Health Risk Assessment of Essential Metals

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McLaughlin Centre for Population Health Risk Assessment

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International perspective on risk assessment for essential metals

Workshop objectives:
- risk assessment methodologies
- challenges in metals risk assessment (U-shaped dose-response)
- applications: Cu, Zn, Mn
- facilitate discussion among stakeholders
Beverly Hale  
University of Guelph

• Network on metals risk assessment (MITHE-SE)
• Focus on human exposure to metals (including bioavailability and bioaccessibility)
• Major themes:
  – aquatic ecosystems
  – soils and plants (cadmium)
  – food and ingested particles
• Improved risk assessment and (cost-effective) risk management strategies
Lorraine Gambling
Rowett Research Institute

• REACH
  – effective June 4, 2007
  – phased-in over 11 years

• Risk assessment guidance prepared by metals industry (MERAG, HERAG)

• Need to consider both toxicity and essentiality of metals

• Cu, Mn, and Zn represent 3 of about a dozen essential trace elements

Five principles:
- metals are naturally occurring
- often occur as mixtures
- many metals essential to health
- metals can change states (organic to inorganic)
- consider toxicokinetics of metals

Science policy issues:
- BAF/BCF factors useful at a single site (but not in hazard ranking)
- incorporate bioavailability into risk assessment
- essentiality: U-shaped dose-response, RFDs ≥ RDA
- environmental chemistry: speciation, pH, Kd values, bioavailability
- human health issues: target organs, route of exposure, sensitive populations
Bonnie Stern  
BR Stern Associates

- Copper interacts with a number of enzymes to maintain normal biological function
- Menkes and Wilson’s diseases associated with inborn errors of copper metabolism
- U-shaped dose-response for copper: seek acceptable range of oral intake (AROI)
- Rich Cu toxicity database available to characterize copper dose-response
• Upper limit on deficiency overlaps with lower limit on toxicity

• Data gaps:
  – effects of occupational exposure
  – effects of inhalation exposures
  – integrated dose-response modeling
  – early warning biomarkers
  – toxicokinetics

• Different exposure guidelines established by different agencies throughout the world (harmonize?)
Joyce Donohue
U.S. Environmental Protection Agency

- Narrow boundary (<10 mg/day) between excess and deficiency
- Portal of entry important
- Complex homeostatic mechanism
- Major challenges:
  - understand uncertainty
  - establish boundaries between excess and deficiency
Annette Santamaria
ENVIRON International

- Mn occurs naturally in soil, air, fresh water (98.8% from food and water)
- Primary (90%) anthropogenic source of Mn is steel production
- EPA RfD: 0.14 mg/kg/day (10 mg/day adult)
- IOM AI: from 0.003 (infants) to 2.3 (adults) mg/day
- Inhalation exposure guidelines established/proposed by a number of agencies (harmonize?)
- New toxicokinetic data available for use in Mn risk assessment
Bruce Winder
California Environmental Protection Agency

- California EPA currently developing inhalation exposure guideline for Mn
- Need to consider susceptibility of infants and children under Children’s Environmental Protection Act: inhalation infant exposure to Mn approaching toxic levels
• Human neurotoxicity not emulated in rodents – therefore focus on primates
• Mn clearance from neural tissue in primates faster than expected
• MnSO₄ tested because of high solubility/bioavailability
• Mn accumulation in globus pallidus
• Many biological processes involve zinc containing enzymes
• Half the world’s population is zinc deficient
• IOM RDAs range from 3 – 12 mg/day (depending on age, sex, and pregnancy status)
• Health protective exposure guidelines:
  – oral intake: 21-60 mg/day
  – occupational air limits: 5-10 mg/m³
• Again, narrow boundary between deficiency and excess
Ian Arnold
International Aluminum Institute

• Opportunity to mitigate population health impacts of zinc deficiency
• Need to characterize upper end of zinc toxicity curve: prostate cancer?
• ‘Metal balance’: understand interaction between zinc and other metals
• Continued attention occupational health issues related to zinc needed
Joyce Donohue
U.S. Environmental Protection Agency

- Tight boundary between dietary needs and overload
- Grain content of diet (phytate) affects bioavailability
- Do HDL levels affect response to zinc?
• Nutrition (deficiency) and toxicology (excess) key disciplines in evaluating benefit-risk aspects of essential metals
• Consider biology: metabolic template for metals
• Consider spectrum of health effects (links to severity scoring in categorical regression) and biomarkers of effects
Michael Dourson
Toxicology Excellence for Risk Assessment

- Development of ‘safe’ exposure guidelines (TDI, RfD, RSD) based on dose-response analysis
  - POD = NOAEL or BMD
  - RfD = POD/UF [or CSAF]
  - choose risk level (e.g., $10^{-6}$) for RSD
  - Integrated approach to cancer and non-cancer risk assessment?

