History and Current Recommendations for Provoked Challenge Urine Testing

Anne-Michelle Ruha, M.D., FACMT
Department of Medical Toxicology
Banner Good Samaritan Medical Center
Phoenix, Arizona
Provoked / Challenge Urine Testing for Metals
Post-Chelator Challenge Urinary Metal Testing

by Nathan Charlton, MD and Kevin L. Wallace, MD FACMT, posted on 10:35 AM, July 27, 2009

American College of Medical Toxicology Position Statement on Post-Chelator Challenge Urinary Metal Testing

Mercury Exposure: Evaluation and Intervention
The Inappropriate Use of Chelating Agents in the Diagnosis and Treatment of Putative Mercury Poisoning

John F. Risher 1,* , Sheralta N. Amler 2,†

1 Agency for Toxic Substances and Disease Registry, Division of Toxicology (F-32), 1600 Clifton Road, Atlanta, GA 30333, USA
2 Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, GA, USA
Search: ‘urine test for metal poisoning’

How the "Urine Toxic Metals" Test Is Used to Defraud Patients
www.quackwatch.org/t/
The report pictured to the right is a "urine toxic metals" test from Doctor's Data, ... The standard way to measure urinary mercury and lead levels is by collecting a ...

Safe Detoxification for Heavy Metal Poisoning
www.evenbetterhealth.com/heavy-metal-poisoning.asp
Tests that help to diagnose metal and chemical toxicity include blood tests, urine tests, and the analysis of hair, nails or other tissues. The most accurate of these ...

Metals Urine Test
www.greatplainslaboratory.com/home/eng/metals_uran.is.asp
Heavy metals toxicity caused by increasing levels of pollution and use of chemicals in ...

Urine toxic and essential elements analysis is an invaluable tool for the ...

Heavy Metal Toxicity Testing Overview
www.patientsmedical.com › Health AZ
The doctor in charge reports any findings in his medical notes. Specific Heavy Metal Toxicity Testing: A. Urine Analysis. What is a Urine Analysis (Urinalysis)? ...
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Test Yourself For Toxic Metals

Tests that help to diagnose metal and chemical toxicity include blood tests, urine tests, and the analysis of hair, nails or other tissues. The most accurate of these are a chelation challenge test or a hair analysis.

Metals Urine Test
www.greatplainslaboratory.com/home/eng/metals_urine.asp
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Analysis of the levels of toxic metals in urine after the administration of a metal detoxification agent is an objective way to evaluate the accumulation of toxic metals. Acute metal poisoning is rare. More common, however, is a chronic, low-level exposure to toxic metals that can result in significant retention in the body that can be associated with a vast array of adverse health effects

Heavy Metal Toxicity Testing Overview
www.patientsmedical.com › Health AZ
The doctor in charge reports any findings in his medical notes. Specific Heavy Metal Toxicity Testing: A. Urine Analysis. What is a Urine Analysis (Urinalysis)? ...
The approach to this test is that any increase in heavy metals after DMSA challenge is considered significant. The patient is then treated with DMSA treatment until the toxic metals in the urine are within the normal range after a DMSA challenge. An additional complication for children is that even a six-hour urine collection may be difficult. Therefore, a single urine sample collection after DMSA may sometimes be used.

DMSA Dosing Chart for challenge test:

<table>
<thead>
<tr>
<th>Body Weight (lbs)</th>
<th>Dose (mg)</th>
<th>No. Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-35</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>36-55</td>
<td>200</td>
<td>2</td>
</tr>
<tr>
<td>56-75</td>
<td>300</td>
<td>3</td>
</tr>
<tr>
<td>76-100</td>
<td>400</td>
<td>4</td>
</tr>
<tr>
<td>&gt;100</td>
<td>500</td>
<td>5</td>
</tr>
</tbody>
</table>
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Heavy metals toxicity caused by increasing levels of pollution and use of chemicals in ... Urine toxic and essential elements analysis is an invaluable tool for the ...

