Environmental Toxins and Neurodegeneration

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Potential Conflict of Interest

Dr. Pizzorno is Chair of the Science Advisory Board for Bioclinic Naturals

No Bioclinic Natural Products are recommended
Overview

1. Worldwide Epidemic of Brain Disorders
2. Toxins Damage Neurons and Brain Function
3. Methodology: Disease Risk to Disease Cause
4. The Worst Toxins
5. Sources of Toxins
6. Assessment of Toxin Load
7. Key Interventions
8. Case Histories
A Note About the Data

- All human data
- Primarily US as a lot more research available
- Spot checking toxins in other countries shows the same toxin overload, but variations in which are most prevalent:
  - Australia (higher PDBEs)
  - Canada (higher lead)
  - New Zealand (higher cadmium)
  - Sweden (higher most toxic metals)
  - UK (highest PDBEs in world, 3x OCP of US)
Virtually every disease and clinical condition caused by neurological damage has increased in every age group the past 50 years.
Significant Clinical and/or Epidemiological Research Support for Neurotoxin Exposure

### Diseases
- Attention deficit hyperactive disorder (ADHD)
- Autism spectrum disorder (ASD)
- Amyotrophic lateral sclerosis (ALS)
- Alzheimer’s disease (AD)
- Parkinson’s disease (PD)

### Conditions
- Cognitive decline
- Dementia
- Headache
- IQ loss (esp children)
- Mood disorders
- Motor neuron disorders

Crinnion W, Pizzorno J. Neurotoxicity in, *Clinical Environmental Medicine*. Elsevier, 2018
### The Worst Neurotoxins (?)

<table>
<thead>
<tr>
<th>Prenatal</th>
<th>Postnatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Methylmercury</td>
<td>- Arsenic</td>
</tr>
<tr>
<td>- Organophosphate pesticides</td>
<td>- Cadmium</td>
</tr>
<tr>
<td>- PCBs</td>
<td>- DDT/DDE</td>
</tr>
<tr>
<td>- Phthalates</td>
<td>- Lead</td>
</tr>
<tr>
<td>- Polyfluoroalkyl chemicals</td>
<td>- Mercury</td>
</tr>
<tr>
<td></td>
<td>- OCPs</td>
</tr>
<tr>
<td></td>
<td>- PCBs</td>
</tr>
<tr>
<td></td>
<td>- Particulate matter (Vehicular exhaust)</td>
</tr>
</tbody>
</table>
Primary Mechanisms of Neuron Damage

1. Oxidative stress
2. Inappropriate microglial activation
3. Mitochondrial damage
4. Methyl group depletion
5. Decreased production of BDNF
SOURCES OF NEUROTOXINS
Daily Arsenic Exposure Common

- <50% of US water supplies tested
- Average US water supply = 1 ug/L
- >10 ug/L increases risk of many diseases
- >10% of public water supplies has As >10 ug/L
- Some:
  - Maine wells 3,100 ug/L!
  - Similar to Taiwan & China


Mercury Exposure Common

• Average exposure in non-industrial populations
  ▪ Amalgams: 10 ug/d
  ▪ Fish: 2.3 ug/d
  ▪ Water: 0.3 ug/d
  ▪ Air
  ▪ Vaccinations

• Industrial

Amalgams Put Mercury Into the Brain

- Mercury accumulates in the brain in proportion to surface area of amalgams.
- Study of 18 cadavers:
  - Hg in brain, thyroid and kidneys proportional to the number of amalgam surfaces.
  - For those with more than 12, Hg in brain disproportionately higher.
  - Suggests that at higher levels of exposure the brain’s mercury excretion pathways become overloaded.


Guzzi 2006
Hg From Fish

- Total Hg urinary excretion proportional to amount of fish eaten
- Impaired psychomotor performance
  - R = 0.38 blood
  - R = 0.77 urine
- Huge variation in amount of Hg in fish

Mercury in the Air
Mercury Neurological Symptoms


Figure 1  Symptom frequency in exposed and control groups.
# Persistent Organic Pollutant (POPs)

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Abbr.</th>
<th>Uses</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphenol A</td>
<td>BPA</td>
<td>Plastics, can lining</td>
<td>Canned food</td>
</tr>
<tr>
<td>Organochlorine pesticides</td>
<td>OCPs</td>
<td>Pesticide</td>
<td>Food, fumigation</td>
</tr>
<tr>
<td>Organophosphate pesticides</td>
<td>OPPs</td>
<td>Pesticide</td>
<td>Food</td>
</tr>
<tr>
<td>Polybrominated diphenyl ethers</td>
<td>PBDEs</td>
<td>Flame retardant</td>
<td>Clothing</td>
</tr>
<tr>
<td>Polychlorinated biphenyls</td>
<td>PCBs</td>
<td>Industrial</td>
<td>Everywhere</td>
</tr>
<tr>
<td>Perflourinated</td>
<td>PFOAs</td>
<td>Non-stick, stain prevention, water repellant</td>
<td>Teflon, Gortex, Scotchguard</td>
</tr>
<tr>
<td>Phthalates</td>
<td></td>
<td>Plastics, fragrances</td>
<td>Shower curtains, cosmetics</td>
</tr>
</tbody>
</table>
Persistent Organic Pollutant Production

- Designed to be difficult to breakdown by biological processes
- Many neurotoxic
- Accumulate in humans with age
- Interfere with neurogenesis

Neel BA, Robert M. Sargis RM. The paradox of progress: Environmental disruption of metabolism and the diabetes epidemic. DIABETES, 2011; 60:1838-48
NEUROTOXICITY
POPs – Prenatal Effects

• Prenatal exposure particularly harmful - 3 studies
  ▪ Higher levels of OP metabolites associated with poorer cognitive scores, (memory, processing speed, comprehension, and perceptual reasoning).
  ▪ **Average deficit in IQ of 7 comparing highest to lowest quintile.**
  ▪ 25% of pregnant women in US have levels exceeding the median in this study

POPS – Prenatal Effects

- Higher maternal levels were associated with **decrease in total IQ of children 7 years later**, as well as working memory.
- Most experts agree that working memory is related to a limited attention capacity.
- Children with higher levels of OP metabolites had up to **2x increased risk for ADHD**, and the levels associated with risk were commonly found in the US population among children.

POPS – Prenatal Effects

• Prenatal exposure to OPs also associated with cognitive impairment
• **Effect magnified in those with genetic variant for PON1 gene**, which reduces ability to detoxify chlorpyrifos
• **Same polymorphism increases risk for Parkinson’s disease** when exposed to OP pesticides
• **Nearly 100% of US homes sampled had detectable OP and other pesticides on their floors**

Chlorpyrifos (CPF) & Brain Anomalies

- Prenatal exposures to CPF and other OP pesticides linked to smaller head size, lower birth weight, abnormal neonatal reflexes, and attention problems.
- Recent study found prenatal CPF exposure at high but routine levels had measurable effects on brain structure in children (MRI).
  - Random sample from Cincinnati blood bank during same time period had levels 2x as high in adults.
- Affected areas involved in attention and receptive function, social cognition, reward, emotion, and inhibitory control as well as executive functioning – changes documented in size & morphology.
- Those with high exposure also had disruption in normal sex-specific brain differences.
- Exposure x IQ interaction – normal positive associations between surface area of some areas and IQ were not found in high exposure group.
- Persistence of effects suggests they are irreversible.

