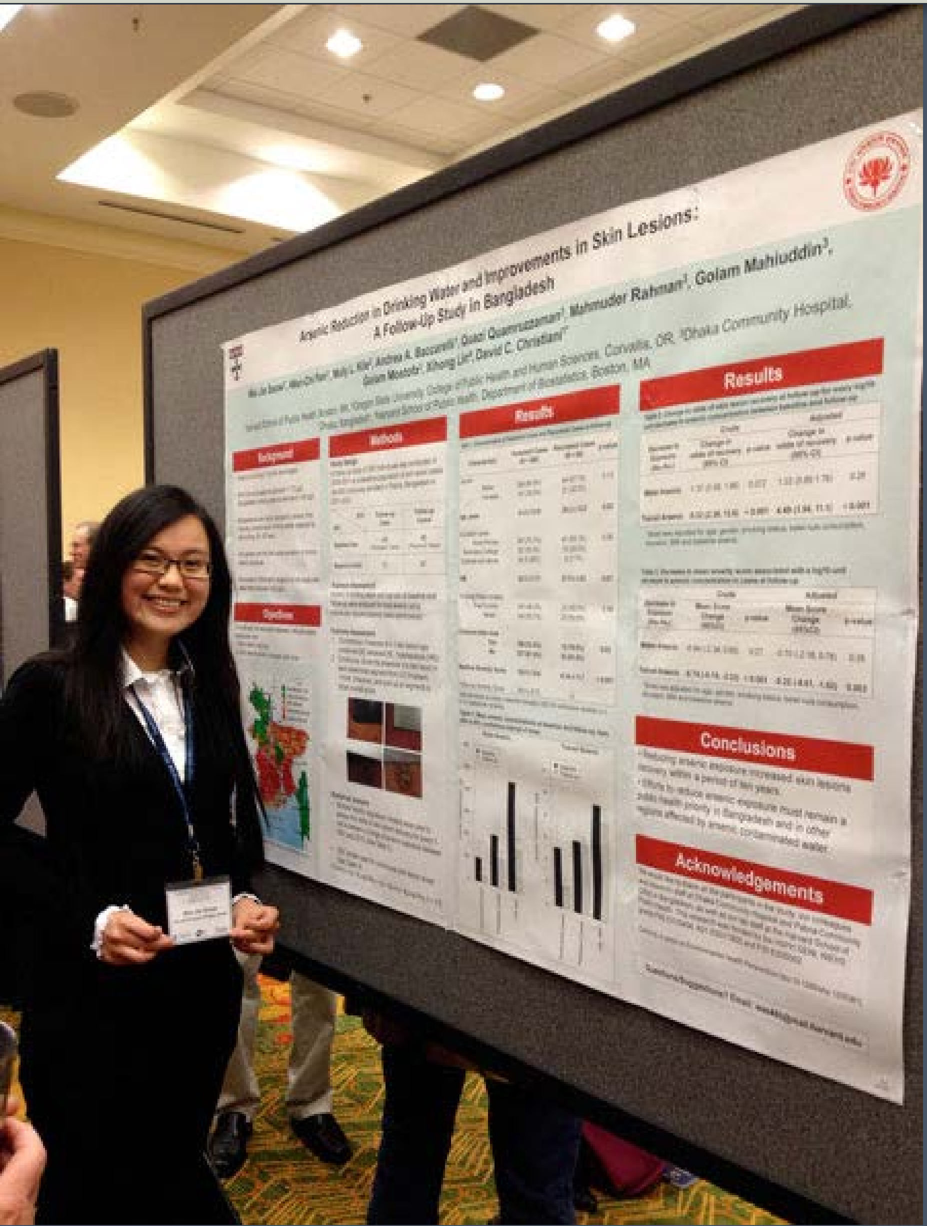
HARVARD | SCHOOL OF PUBLIC HEALTH

P42ES016454




# Mixtures, Metals, Genes and Pathways: A Systematic Review

Katherine von Stackelberg
kvon@hsph.harvard.edu
Liz Guzy, Tian Chu, Birgit Claus-Henn

