Review of Chiu, “Chemical Risk Assessment and Translation to Socioeconomic Assessments”

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Overview

• Strong review of basic steps to chemical risk assessment
  – Comment for emphasis that “risk” implies probability when these are more typically impact assessments
  – Four case studies of risk assessment as used in socioeconomic analyses (HBCD human and ecological; DCM and PFOA)
Main findings

• Most methods poorly adapted to look at entirety of exposure-response function
  – Focused instead on points of departure (Probabilistic Dose-Response Framework an alternative)
  – Heavily reliant on animal data with crucial assumptions about extrapolation to humans (internal dose, species variability)
Main findings

• Methods weak for non-cancer endpoints
• Work from “central tendency” of exposure
  – Fail to consider high-exposure or otherwise vulnerable populations
• Not all end points monetize readily
  – Toxicology needs to adapt better to health and economic outcomes
• Causal framework rigid
  – Misapplied notions of Bradford Hill
Other concerns

- Toxicology studies are limited foundation for imputing effects
  - Small sample size (limited power)
  - Limited and wide range of doses
  - PBPK models not proven to have good fit for many exposures
  - Old assays (e.g., uterotrophic) crude and insensitive
    - Also cannot be extrapolated to humans readily
Other concerns

• Integrated Probabilistic Risk Assessment and Probabilistic Dose-Response Frameworks may particularly compound error from toxicology studies
  – Extrapolating from toxicology studies to assume a distribution of margins of exposure for humans
  – Assumes variability in exposure and response can be modeled in humans (assuming interspecies and intraspecies factors)
Case in point: Triclosan

• IPRA from REACH: 4,894 men could have reproductive deficits based on the decreased vas deferens weights observed in rats

• Extrapolations from human data suggest missed 282,000 girls per year with earlier pubertal development and 428,000 cases per year with increased total \( T_3 \) hormone levels

Radka et al in preparation
Other concerns

• Nonmonotonicity, nonlinearity
  – Even newest methods fail to account for this reality
• "Good laboratory practice" (GLP) hardly represents a proper or even gold standard for laboratory studies, with concerns including:
  – Contamination of negative controls
  – Responsiveness to positive controls
  – Dissection techniques.
  – Flaws in many GLP studies have been identified, yet regulatory agencies rely upon these flawed studies.

Caution about newer methods

- Flaws in ToxCast have recently been exposed in detecting synthetic chemical obesogens.
  
  Janesick et al. EHP 2016

- Thyroid, sex steroids are not the only hormonal systems.

- Subclinical effects matter (decrements within euthyroid range associated with adverse neurodevelopmental outcomes, e.g. autism and ADHD).

  Bellanger et al. JCEM 2015
Models are only as good as their inputs

• If toxicology data are flawed, then burden of disease and cost estimates are meaningless.

• Strengths of lead, mercury, air pollution risk assessments derived from strong human and animal data.
Needed improvements

- Stronger pre-market data and follow-up toxicology studies
- Clinical and subclinically relevant endpoints
- Powered, independent peer-reviewed studies
- Careful consideration of endocrine system
Way forward?

• We’re not getting anywhere by singling out disciplines
  – Risk assessors, toxicologists, economists epidemiologists can all be blamed for working in silos and failing to provide robust data
  – Socioeconomic analyses are only as good as primary disease/disability estimates (i.e., worry about the money later)
  – Subclinical endpoints are valuable to society (e.g., IQ, Body Mass Index, Blood Pressure, Time to Pregnancy)
Modeling disease burden

• Suggest epidemiologic evidence as first choice for extrapolation

• If toxicologic studies used, cannot simply rely on safety factor for threshold
  – Presumption of steeper exposure-response relationship (with sensitivity analyses), or adapt probabilistic range for main effects in entire population
  – Could still adapt probabilistic ranges for individual-level variability
Modeling disease burden for EDCs

Epidemiologists, toxicologists and economists all served on expert panels

IPCC framework for probability of causation; WHO GRADE Working Group criteria for grading epidemiology; Danish EPA criteria for grading toxicology

• Fifteen exposure-outcome relationships → Monte Carlo simulations yielded median of €163 billion
  – <5% of EDCs considered
  – Breast cancer and many other conditions not included
  – Only considered published costs associated with these chronic conditions
  – COI approach misses substantial welfare costs

Trasande et al JCEM 2015; Andrology 2016
Benefits and costs of replacing BPA

• Potential cost of one BPA alternative, oleoresin = $0.022 per can
  • 100 billion aluminum cans are produced annually
  • 100 billion x $0.022 = $2.2 billion

• Potential benefit of replacing BPA with lining free of health effects = $1.74 billion
  • Does not include other effects (cognitive, asthma, breast cancer)

• Sensitivity analyses suggest as high as $13.8 billion

Trasande Health Affairs 2014
Context for the GBD

• GBD meant to provide common framework for comparing investments in health
• Environmental health interventions reverse externalities, and do not require health ministry expenditures
• Strict causal framework correct for health ministry investment decisions, but not for regulatory decisions in environmental health
Beware the DALY

• Because DALY values have been estimated only for intellectual disability, approach taken in GBD would include DALY losses only from the 3,290 annual cases in the EU found to suffer intellectual disability attributable to PBDE exposure and 59,300 for organophosphates.

  – For the EU, costs from intellectual disability alone were calculated at more modest amounts of €1.2 billion and €21.4 billion, respectively.
  – The more inclusive approach yielded estimates of €9.6 billion and €146 billion, respectively.
Measuring the true chemical GBD

- Quasi-representative biomonitoring from selected countries
  - Current estimate of childhood lead costs: 98.6 million IQ points lost, $134.7 million international dollars = 4.03% of GDP PPP
    
    Attina and Trasande EHP 2013

- Based on data from five African countries (South Africa, Nigeria, Kenya, Botswana, Uganda)

- Measurements of biomarkers in populations of concern (adult men, women of childbearing age, children)

- Suggest not limiting to POPs (phthalate, bisphenol, organophosphates, Hg, Pb, As, Cd)
Summary

• Beware toxicology as input to socioeconomic modeling
• Engage broadly with health scientists
• Embrace probability throughout (causation, reference level, exposure response relationship)
• Disease burden first, counterfactuals, costs last
• COI first, WTP later