Polyfluoroalkyl Chemicals - Children

- **Developmental neurotoxicants**
- Associated with ADHD in children age 12-15
- Eliminated very slowly from the body – serum ½ life of 2 to 8.5 years
- Gore-Tex, Scotchgard and STAINMASTER all PFCs
- Serum levels directly associated with income (opposite of BPA, with higher levels seen in lower income)


Phthalates

- Found in building materials, **personal cosmetics**, **pharmaceuticals**, **nutritional supplements**, solvents, adhesives, paints, lacquers, insecticides, air fresheners, shampoos, cleaning materials, **children’s toys**, and **food packaging**
- May be listed as “**fragrance**”
- Dietary sources – chickens and eggs had DEHP metabolites, suggesting **chickens** (vs. packaging) are contaminated
- More than 75% of the U.S. population has measurable levels of several phthalate metabolites in the urine

Phthalates are Endocrine and Neurological Poisons

- Prenatal exposure associated with **conduct & attention disorders**
- Act as anti-androgens, and endocrine disruptors
  - **Inverse relationships between urinary DEHP metabolites and total T4, free T4, total T3, and thyroglobulin**
  - Positive relationships with TSH
  - Associated with both diabetes prevalence as well as insulin secretion & resistance
  - Longitudinal study in children - higher urinary phthalate excretion associated with lower adrenal androgens in girls and boys (age 11), and higher testosterone in boys (age 13).


PBDE – The New PCBs

• Polybrominated diphenyl ethers
• Breast milk samples found PBDEs replacing PCBs
  ▪ 30% of mothers more PBDEs than PCBs, and 65% had 3-fold higher levels.

• Prenatal exposure linked to lower IQ, and lower scores on tests of physical and mental development at 12-28, and 72 months

• Postnatal exposure linked to poor social competence and attention deficit in 4 year old children

She J, et al. Polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in breast milk from the Pacific Northwest. Chemosphere. 2007 Apr;67(9):S307-17
Gascon M, et al. Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age. Environ Int. 2011 Apr;37(3):605-11.
Organochlorine Pesticides and Dementia

Parkinson’s & Epigenetic Modulation

• Animal-based study: Dieldrin increases histones acetylation in dopaminergic neuronal cells,
  - It rapidly induces hyperacetylation of histones, as early as 10 min after the start of dieldrin exposure in dopaminergic neuronal cells
  - Long-term exposure also induces histone hyperacetylation in the striatum and substantia nigra
  - HAT inhibitor, anacardic acid had neuroprotective effect independent of antioxidant mechanism
  - Conclusion: “hyperacetylation is an early signaling event in the execution of apoptosis after neurotoxic exposure to the environmental toxicant dieldrin”

Solvents Impair Neurological and Psychological Function

- Compared auto repair workers exposed 2.3 hr/day to those exposed most of day to toluene
- All wore face masks and protective gear
- **Impairment of sympathetic nerves** (OR = 4.1)
- **Impairment of peripheral nerves** (OR = 6.9)
- Positive relationship between **neurological abnormalities** and a self-reported **neuropsychiatric** measurement (r = 0.35-0.66)

% OF CHRONIC DISEASE DUE TO NEUROTOXINS
Converting Disease Risk to % Caused: Attributable Fraction Calculation

\[ AF = \frac{p(rr-1)}{p(rr-1) + 1} \]

- \( p \) = underlying prevalence of risk factor in the population
- \( rr \) = relative risk (risk of contracting a disease in an exposed population divided by the risk of contracting the disease in an unexposed population)

\( AF = \% \) of disease due to the identified cause

Example: Smoking and Lung Cancer

\[ AF = \frac{A}{A + B + C} \]

\( A = 5 \)  
Number of smokers who contract Lung Cancer due to smoking

\( B = 5 \)  
Number of smokers who contract Lung Cancer not due to smoking

\( C = 15 \)  
Number of nonsmokers who contract Lung Cancer

Rosen L. An Intuitive Approach to Understanding the Attributable Fraction of Disease Due to a Risk Factor: The Case of Smoking. Int. J. Environ. Res. Public Health 2013, 10, 2932-2943
Our Process In Summary

1. Determine incidence of disease in “unexposed” population
2. Determine threshold for increased disease risk
3. Determine % of population above threshold
4. Determine incidence of disease (OR) in those above threshold
5. Calculate AF, i.e., % of disease

Whole population is exposed, so probably UNDERESTIMATES % of disease.

However, independence almost impossible, so OVERESTIMATES as well.
Status of Our Research

• 26 toxins and toxin classes, e.g. lead, mercury, BPA, OCPs
  ▪ 100s of chemicals and POPs in some classes
• 18 cancers
• 24 chronic diseases

• 1,092 cells in spreadsheet

Large Personal Ongoing Research Investment
Huge Amount of Research Work!
Toxins Studied

Aluminum
Arsenic
Cadmium
Fluoride
Lead
Manganese
Mercury

Acrylamide
Acrylonitrile
Benzene
Bisphenol A (BPA)
Chloroform
DDT
Dioxins
Glyphosate
Organochlorine pesticides (OCPs)
Organophosphate pesticides
Parabens
Phthalates
Polybrominated diphenyl ethers (PBDEs)
Polycyclic aromatic hydrocarbons (PAHs)
Polychlorinated biphenols (PCBs)
Vinyl chloride
Diseases Studied

ADHD
Alzheimer's Disease
ALS
Angiosarcoma
Anxiety
Atopic Conditions
Diabetes
Dyslipidemia
Gout
Fetal Abnormalities
Hyperuricemia
Infertility
Juvenile IQ

Juvenile Obesity
Metabolic Syndrome
Mitochondrial dysfunction
Myocardial Infarction
Obstructive Lung Disease
Osteoporosis
Peripheral Artery Disease
Peripheral Neuropathy
Prediabetes
Renal Disease
Rheumatoid Arthritis
Thyroid Dysfunction

Cancer, Bladder
Cancer, Bone
Cancer, Breast
Cancer, Cervix
Cancer, Colorectal
Cancer, Endometrial
Cancer, Head & Neck
Cancer, Liver
Cancer, Lung
Cancer, Lymph & Blood
Cancer, Ovarian
Cancer, Pancreatic
Cancer, Prostate
Cancer, Renal
Cancer, Skin
Cancer, Testicular
Cancer, Thyroid
How to Interpret the Following Slides

Threshold – Threshold exposure at which there is an increased risk of disease outcome

% Above Threshold – Percentage of the population with higher exposure than the threshold