Heavy Metal Toxicity Testing Overview
www.patientsmedical.com › Health AZ
request some testing that is and not commonly performed in more "mainstream" medical clinics. 24-hour heavy metal testing with provoking agent, neurotransmitter analysis, food sensitivity

3 of top 4 sites advise challenge test
Advocates state:
- Current and past exposures result in increased body stores
- Challenge reveals ‘body burden’

Advocates advise:
- Comprehensive search for potential sources of Hg exposure
  - geography, amalgams, fish, high fructose corn syrup, second hand smoke in childhood, exposures of mother prior to conception

## Toxic Metals; Urine

<table>
<thead>
<tr>
<th>TOXIC METALS</th>
<th>RESULT µg/g creat</th>
<th>REFERENCE INTERVAL</th>
<th>WITHIN REFERENCE</th>
<th>OUTSIDE REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>120</td>
<td>&lt; 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony</td>
<td>0.1</td>
<td>&lt; 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>49</td>
<td>&lt; 117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barium</td>
<td>8.3</td>
<td>&lt; 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beryllium</td>
<td>&lt; dl</td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth</td>
<td>0.6</td>
<td>&lt; 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.8</td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesium</td>
<td>5.3</td>
<td>&lt; 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadolinium</td>
<td>0.2</td>
<td>&lt; 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>7.3</td>
<td>&lt; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury</td>
<td>21</td>
<td>&lt; 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>12</td>
<td>&lt; 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palladium</td>
<td>&lt; dl</td>
<td>&lt; 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum</td>
<td>&lt; dl</td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tellurium</td>
<td>&lt; dl</td>
<td>&lt; 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thallium</td>
<td>0.4</td>
<td>&lt; 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thorium</td>
<td>&lt; dl</td>
<td>&lt; 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tin</td>
<td>0.4</td>
<td>&lt; 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tungsten</td>
<td>&lt; dl</td>
<td>&lt; 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uranium</td>
<td>0.1</td>
<td>&lt; 0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Specimen Data

- **Date Collected:** 12/5/2011  
- **pH upon receipt:** Acceptable  
- **Collection Period:** timed: 6 hours  
- **Date Received:** 12/8/2011  
- **<dl:** less than detection limit  
- **Volume:**  
- **Date Completed:** 12/9/2011  
- **Provoking Agent:** CAEDEA DMSA  
- **Provocation:** POST PROVOCATIVE  
- **Method:** ICP-MS  
- **Creatinine by Jaffe Method**

Results are creatinine corrected to account for urine dilution variations. Reference intervals and corresponding graphs are representative of a healthy population under non-provoked conditions. Chelation (provocation) agents can increase urinary excretion of metals/elements.
Questions?

- What are normal reference ranges for metals in urine after a dose of chelator?
- Diagnostic value?
  - Can toxicity be ruled in or out based on this test?
- Is it safe?
- Does the evidence support use of a challenge test?
Early Challenge Tests in Medicine: Deferoxamine for Iron

- 1960s
  - Fielding proposed a test for measuring ‘chelatable’ iron
  - A single dose of IV deferoxamine followed by 6 hour urine test

J Clin Path 1965;18:88–9
Deferoxamine for Iron

- Rabbit model (Keberle 1964)
  - Fe loaded rabbits – 16x increase UFe with red-brown urine
  - *Normal rabbits – 5x increase UFe
Deferoxamine Challenge Test

- IM deferoxamine (about 50 mg/kg)

- If ‘vin rose urine’ within 4–6 hours this would indicate excretion of ferrioxamine

- Imply a toxic level prompting treatment, until urine no longer red
End of Deferoxamine Challenge

- No change in urine color in 70% of patients with serum Fe concentrations exceeding expected TIBC

- Recommended that the deferoxamine challenge test be abandoned

Proudfoot AT. Tox Let 1995;82/83:770–783.
EDTA Challenge for Lead

EDATHAMIL CALCIUM DISODIUM (VERSENATE) DIAGNOSTIC TEST FOR LEAD POISONING
Jo Anne Whitaker, Wm. Austin and John D. Nelson
Pediatrics 1962;29:384

- Lead mobilization test:
  - 24 h urine
  - 3 doses IM CaNa$_2$EDTA
    - Every 8 h
  - 24 h urine

