Mixtures, Metals, Genes and Pathways: A Systematic Review

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Prenatal and perinatal exposures to mixtures of metals (arsenic, lead, manganese; cadmium) and neurodevelopmental health outcomes in children
Emerging Issues in Risk Assessment

- Cumulative risk
- Non-chemical stressors
- Chemical mixtures
- Susceptibility
- Environmental equity / justice
- Gene-environment interaction
- Epigenetics
- Exposure
- Bioavailability
- Exposome
- Timing of exposure
Synthesizing Evidence from Exposure to Health Outcome

EXPOSURE biomonitoring modeling PBPK

EFFECT in vivo and in vitro tox assays epidemiology molecular epidemiology

DISEASE ETIOLOGY cellular events subclinical disease

· Genetic susceptibility/interaction

Intersection and synthesis of effect data, exposures in the environment, and disease etiology

Dose
Exposure models
PBPK models
Exposure
Internal
Dose
Target tissue dose

Mode(s) of action
BBDR models
Early biological effects
Altered structure function
Disease models
Disease

Disease etiology
Systems models
Disease models
Adverse Outcome Pathway

Exposure

Uptake Delivery to Target Tissues

Perturbation

Cellular response pathway

Biologic inputs

Early cellular changes

Adaptive responses

Molecular initiating event

Perturbed cellular response pathway

Cell injury, inability to regulate

Adverse outcome relevant to risk assessment

Expected Biological Function

Adverse outcomes (e.g., reduced performance on developmental tests)

Toxicity Pathway

Adverse Outcome Pathway
Components of Systematic Review

**EPI** | **TOX** | **GENE INTERACTION** | **EXPOSURE** | **HEALTH OUTCOME**
---|---|---|---|---
22 studies | 11 *in vitro*; 32 *in vivo* | Genes within a health outcome; genes across health outcomes within a metal; genes relevant to pathways | Compare exposure levels from epi studies to NHANES; other biomonitoring studies | Autism ADHD Neuronal function in cognition and learning

**Notes:** Red - gene in common across all four metals; Blue - gene in common across three metals; Green - gene in common across two metals

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**Stages of Systematic Review**

EPI TOX GENE INTERACTION EXPOSURE HEALTH OUTCOME

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Evidence Along the AOP Continuum

Genetics
Polymorphisms in metal uptake and metabolism

Epigenetics
DNA methylation

Molecular Initiating Event
Phosphorylation of MEK
Inhibition of Na⁺/K⁺-ATPase
Increase in Ca²⁺

Cellular response
Neurotransmitter release
Apoptosis
ROS formation
Heme biosynthesis

Organ Response
Disruptions in neuronal signaling
Disruptions in neuronal function

Organism response
Decreased performance on developmental tests
IQ point decrements
Specific developmental disorders such as ADHD, autism
What criteria should be used to evaluate the applicability of different research synthesis methods to particular types of problems and data?

- Criteria will vary given decision context
  - Resource availability
  - Time constraints
  - External review
  - Qualitative vs. quantitative
  - Within our review, used different criteria across domains
- Decision tree or flow chart
What particular characteristics of the problem and data make the research synthesis method(s) you address particularly well (or poorly) suited for that context?

- Context: risk, public health, exposure, regulatory toxicology
  - Synthesizing evidence across domains
  - Moving toward mechanistic understanding of complex interactions leading to health outcomes
What are the strengths and limitations of the outputs provided, and the implications for their use in policy analysis?

- Establish a baseline
- Integrative
- Qualitative
- Policy context (risk assessment)
What are the most important research needs, in terms of methodological development, given your findings?

- Quantitative methods for translating AOP into regulatory values (e.g., IRIS)
- Implications for risk assessment more broadly
- Standardized approach(es) within a domain?
  - “universal” standards for judging acceptability/suitability of specific studies
Concluding Ideas

- Evidence that prenatal or perinatal exposures to mixtures of metals are associated with greater than additive neurodevelopmental health outcomes in children
  - Several modes of action by which this could occur
  - Support for proposed adverse outcome pathway

- Complexity across the continuum from exposure to health outcome requires synthesis and integration in an evidence-based analysis
  - Greater reliance on high-throughput methods
  - Tiered modeling approaches
  - Method development within a domain
    - Kernel machine regression
    - Variety of methods discussed here
  - Meta analysis
  - Weight of evidence
  - Systems based approaches
  - Bayesian structural equation models