Odds Ratio – Increased disease risk in those above threshold

% of Dz – Percent contribution of the toxin to that disease outcome
## Attention Deficit Hyperactivity Disorder

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Threshold</th>
<th>% Above Threshold</th>
<th>Odds Ratio</th>
<th>% of Dz</th>
<th>Reference PMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDT</td>
<td>1.26 ng/g serum (p,p’-DDE)</td>
<td>25.0%</td>
<td>1.8</td>
<td>16.6%</td>
<td>20106937</td>
</tr>
<tr>
<td>Lead</td>
<td>2.3 ug/dL</td>
<td>1.3%</td>
<td>2.54</td>
<td>2.0%</td>
<td>27659349</td>
</tr>
<tr>
<td>Mercury</td>
<td>~3.5ug/dL maternal whole blood</td>
<td>Difficult to determine, ~8-9%</td>
<td>1.6</td>
<td>Difficult to determine, 3.2%</td>
<td>24952233</td>
</tr>
<tr>
<td>Organophosphate pesticides</td>
<td>~413nm/L</td>
<td>NAD</td>
<td>1.55</td>
<td>NAD</td>
<td>20478945</td>
</tr>
<tr>
<td>Polycyclic Aromatic Hydrocarbons</td>
<td>2.27 ng/m3</td>
<td>94.0%</td>
<td>1.25</td>
<td>19.0%</td>
<td>22440811</td>
</tr>
<tr>
<td>PCBs</td>
<td>1.04 ng/g serum (sum of 50 PCBs)</td>
<td>25.0%</td>
<td>1.76</td>
<td>16.0%</td>
<td>20106937</td>
</tr>
</tbody>
</table>
## Juvenile IQ

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Threshold</th>
<th>% Above Threshold</th>
<th>Odds Ratio</th>
<th>% of Dz Change</th>
<th>IQ Reference</th>
<th>PMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>&gt;50ug/L urine</td>
<td>~5%</td>
<td>Reported as Beta</td>
<td>NAD</td>
<td>0.5 point decrease</td>
<td>23570911</td>
</tr>
<tr>
<td>Fluoride</td>
<td>0.7mg/L urine</td>
<td>NAD</td>
<td>Not Reported</td>
<td>NAD</td>
<td>0.59 point decrease per 1mg/mL fluoride</td>
<td>21237562</td>
</tr>
<tr>
<td>Lead</td>
<td>5-10ug/dL</td>
<td>~5%</td>
<td>Reported as Beta</td>
<td>NAD</td>
<td>4.9 point decrease</td>
<td>21450073</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>75nmol/L</td>
<td>NAD</td>
<td>Reported as Beta</td>
<td>NAD</td>
<td>5.6 point decrease</td>
<td>21507776</td>
</tr>
<tr>
<td>PAHs</td>
<td>17.96ng/m3</td>
<td>NAD</td>
<td>Reported as Beta</td>
<td>NAD</td>
<td>3.8 point decrease</td>
<td>20406721</td>
</tr>
<tr>
<td>Phthalates</td>
<td>19.4 &amp; 5.0 ug/L (MnBP/MiBP)</td>
<td>~41% ~57%</td>
<td>Reported as Beta</td>
<td>NAD</td>
<td>6.7-7.6 point decrease</td>
<td>25493564</td>
</tr>
</tbody>
</table>
### Neurological Diseases—Adults

<table>
<thead>
<tr>
<th>Disease</th>
<th>Toxin</th>
<th>Threshold</th>
<th>% Above Threshold</th>
<th>Odds Ratio</th>
<th>% of Dz</th>
<th>Reference PMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's</td>
<td>Aluminum</td>
<td>0.1 mg/L drinking water</td>
<td>40%</td>
<td>2.0</td>
<td>~30.0%</td>
<td>10901330</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>DDE</td>
<td>1.66 ng/mg cholesterol</td>
<td>6%</td>
<td>3.4</td>
<td>12.6%</td>
<td>24473795</td>
</tr>
<tr>
<td>ALS</td>
<td>Lead</td>
<td>2.38 ug/dL blood</td>
<td>33%</td>
<td>1.81</td>
<td>21.0%</td>
<td>25479292</td>
</tr>
<tr>
<td>ALS</td>
<td>DDT</td>
<td>Any exposure</td>
<td>&gt;95% below LOD</td>
<td>2.1</td>
<td>Unknown at this time</td>
<td>PMC3358481</td>
</tr>
<tr>
<td>Brain CA</td>
<td>Lead</td>
<td>0.005 ug/dL</td>
<td>14%</td>
<td>1.9</td>
<td>~50.0%</td>
<td>17164378</td>
</tr>
<tr>
<td>Emotional disturbance in boys 3-5</td>
<td>BPA</td>
<td>8.50 ug/L</td>
<td>7%</td>
<td>1.62</td>
<td>2.7%</td>
<td>22543054</td>
</tr>
</tbody>
</table>
# In-Process Example – Alzheimer’s Dz

## How to Interpret

<table>
<thead>
<tr>
<th>Term</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No association</td>
<td>No apparent disease association</td>
</tr>
<tr>
<td>#.#</td>
<td>Disease risk (not yet converted to %)</td>
</tr>
<tr>
<td>%</td>
<td>% of Disease due to toxin</td>
</tr>
<tr>
<td>NAD</td>
<td>No available data</td>
</tr>
<tr>
<td>Insufficient data</td>
<td>Inadequate or contradictory data</td>
</tr>
<tr>
<td>Theoretical</td>
<td>Known mechanism but no research</td>
</tr>
<tr>
<td>??</td>
<td>Data very dirty</td>
</tr>
<tr>
<td>Blank</td>
<td>Research not yet reviewed</td>
</tr>
<tr>
<td>Substance</td>
<td>Alzheimer's Disease</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Aluminum</td>
<td>3-33% (Dirty data!)</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Theoretical</td>
</tr>
<tr>
<td>Benzene</td>
<td>NAD</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>Theoretical</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>DDT/DDE</td>
<td>12%</td>
</tr>
<tr>
<td>Dioxins</td>
<td>Theoretical</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Annecdotal - dentistry</td>
</tr>
<tr>
<td>Glyphosate</td>
<td>Theoretical</td>
</tr>
<tr>
<td>Lead</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Mercury</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Organochlorine pesticides</td>
<td>Theoretical</td>
</tr>
<tr>
<td>Organophosphate pesticides</td>
<td>2.0</td>
</tr>
<tr>
<td>Phthalates</td>
<td>Possible correlation, insuf. data</td>
</tr>
<tr>
<td>Polybrominated diphenyl ethers</td>
<td>NAD</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>NAD</td>
</tr>
<tr>
<td>PCBs</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>
Applying Same AF Formula to AD for “Conventional” Risk Factors