- Choose outcome of interest: adverse health effect or known precursor

- U-shaped dose-response for essential metals: define AROI (between ADI and RfD)

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Categorical regression provides a useful tool for combining data from different sources, using a common severity metric to put disparate health outcomes on the same scale.

Rich copper toxicity database provides an opportunity to apply this technique to get an omnibus description of copper dose response (including both excess and deficiency).
Melvin Andersen
Hamner Institutes for Health Research

- PBPK models now widely used for tissue dosimetry
- Models provide a basis for dose, route, and species extrapolation
- Models link to recent work by Hayes et al. on the use of ‘biomonitoring equivalents’ in risk assessment
- PBPK model now available for Mn
Panel Discussion:
Bette Meek, University of Ottawa

• Challenge to Panel: explore further aspects of essential metals risk assessment, drawing on experience from other areas of risk assessment
Panel Discussion:
Leonard Levy, Cranfield University

- Clarify which metals are essential for health (e.g., silicon, boron, vanadium)
- Which metals have carcinogenic potential (e.g., chromium VI), and how should they be assessed?
- Read-across (used in REACH) depends on knowledge of mode of action
- Need to evaluate subtle neurotoxic effects of metals
Panel Discussion:
Donna Mergler: Université du Québec à Montréal

• Current risk assessments of Mn based largely on occupational exposures to men
• Life-span approach to risk assessment needed to accommodate changing biology, and changing environmental health impacts
• Gender differences also warrant attention
‘Science is what we know, risk assessment is what we don’t know’ (adapted from Bertrand Russell): how do we handle essential nutrients?

Need unified assessment to understand manganese body burden from all different routes of exposure, and when normal homeostatic controls are exceeded
Panel Discussion: Barbara Beck, Gradient Corporation

- Explore in vitro models for bioaccessibility of metals
- Explore use of ‘omics technologies and computational biology in metals risk assessment (NRC, 2007)
- Need to better understand pathways associated with deficiency, sufficiency, and toxicity
Panel Discussion: Michelle Deveau, Health Canada

- Canadian drinking water guidelines based on aesthetic criteria:
  - Cu: 1 mg/L
  - Mn: 0.05 mg/L (prevents staining)
  - Zn: 5 mg/L (water unpalatable at higher levels of health concern)

- Except for infants and young children, DRI levels for Mn or Zn not met by water alone, assuming these metals are present at the guideline level

- Average Cu levels in water will however meet 23-66% of DRI for copper

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Panel Discussion:
Ruth Danzeisen, International Copper Association

• HERAG provides guidance on risk assessment approaches for metals
• Builds on exposure assessment, effects assessment, and risk characterization
• Summary document and eight fact sheets on aspects of risk assessment available
Next Steps

- Workshop report summarizing today’s discussions
- Workshop proceedings
- Application of new risk assessment methods and data (PBPK, CatReg) to essential metals

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• Workshop evaluations
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Related Events

20th International Conference on Epidemiology in Occupational Health
(June 9-11, 2008)

11th International Symposium on Neurobehavioral Methods and Effects in Environmental and Occupational Health
(June 11-13, 2008)

www.EPICOH-NEUREOH2008.com

Costa Rica
Related Events

Human Relevance of Animal Modes of Action and Chemical Specific Adjustment Factors

McLaughlin Centre for Population Health Risk Assessment
(in collaboration with the ILSI Research Foundation)

July 22-23, 2008

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Related Events:
Toxicity Testing in the 21st Century

www.nas.edu
Contributions to Proceedings Volume

Papers should be sent directly to:
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Submissions by
June 15, 2008
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Adjourned!