- Study groups:
  - Control
  - Suspected Pb poisoning
  - Confirmed Pb poisoning

*All children had increase UPb after challenge Lead poisoned higher UPb than controls

CaNa$_2$EDTA for Lead

- **1980s**
  - Used routinely in children with elevated BPb levels (25–55 ug/dL) to detect ‘mobilizable’ lead
  - CDC recommended use of lead mobilization test to determine which children would respond to chelation
End of EDTA Lead Challenge

- Concerns regarding safety
  - Concern for redistribution of lead
  - Depletes other metals
  - Renal toxicity

- Difficult to perform in children

- Data showing lead initially mobilized mainly from bone

Chisolm JJ. AJDC 1987;141:1256-1257
Penicillamine Challenge for Copper

- Used as an adjunctive test in the diagnosis of Wilson Disease
  - One recommendation is use in symptomatic children if WD is suspected but basal urinary copper excretion is normal

- D–penicillamine 500 mg administered at the onset and 12 hours into a 24 hour urine collection
Re-evaluation of the Diagnostic Criteria for Wilson Disease in Children With Mild Liver Disease

Emanuele Nicastro*, Giusy Ranucci*, Pietro Vajro, Angela Vegnente, and Raffaele Iorio

- **Purpose**: to re-evaluate conventional diagnostic criteria for WD in children with mild liver disease

- **Subjects**
  - 40 with diagnosis of WD
  - 58 controls – other liver disease and siblings of WD

Concluded the PCT is of little value for diagnosis in these patients.
Challenge Tests in ‘Mainstream Medicine’

- Not recommended:
  - CaNa2EDTA for lead
  - Deferoxamine for iron

- Unclear role in dx of Wilson Disease
  - Penicillamine for copper
DMSA and DMPS

- **DMSA** approved in the US in 1990 for treatment of Pb intoxication

- **DMPS**
  - Not approved in US
  - Used in Russia since 1950s
  - Approved in Europe in 1970s

  - Studied as early as the 1950s in Soviet Union and China for treatment of Pb and Hg toxicity
19 healthy college and grad students

No seafood x 30 days

Amalgam score determined by a dentist (10 with amalgams)

11 hr pre-DMPS urine collection
Oral DMPS 300 mg
9 hr post-DMPS urine collection
• Amalgam group had higher baseline UHg
• Both groups had rise in UHg (19 fold vs 25 fold)
• Individual cases UHg increased 12–70 fold

*healthy subjects had up to 70 fold increase in UHg after DMPS
Adverse effects in healthy subjects

2/19 nausea, one vomited

1 rash a week out
Dimercaptosuccinic acid loading test for assessing mercury burden in healthy individuals

GP Archbold¹, Roisin M McGuckin¹ and NA Campbell²

- To assess change in UHg in healthy people given a DMSA challenge test
  - Fasting urine sample
  - Oral DMSA 30 mg/kg
  - 2 h urine sample discarded
  - 3 h urine sample collected