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>POPULATION PREVALENCE</th>
<th>RELATIVE RISK (95% CI)</th>
<th>PAR% (Confidence Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical inactivity</td>
<td>32.5%</td>
<td>1.82 (1.19, 2.78)</td>
<td>21.0% (5.8%, 36.6%)</td>
</tr>
<tr>
<td>Depression</td>
<td>19.2%</td>
<td>1.90 (1.55, 2.33)</td>
<td>14.7% (9.6%, 20.3%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>20.6%</td>
<td>1.59 (1.15, 2.20)</td>
<td>10.8% (3.0%, 19.8%)</td>
</tr>
<tr>
<td>Mid-life hypertension</td>
<td>14.3%</td>
<td>1.61 (1.16, 2.24)</td>
<td>8.0% (2.2%, 15.1%)</td>
</tr>
<tr>
<td>Mid-life obesity</td>
<td>13.1%</td>
<td>1.60 (1.34, 1.92)</td>
<td>7.3% (4.3%, 10.8%)</td>
</tr>
<tr>
<td>Low education</td>
<td>13.3%</td>
<td>1.59 (1.35, 1.86)</td>
<td>7.3% (4.4%, 10.3%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.7%</td>
<td>1.39 (1.17, 1.66)</td>
<td>3.3% (1.5%, 5.4%)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td>30.8% - 54.1%</td>
</tr>
</tbody>
</table>

## Portion of Population with Toxin Load Which Doubles Disease Risk

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Disease</th>
<th>% with Doubled Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>Asthma</td>
<td>94%</td>
</tr>
<tr>
<td>PCB187</td>
<td>Breast Cancer</td>
<td>60%</td>
</tr>
<tr>
<td>Phthalates</td>
<td>Diabetes</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Lead</strong></td>
<td>ALS</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Aluminum</strong></td>
<td>Alzheimer's Disease</td>
<td>25%</td>
</tr>
<tr>
<td><strong>DDT</strong></td>
<td>ADHD</td>
<td>25%</td>
</tr>
<tr>
<td>PCBs</td>
<td>Diabetes</td>
<td>25%</td>
</tr>
<tr>
<td>Dioxin-like PCBs</td>
<td>Rheumatoid Arthritis</td>
<td>25%</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Gout</td>
<td>23%</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>Diabetes</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Cigarette smoking</strong></td>
<td>Lung Cancer</td>
<td>21%</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Diabetes</td>
<td>20%</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>Diabetes</td>
<td>20%</td>
</tr>
</tbody>
</table>
BIOACCUMULATION AND MECHANISMS OF DAMAGE
# Toxin Half Lives in Blood and Tissues

<table>
<thead>
<tr>
<th>Toxin</th>
<th>“Normal” (mg/L)</th>
<th>Acute Toxic (mg/L)</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>0.002-0.07</td>
<td>0.05-0.25</td>
<td>2-4 days (CDC)</td>
</tr>
<tr>
<td>Benzene</td>
<td>0.0002</td>
<td>60ppm</td>
<td>0.5-1.0 days</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.0003-0.0065</td>
<td>0.015-0.05</td>
<td>16 years</td>
</tr>
<tr>
<td>Chlordane</td>
<td>0.001</td>
<td>0.0025</td>
<td>3-4 days</td>
</tr>
<tr>
<td>DDT/DDE</td>
<td>Absent</td>
<td>285mg/kg</td>
<td>2-10 years</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>0.0015</td>
<td>0.15-0.30</td>
<td>2-12 months</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Absent</td>
<td>1000-2000</td>
<td>15%/hour</td>
</tr>
<tr>
<td>Lead</td>
<td>0.09</td>
<td>0.4-0.6</td>
<td>1-1.5 mo (2+ yrs bone)</td>
</tr>
<tr>
<td>Mercury</td>
<td>0.0015-0.002</td>
<td>0.05-0.2</td>
<td>2 months (CDC)</td>
</tr>
<tr>
<td>PCBs</td>
<td>&lt;700ng/g lipid</td>
<td>700-1000ng/g lipid</td>
<td>3-25 years!</td>
</tr>
<tr>
<td>Toluene (hippuric acid)</td>
<td>1.5-1.6g/g creatinine</td>
<td>2.5g/g creatinine</td>
<td>0.5-3 days</td>
</tr>
</tbody>
</table>

Bioaccumulation of Neurotoxins

DDT banned in 1972       PCBs banned in 1977

Neurotoxin Synergy

- Neuron cell study
- Damage (units):
  - 400 (OCP)
  - +
  - 600 (AL)
  - =
  - 2,000

Which are the Worst Toxins?

• According to the CDC
  ▪ Toxicity
  ▪ Population toxic load
  ▪ Prevalence in toxic waste sites
• According to clinical importance (our research)
  ▪ Exposure
  ▪ % of disease
  ▪ Ability of the body to detoxify/excrete
<table>
<thead>
<tr>
<th>2013 RANK</th>
<th>SUBSTANCE NAME</th>
<th>TOTAL POINTS</th>
<th>2011 RANK</th>
<th>CAS RN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ARSENIC</td>
<td>1670.4</td>
<td>1</td>
<td>0077440-38-2</td>
</tr>
<tr>
<td>2</td>
<td>LEAD</td>
<td>1529.2</td>
<td>2</td>
<td>0077439-92-1</td>
</tr>
<tr>
<td>3</td>
<td>MERCURY</td>
<td>1458.6</td>
<td>3</td>
<td>0077439-97-6</td>
</tr>
<tr>
<td>4</td>
<td>VINYL CHLORIDE</td>
<td>1359.8</td>
<td>4</td>
<td>000075-01-4</td>
</tr>
<tr>
<td>5</td>
<td>POLYCHLORINATED BIPHENYLS</td>
<td>1343.5</td>
<td>5</td>
<td>001336-36-3</td>
</tr>
<tr>
<td>6</td>
<td>BENZENE</td>
<td>1328.5</td>
<td>6</td>
<td>000071-43-2</td>
</tr>
<tr>
<td>7</td>
<td>CADMIUM</td>
<td>1318.7</td>
<td>7</td>
<td>0077440-43-9</td>
</tr>
<tr>
<td>8</td>
<td>BENZO(A)PYRENE</td>
<td>1304.7</td>
<td>8</td>
<td>000050-32-8</td>
</tr>
<tr>
<td>9</td>
<td>POLYCYCLIC AROMATIC HYDROCARBONS</td>
<td>1279.7</td>
<td>9</td>
<td>130498-29-2</td>
</tr>
<tr>
<td>10</td>
<td>BENZO(B)FLUORANTHENE</td>
<td>1251.2</td>
<td>10</td>
<td>000205-99-2</td>
</tr>
<tr>
<td>11</td>
<td>CHLOROFORM</td>
<td>1203.5</td>
<td>11</td>
<td>000067-66-3</td>
</tr>
<tr>
<td>12</td>
<td>AROCLOR 1260</td>
<td>1190.3</td>
<td>12</td>
<td>011096-82-5</td>
</tr>
<tr>
<td>13</td>
<td>DDT, P,P’-</td>
<td>1181.5</td>
<td>13</td>
<td>000050-29-3</td>
</tr>
<tr>
<td>14</td>
<td>AROCLOR 1254</td>
<td>1171.2</td>
<td>14</td>
<td>011097-69-1</td>
</tr>
<tr>
<td>15</td>
<td>DIBENZO(A,H)ANTHRACENE</td>
<td>1155.4</td>
<td>15</td>
<td>000053-70-3</td>
</tr>
<tr>
<td>16</td>
<td>TRICHLOROETHYLENE</td>
<td>1151.4</td>
<td>16</td>
<td>000079-01-6</td>
</tr>
<tr>
<td>17</td>
<td>CHROMIUM, HEXAVALENT</td>
<td>1146.9</td>
<td>17</td>
<td>018540-29-9</td>
</tr>
<tr>
<td>18</td>
<td>DIELDRIN</td>
<td>1142.5</td>
<td>18</td>
<td>000060-57-1</td>
</tr>
<tr>
<td>19</td>
<td>PHOSPHORUS, WHITE</td>
<td>1141.4</td>
<td>19</td>
<td>007723-14-0</td>
</tr>
<tr>
<td>20</td>
<td>HEXACHLOROBUTADIENE</td>
<td>1128.2</td>
<td>20</td>
<td>000087-68-3</td>
</tr>
<tr>
<td>21</td>
<td>DDE, P,P’-</td>
<td>1126.2</td>
<td>21</td>
<td>000072-55-9</td>
</tr>
<tr>
<td>22</td>
<td>CHLORDANE</td>
<td>1125.9</td>
<td>22</td>
<td>000057-74-9</td>
</tr>
<tr>
<td>23</td>
<td>COAL TAR CREOSOTE</td>
<td>1124.5</td>
<td>23</td>
<td>008001-58-9</td>
</tr>
</tbody>
</table>
# The Worst Toxins Clinically

