelation for chronic intoxication by As or Hg may accelerate metal excretion and diminish concentration in some organs, therapeutic efficacy in terms of decreased morbidity and mortality is largely unestablished.
The Role of Chelation in the Treatment of Other Metal Poisonings

Silas W. Smith, MD
NYU School of Medicine
Bellevue Hospital Center
NYU Langone Medical Center
New York City Poison Control Center

Declarations and Disclaimers

Salaried, academic physician.

Nearly everything I will talk about is off-label, if one exists.

Trade, product, and commercial names are for identification purposes only and do not constitute endorsement.

My views do not necessarily reflect the those of my employers, affiliations, conference participants, or conference supporters.
Chelation of Other Metals
*(Reductio ad absurdum)*

Administer Chelation

Purge Metal
(Entirely beneficial effects)
Bycatch

• “Bycatch occurs if a fishing method is not perfectly selective.... A fishing method is perfectly selective if it results in the catch and retention only of the desired size, sex, quality, and quantity of target species without other fishing-related mortality. Very few fishing methods meet this criterion.”
National Oceanic and Atmospheric Administration

Chelation “Bycatch”

• Bycatch occurs if a chelation method is not perfectly selective.... A chelation method is perfectly selective if it results in the chelation and elimination only of the desired form (speciation), quality, and quantity of target metal without other chelation-related mobility or mortality. Very few [if any] chelation methods meet this criterion.

Dose-response

- Deficiency
- Homeostasis
- Toxicity

Adverse Effect

Dose
Aluminum (Al)
Exposures

• Food, water, and antiperspirant
• Bladder hemorrhage
• TPN
  – Adult
  – Pediatric
• Renal failure
  – Phosphorous “chelators”
  – Dialysis
• Drug abuse

Aluminum (Al)
Toxicity

• Central nervous system (“dialysis dementia”)
• Metabolic bone disease
• Anemia
• Cardiomyopathy
Aluminum Chelation Considerations

• Metals
  – Aluminum (Al)
  – Iron (Fe)
• Binding proteins
  – Transferrin (unbound)
  – Transferrin-aluminum
  – Transferrin-iron
• Chelator (unbound)
  – Deferoxamine (DFO)
• Chelates
  – Aluminoxamine (AlO)
  – Ferroxamine (FO)

Aluminum Chelation Considerations

• Acute vs. chronic exposure
• DFO adverse effects
  – Precipitated aluminum encephalopathy and death
  • Redistribution of DFO-mobilized aluminum into brain
  • Ability of AlO complex to cross blood/brain barrier
  – Hypocalcemia
  – Hyperparathyroidism
  – Systemic hypersensitivity reactions
  – Infection

Lillevang ST, 1989.
Novars, 2011.
Aluminum Chelation Considerations

- Timing
- Dose
- Dialysis
- Bycatch

Alternative Potential Chelators

- Deferiprone
  - L1, 1,2-dimethyl-3-hydroxypyrid-4-one

- Deferasirox
  - 4-[3,5-Bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]-benzoic acid

Alternative Chelator Issues

- Deferiprone\(^1,2\)
  - Stoichiometry, 3:1
  - Agranulocytosis
  - Copper, zinc bycatch

- Deferasirox\(^2,3\)
  - Stoichiometry, 2:1
  - Renal impairment (failure)
  - Hepatic impairment (failure)
  - Gastrointestinal hemorrhage
  - Copper, zinc bycatch

Al Chelation Summary

- Chelator = deferrioxamine (DFO)
- Labeled indication (DFO)
  - Acute iron intoxication
  - Chronic iron overload
- Evidence of “technical” and “clinical” efficacy
- Potential for worsening Al toxicity
- Consider chelate (AlO) elimination

Chromium (Cr) Exposures

- Essential nutrient
- Environment
  - Water
  - Food
  - Supplements
  - CCA
- Industrial
- Biomedical
  - Prostheses
  - Stents

Chromium

http://upload.wikimedia.org/wikipedia/commons/0/08/Chromium_crystals_and_1cm3_cube.jpg (Creative Commons)

Chromium (Cr)


http://www.ecy.wa.gov/programs/tcp/sites_brochure/dirt_alert/other_info/arsenic_treated_wood.html

http://www.arb.ca.gov/training/images/290.7.jpg
Chromium (Cr)