- UHg correlates with amalgam surfaces

Mean factor increase = 7  
Range = 1 to 27

*healthy subjects had up to 27 fold increase in UHg after DMSA

Table 1. Demographic, dental and biochemical data on the studied volunteers

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Amalgam surfaces</th>
<th>Time (months) from last dental work</th>
<th>Urinary mercury : creatinine ratio nmol:mol</th>
<th>Incremental factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M/F</td>
<td></td>
<td>Total Occlusal</td>
<td>Pre-dose Post-dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>46</td>
<td>34 12</td>
<td>5.0</td>
<td>2.1 19.2</td>
<td>8.1</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>27</td>
<td>28 11</td>
<td>7.0</td>
<td>2.4 9.2</td>
<td>2.8</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>22</td>
<td>6 4</td>
<td>7.0</td>
<td>0.1 2.8</td>
<td>27.0</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>38</td>
<td>16 9</td>
<td>36.0</td>
<td>0.3 1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>50</td>
<td>41 13</td>
<td>4.0</td>
<td>1.0 7.9</td>
<td>6.9</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>33</td>
<td>47 16</td>
<td>14.0</td>
<td>1.0 11.7</td>
<td>10.7</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>59</td>
<td>5 3</td>
<td>36.0</td>
<td>0.6 2.1</td>
<td>2.5</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>36</td>
<td>10 5</td>
<td>1.5</td>
<td>0.6 3.3</td>
<td>4.5</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>59</td>
<td>32 12</td>
<td>1.5</td>
<td>2.1 11.8</td>
<td>4.6</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>53</td>
<td>24 10</td>
<td>27.0</td>
<td>0.2 1.6</td>
<td>7.0</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>26</td>
<td>17 13</td>
<td>3.5</td>
<td>1.1 8.3</td>
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<tr>
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<td>M</td>
<td>54</td>
<td>27 11</td>
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<tr>
<td>13</td>
<td>F</td>
<td>53</td>
<td>36 12</td>
<td>3.0</td>
<td>1.8 3.6</td>
<td>1.0</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>28</td>
<td>0 0</td>
<td>—</td>
<td>0.5 2.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

M = male; F = female.
Adverse effects...

- Intention to include 20 subjects
  - study closed after 14 completed

- 15th developed vomiting, tight chest, urticarial rash 6 minutes after ingestion of DMSA

- 3 other subjects with nausea and all reported foul smelling urine x 24 h

Urine Mercury Excretion Following \textit{meso}-Dimercaptosuccinic Acid Challenge in Fish Eaters

Anne-Michelle Ruha, MD; Steven C. Curry, MD; Richard D. Gerkin, MD; Kathleen L. Caldwell, PhD; John D. Osterloh, MD, MS; Paul M. Wax, MD

- DMSA challenge in healthy individuals with varying amounts of fish intake
- 22 volunteers, 30mg/kg oral DMSA

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
                   & Group 1 & Group 2 & Group 3 & \( P^\dagger \) \\
\hline
\text{Urine mercury excretion, \( \mu g \) Hg/g Cr} & & & & \\
Before DMSA       & \(0.74 \ (0.61) \ [0.17-1.58]\) & \(1.06 \ (1) \ [0.12-2.2]\) & \(1.21 \ (1.5) \ [0.62-1.9]\) & \(0.37\) \\
After DMSA        & \(2.92 \ (3.15) \ [0.81-4.78]\) & \(10.08 \ (8.86) \ [0.57-28.56]\) & \(13.04 \ (11.36) \ [2.55-32.63]\) & \(0.05\) \\
\( P^\ddagger \)   & \(0.02\) & \(0.01\) & \(0.02\) & \\
\hline
\end{tabular}
\end{table}
UHg rises in everyone after DMSA challenge.

Rise is greater with increased fish intake.

Healthy People with Mercury Exposure via Amalgams or Fish

- All have urinary Hg excretion even without use of a chelator
- Urinary Hg excretion rises in everyone after a chelation challenge
Sodium 2,3-Dimercaptopropylamine-1-Sulfonate Challenge Test for Mercury in Humans: II. Urinary Mercury, Porphyrisms and Neurobehavioral Changes of Dental Workers in Monterrey, Mexico

DIEGO GONZALEZ-RAMIREZ, RICHARD M. MAIORINO, MIGUEL ZUNIGA-CHARLES, ZHAOFA XU, KATHERINE M. HURLBUT, PABLO JUNCO-MUNOZ, MARY M. APOSHIAN, RICHARD C. DART, JOSE HORACIO DIAZ GAMA, DIANA ECHEVERRIA, JAMES S. WOODS and H. VASKEN APOSHIAN

### TABLE 1
**DMPS challenge test protocol**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>-11 hr</td>
<td>Begin fasting</td>
</tr>
<tr>
<td></td>
<td>Begin overnight urine collection</td>
</tr>
<tr>
<td>0 hr</td>
<td>End overnight urine collection</td>
</tr>
<tr>
<td></td>
<td>Collect blood sample</td>
</tr>
<tr>
<td></td>
<td>Administer 300 mg of DMPS p.o.</td>
</tr>
<tr>
<td></td>
<td>Begin 0–6-hr urine collection</td>
</tr>
<tr>
<td>+4 hr</td>
<td>End fast</td>
</tr>
<tr>
<td>+6 hr</td>
<td>End 0–6-hr urine collection</td>
</tr>
<tr>
<td></td>
<td>Collect blood sample</td>
</tr>
</tbody>
</table>

- 10 dental technicians
- 5 dentists
- 13 non–dental personnel

J Pharm and Exp Therapeut 1995;272:264–274
Pre-DMPS
All groups excrete Hg at baseline. Exposed groups more so than controls.