<table>
<thead>
<tr>
<th>My Rank</th>
<th>Toxin</th>
<th>Diseases</th>
<th>Primary Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Arsenic</td>
<td>Cancers, diabetes, gout</td>
<td>Water, chicken, rice</td>
</tr>
<tr>
<td>2</td>
<td>DDT</td>
<td>ADHD, dementia, diabetes</td>
<td>Everywhere</td>
</tr>
<tr>
<td>3</td>
<td>Phthalates</td>
<td>ADHD, diabetes</td>
<td>Soft plastics, HABAs</td>
</tr>
<tr>
<td>4</td>
<td>PBDEs</td>
<td>ADHD, diabetes</td>
<td>Flame retardant fabrics</td>
</tr>
<tr>
<td>5</td>
<td>PAHs</td>
<td>ADHD, cancers, dyslipidemia</td>
<td>Smoking, charbroiling</td>
</tr>
<tr>
<td>6</td>
<td>PCBs</td>
<td>Cancers, diabetes, MI, RA</td>
<td>Everywhere</td>
</tr>
<tr>
<td>7</td>
<td>Mercury</td>
<td>Dementia</td>
<td>“Silver” fillings, fish</td>
</tr>
<tr>
<td>8</td>
<td>Lead</td>
<td>Cardiovascular disease, IQ</td>
<td>Paint, water</td>
</tr>
<tr>
<td>?</td>
<td>Glyphosate</td>
<td>Pending</td>
<td>Research invalid</td>
</tr>
</tbody>
</table>
Assessment

• Direct measurement
• Body load/Historic exposure
  ▪ Challenge testing
  ▪ Toenails
  ▪ Hair
• Indirect measures
  ▪ GGTP
  ▪ 8-OHdG
  ▪ Conventional laboratory tests
Direct Assessment

• Toxic metals:
  ▪ Urine or blood levels considered the gold standard
    • Primarily indicate current exposure
    • Poor intercorrelations
    • Correlation with body load controversial
    • 95% standard questionable

• Persistent organic pollutants and solvents
  ▪ Direct measure in blood and urine now available
  ▪ Fat biopsy measurement more indicative of body load
    • Invasive and expensive
“Safe” Lead Levels 6-Fold Lower Than Original 1965 95% Standard
Poor Hg Inter-Test Correlation

- Poor correlation between blood and urine, $r = 0.30$
- Better correlation between blood and hair, $r = 0.56$


## 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>&lt; dl</td>
<td>&lt; 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony (Sb)</td>
<td>&lt; dl</td>
<td>&lt; 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic (As)</td>
<td>39</td>
<td>&lt; 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barium (Ba)</td>
<td>0.5</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>&lt; dl</td>
<td>&lt; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium (Cd)</td>
<td>0.4</td>
<td>&lt; 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesium (Cs)</td>
<td>5.3</td>
<td>&lt; 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadolinium (Gd)</td>
<td>&lt; dl</td>
<td>&lt; 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>0.1</td>
<td>&lt; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury (Hg)</td>
<td>2.4</td>
<td>&lt; 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel (Ni)</td>
<td>1.1</td>
<td>&lt; 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palladium (Pd)</td>
<td>&lt; dl</td>
<td>&lt; 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum (Pt)</td>
<td>&lt; dl</td>
<td>&lt; 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tellurium (Te)</td>
<td>&lt; dl</td>
<td>&lt; 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thallium (Tl)</td>
<td>0.4</td>
<td>&lt; 0.5</td>
<td></td>
<td></td>
</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; 4</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>&lt; dl</td>
<td>&lt; 0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Urine Creatinine

<table>
<thead>
<tr>
<th>RESULT mg/dL</th>
<th>REFERENCE INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>35 - 240</td>
</tr>
</tbody>
</table>

### Specimen Data

- **Date Collected:** 01/09/2017
- **pH upon receipt:** Acceptable
- **Volume:** Random
- **Proving Agent:** PRE PROVOCATIVE
- **Date Received:** 01/11/2017
- **Date Completed:** 01/12/2017

**Comments:**

- **<dl:** less than detection limit
<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>5.2</td>
<td>&lt; 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony (Sb)</td>
<td>0.2</td>
<td>&lt; 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic (As)</td>
<td>140</td>
<td>&lt; 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barium (Ba)</td>
<td>0.8</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>0.3</td>
<td>&lt; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium (Cd)</td>
<td>0.4</td>
<td>&lt; 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesium (Cs)</td>
<td>6.3</td>
<td>&lt; 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadolinium (Gd)</td>
<td>&lt; dl</td>
<td>&lt; 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>6.9</td>
<td>&lt; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury (Hg)</td>
<td>53</td>
<td>&lt; 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel (Ni)</td>
<td>1.7</td>
<td>&lt; 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palladium (Pd)</td>
<td>&lt; dl</td>
<td>&lt; 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum (Pt)</td>
<td>&lt; dl</td>
<td>&lt; 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tellurium (Te)</td>
<td>&lt; dl</td>
<td>&lt; 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thallium (Tl)</td>
<td>0.5</td>
<td>&lt; 0.5</td>
<td></td>
<td></td>
</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>14</td>
<td>&lt; 4</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>&lt; dl</td>
<td>&lt; 0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>URINE CREATININE</th>
<th>RESULT mg/dL</th>
<th>REFERENCE INTERVAL</th>
<th>-2SD</th>
<th>-1SD</th>
<th>MEAN</th>
<th>+1SD</th>
<th>+2SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>82.5</td>
<td>35-240</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**
- Date Collected: 01/09/2017
- pH upon receipt: Acceptable
- Date Completed: 01/13/2017
- Collection Period: Random
- Provoking Agent: DMPS 500MG, DMSA
- Volume: Random
Hg Assessment Correlations