Kinetics

- Trivalent (Cr\(^{3+}\))
  - Limited oral absorption of Cr\(^{3+}\) salts (0.4-2.5%)
  - 98% fecal elimination post oral exposure
  - Rapid urinary elimination
  - Poor dermal absorption of Cr\(^{3+}\) salts (absent disruption)
  - Cellular diffusion
- Hexavalent (Cr\(^{6+}\))
  - Endogenous gastrointestinal tract reducing agents
  - Greater absorption than Cr\(^{3+}\)
  - Facilitated cellular uptake
- Concentration in liver, kidney, spleen, soft tissues, bone
- Increased urinary excretion in stress, exercise, glucose loads, and in higher insulin resistance
- Pulmonary kinetics (soluble vs. insoluble compounds)

Chromium (Cr)

Toxicity

- Hexavalent (Cr\(^{6+}\)) vs. trivalent (Cr\(^{3+}\))
- Respiratory irritation and compromise
- "Blackjack" dermatitis, "chrome holes" and type IV (delayed-type) hypersensitivity reactions
- Gastrointestinal irritation/ulceration
- Anemia/hemolysis
- Oligospermia
- Cr\(^{6+}\): IARC Group I carcinogen\(^1,2\)

Chromium Chelation Considerations

Human Experience

- Cr(VI) → Cr(V) → Cr(IV) → Cr(III)
- BAL: unclear effects.\(^3\) No effect\(^4\)
- EDTA: uninterpretable increased urinary elimination over 48 hours\(^5\)
- EDTA: relatively ineffective short term lowering\(^6\)
- EDTA: no increased urinary elimination, 4x HD removal\(^7\)
- DMPS: "challenge" → unchanged chromium excretion\(^6\)
- NAC plus DMPS: "adjuvant therapy"\(^7\)
- NAC: without apparent renal toxicity\(^8\)
Chromium Chelation Considerations
Human Experience (Adjuvant Therapies)

- Exchange transfusion
  - Double: $Cr_{plasma} \rightarrow 4.163 \rightarrow 1.043 \mu g/L; Cr_{RBC} \rightarrow 7.795 \rightarrow 1.474 \mu g/L$  
  - $\sim$ Double: $Cr_{plasma} \rightarrow 5.9 \rightarrow 1.9 \mu g/L; Cr_{RBC} \rightarrow 0.43 \rightarrow 0.15 \mu g/L$
- Hemodialysis
  - $Cr_{plasma} \rightarrow 1.249 \rightarrow 974 \mu g/L; Cr_{RBC} \rightarrow 990 \rightarrow 917 \mu g/L$
  - $Cl_{dialysis} = 12.4 \pm 2.4 \text{ mL/min (62 mg/8 hours)}$
  - $Cl_{dialysis} = 2.5 \pm 0.8 \text{ mL/min}$
  - $3.3 \text{ mg/9 hours (vs. 3.74 mg/9 hours endogenous)}$

- Ascorbic acid (AA) therapy$^1,4,6-9$

Chromium Chelation Considerations
Animal Experience

- AA: time-dependent mortality and renal effects$^1$
- ALA: no change in urinary clearance$^2$
- BAL
  - Decreased urinary and stool clearance$^2$
  - No increase in dialysis or urinary clearance$^3$
- DFO: effective pre-exposure; ineffective post-exposure$^4$
- D-PCA: decreased urinary clearance$^3$
- EDTA: no increase in urinary clearance$^2$
- NAC: $>3 \times$ increased urinary clearance ($\sim$ volume)$^5$

Cr Chelation Summary

- Species effects
- Address chromium source
- There is little evidence to suggest currently available chelators are efficacious
- NAC
  - Anecdotal human use
  - Limited supportive animal study
  - Familiar risk-benefit profile
- Ascorbic acid
  - Anecdotal human use
  - Potential time-dependent risk-benefit profile
Cobalt (Co)
Exposures

- Essential nutrient
- Environment
- Industry
- Biomedical therapy and research
- Prostheses
- Antidote

Cobalt (Co)
Kinetics

- Variable GI absorption (∼ iron, ∼ age)
- Dermal absorption (∼ integrity)
- Hepatic concentration
- RBC uptake
- Oral exposure → fecal elimination (∼ variable GI absorption)
- Parenteral exposure → urinary elimination
- Pulmonary exposure → prolonged retention (insoluble Co)
Cobalt (Co) Toxicity