Superfund Research Program

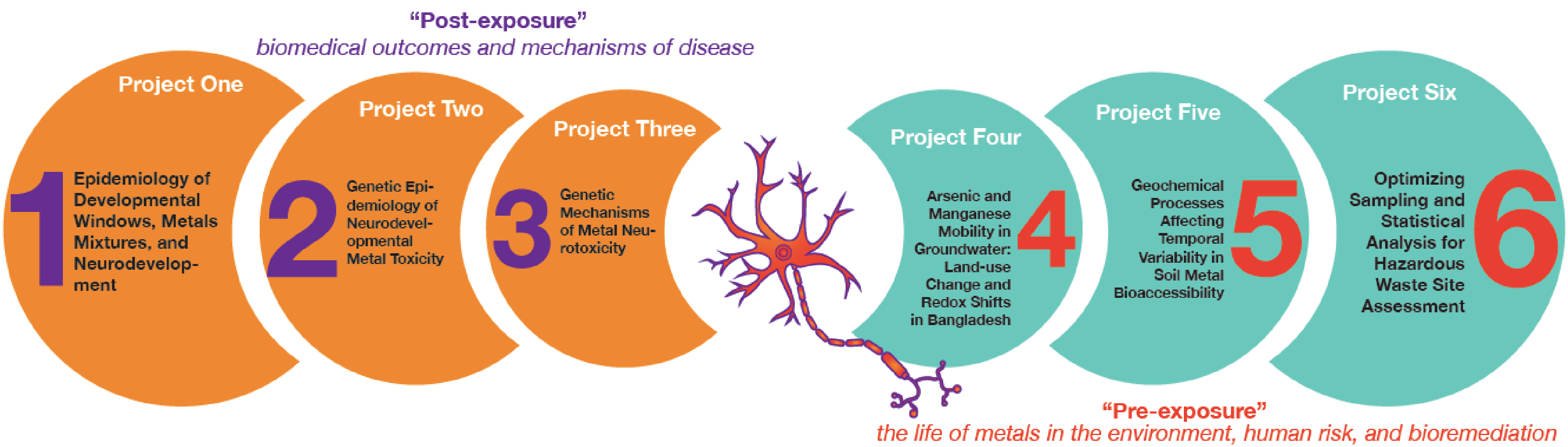
HCRA

SUPERFUND RESEARCH PROGRAM

HARVARD | SCHOOL OF PUBLIC HEALTH

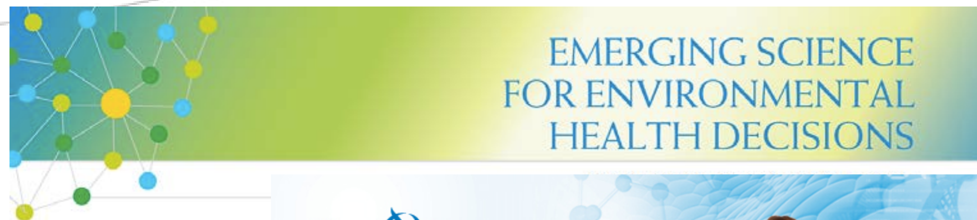
# Superfund Research Program at HSPH

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

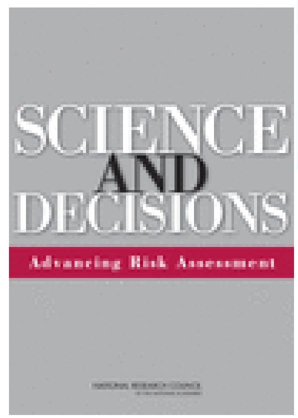


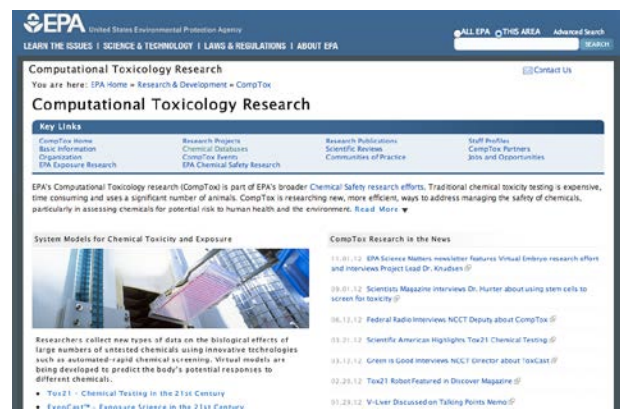
# Emerging Issues in Risk Assessment

- Cumulative risk
  - Non-chemical stressors
  - Chemical mixtures
- Susceptibility
  - Environmental equity / justice
  - Gene-environment interaction
- Epigenetics
- Exposure
  - Bioavailability
  - Exposome
    - Timing of exposure