Post-DMPS
All groups have rise in UHg.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mercury level ± S.E.</th>
<th>Mercury Concentration ± S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-6 to 0 hr (before)</td>
<td>0 to +6 hr (after)</td>
</tr>
<tr>
<td>Dental technicians</td>
<td>10</td>
<td>4.84 ± 0.742</td>
<td>424.0 ± 84.9</td>
</tr>
<tr>
<td>Dentists</td>
<td>5</td>
<td>3.28 ± 1.11</td>
<td>162.0 ± 51.2</td>
</tr>
<tr>
<td>Nondental</td>
<td>13</td>
<td>0.783 ± 0.189</td>
<td>27.3 ± 3.19</td>
</tr>
</tbody>
</table>

Controls 35 fold increase
Dentists 49 fold increase
Dental techs 88 fold increase

Overlapping ranges
14–132
45–76
11–335

*Healthy controls with up to 132x rise in UHg after DMPS

*one subject nausea/diarrhea
DMPS challenge to:

- 11 factory workers
  - (made HgCl – containing skin lotion)
- 8 lotion users
- 9 controls

JPET 1996;277:938–944
<table>
<thead>
<tr>
<th>Group</th>
<th>μg of Hg ± S.E.M. -6 to 0 hr (Before)</th>
<th>0 to +6 hr (After)</th>
<th>μg of Hg/mL ± S.E.M. -6 to 0 hr (Before)</th>
<th>0 to +6 hr (After)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin lotion makers</td>
<td>113 ± 26 (11)</td>
<td>5037 ± 682 (11)</td>
<td>333 ± 96 (11)</td>
<td>4282 ± 479 (11)</td>
</tr>
<tr>
<td>Range</td>
<td>16.0 to 314</td>
<td>1728 to 10307</td>
<td>57.7 to 1077</td>
<td>2051 to 7956</td>
</tr>
<tr>
<td>Skin lotion users</td>
<td>16.2 ± 3.4 (8)</td>
<td>1410 ± 346 (8)</td>
<td>63.5 ± 22.2 (8)</td>
<td>708 ± 197 (7)</td>
</tr>
<tr>
<td>Range</td>
<td>1.91 to 35.3</td>
<td>71.3 to 3075</td>
<td>3.06 to 186</td>
<td>116 to 1625</td>
</tr>
<tr>
<td>Controls</td>
<td>0.49 ± 0.11 (8)</td>
<td>18.4 ± 7.1 (8)</td>
<td>1.32 ± 0.37 (8)</td>
<td>22.2 ± 9.8 (9)</td>
</tr>
<tr>
<td>Range</td>
<td>0.07 to 0.98</td>
<td>3.17 to 54.2</td>
<td>0.15 to 2.82</td>
<td>1.31 to 73.1</td>
</tr>
</tbody>
</table>

All groups excrete Hg before DMPS
Large baseline differences in UHg

Makers: increased 45 x
Users: increased 87 x
Controls: increased 38 x
Also reported urine lead excretion
Test whether DMPS challenge could provide index of the Hg body burden due to long-term exposure

All healthy subjects with little fish intake

41 men in 4 groups
  - 10 industrial workers (m exposure = 11 yrs)
  - 8 dentists (m = 33 yrs)
  - 18 occupationally unexposed
  - 5 occ unexposed and amalgam free

Challenge: spot urine, 300 mg DMPS, 24 h urine

All groups excrete Hg at baseline
Exposed populations have greater baseline UHg
UHg excretion rises in all groups after DMPS
Molin et al...