- “Hard metal” or “diamond polisher’s” pulmonary disease
- “Beer drinkers” cardiomyopathy
- Thyroid disease
- Hepatotoxicity
- Neuropathy
- Dermatitis/hypersensitivity
- Polycythemia

Regulatory Guidance

- **U.S. Food and Drug Administration**
  - “...there is no evidence to support the need for checking metal ion levels in the blood or special imaging if patients with MoM hip implants have none of the signs or symptoms described above and the orthopaedic surgeon feels the hip is functioning properly.”
  - “There are currently insufficient data to identify any specific metal ion levels that would cause adverse systemic effects. As a result, it is not possible to cite a metal ion threshold value in the blood that would serve to confirm the etiology of the symptoms.”
  - “If metal ion (e.g. cobalt and chromium) levels are assessed, interpret the values in the context of the overall specific clinical scenario including symptoms, physical findings, and other diagnostic results when considering further actions. If clinical and imaging evaluations lead to the suspicion of an adverse reaction to metal debris (e.g., soft tissue mass), consider assessing and monitoring serial metal ion levels.”

- **U.K. Medicines and Healthcare Products Regulatory Agency**
  - “…investigate patients with painful MoM hip replacements. Specific tests should include evaluation of cobalt and chromium ion levels in the patient’s blood and cross sectional imaging including MRI or ultrasound scan.”
  - “…if either cobalt or chromium ion levels are elevated above seven parts per billion (ppb), then a second test should be performed three months after the first in order to identify patients who require closer surveillance, which may include cross sectional imaging.”

Cobalt Chelation Considerations

Human Experience

- **CaNa₂EDTA**
  - Short-term Co lowering (prosthesis)\(^1\)
  - Four-fold increase in urinary Co excretion (ingestion)\(^2\)
  - Small non-significant increase in urinary Co (infusion)\(^3\)

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Cobalt Chelation Considerations
Animal Studies

N-acetylcysteine (NAC)  D-penicillamine (PCA)

Trientine

Diethylenetriaminepentaacetic acid (DTPA)  meso-2,3-dimercaptosuccinic acid (DMSA, succimer)

Cobalt Chelation Considerations
Animal Studies

Mortality

Control  L-Cys  NAC  L-Met

Mortality

CoCl₂ PO  CoCl₂ IP  CoCl₂ Chelated pre-administration, PO  CoCl₂ Chelated pre-administration, IP
Cobalt Chelation Considerations
Animal Studies

Survival

Cobalt Chloride (mmol/kg IP)

EDTA

DTPA

NAC

L-Cys

DMPSA

r-PCA

Redrawn from data in Llobet JM, 1986.

Survival

Cobalt Chloride (mmol/kg IP)

Elimination

Control

GSH

L-Cys

Redrawn from data in Levitskaia TG, 2010.

Elimination

Control

D-PCA

Trientine

Redrawn from data in Levitskaia TG, 2010.
Co Chelation Considerations

Animal Studies

Co Chelation Summary

- Evaluate appropriate organ systems for toxicity
- Address cobalt source
- There is little human evidence at all with which to provide a specific chelation recommendation
  - For $^{60}$Co (per REAC/TS and NCRP)$^{1,2}$
    - DTPA preferred
    - DMSA, EDTA, NAC suggested
  - For others
    - NAC & EDTA considered

---

1. IAEA Co Chelation Course Training
Uranium (U) Exposure

- Environment
  - Background
  - Remediation
- Industry
  - Mining/Milling
  - Refining
  - Nuclear fuel processing
- Military conflict
  - Weapons assembly
  - Combat
  - Firefighting
- Terrorism

---

Uranium (U) Kinetics

- Ingestion
  - Poor absorption (0.1%-6%)
- Inhalation
  - Pulmonary retention ($t_{1/2}$ = weeks-years)
  - Limited absorption ($\leq$ 5%)
- Absorption
- Shrapnel (DU)
- Accumulation
  - Skeletal, renal, hepatic
- Elimination
  - $>50\%$ urinary elimination within 24 hours (parenteral exposure)
  - $>50\%$ fecal elimination (oral exposure)