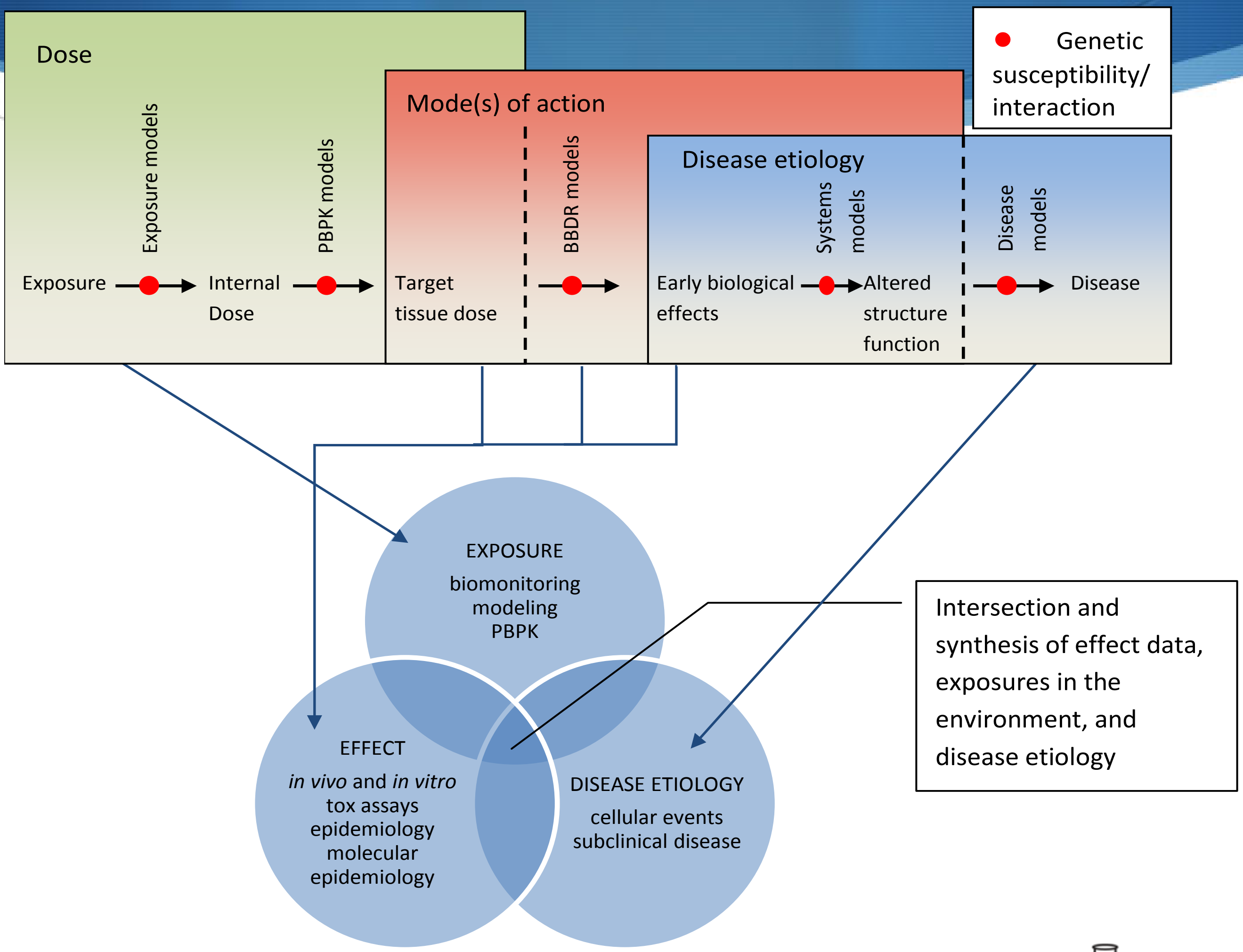






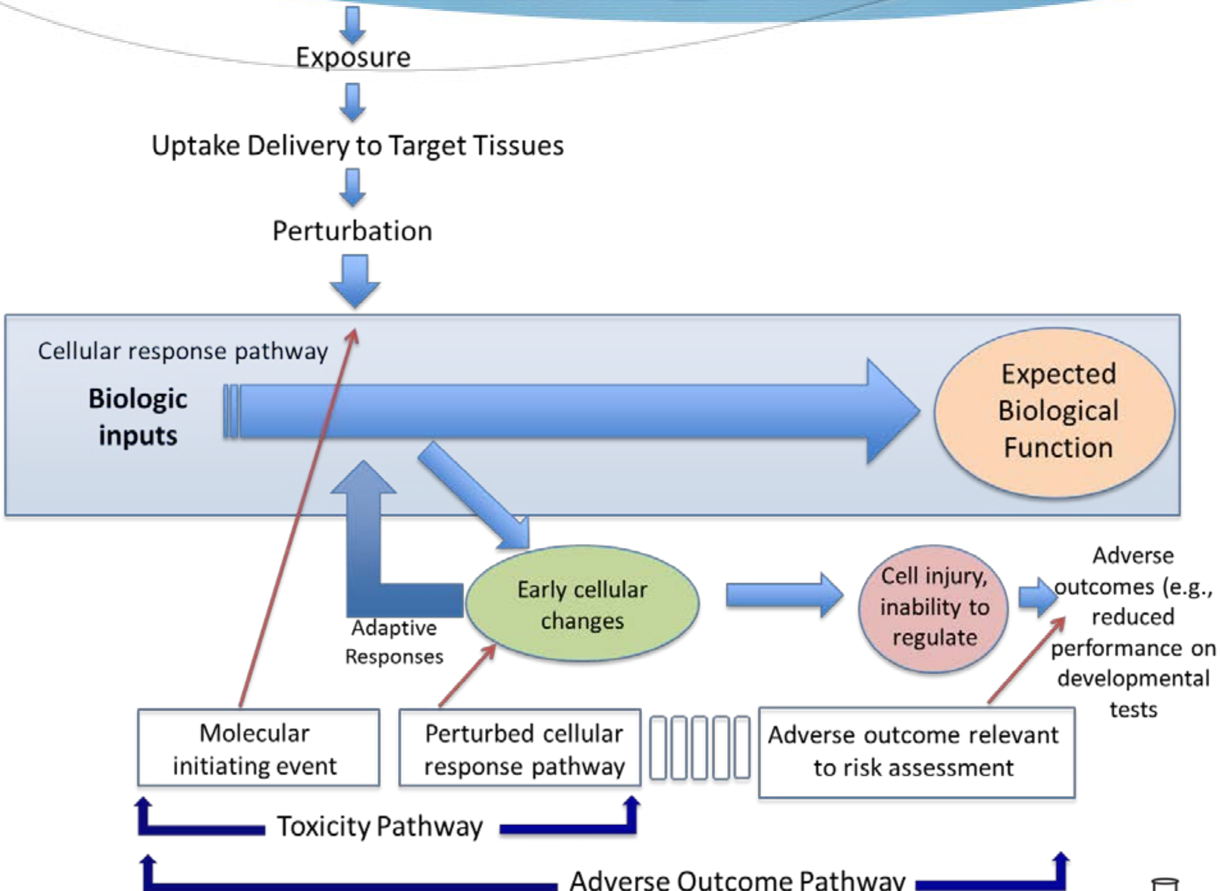



# Synthesizing Evidence from Exposure to Health Outcome




SUPERFUND RESEARCH PROGRAM
HARVARD SCHOOL OF PUBLIC HEALTH

# Adverse Outcome Pathway



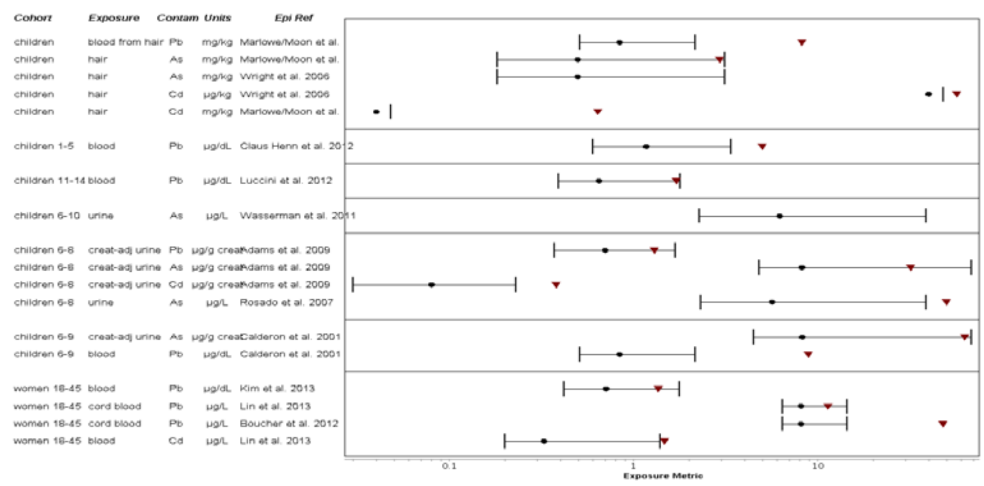

SUPERFUND RESEARCH PROGRAM
HARVARD SCHOOL OF PUBLIC HEALTH

# 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<br>ADHD<br>Neuronal function in cognition and learning |

| Outcome | Pb | As | Mn | Cd |
|---|---|---|---|---|
| ADHD | DRD2, GRM5 | LPHN3 | DRD2, SLC6A3, TACR1 | DRD2, DRD4, TACR1 |
| Anxiety Disorders | MAOA | CRHR1, FOS, SLC6A4, TNF | APP, DRD2, FOS, SLC6A3, TNF, UCN | ADORA2A, APP, CRP, DRD2, FOS, MIF, NPY, SERPINA1, SLC6A4, TNF |
| Asperger Syndrome | | SLC6A4 | | SLC6A4 |
| Autism | BCL2, BDNF, CAT, CP, GABRA1, GAD1, GRIN2A, HLA-, DRB1, HRAS, IFNG, IGF1, ITGB3, JMJD1C, MAOA, MECP2, MET, NOS2, NTRK2, PON1, PRKCB, PTGS2, ROBO1, SLC1A3, SND1, TF, TNFRSF1B, XDH | ADM, BCL2, BDNF, CAT, GSTM1, GSTP1, HLA-, DRB1, IGF1, IL10, IL1RN, IL2, IL6, LAMB1, LEP, MEF2C, MTHFR, NOS2, PDE4B, PER1, PLAUR, PON1, PRF1, PTGS2, SCN7A, SERPINE1, SLC6A4, XPC | ADM, AQP4, BDNF, CAT, FOXP2, GRIN2A, IFNG, IL2, IL6, LEP, NOS2, PARK2, PTGS2, SLC1A3, TF | ADM, AR, BCL2, BDNF, CAT, DRD3, EGR2, GHR, GJA1, GPX1, GSTP1, IFNG, IGF1, IGF2, IL10, IL1RN, IL4, IL6, MET, MIF, MTF1, NOS2, PER1, PLA2G4A, PLAUR, POMC, PRL, PTGS2, SCT, SEMA5A, SERPINE1, SLC40A1, SLC6A4, TF |
| Child development disorders, pervasive | GRIN2B, HFE, ITGB3, LAMC3, MECP2 | FOXP1, MEF2C, SOX9 | GRIN2B, HFE | DRD4 |
| Cognition disorders | APOE, APP, DRD2, MET, PTGS2, SLC1A1 | APOE, MT1, MT2, PTGS2, SLC6A4 | APP, DRD2, EPO, PTGS2, SLC4A10 | APP, DRD2, DRD3, EPO, IGF2, MET, MT1, MT2, PTGS2, SLC6A4 |
| Intellectual disability | BDNF, GAMT, GNAS, GRIN2B, MECP2 | BDNF, MEF2C | BDNF, GRIN2B, SLC4A10 | BDNF, FGFR2 |
| Iron metabolism disorders | CP, HMOX1 | HMOX1, SLC11A2, SOD1, TNF | HMOX1, TFRC | BMP2, FTH1, FTL, HAMP, HMOX1, SLC11A2, SLC40A1, SOD1, TF, TFNC, TNF |
| Learning Disorder | ACHE, APP, BCL2, CASP3, HMOX1, IL1B, MAPT, MECP2, TH, TRH | ACHE, BCL2, CASP3, HMOX1, HTR1A,IL1B, MAPT, MT1, MT2 , TH, VEGFA | APP, CASP3, HMOX1, HTR1A, IL1B, PARK2, TH, VEGFA | ACHE, APP, BCL2, CASP3, HMOX1, IL1B, MT1, MT2, TH, VEGFA |
| Memory disorders | ACHE, APP, BCL2, HTR6, IL1B, MAPT | | | |
| Notes: | | | | |

Red - gene in common across all four metals; blue - gene in common across three metals; green - gene in common across two metals



# Evidence Along the AOP Continuum

| Genetics | Epigenetics | Molecular Initiating Event | Cellular response | Organ Response | Organism response |
|---|---|---|---|---|---|
| Polymorphisms in metal uptake and metabolism | DNA methylation | Phosphorylation of MEK<br>Inhibition of $Na^+/K^+$-ATPase<br>Increase in $Ca^{2+}$ | Neurotransmitter release<br>Apoptosis<br>ROS formation<br>Heme biosynthesis | Disruptions in neuronal signaling<br>Disruptions in neuronal function | Decreased performance on developmental tests<br>IQ point decrements<br>Specific developmental disorders such as ADHD, autism |

# Question Review

- 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

# Question Review

- 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

# Question Review

- 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)

# Question Review

- 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