Conventional Laboratory Tests to Assess Toxic Load

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Overview

1. Toxicity has Become the New Normal
   ⇒ “Normal” laboratory ranges are toxic ranges
2. Conventional Measures of Toxic Load are Flawed
3. Conventional Lab Tests as Indirect Measure of Toxic Load
4. Summary Interpretation
<table>
<thead>
<tr>
<th>Toxin</th>
<th>Type</th>
<th>Use</th>
<th>Threshold for disease association</th>
<th>% of US above threshold</th>
<th>Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordane</td>
<td>OC pesticide</td>
<td>Termites, corn, citrus, lawns, gardens</td>
<td>14.5ng/g lipid</td>
<td>63% (diabetes)</td>
<td>Diabetes (2.0)</td>
</tr>
<tr>
<td>BPA</td>
<td>Plasticizer</td>
<td>Water bottles, canned food, water pipes, thermal sales receipts</td>
<td>4.8 men; 5.1 women (urine, ng/mL)</td>
<td>~18% (diabetes)</td>
<td>Diabetes, hypertension</td>
</tr>
<tr>
<td>Octachlorodibenzo-p-dioxin (OCDD)</td>
<td>Polychlorinated dibenzo-p-dioxin</td>
<td>Incineration or burning of waste; bleaching processes used in pulp and paper mills</td>
<td>1010 pg/g lipid (highest quartile)</td>
<td>10-25% (hypertension)</td>
<td>Hypertension (7.9 for women, highest quartile), diabetes (2.1), obesity, learning disability (2.72)</td>
</tr>
<tr>
<td>MEP (mono-ethyl phthalate)</td>
<td>Phthalate</td>
<td>Toothbrushes, automobile parts, tools, toys, and food packaging; aspirin, cosmetics, food packaging</td>
<td>&gt;17.5 ng/mL (urine)</td>
<td>~60% (diabetes)</td>
<td>Diabetes (1.48), lower BMD, obesity</td>
</tr>
<tr>
<td>p,p'-DDE</td>
<td>DDT metabolite (OC pesticide)</td>
<td>Agricultural crops</td>
<td>1,560ng/g lipid</td>
<td>25% (diabetes)</td>
<td>Diabetes (2.3-4.3), early menopause, impaired cognitive function (2-3x; 6.5x in highest 5th percentile), peripheral arterial disease</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Toxic metal</td>
<td>Mining/smelting, wood preservative, pesticides</td>
<td>7.4ug/L total arsenic (urine)</td>
<td>20% (diabetes)</td>
<td>Cancers, diabetes (2.6-4.6), dyslipidemia, gout</td>
</tr>
</tbody>
</table>
Conventional Toxin Tests are Flawed

1. Blood and urine primarily only reflect acute exposure
2. Toxicity primarily defined as >95 percentile
3. Poor inter-test correlations
Blood Primarily Reflects Acute Exposure

Centers for Disease Control

*Elevated blood cadmium levels confirm recent acute exposure, but do not correlate with body burden or clinical outcome, and should not be used to determine the need for treatment.*

California Poison Control System

*Whole blood mercury is a useful marker of acute exposure. However, as mercury redistributes into tissues the blood level will decline even as organ toxicity manifests.*

The Official Newsletter of the California Poison Control System. Volume 9, Number 1, Spring 2011
“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, $r = 0.56$


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, AST, ALP, 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

**WBC Lowered by PCB and OCP Exposure**

- Strong inverse correlation with PCBs and OCPs and CBC
- Linear with almost all PCBs
- High variability with OCPs
- Within “normal” range!
Effects on WBC Worsen with Years of Exposure to Benzene and CO

- Petrol filling workers
- “Healthy” non-smokers

Platelet Count Decreases with Years of Exposure to Benzene and CO

- Petrol filling workers
- “Healthy” non-smokers

Solvents Decrease Platelet Count

- Compared workers exposed 2.3 hr/day to those exposed most of day to toluene
- All wore face masks and protective gear
- Platelet count 14% lower: 252 versus 216/ml
- Impairment of sympathetic nerves (OR = 4.13)
- Impairment of peripheral nerves (OR = 6.94)
- Positive relationship between neurological abnormalities and a self-reported neuropsychiatric measurement (r = 0.35-0.66)

## Basophilic Stippling of Red Cells

<table>
<thead>
<tr>
<th>Toxins</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>Alpha-thalassemia, HbH Disease</td>
</tr>
<tr>
<td>Lead</td>
<td>Beta thalassemia</td>
</tr>
<tr>
<td></td>
<td>Hereditary pyrimidine 5'-nucleotidase deficiency</td>
</tr>
<tr>
<td></td>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td></td>
<td>Sideroblastic anemia</td>
</tr>
<tr>
<td></td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
</tbody>
</table>
GGT: Indirect Measure of Toxic Load