---

Uranium (U) Toxicity

- Radiological considerations:
  - $^{238}\text{U} \rightarrow ^{234}\text{Th} \rightarrow ^{234}\text{Pa} \rightarrow ^{234}\text{U} \rightarrow ^{230}\text{Th} \rightarrow ^{226}\text{Ra} \rightarrow ^{222}\text{Rn} \rightarrow$
  - No IARC classification
- While $^{239}\text{U}$, $^{235}\text{U}$, $^{234}\text{U}$ are “radioactive,” their half-lives of are on the order of billions, millions, and thousands of years (respectively), making them primarily chemical toxicants.
- Chemical toxicities of uranium species and forms with variant isotopic ratios (natural, depleted, and enriched) are identical.
Uranium (U) Toxicity

- Hexavalent uranium (U(VI)), as the dioxo uranyl cation \([\text{UO}_2]^{2+}\), is the most stable state \textit{in vivo}.\textsuperscript{1,2}
- \textit{Renal tubular epithelium}
- Respiratory tract (inhalation)
- Hepatic dysfunction
- Anemia
- Myocarditis

Uranium Speciation and Solubility

DTPA

- Negligible GI absorption
- Cleared by glomerular filtration
- Ineffective
  - Bone / total body
  - Package inserts: Ca-DTPA and Zn-DTPA "treatments are not expected to be effective for uranium and neptunium."
- Nephrotoxicity
- Suppressed hematopoiesis
- Teratogenicity/embryotoxicity
- "Bycatch"
DTPA
“Bycatch”

- Zinc, magnesium, manganese, and metalloproteinase depletion
- Animal models
  - U-DTPA → cardiac arrest (porcine)\(^1\)
  - Significantly increased urinary elimination of Ca, Cu, Fe, Zn, and Mn (murine)\(^2,3\)
  - Concomitant inter-tissue distribution
  - Enhanced fecal excretion of Mn (lapine)\(^4\)

---

Other Chelators
Tiron (Tiferron)

- Favorable removal as U(VI)-tiron, only at large molar ratios
- Limited practical value for treatment of uranium exposures

---

Other Chelators
Hydroxypyridonates (HOPOs)

- 5-LIO(Me-3,2-HOPO) and 3,4,3-LI(1,2-HOPO)
Other Chelators
Hydroxypyridonates (HOPOs)

percent of injected 232U or 233U
drawn from data in Durbin PW, 2008.

0.1% 1.0% 10.0% 100.0%

Skeleton Soft tissue Kidneys Whole body Urine Feces + GI contents

Other Considerations

• Address uranium source
• Dialysis
• Sodium bicarbonate (NaHCO₃)

A STUDY OF THE ACIDOSIS, BLOOD UREA, AND PLASMA CHLORIDES IN URANIUM NEPHRITIS IN THE DOG, AND OF THE PROTECTIVE ACTION OF SODIUM BICARBONATE.

By EUGEN S. COPIN, M.D.

(FROM THE WILLIAM PENN LABORATORIES OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.)

July 15th, 1936.

(Readed for publication, November 29, 1936.)

Sodium Bicarbonate (NaHCO₃)

• National Council on Radiation Protection and Measurements (NCRP) preferred¹,²
• Label
  – “Sodium Bicarbonate is further indicated in the treatment of certain drug intoxications, including barbiturates (where dissociation of the barbiturate-protein complex is desired), in poisoning by salicylates or methyl alcohol and in hemolytic reactions requiring alkalization of the urine to diminish nephrotoxicity of hemoglobin and its breakdown products.”

² National Council on Radiation Protection and Measurements (NCRP), 1968.
Uranium Chelation Summary

- Not supported: DTPA
- Current recommendation: sodium bicarbonate
- Consider dialysis
- Experimental: hydroxypyridonates

Cadmium

Cadmium (Cd) Exposure

- Background/Environment
- Industry
  - Mining
  - Refining
  - Metalworking
Cadmium (Cd)
Kinetics

• *Ingestion*
  – Poor absorption (5%-20%)
• *Inhalation*
  – Excellent absorption (≤5%)
• *Accumulation*
  – Hepatic
  – Renal
• *Elimination*
  – $t_\text{1/2} = \text{years}$