- Pre–DMPS UHg excretion was associated with post–DMPS UHg excretion in all groups

- Authors concluded the challenge test did not reflect long term exposure (body burden)
Does DMSA challenge reveal increased body burden of Hg with remote occupational exposure to Hg?

Chloralkali plant workers with long-term, high-level exposure; controls

Exposure profiles – based on specific jobs, historical air sampling data
  ◦ Average, cumulative, and peak exp

DMSA Challenge: 24 h UHg, DMSA 10 mg/kg x 2 (8 h interval), 24 h UHg

Authors conclude DMSA challenge not useful in quantifying past mercury exposure
Table 2. Association of exposure ranks and chelation challenge response ranks among the most heavily exposed subjects.

<table>
<thead>
<tr>
<th>Exposure rank</th>
<th>Cumulative exposure difference</th>
<th>Cumulative exposure ratio</th>
<th>Mean exposure difference</th>
<th>Mean exposure ratio</th>
<th>Peak exposure difference</th>
<th>Peak exposure ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>6</td>
<td>80</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>8</td>
<td>56</td>
<td>64</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>86</td>
<td>71</td>
<td>64</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>15</td>
<td>109</td>
<td>114</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>81</td>
<td>88</td>
<td>59</td>
<td>22</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>33</td>
<td>23</td>
<td>29</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>96</td>
<td>91</td>
<td>14</td>
<td>19</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>37</td>
<td>69</td>
<td>85</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>74</td>
<td>35</td>
<td>34</td>
<td>38</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td>111</td>
<td>108</td>
<td>39</td>
<td>70</td>
<td>73</td>
<td>83</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>16</td>
<td>103</td>
<td>100</td>
<td>69</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>7</td>
<td>31</td>
<td>39</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>3</td>
<td>19</td>
<td>33</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>14</td>
<td>81</td>
<td>89</td>
<td>38</td>
<td>57</td>
<td>39</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>75</td>
<td>56</td>
<td>93</td>
<td>96</td>
<td>28</td>
<td>25</td>
</tr>
</tbody>
</table>

n = 119; ranks can range between 1 and 119.

Range for this highest exposure group 3x -114x increase
What can we conclude from these studies?

- Recognize
  - UHg concentrations reported differently (mcg, mcg/L, mcg/gCr)
  - Urine collections vary (spot – 24 h)
  - Dose of chelating agent varies
  - Results may not be comparable with different chelators
What can we conclude from these studies?

- Baseline urine Hg concentrations are higher in exposed populations than in unexposed populations
- DMPS and DMSA challenges produce a rise in urine Hg excretion in all groups
- There is great overlap in factor increase between and within exposure groups
<table>
<thead>
<tr>
<th>Study</th>
<th>Chelator</th>
<th># subjects</th>
<th>Hg (mean; upper range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aposhian</td>
<td>DMPS</td>
<td>10 (no amal)</td>
<td>5±1mcg/9h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (amal)</td>
<td>17±3 mcg/9h</td>
</tr>
<tr>
<td>Archbold</td>
<td>DMSA</td>
<td>14</td>
<td>14 ± 14 mcg/L</td>
</tr>
<tr>
<td>Ruha</td>
<td>DMSA</td>
<td>22</td>
<td>3/10/13; 33 mcg/gCr</td>
</tr>
<tr>
<td>Gonzalez–Ramirez</td>
<td>DMPS</td>
<td>13</td>
<td>27 ±3 mcg/6h OR 37±15 mcg/L</td>
</tr>
<tr>
<td>Maiorino</td>
<td>DMPS</td>
<td>9</td>
<td>18±7; 54 mcg/6h OR 22±10; 73 mcg/L</td>
</tr>
<tr>
<td>Molin</td>
<td>DMPS</td>
<td>5 (no amal)</td>
<td>3.2 mcg/24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 (no amal)</td>
<td>14; 56 mcg/24h</td>
</tr>
<tr>
<td>Frumkin</td>
<td>DMSA</td>
<td>101</td>
<td>8±6; 28 mcg/24h</td>
</tr>
</tbody>
</table>
# Toxic Metals; Urine