- Glutathione is key intracellular defense against oxidative stress
- Cellular GGT metabolizes extracellular GSH, allowing precursor amino acids to be reutilized for intracellular GSH.
- Exposure to POPs induces GGT as a defensive mechanism.
- Within normal range predicts type 2 diabetes, coronary heart disease, hypertension, stroke, dyslipidemia, chronic kidney disease and cancer.
- **Men with GGT >50 U/l had ~26 fold risk for diabetes compared to those with <10. Those with 40-49 had a ~20 fold risk.**
- Levels within normal range occur with obesity, xs alcohol, cigarette smoking, physical inactivity, high meat /low fruit and vegetable intake
- Cumulative biomarker for environmental pollutants.

GGT Increases with Alcohol Consumption

- GGT directly correlates with alcohol consumption
- In a non-uniform population, 40 g/d will elevate 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 Increases with Lead and Cadmium Levels

GGT Increases with Mercury Levels

GGT Increases with OCPs and PAHs

- Serum GGT, within its reference range, increases with organochlorine pesticides and polycyclic aromatic hydrocarbons.

GGT Levels Correlate with Risk of Death

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

GGT Data from Canadian Oil Field Workers

20-fold increased risk of diabetes
GGT From Small US Company with Young Workers
Uric Acid Increases with Perfluorinateds

- Perfluorinated hydrocarbons (PFOA and PFOS) associated with increased serum uric acid

Steenland K et al. Association of perfluoroctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA. Environ Health Perspect. 2010 Feb;118:229-33.
ALT Increases with Cd, Pb, Hg and PCBs

- ALT (proxy marker) elevation in 10.4% (not including viral hepatitis, hemochromatosis, or alcoholic liver disease) of NHANES 03-04 subset
- Risk of elevated ALT increased dose-dependently with cadmium, lead, mercury, and PCB exposure
- 100% of individuals had detectable PCBs, 92.5% mercury, and 99.6% had detectable lead
- In 2005-08, prevalence of NAFLD in US was 11%, a growing cause of chronic liver disease.

ALT Increases with PAHs and PFOAs

- ALT increases in a dose-dependent manner with body load of blood cadmium, lead, mercury, and PCBs within and above the normal range.
- Exposure to polycyclic aromatic hydrocarbons causes elevations in AST and ALT. When serum log-perfluorooctanic acid (PFOA – a perfluorinated chemical) increases by one unit, serum ALT increases by 1.86 units.

Alkaline phosphatase (ALP) Increases with Pesticides

- ALP is a hydrolase enzyme responsible for dephosphorylation. Present in higher concentration in the liver, kidney, and bone.
- Chronic exposure of pesticides in agricultural workers was found to be associated with significantly higher activities of ALP compared to controls, and the number of years exposed to pesticides predicted higher activities of ALP.

Bilirubin Increases with PCBs

• Degree of serum bilirubin increase is prognostically significant in chronic liver dysfunction.

• Mono-ortho PCB TEQ values were found to be significantly positively associated with bilirubin ($\beta=0.71$, $P=0.008$) following adjustment for multiple potential confounders.

• Bilirubin levels significantly correlated with PCBs -105, -118, -126, and -194.

• Smoking appears to be the biggest confounder.


Liver Enzymes Reflect Toxic Load

- AST, ALT and GGT increase with body load of PCBs and OCPs
- Some non-linear
- Oxychlordane top quartile:
  - ALT $\uparrow$10%
  - GGT $\uparrow$25%