Cadmium (Cd)
Toxicity

• Renal injury
• "Itai-itai" osteomalacia
• Respiratory tract (inhalation)
• Gastrointestinal injury (acute ingestion)

Cadmium Chelation Considerations

• Metals
  – Cadmium (Cd)
• Binding proteins
  – Albumin
  – α2-macroglobulin
  – Metallothionein
• Chelators
• Chelates
Cadmium Chelation Considerations

Human Experience

- DMPS
  - Increased cadmium excretion in "mobilisation" tests, unchanged Cd_{serum}.
- EDTA
  - No beneficial effects on chronic Cd-induced renal dysfunction.
  - Unchanged clinical status; unchanged Cd_{serum}.
  - +GSH: increased Cd_{serum}.
  - Increased urinary excretion.

Animal Experience

- Marked temporal dependence.
- Acyclic polyamines: significant renal damage.
- BAL: increased renal and hepatic cadmium burden. Decreased survival.
- Carbodithioates: highly dependent upon agent and experimental conditions.
  - DMPS: increased renal cadmium burden.
  - DMSA: improved survival. Modestly decreased retention. Dose-dependent survival benefit with increased renal burden.
  - D-PCA: increased renal cadmium burden. No survival benefit. Ineffective.
  - DTPA: Dose dependent increased survival. Decreased retention. Decreased residual cadmium.
- EDTA: increased renal cadmium burden. Survival at lower Cd doses. Renal damage.
- NAC: improved oxidative stress markers with concomitant chelator.

Cadmium Chelation Summary

- Address cadmium source
- Minimal treatment window
- Acute toxicity: no definitive chelation benefit
  - DMSA, DTPA, EDTA
- Chronic toxicity: chelation unsupported
- Experimental: carbodithioates
References

- Provided separately

Thank You
The use and abuse of chelation therapy in patients with autism spectrum disorders

JEFFREY BRENT, M.D., PH.D.
TOXICOLOGY ASSOCIATES
UNIVERSITY OF COLORADO
SCHOOL OF MEDICINE

DISCLAIMER
I have been a consultant to the US National Vaccine program and was a witness, on behalf of the US Government, in the National Omnibus Vaccine Hearings.

4 year old female diagnosed with PDD is referred by her pediatrician because a hair analysis found that she was high on As, Hg, Zn, Th, Te and her mother wanted her chelated. No environmental source of unusual exposure to any of these elements could be found. Work up was negative.

Chelate?
A typical hair analysis report

PT: 6 yr old autistic male – parents want him chelated because on a post-chelation urine sample he was high on:
  Cadmium
  Lead
  Tin
  Uranium

Exam normal except for autistic behavior

Environmental history unremarkable

Work up:
  Cadmium: Blood and urine within ref range
  Beta-2-microglobulin normal
  No microalbuminuria
  Lead: Blood lead 69 ug/dl
  Tin: Blood within ref range
  Uranium: Urine within ref range

-Chelate?
The prevalence of the diagnosis of Autism Spectrum Disorder has been increasing.

- The increased prevalence temporally correlates with the increase in the number of vaccinations.
- The increase is in ASD, the rates of classical autism are largely unchanged.

Two hypotheses have emerged linking vaccinations to autism/ASD:

- MMR
- Thimerosal

US FDA’s Analysis of Thimerosal in vaccines

(Ball LK et al, Pediatrics 107, 1147-1154, 2001)
It was possible to exceed the US EPA's Reference Dose for methyl mercury from the ethyl mercury in vaccines:

RfD = daily dose determined by US EPA To be acceptably safe when averaged over a lifetime

Ball, 2001

Blood mercury levels before and after receipt of vaccines that contained thimerosal preservative:

Newborns

2 Month olds

6 Month olds

Ethyl mercury poisoning and ASD are completely different diseases:

<table>
<thead>
<tr>
<th>ASD</th>
<th>Ethylmercury poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large head size</td>
<td>Small head size</td>
</tr>
<tr>
<td>Lack of social reciprocity</td>
<td>No lack of reciprocity</td>
</tr>
<tr>
<td>Stereotypical behavior</td>
<td>No stereotypical behavior</td>
</tr>
<tr>
<td>Purkinje cells affected</td>
<td>Granular cells affected</td>
</tr>
<tr>
<td>Normal renal function</td>
<td>Abnormal renal function</td>
</tr>
<tr>
<td>No tunnel vision</td>
<td>Tunnel vision</td>
</tr>
<tr>
<td>No tremor</td>
<td>Tremor</td>
</tr>
<tr>
<td>No paresthesias</td>
<td>Paresthesias</td>
</tr>
<tr>
<td>No ataxia</td>
<td>Ataxia</td>
</tr>
<tr>
<td>No dysarthria</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>Associated with relatively normal blood mercury levels (normal approx. 1 ug/L)</td>
<td>Associated with high blood mercury levels (&gt; 500 ug/L)</td>
</tr>
</tbody>
</table>
Is immunization with thimerosal containing vaccines associated with higher rates of autism or ASD?

The Studies of the Geier's

- Published numerous studies with positive association between THI exposure and ASD
- Most published in marginal journals
- US NAS, IOM: “Geier studies are uninterpretable and thus non-contributory.”
  - Criticized methodology, calculations, conclusions
Ten human epidemiological studies have found no link between ASD and Thimerosal

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verstraeten, 2003</td>
<td>Cohort</td>
<td>124,170</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>Madsen, 2003</td>
<td>Ecological</td>
<td>Danish pop</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>Stehr-Green, 2003</td>
<td>Ecological</td>
<td>Danish and Swedish pops</td>
<td>A J Pub Health</td>
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<tr>
<td>Hvid, 2003</td>
<td>Cohort</td>
<td>Danish pop</td>
<td>JAMA</td>
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<td>Andrews, 2004</td>
<td>Cohort</td>
<td>103,043</td>
<td>Pediatrics</td>
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</thead>
<tbody>
<tr>
<td>Jick, 2004</td>
<td>Case-control</td>
<td>709</td>
<td>NEJM</td>
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<tr>
<td>Heron, 2004</td>
<td>Cohort</td>
<td>12,956</td>
<td>Pediatrics</td>
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<tr>
<td>Fombonne, 2008</td>
<td>Ecological</td>
<td>27,749</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>Schecter, 2008</td>
<td>Ecological</td>
<td>California</td>
<td>Arch Gen Psychiatry</td>
</tr>
<tr>
<td>Price, 2010</td>
<td>Case-control</td>
<td>1,008</td>
<td>Pediatrics</td>
</tr>
</tbody>
</table>

PROONENTS OF THE VACCINE AUTISM THEORY RESPOND BY SAYING THE EPIDEMIOLOGY IS NON-APPLICABLE BECAUSE THERE IS A HYPOTHESIZED SMALL SUSCEPTIBLE POPULATION
The syllogism that does not work

- Proponents of an ASD-thimerosal link:
  1. The large increase is ASD is due to thimerosal
  2. The epi studies do not show a relationship btw thimerosal and ASD
  3. That is because it is only the few susceptible cases that are caused by thimerosal
  4. ?

There are many reasons for the increase in ASD

- Broadening of the concept of ASD
- Changes in diagnostic criteria
- Diagnostic substitution
  - Inverse relationship between incidence of mental retardation and ASD
- Educational advantages for students diagnosed with ASD
- Increased awareness
- Promotion by organizations favoring expensive but ineffective therapies (e.g. Doctors Against Autism) and attorneys

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- Tin
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- Lead: Blood lead 69 ug/dl
- Tin: Blood within ref range
- Uranium: Urine within ref range

Chelate?

“To evaluate net retention, one compares the levels of metals in urine before and after the administration of a pharmaceutical metal detoxification agent such as EDTA, DMSA or DMPS”
Thanks for your attention, I hope this was interesting

If you would like to have a copy of these slides in PowerPoint format please e-mail me at: jeffrey.brent@ucdenver.edu
Panel Discussion: Practical Application of Evidence-Based Chelation Recommendations
Moderator: Charles McKay MD, FACMT

Panel Members

- Jeffrey Brent, MD, PhD, FACMT
- Michael Kosnett, MD, MPH, FACMT
- Charles Lee, MD
- Walter Rogan, MD, MPH
- Silas Smith, MD
- Richard Wang, DO, FACMT
- Paul Wax, MD, FACMT

