Approaches to Exposure Assessment for Metals

Submitted by: McLaughlin Centre for Population Health Risk Assessment
Approaches to Exposure Assessment for Metals

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Professor and Director
McLaughlin Centre for Population Health Risk Assessment

Outline

1. New directions in risk science
2. Exposomics
   - Biomarkers of exposure
   - Biomonitoring equivalents
   - High throughput techniques
3. Metals-specific exposure assessment
   - Aluminum
   - Manganese
   - Copper
4. Conclusions
Three Cornerstones

- New paradigm for toxicity testing (TT21C), based on perturbation of toxicity pathways
- Advanced risk assessment methodologies, including those addressed in *Science and Decisions*
- Population health approach: multiple health determinants and multiple interventions
Exposure Assessment

McLaughlin Centre for Population Health Risk Assessment

Hubal et al. (2010,) JTEH 13:299
Exposomics

Exposomics

McLaughlin Centre for Population Health Risk Assessment

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The exposome represents the combined exposures from all sources that reach the internal chemical environment. Toxicologically important classes of exposome chemicals are shown. Signatures and biomarkers can detect these agents in blood or serum.```

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Environment and Disease Risks
Stephen M. Rappaport, et al.
Science 330, 460 (2010);
DOI: 10.1126/science.1192603
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Two Approaches to Exposomics

Bottom-up Exposomics
Identify important exogenous exposures
Measure chemicals in air, water & food

Top-down Exposomics
Measure chemicals in blood
Identify all important exposures

Rappaport et al. (2011)
J. Exp. Sci. Env. Epi. 21:5

Biomarkers of Exposure

McLaughlin Centre for Population Health Risk Assessment
Establishing Biomonitoring Equivalents

Guidelines for the derivation of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop

Sean M. Hays a, Lesa L. Aylward b, Judy S. LaKind c, Michael J. Bartels d, Hugh A. Barton e, Peter J. Boogaard f, Conrad Brunk g, Stephen DiZio h, Michael Dourson i, Daniel A. Goldstein j, John Lipscomb k, Michael E. Kilpatrick l, Daniel Krewski m, Kannan Krishnan n, Monica Nordberg o, Miles Okino p, Yu-Mei Tan q, Claude Vieu r, Janice W. Yager s
- 2,4-D
- Acrylamide
- Cadmium
- Cyfluthrin
- Di(2-ethylhexyl)phthalate
- Phthalate Esters:
  - Diethyl phthalate
  - Di-n-butyl phthalate
  - Benzylbutyl phthalate
- Polychlorinated dibenzo-p-dioxins and dibenzofurans
- Toluene
- Trihalomethanes:
  - Chloroform
  - Dibromochloromethane
  - Bromodichloromethane
  - Bromoform

http://www.biomonitoringequivalents.net/html/chemical_specific_bes.html

Exposure Assessment Guidance
Exposure Science in the 21st Century

Remote Sensing Techniques: Global PM2.5 Levels

With dust

Without dust

Evans et al. (2013)
Env. Res. 120:33
• **ExpoCast** provides high-throughput exposure estimations for thousands of chemicals via multiple routes
• **Farfield exposure models** used to estimate exposure from chemicals that are released into the environment
• **Nearfield exposure models** used to estimate exposure to chemicals in consumer products and in-home sources
• **CPCat** database catalogs the use of over 40,000 chemicals in different consumer products

Margins of Exposure based on *In Vitro* Toxicity Testing
High-throughput Biomonitoring

A. The environmental metabolome

- The human metabolome contains 1 million chemicals
  - 40 nutrients
  - 2000 intermediary metabolites
  - 500,000 lipids
  - 200,000 food components
  - 100,000 microbial metabolites
  - 100,000 commercial products
  - Environmental chemicals & metabolites

- The human exposure is likely to include 400,000 chemicals

B. Cost comparisons for chemical profiling

- Targeted chemical assay

- High-resolution metabolomics

C. High-resolution metabolomics

- Unprecedented detection of low abundance ions

D. Profiling and centroid mode MS data

- High Res Profile
- Low Res Profile

Metal Specific Exposure Assessment: Aluminum

Critical Reviews in Toxicology

REVIEW ARTICLE

Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts

Calvin C. Willihite1,2, Nataliya A. Karyakina1, Robert A. Yoke3, Nagarajkumar Yenugadhati2, Thomas M. Wisniewski4, Ian M.F. Arnold5, Franco Momoli6,7, and Daniel Krewski1,2,7
Food is the primary source of aluminum for most healthy people: the typical American diet contributes about 5 mg/d to human exposure.

Drinking water contributes much less Al than food: about 0.2 mg/d at the WHO drinking water guideline.

Non-prescription medicines can lead to much higher exposures: 120-7,200 mg/d for antacids and 200-1,000 mg/day for buffered aspirin.

Occupational exposures can also be appreciable: 3-21 mg/d for Al smelting or welding.