<table>
<thead>
<tr>
<th>Blood marker</th>
<th>n</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate aminotransferase AST (U/L)</td>
<td>1951</td>
<td>23.2 (22.7, 23.6)</td>
<td>23.7 (22.3, 25.3)</td>
<td>24.3 (22.2, 25.5)</td>
<td>25* (23.6, 26.5)</td>
</tr>
<tr>
<td>Gamma glutamyl transferase GGT (U/L)</td>
<td>1951</td>
<td>18.8 (18.2, 19.4)</td>
<td>22.2* (20.2, 24.4)</td>
<td>22* (19, 23.3)</td>
<td>19.7 (16.6, 23.2)</td>
</tr>
<tr>
<td>Oxychlordane</td>
<td></td>
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<tr>
<td>p,p'-DDE</td>
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<tr>
<td>Alanine aminotransferase ALT (U/L)</td>
<td>1956</td>
<td>20.9 (20, 21.8)</td>
<td>22.9 (21.3, 24.3)</td>
<td>22.7* (21.7, 23.7)</td>
<td>22.3* (21.4, 23.6)</td>
</tr>
<tr>
<td>p,p'-DDT</td>
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<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase AST (U/L)</td>
<td>1965</td>
<td>22.6 (22, 23.2)</td>
<td>24.1* (23.1, 25.3)</td>
<td>23.8 (22.8, 24.7)</td>
<td>24* (23.3, 24.7)</td>
</tr>
<tr>
<td>Gamma glutamyl transferase GGT (U/L)</td>
<td>1965</td>
<td>18.1 (17.9, 19.2)</td>
<td>20.7* (18.9, 22.6)</td>
<td>20.3* (18.7, 22)</td>
<td>19.8 (17.8, 21.9)</td>
</tr>
<tr>
<td>Trans-nonachlor</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase ALT (U/L)</td>
<td>1955</td>
<td>19.3 (17.9, 20.8)</td>
<td>21 (20.2, 21.8)</td>
<td>23.1* (22.1, 24.1)</td>
<td>23.3* (21.9, 24.9)</td>
</tr>
<tr>
<td>Gamma glutamyl transferase (U/L)</td>
<td></td>
<td>15.4 (14.1, 16.9)</td>
<td>19* (18, 20)</td>
<td>20.4* (19, 21.9)</td>
<td>21.3* (18.9, 24)</td>
</tr>
<tr>
<td>Oxychlordane</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase ALT (U/L)</td>
<td>1978</td>
<td>20.1 (19.2, 21.1)</td>
<td>22* (20.9, 23.1)</td>
<td>23.7* (22.5, 25)</td>
<td>22* (20.7, 23.4)</td>
</tr>
<tr>
<td>Gamma glutamyl transferase GGT (U/L)</td>
<td>1978</td>
<td>16.1 (14.6, 17.9)</td>
<td>19.9* (18.6, 21.3)</td>
<td>21.4* (19.6, 23.3)</td>
<td>20.5* (18.2, 23.2)</td>
</tr>
</tbody>
</table>
Inflammatory Markers Increase with OCPs, PCBs, PBDE

Schæbel LK, Bonefeld-Jørgensen EC, Vestergaard H, Andersen S.
POPs and CRP Interact to Increase Insulin Resistance

**LDL-Cholesterol as Measure of POPs?**

- **5-year prospective study** to determine if POP levels predict future elevation in LDL-cholesterol
- 598 subjects initially at age 70
- Looked at 23 POPs
- Best correlation with PCB 194

oxLDL as Measure of POPs?

- 992 70-year old individuals (50% women)
- Sum of PCBs showed strong, significant positive associations with ox-LDL, and significant negative associations with glutathione-related markers (GSSG and GSSG/GSH)
- A number of POPs (PCB-99, 138, 153, 156, 170, 180, 194, 206 and 209) showed strong significant positive association with ox-LDL

Homocysteine Increases with Pb & Cd

Nutrient Deficiencies Accentuate Effects of Lead on Homocysteine

- Deficiencies in folate, B6 or B12 make lead more toxic!

T4 & T3 Decrease with PCBs

- PCBs decrease T4 production
- PCBs inhibit iodotyrosine deiodinase activity
- Study done in pregnant women which implies effect on fetus IQ

Kim S, Park J, Kim HJ, et al. Association between several persistent organic pollutants and thyroid hormone levels in serum among the pregnant women of Korea. Environ Int. 2013 Sep;59:442-8

T4 & T3 Decrease w PCBs

- Not just humans being affected
- Large study of dolphins shows exactly the same effects

8-OHdG

- Oxidized nucleoside
- Direct measure of DNA damage
- Indirect measure of oxidative stress and toxin load
- Correlates with:
  - Multiple cancers
  - Mitochondrial damage
  - Rate of aging
  - Smoking
  - Several toxins

Walter Crinnion “Total Toxic Load,” AANP 2015
8-OHdG Increases with Pack-Years of Smoking

8-OHdG Increases with Mercury

Recommendations

High body toxic load:
- GGT: > 25
- Uric acid: > 5.0 mg/dl
- ALT: > 30 U/L
- Bilirubin: > 0.8 mg/dl
- CBC: < 6,000
- Platelet: < 250,000
- Low T3 and/or T4

Monitor Total Toxic Load
- 8-OHdG: > 4