Overview

- Apply material from today’s symposium to case examples
  - We will focus on Pb, As, Hg, U
  - Framework should be applicable to other metals
- For each case, identify:
  - Patient concern
  - Misinformation
  - Role of testing
  - Role for chelation therapy
  - Systemic issues or information to reduce confusion
Case 1: Lead Poisoning in Extended Family Linked To Ethnic Food Coloring Agent – CT and MA, 2008-2009 (Epi-X report)

- 4-year-old Pakistani child: blood Pb of 105 µg/dL
  - Delayed Pb screening at pre-school entry
- All family members living in the same residence were also identified as having elevated blood Pb levels ranging from 68 to 84 µg/dL
  - Reported symptoms: crampy abdominal pain, constipation, weakness, difficulty concentrating
  - One female who had a whole blood Pb of 51 µg/dL recently had a first trimester miscarriage
  - Exception of an infant: blood Pb > detection limit of 2 µg/dL
- Continuing investigation by local and state public health departments identified an orange powder used by the family as a “yellow food coloring” as containing 47% (470,000 µg/g) Pb by weight.
  - The family has not identified the brand name and location of purchase
  - Extended family members: blood Pb ranging from 51 to 84 µg/dL
  - Related family in a neighboring state that had shared meals was also identified: blood Pb ranging from 13 to 36 µg/dL, in 5 of 7 members.

Case 1: Time course with treatment

Blood Lead Levels - Family

Case 1

- Patient concern?
- Misinformation?
- Role of testing?
- Role for chelation therapy?
- Systemic issues or information to reduce confusion?
Mercury 0.010 (<0.01 ug/g) 95% percentile

Urine Mercury VERY ELEVATED
Mercury 21 (0-3 ug/g creatinine)

Comment: Post provocative challenge
Case 2

- Patient concern?
- Misinformation?
- Role of testing?
- Role for chelation therapy?
- Systemic issues or information to reduce confusion?

Case 3: Dietary Arsenic

- After seeing a Dr. Oz show, a mother calls the PCC concerned that she may have poisoned her child by serving apple juice
- Wonders about having her child tested and perhaps treated for "arsenic poisoning"
- Data:
  - 5 brands from 3 cities
  - 1/3 of samples >10ppb(mcg/L)
    - Highest value 36 mcg/L
  - Subsequent CR study: 10% of samples similar results

Consumer Reports: 88 samples tested for As and Pb

- One [As] value: almost 25 ppb
- Most of 9 "elevated" measurements ~ 10ppb

- Pb comparisons to 'bottled water' standard
  - Why?
    - Tap water standard of 15 ppb was 'exceeded' once
Case 3

- Patient concern?
- Misinformation?
- Role of testing?
- Role for chelation therapy?
- Systemic issues or information to reduce confusion?

Arsenic Contamination of Drinking Water in Bangladesh

This is the greatest case of poisoning in the history of mankind: In Bangladesh, the health of 35 to 80 million people is endangered due to water contaminated by arsenic. The problem was first detected in the early 1980s in the Indian state of Western Bengal, a neighbor of Bangladesh. It quickly became evident that this contamination also existed in Bangladesh. Another ten years would pass, however, before the authorities and the international community mobilized their efforts. The aim is simple: to make sure the people of Bangladesh have safe drinking water. Achieving it, however, is far more complex. There is no miracle solution in sight and, meanwhile, millions of people are slowly becoming poisoned.

Real Arsenic Poisoning

- Daily exposure to more than 2 liters (hot climate) at amounts as high as 2000ppb
  - Equivalent to 2 mg/L
  - U.S. drinking standard decreased from 50 to 10 mcg/L

Source: Danish Consultants, Japan
**Case 4: Broad Screening “Heavy Metal Testing”**

Caller wants help because of testing:
- “found 33 times the limit for aluminum and uranium and all these things…”
- “Find out where I have been exposed and how to get rid of these things so I can become a well person again.”