- Extensive measurements in 65
  - Whole blood Hg
  - Oral DMPS challenge
  - Amalgam surfaces

- Correlations
  - Whole blood w pre urine: $r = 0.40$
  - Whole blood w post urine: $r = 0.57$
  - Pre urine w post urine: $r = 0.68$
  - Amalgams w pre urine: $r = 0.26$
  - Amalgams w whole blood: $r = 0.36$
  - **Amalgams with post urine: 0.44**

- Preliminary support that challenge testing is better

Pizzorno J, Markin A. Unpublished research. 2010
Challenge Testing: Correlates with Fish Consumption

- Compared 0 to 1-2 to 3 or more servings per week
- First urine showed essentially no differentiation
- Challenge testing showed clear correlation
- Still a lot of variation

Historic: Toenail Arsenic Correlates with Diabetes

**How As causes diabetes**

- Blocks sugar stimulating insulin secretion
- Epigenetic inhibition of sugar regulation

Direct: Chemicals

- Measuring chemicals and POP load directly
  - Urine sample
  - 150+ environmental chemicals

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Result μg/g creatinine</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Industrial Toxicants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) 2-Hydroxysobutyric Acid (2HIB)</td>
<td>3,955</td>
<td>75th</td>
</tr>
<tr>
<td>Parent: MTBE/ETBE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTBE and ETBE are gasoline additives used to improve octane ratings. Exposure to these compounds is most likely due to groundwater contamination, inhalation or skin exposure to gasoline or its vapors, and exhaust fumes. MTBE has been demonstrated to cause hepatic, kidney, and central nervous system toxicity, peripheral neurotoxicity, and cancer in animals. Very high values have been reported in genetic disorders. Because the metabolites of these compounds are the same, ETBE may be similarly toxic.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Monoethylphthalate (MEP)</td>
<td>20</td>
<td>75th</td>
</tr>
<tr>
<td>Parent: Diethylphthalates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phthalates may be the most widespread group of toxins in our environment, commonly found in many bath and beauty products, cosmetics, perfumes, oral pharmaceuticals, insect repellants, adhesives, niks, and varnishes. Phthalates have been implicated in reproductive damage, depressed leukocyte function, and cancer. Phthalates have also been found to increase blood coagulation, lower testosterone, and alter sexual development in children. Low levels of phthalates can feminize the male brain of the fetus, while higher levels can hyper-masculinize the developing male brain.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) 2,3,4-Methylhippuric Acid (2,3,4-MHA)</td>
<td>347</td>
<td>75th</td>
</tr>
<tr>
<td>Parent: Xylene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xylens (directly phthalates) are found not only in common products such as paints, lacquers, pesticides, cleaning fluids, fuel and exhaust fumes, but also in perfumes and insect repellents. Xylens are oxidized in the liver and bound to glycine before eliminated in urine. High exposures to xylene create a rise in oxidative stress, causing symptoms such as nausea, vomiting, dizziness, central nervous system depression, and death. Occupational exposure is often found in pathology laboratories where xylene is used for tissue processing.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4) Phenylglyoxylic Acid (PGO)</td>
<td>279</td>
<td>75th</td>
</tr>
<tr>
<td>Parent: Styrene/Ethylenebenzene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Styrene is used in the manufacturing of plastics, in building materials, and is found in car exhaust fumes. Polystyrene and its copolymers are widely used in food packaging materials. The ability of styrene monomer to leach from polystyrene packaging to food has been reported. Occupational exposure due to inhalation of large amounts of styrene adversely impacts the central nervous system. Causes concentration problems, muscle weakness, fatigue, and nausea, and irritates the mucous membranes of the eyes, nose, and throat.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LLQO - Lower Limit of Quantitation
*N.D. - Not Detected

Testing performed by The Great Plains Laboratory, Inc., Lenexa, Kansas. The Great Plains Laboratory has developed and determined the performance characteristics of this test. This test has not been evaluated by the U.S. FDA; the FDA does not currently regulate such testing.
Conventional Laboratory Tests Reflect Toxic Load in “Normal” Range

• Surprising number show toxin exposure
  - CBC: RBC, WBC, platelet count, hemoglobin, basophilic stippling
  - Liver enzymes: ALT, GGTP
  - Inflammatory markers: CRP
  - Lipids: LDL, oxLDL, triglycerides
  - Blood sugar: insulin, FBS, 2-hour PP
  - Metabolites: bilirubin, uric acid, homocysteine, 8-OHdG
  - Thyroid: T3, T4, TSH

• The historic “normal” range has been changing as the population has become more toxic
GGT: Indirect Measure of Toxin Load

- Exposure to POPs and metals induces GGTP as a defensive mechanism.
- **Within normal range** predicts:
  - All cause mortality
  - Type 2 diabetes
  - Coronary heart disease, hypertension, stroke, dyslipidemia,
  - Chronic kidney disease
  - Cancer.
- Cumulative biomarker for environmental pollutants.
- But not useful in the 10% with certain polymorphisms

GGT and Alcohol Consumption

- GGT directly correlates with alcohol consumption
- 40 g/d elevates GGT ~15%
- Watch for false negatives
  - Genomic variation
  - Are these the ones most sensitive to/damaged by chemical toxins?
- Could up-regulation of GGT in light alcohol consumption be reason for benefit?

GGT Correlates With Toxic Metal Levels

GGT Levels Correlate with Risk of Death

- GGT over 50 associated with tripling of death rate!
- 30-40 associated with doubling

Homocysteine is Increased by Pb & Cd

8-OHdG Correlates with Mercury

8-OHdG Correlates with Arsenic Load

- Urinary 8-OHdG measures DNA damage
- Many studies have found significant correlation with levels of typical forms of As

INTERVENTION
Intervention

- Avoidance, AVIODANCE, **AVOIDANCE**
- Facilitate detoxification
- Increase excretion
- Supply competitive nutrients
- Decrease damage
Sources of Toxins

- 60% Food
- 10% Water
- 10% House and yard chemicals
- 10% Health and beauty aids
- 5% Air

These are my best estimates, will likely change as new research becomes available
Public Health Can Decrease Toxic Load

- Banning lead in gasoline and paint worked—blood levels down dramatically.
- No threshold for safety –
  - **Children who had whole blood lead concentrations of <5 µg/dL (supposedly safe) associated with decreased IQ**
  - **2.4 million children at levels between 5 and 9.9 ug/dL**
- July 2012: CDC changed recommended level to intervene in children from 10 to 5.0 ug/dL. Eliminated term “level of concern”, to avoid false sense of safety.