Other sources, including cosmetics and anti-perspirants, are comparatively small.
Metal Specific Exposure Assessment: Manganese

Main Health Issues Associated with Manganese Exposure

- **Neurotoxicity** (mood changes, tremors, altered gait, facial muscle spasms)
- Lung toxicity (inflammation, pneumonia)
- Effects on reproductive system (loss of libido, impaired fertility in men)
- Developmental toxicity (reduced IQ)
Multi-route PBPK model for Manganese Tissue Kinetics in Adult Monkeys and Humans

Predicted Mn Concentrations in the Globus Pallidus of Monkeys Exposed to 0 or 1.5 mg Mn/m³ in air (6 h/d, 5 d/wk) and 133 ppm Mn in diet for 13 weeks (diet-only post-exposure up to 90 days)
Currently Available PBPK Models for Mn

- Rats (adult, pregnant, lactating, and neonatal)
- Nonhuman primates (adult)
- Human (adult, pregnant, lactating, and neonatal)

Metal Specific Exposure Assessment: Copper
Estimates and Assumptions in Assessing Copper Intake

<table>
<thead>
<tr>
<th>Ref (126)</th>
<th>Weight at T1 (kg)</th>
<th>Age at T1 (days)</th>
<th>Exposure T (days)</th>
<th>Weight at T2 (kg)</th>
<th>Age at Midpoint (days)</th>
<th>Weight at Midpoint (kg)</th>
<th>Consumption Free (g)</th>
<th>Consumption weight (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>NA</td>
<td>42</td>
<td>NS/NA</td>
<td>NA</td>
<td>0.25</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>NA</td>
<td>42</td>
<td>NS/NA</td>
<td>NS</td>
<td>0.13</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

No need to estimate amount of copper in feed consumed – exposure was given via a capsule with copper content reported in milligrams per day. Weight and age is assumed to be constant.

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<th>Weight at Midpoint (kg)</th>
<th>Consumption Free (g)</th>
<th>Consumption weight (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.66</td>
<td>27</td>
<td>26</td>
<td>NS/NA</td>
<td>27</td>
<td>0.165</td>
<td>10</td>
<td>NA</td>
</tr>
</tbody>
</table>

Weight was gross but assumed to be 100g. No need to estimate amount of copper in feed consumed – exposure was given via a capsule with copper content reported in milligrams.

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<th>Weight at Midpoint (kg)</th>
<th>Consumption Free (g)</th>
<th>Consumption weight (ml)</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>0.06</td>
<td>27</td>
<td>26</td>
<td>NS/NA</td>
<td>27</td>
<td>0.165</td>
<td>10</td>
<td>NA</td>
</tr>
</tbody>
</table>

Weight reported at onset, age and weight at mid-point estimated from Phelps (1992) based on sex, race and weight. Consumption of feed based on NAS (1972) estimates by sex, race and weight.

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<th>Weight at Midpoint (kg)</th>
<th>Consumption Free (g)</th>
<th>Consumption weight (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>0.70</td>
<td>25</td>
<td>28</td>
<td>NS/NA</td>
<td>NA</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Weight at onset assumed to be 60% for adult males. Weight and age is assumed to be constant. Amount of copper consumed provided in the article.

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<th>Consumption weight (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.21</td>
<td>21</td>
<td>14</td>
<td>NS/NA</td>
<td>21</td>
<td>0.25</td>
<td>9</td>
<td>NA</td>
</tr>
<tr>
<td>20</td>
<td>0.21</td>
<td>21</td>
<td>21</td>
<td>NS/NA</td>
<td>21</td>
<td>0.25</td>
<td>9</td>
<td>NA</td>
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<td>0.25</td>
<td>9</td>
<td>NA</td>
</tr>
</tbody>
</table>

Animals reported as being in the weaning stage. Estimates of 21 days for the age of weaning are taken from NAS (2009). Weight at midpoint estimated from Phelps (1992) based on sex, race and age. Consumption of feed based on NAS (1972).

Seven Level Severity Scoring System for Copper Toxicity due to Excess and Deficiency

<table>
<thead>
<tr>
<th>Severity Score (S)</th>
<th>Physiological Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>Serious irreversible gross deficiency</td>
</tr>
<tr>
<td>4</td>
<td>Reversible gross deficiency</td>
</tr>
<tr>
<td>3</td>
<td>Metabolic perturbation</td>
</tr>
<tr>
<td>2</td>
<td>Early biological indicators of deficient Cu levels</td>
</tr>
<tr>
<td>1</td>
<td>Homeostatic adaptations to low intakes</td>
</tr>
<tr>
<td>0</td>
<td>No effect</td>
</tr>
<tr>
<td>1</td>
<td>Homeostatic adaptation to high intakes</td>
</tr>
<tr>
<td>2</td>
<td>Early biological indicators of accumulated Cu</td>
</tr>
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<tr>
<td>6</td>
<td>Death</td>
</tr>
</tbody>
</table>

U-Shaped Dose-response Curve for Copper Toxicity due to Excess and Deficiency

Optimal intake of copper is 2.73 mg/day (95% CI: 1.54 – 4.58 mg/day)

**Key Issues in Assessing Human Exposure to Metals**

- Physical form (insoluble bauxite dust vs Al welding fumes)
- Chemical form (insoluble Al silicates vs highly soluble Al organics)
- Route of exposure and bioavailability (intravenous Al injection during kidney dialysis vs ingested baking powder)
- Target organ (inhaled bauxite particulates and emphysema vs systemic Al and adynamic bone disease)
- Substance-specific adjustment factors

**Future Directions in Exposure Science**

- NRC TT21C/EPA NexGen future risk assessment paradigms built on understanding of toxicity pathways, and HTS assays to detect pathway perturbations: *a concomitant shift in exposure science is needed to complete this transition:*
  - Biomarkers of exposure linked to toxicity pathway perturbations
  - High-throughput exposure assessment (biomonitoring and computational approaches)
  - *In vitro to in vivo* extrapolation (IVIVE) for dosimetric calibration of HTS assays
  - Human exposure guidelines based on biomonitoring equivalents (BEs)
Contributors

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