**Environmental Testing: Uranium**

- Well water uranium: 100 mcg/L
  - EPA standard for public drinking water systems: 30 mcg/L (ppb)
- Urinary uranium (post-provocation):
  - 0.8 mcg/L (“normal <0.013”)
- Health status:
  - Fear about possible future health effects
    - Renal impairment
    - Cancer

**Case 4**

- Patient concern?
- Misinformation?
- Role of testing?
- Role for chelation therapy?
- Systemic issues or information to reduce confusion?
Chelation: Efficacy to Effectiveness

• Not false manipulation of laboratory data
• Not just a drop in measured body concentrations
  – Particularly for chronic exposures
• Combination of demonstrated removal and improvement of causally-related symptoms
  – Combined with identification and removal of significant exposure source

Touchpoints for Metal Chelation Decisions

• Valid clinical suspicion
• Proper patient and specimen preparation
• Valid comparison groups
  – No role for provoked challenge in screening/diagnosis
  – Laboratory normal vs population norms vs toxicity ranges
• Distinguish and communicate the difference between “individual health effect” and “public health concern”
  – Biochemical changes vs organ dysfunction vs clinical symptoms
  – At-risk population vs entire population

Appendix

• Perspective and comparisons
• Reference ranges
• Advocacy
Organic (vs. other forms) of Mercury

- Conflation of numbers
- Argument for special risk for special groups
  - Extrapolate small biochemical effects to organ effects to entire being effects
    - Discount any feedback, reparative, compensatory response
  - Argue from statistical minimums to large effects for large populations

Normal Range – What is the Reference Group?

- "Not based on large samples"
- "Consensus opinion"
- Population-based
  - U.S. hair Hg for an "average fish-eating population": 0.4-7.6 ppm
  - NHANES sampling total blood mercury
    - Children (1-5yo, all races): 705 studied
      - 25th percentile: <0.14 µg/L
      - 50th percentile: 0.3 µg/L
      - 95th percentile: 2.3 µg/L
  - Similar results from other population studies of thousands of individuals

What Reference Group?

- Occupational/BEI
  - <15 µg/L blood inorganic mercury (ACGIH)
  - <50 µg/g creatinine urinary mercury (BEI-renal)
- "Clinical effect"
  - Methylmercury death Nierenberg et al. NEJM 1996;335:1872
    - Whole blood Hg 4000 µg/L (reference 1-8 µg/L)
    - Plasma Hg 600 µg/L
    - Urine Hg 234 µg/L (ref 1-5 µg/L)
    - Hair Hg 1100 ppm (ref < 0.26 ppm)
Reference Range – Exposed?

- Organic Hg
  - Subsistence fish diet (Faroe Island)
    - 22.9 µg/L cord blood (interquartile range 13.4-41.3)
    - 4.27 µg/g maternal hair (interquartile range 2.6-7.7)
  - Polluted Japanese bays (Fukuda et al. Env Res 1999;81:100)
    - RBC Hg 28.5 +/- 11.5 ng/g (equiv. ~40 µg/L whole blood)

Normal range v. Clinical Effect

- Cord blood and/or maternal hair measurements (confounders of nutrition, “heavy” exposure)
  - NOAEL – neurocognitive battery (Seychelles)
    - 15 ppm maternal hair (equivalent to ~75 µg/L whole blood)
  - LOAEL – subtests of neurocognitive battery (Faroe)
    - 12 ppm maternal hair
  - NOAEL – Delayed walking (Iraq)
    - 10 ppm maternal hair
  - NOAEL – Obvious neurologic deficits (Iraq)
    - Paresthesias 100 ppm hair
    - Dysarthria 300 ppm hair
    - Death 800 ppm hair

Best Graphical Depiction?

- Population Distribution of Blood Hg Levels in US Woman of Childbearing Age
  - BMQL: the lower statistical bound (95% confidence interval) dose level (99 µg mercury/l blood) corresponding to a 10% increase in the probability of an adverse health effect, in this case neurologic injury.
• Is the “abnormal” value:
  – Outside that of an appropriate referent population
  – Abnormal for clinically relevant norms
  – Of any meaning in your patient
• Contrast individual health risk and public health “concern” for susceptible populations


Epidemiologic studies of chronic “low-level” exposures

Ecologic Fallacies and Confounders

Arsenic Exposure and Prevalence of Type 2 Diabetes in US Adults
Advocacy Sites

- Promotional – GUNA or others
- American College for the Advancement of Medicine (ACAM)
- American Academy of Anti-aging Medicine (A4M)
- Foundation for the Advancement of Innovative Medicine (FAIM)
- International Academy of Oral Medicine and Toxicology
- British Society for Homotoxicology

Advocacy Sites: How to respond?

- Absence of scientific basis?
- Harmless placebo effect?
- Misdirection/adverse effects?