http://www.environment.ucla.edu/reportcard/article3772.html
Mercury In Fish

- 10-fold variation from lowest to highest
- All fish contain some mercury
- Pick those with highest omega-3 and lowest Hg:
  - Sardines
  - Anchovies
  - Small salmon

Source: http://www.fda.gov/Food/FoodSafety/ProductspecificInformation/Seafood/FoodbornePathogensContaminants/Methylmercury/ucm115644.htm
Fish (esp farmed) a Significant Source of POPs

Bjermo H, et al. Fish intake and breastfeeding time are associated with serum concentrations of organochlorines in a Swedish population. Environ Int. 2013 Jan;51:88-96
# Worst/Best Foods

(www.ewg.org 4/17)

<table>
<thead>
<tr>
<th>Dirty Dozen™</th>
<th>Clean 15™</th>
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<tbody>
<tr>
<td>1. Strawberries</td>
<td>1. Sweet Corn</td>
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<td>2. Spinach</td>
<td>2. Avocado</td>
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<tr>
<td>5. Peaches</td>
<td>5. Onions</td>
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<tr>
<td>7. Cherries</td>
<td>7. Papayas</td>
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<tr>
<td>8. Grapes</td>
<td>8. Asparagus</td>
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<tr>
<td>10. Tomatoes</td>
<td>10. Eggplant</td>
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<tr>
<td>11. Sweet Bell Peppers</td>
<td>11. Honeydew melon</td>
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<tr>
<td>• Hot peppers</td>
<td>13. Cantaloupe</td>
</tr>
<tr>
<td>• Kale</td>
<td>14. Cauliflower</td>
</tr>
<tr>
<td></td>
<td>15. Grapefruit</td>
</tr>
</tbody>
</table>
Eating Organically Grown Foods Dramatically Decreases Neurotoxins

- Study done in Seattle children
- 10-fold increase in POPs doubles ADHD
- **Blood levels drop measurably within 3 days of eating only organically grown foods**


BPA: Home-Made or Glass Containers

- One 12oz serving daily for 1 week of either fresh soup or canned soup (Progresso)
  - 12-fold increase in BPA
- 2 servings of 6 ounces Soy milk in can compared to glass
  - 16-fold increase in BPA
  - Systolic BP elevated 4.5 mm Hg
- Diabetes 2X risk threshold?


Bae S1, Hong YC2. Exposure to bisphenol A from drinking canned beverages increases blood pressure: randomized crossover trial. Hypertension. 2015 Feb;65(2):313-9.
HABAs Can Be Significant Source of POPs

Breast Feeding Decreases POPs

Bjermo H, et al. Fish intake and breastfeeding time are associated with serum concentrations of organochlorines in a Swedish population. Environ Int. 2013 Jan;51:88-96
FACILITATE DETOXIFICATION AND EXCRETION
Mediterranean Diet Slows Aging and Prevents Neurological disease

- Those following most closely this dietary pattern have a longer lifespan and a reduced risk of neurodegenerative disease, including Alzheimer’s.
- Review of all prospective cohort studies (nearly 600,000 subjects)
- Greater adherence to a Mediterranean diet is associated with a significant reduction in:
  - Overall mortality (-8%),
  - Mortality/incidence of cardiovascular diseases (-10%),
  - Incidence of or mortality from cancer (-6%),
  - Incidence of Parkinson’s disease and Alzheimer’s disease (-13%)

Fiber Decreases POPs

• Fiber
  ▪ Rice bran (PCBs, PCDFs, dioxins)
  ▪ Wheat bran (PCBs)
  ▪ 5g/day
  ▪ Slow!!

• Bile sequestrants
  ▪ Cholestamide, Cholestyramine, Olestra

Colestimide Reduces PCBs

- 5 g/d (?)
- 6 months
- Average reduction 23%
- Those who did not take increased 24%

Olestra Decreases PCBs and DDE

- Potato chips made with olestra or vegetable oil
- 12 months
- 15 g of olestra per day
  - 22 Pringles Light crisps
- No change in diet
- Higher body fat = lower % decrease
- 25% loose stools

% Decrease in Blood PCBs

\( \frac{1}{2} \) life decreased from 20+ years to 8.5 years

Cadmium – Sweat it Out!

- **Cadmium eliminated efficiently through sweat**
- 20 individuals sweat via exercise, steam or infrared sauna
- Cadmium found in sweat in those with undetectable serum levels, suggesting it could be used for assessment of burden
- Elimination of other minerals (Cu, Mn) suggests need replenishment during induced sweat

DMSA to Excrete Lead and Mercury

- 2,3-Dimercaptosuccinic acid
- SH-containing, water-soluble, low-toxicity, oral (IV toxic)
- Developed in 1950s as alternative to more toxic chelating agents
- 10-20% of oral dose absorbed
- Chelates all forms of mercury (more effective for Pb)
- ½ through urine, ½ through bile
- Amount of Hg bound: ~7.5 ug/g of oral DMSA
- Increases glutathione production
- ½ life in blood 2-3 hours

DMSA

- Nutrients to improve efficacy
  - Alpha lipoic acid
  - NAC
  - Probiotics
  - Fiber
- Research studies use 30 mg/kg/day
  - 7 days on, 7 off
  - Not recommended
- Protocol we used:
  - 50 mg trial dose; if no reaction within 2 hours:
    - 250 mg qd for 3 days then off for 11 days, or
    - 250 mg every 3rd day before bed

NAC

- Most research animal and human cell lines
- Multiple benefits:
  - Increases production of glutathione
  - Protects human neurological cells from Hg toxicity
  - Reverses damage to human pancreatic cells from Hg
  - Directly binds to Hg, esp. MeHg, and excrete through kidneys

Watch for Sulfur Sensitive Patients

- Clinical indications:
  - Allergies  Onion and/or garlic intolerance
  - GURD  Sulfite sensitivity
  - IBS

- Laboratory:
  - Increased sulfite/sulfate ratio in urine
  - Decreased Phase II sulfation

- Intervention:
  - Molybdenum 300 ug/d
  - Manganese 20 mg/d
  - DMSA and possibly NAC contraindicated until S metabolism improved
Lead Detoxification

- Chelators: DMPS, DMSA, EDTA, d-penicillamine (DPA)
  - Long history of EDTA use, most often used IV
  - EDTA also depletes Zn, Cu, Fe, Co, and Mn
- **Oral DMSA as effective as IV EDTA**
  - Pt example decreased from 3.7 to 2.4
  - Not clear if DMSA removes lead from bone, but does reduce hippocampal lead
  - Combination of EDTA and DMSA increase excretion

Bradberry, S et al. A comparison of sodium calcium edetate (edetate calcium disodium) and succimer (DMSA) in the treatment of inorganic lead poisoning. Clinical Toxicology 2009

Bradberry Use of oral DMSA in adult patients with inorganic lead poisoning. QJM. 2009

Lee BK, Provocative chelation with DMSA and EDTA: evidence for differential access to lead storage sites. Occup Environ Med. 1995
Glutathione: Critical

- **Difficult to overstate its importance in brain health**
- Most important intracellular and intra-mitochondrial antioxidant
- Binds and transports mercury out of cells and brain
- Irreversibly(?) binds to mercury in the brain
- Neutralizes oxidative damage from mercury and POPs
- Facilitates detoxification of POPs
- Depleted by oxidative stress, metals, alcohol
- Even predictor of healthy aging!