<table>
<thead>
<tr>
<th>TOXIC METALS</th>
<th>RESULT µg/g creat</th>
<th>REFERENCE INTERVAL</th>
<th>WITHIN REFERENCE</th>
<th>OUTSIDE REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum (Al)</td>
<td>120</td>
<td>&lt; 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony (Sb)</td>
<td>0.1</td>
<td>&lt; 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic (As)</td>
<td>49</td>
<td>&lt; 117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barium (Ba)</td>
<td>8.3</td>
<td>&lt; 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beryllium (Be)</td>
<td>&lt; dl</td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth (Bi)</td>
<td>0.6</td>
<td>&lt; 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium (Cd)</td>
<td>0.8</td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesium (Cs)</td>
<td>5.3</td>
<td>&lt; 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadolinium (Gd)</td>
<td>0.2</td>
<td>&lt; 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>7.3</td>
<td>&lt; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury (Hg)</td>
<td>21</td>
<td>&lt; 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel (Ni)</td>
<td>12</td>
<td>&lt; 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palladium (Pd)</td>
<td>&lt; dl</td>
<td>&lt; 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum (Pt)</td>
<td>&lt; dl</td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tellurium (Te)</td>
<td>&lt; dl</td>
<td>&lt; 0.8</td>
<td></td>
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<tr>
<td>Thallium (Tl)</td>
<td>0.4</td>
<td>&lt; 0.5</td>
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</tr>
<tr>
<td>Thorium (Th)</td>
<td>&lt; dl</td>
<td>&lt; 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tin (Sn)</td>
<td>0.4</td>
<td>&lt; 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tungsten (W)</td>
<td>&lt; dl</td>
<td>&lt; 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uranium (U)</td>
<td>0.1</td>
<td>&lt; 0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## SPECIMEN DATA

**Comments:**
- Date Collected: 12/5/2011
- pH upon receipt: Acceptable
- Date Received: 12/8/2011
- <dl: less than detection limit
- Date Completed: 12/9/2011
- Provoking Agent: CAEDTA DMSA
- Provocation: POST PROVOCATIVE
- Method: ICP-MS
- Creatinine by Jaffe Method

Results are creatinine corrected to account for urine dilution variations. Reference intervals and corresponding graphs are representative of a healthy population under non-provoked conditions. Chelation (provocation) agents can increase urinary excretion of metals/elements.
No randomized, controlled studies comparing use of a challenge test in subjects with metal poisoning to those without metal poisoning

- Metal toxicity would have to be diagnosed based on known exposure and clinical findings consistent with and specific for toxicity
Not acceptable.....

- Reports that describe patients with vague symptoms that are non-diagnostic for Hg toxicity who are given a challenge test and diagnosed on the basis of
  - An increase in metal excretion
  - Report of symptom improvement
Vamnes JS, et al: **Diagnostic value of a chelating agent in patients with symptoms allegedly caused by amalgam fillings**

- DMPS challenge test (2 mg/kg IV) to:
  - 19 without amalgams and healthy
  - 21 with amalgams and healthy
  - 20 with amalgams and self-diagnosed Hg poisoning
  - 20 who had amalgams removed because of self-diagnosed Hg poisoning

The amalgam groups excreted 3x as much Hg as the amalgam free groups.

No difference between amalgam groups with and without symptoms.

- (the symptomatic group did not have a larger ‘body burden’ detected with challenge test)
The Importance of Blinding...


- Double blind RCT

- Patients who attributed symptoms to amalgams (no alternative dx)

- DMSA 30 mg/kg divided TID x 5 days

- Both groups reported improvement

Can we at least state it is risk-free?

- Adverse reactions widely reported
- Potential for mineral deficiencies
- Other unpleasant side-effects
  - Foul-smell
  - Nausea
- Cost

EDTA 850mg Vitaltox Chelation Suppositories,

$115 online
Does the evidence support use?

- No established reference ranges
- No evidence for diagnostic value
- Not universally safe

- NO
References

8. Chisolm JJ. Mobilization of lead by calcium disodium edetate. AJDC. 1987;141:1256–1257
References