Depleted GSH Has Been Implicated In:

- **Neurodegenerative disorders** (Alzheimer's, Parkinson's and Huntington's diseases, amyotrophic lateral sclerosis, Friedreich's ataxia)
- Pulmonary disease (COPD, asthma, and acute respiratory distress syndrome)
- Immune diseases (HIV, autoimmune disease)
- Cardiovascular diseases (hypertension, myocardial infarction, cholesterol oxidation)
- Liver disease
- Cystic fibrosis
- Chronic age-related diseases (cataracts, macular degeneration, hearing impairment, and glaucoma)
- Aging process itself

Glutathione Protects Neurons

- 50% less glutathione (GSH) in the substantia nigra of Parkinson's patients
- But not in other parts of brain => used up in neutralization of local toxins
- GSH 600 mg IV bid x 30 days
  - 42% decline in disability
  - Lasted 2-4 months after stopped
- **Protects both telomeres and mtDNA**

Glutathione

- Tripeptide (cysteine, glycine and glutamic acid)
- Relatively high (5 millimolar) concentrations in most cells
- Exists in reduced state (GSH) and oxidized state (GSSG)
- Ratio determines cell redox status
  - Healthy cells at rest have a GSH/GSSG ratio >100
  - Ratio drops to 1-10 in cells exposed to oxidant stress
- Produced exclusively in the cytosol and actively pumped into mitochondria
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Glutathione: Direct Administration

- IV glutathione
- Nebulized glutathione
- Oral glutathione (basically, expensive cysteine)
- Oral liposomal glutathione
- Topical glutathione
- Intranasal glutathione


NAC Elevates Glutathione

- N-acetylcysteine
- Amino acid cysteine is a rate-limiting factor for GSH synthesis
- Variety of both clinical trials and in-vitro/in-vivo data suggest that supplying cysteine as NAC is an effective strategy for enhancing GSH production and intracellular cysteine.
- Increases intracellular glutathione
- **Dosage dependent increase in glutathione**


NAC Decreases GGT

- 600mg/day for 4 weeks reduced GGT from 62.7 to 46.3 U/L.
- Expected result as decreases need for recycling glutathione

Breast Feeding Decreases PCBs
Case Histories
Patience!

Don’t expect the speed of results seen with drug or even nutrition therapy

1. First must greatly decrease body load
   - Decrease exposure as much as possible
   - Some toxins become apparent only after others removed

2. For damaged enzymes to work:
   - Must displace enzyme poison with nutrient cofactor, or
   - Degrade and replace enzyme
     - ½ life MAO-B in baboon brain = 30 days

3. Then the tissue damage has to be repaired

## It All Started After Amalgams (MB)

### 48 yo male, employee, Calgary

#### Relevant medical history
- Symptoms began 2 mo after amalgams and gold crowns
  - Chest pain followed by weakness, dizziness and shortness of breath.
  - Multiple trips to emergency room with no answers.
  - Neck pain, gastrointestinal problems and insomnia. Extreme fatigue, chronic sinusitis.
- 8 amalgams, 2 gold crowns
- Challenge Hg: 5.8 ug/g creat

### Intervention
- All amalgams removed
- B-complex
- Vitamin C
- Infrared saunas
- IV DMPS

### Results
- “Feel better now both physically and mentally than I have in 15 years.”
- Virtually all symptoms eventually alleviated
- All prescription drugs discontinued
- Improvement within 2 weeks of removal of amalgams
MB Symptoms That Went Away

- Chest pains
- Completely exhausted all the time
- Amalgam tattooing on the gums
- Muscle twitching and muscle tremors
- Burning in the mouth and tongue
- **Numbness in the feet and hands**-feeling of something crawling under the skin
- Insomnia
- Night Sweats
- Tingling on the face
- Tingling and prickly feeling on the scalp and legs
- Severe lower back pain
- Sore muscles and joint pain
- Double vision
- Blurred vision
- Jabbing pain in the eyes
- Dizziness
- Depression
- Anxiety – panic attacks
- Memory loss
- Brain fog – impaired cognitive thinking
- Sour and metallic taste
- Increased saliva production
- Elevated liver enzymes
- Itchy hands
- High pitch whining in the ears
- Persistent cough and sore throat
- Cold hands and feet
- No appetite to eat

Full relief took ~ 2 years
Am I Losing my Mind? April 2012

- 67 yo white woman
- I had the odd feeling that I was living in a fog, that things were very fuzzy and that my memory was very sporadic. I was having trouble sleeping and had a lot of muscle aches during the night. I always had a metal taste in my mouth and felt that my breath lacked freshness other than the first few minutes after brushing my teeth. My skin and scalp were always sore and especially dry.

2 years IV chelation discontinued due to side effects & no benefit
I do know that things really improved once I started your protocol and I was happy to see the light at the end of the Mercury tunnel.
June 2013

- With each successive test the symptoms were lessening and I was feeling more normal.

Hg = 7.3
December 2013

- It was a day of celebration when I received the last test results.
- I would caution people to remember that clearing mercury out of one’s system is a long process but it is worth the effort even if it takes many years. Being healthy is a good reward for all the patience required to do the heavy mercury lifting.
- Good luck with your seminars. I will always be in your debt for your help.
Summary: Assessment

Metals
• First morning urine (current exposure)
• Challenge with, oral:
  • DMSA 500mg
  • DMPs 300 mg
  • Collect urine 6 hours (body load)

Chemicals and POPs
• Urine or blood

Total Toxic Load
• GGT: > 25 (20?)
• 8-OHdG: >4 ng/mg creat
Summary: Intervention

1. Keep the toxins out!
   - Organically grown foods
   - Prepare own food
   - Food stored in glass, not plastic or cans
   - Clean water
   - Safe health and beauty aids

2. Facilitate detoxification and excretion
   - High fiber diet and supplements
   - Good quality multivitamin and mineral
   - DMSA if lead or mercury

3. Protects against damage
   - NAC to increase glutathione to protect against oxidative and damage and for binding POPs
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<td>Osteoporosis</td>
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</table>
Summary

1. Toxins are now ubiquitous in the industrialized world
2. Toxins are now the primary drivers of chronic disease
3. Standard laboratory tests now include in “normal” range the body’s adaptations to, and damage from, toxins

Thank you
Chrissie Cirovic, ND & Geoff Bender, ND
For Your Excellent Research Work