ExpoCast:
Applications to Integrated Bioactivity - Exposure Ratios

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The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA
• The timely characterization of the human and ecological risk posed by thousands of existing and emerging commercial chemicals is a critical challenge facing EPA in its mission to protect public health and the environment.

• While advances have been made in HT toxicity screening, evaluated exposure and dosimetry prediction methods applicable to 1000s of chemicals are needed.
Prioritizing 1000’s of Chemicals for Further Study

- High throughput risk prioritization relies on **three components** – high throughput **hazard** characterization, high throughput **exposure** forecasts, and high throughput **pharmacokinetics**

2007 NRC Report

2007 NRC Report

Potential Hazard from *in vitro* with Reverse Toxicokinetics

Potential Exposure from ExpoCast

mg/kg BW/day

Lower Risk

Medium Risk

Higher Risk

e.g. Judson *et al.*, (2011) Chemical Research in Toxicology
**High-Throughput Bioactivity**

- **Tox21**: Examining >10,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

- **ToxCast**: For a subset (>1000) of Tox21 chemicals ran >500 additional assays (Judson et al., 2010)

- Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function)

- All data is public: http://actor.epa.gov/
In Vitro Bioactivity, In Vivo Toxicokinetics, and Human Exposure

Egeghy et al. (2012):
There is a paucity of data for providing exposure context to HTS data

Number of Chemicals

ToxCast Phase I (Wetmore et al. 2012)
ToxCast Phase II (Wetmore et al. in preparation)
High Throughput Toxicokinetics (HTTK)

Monte Carlo Simulation of Biological Variability

Combination of higher exposure and sensitivities

Populations that are More Sensitive

Images from Thinkstock
There is a paucity of data for providing exposure context to HTS data.
There is a paucity of data for providing exposure context to HTS data. Egeghy et al. (2012): HTTK studies like Wetmore et al. (2012), can address the need for toxicokinetic data.
High Throughput Exposure Forecasts

- New methods for Exposure Forecasting (ExpoCast) currently being considered for prioritization of chemical testing in the Endocrine Disrupter Screening Program (EDSP)
- Favorably reviewed by July 2014 Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP)

https://federalregister.gov/a/2014-12593

Agency/Docket Numbers:
EPA-HQ-OPP-2014-0331
FRL-9910-22
Consensus Model Building with the SEEM Framework

• Incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework**

• Evaluate/calibrate predictions with available measurement data across many chemical classes

• Analogous efforts for both human and ecological exposures
Predicting NHANES exposure rates

$R^2 \approx 0.5$ indicates that we can predict 50% of the chemical to chemical variability in mean NHANES exposure rates.

Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index.

Wambaugh et al., 2014
# High-throughput exposure heuristics

<table>
<thead>
<tr>
<th>Heuristic</th>
<th>Description</th>
<th>Number of Chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACToR “Consumer use &amp; Chemical/Industrial Process use”</td>
<td>Chemical substances in consumer products (e.g., toys, personal care products, clothes, furniture, and home-care products) that are also used in industrial manufacturing processes. Does not include food or pharmaceuticals.</td>
<td>37</td>
</tr>
<tr>
<td>ACToR “Chemical/Industrial Process use with no Consumer use”</td>
<td>Chemical substances and products in industrial manufacturing processes that are not used in consumer products. Does not include food or pharmaceuticals</td>
<td>14</td>
</tr>
<tr>
<td>ACToR UseDB “Pesticide Inert use”</td>
<td>Secondary (i.e., non-active) ingredients in a pesticide which serve a purpose other than repelling pests. Pesticide use of these ingredients is known due to more stringent reporting standards for pesticide ingredients, but many of these chemicals appear to be also used in consumer products</td>
<td>16</td>
</tr>
<tr>
<td>ACToR “Pesticide Active use”</td>
<td>Active ingredients in products designed to prevent, destroy, repel, or reduce pests (e.g., insect repellants, weed killers, and disinfectants).</td>
<td>76</td>
</tr>
<tr>
<td>TSCA IUR 2006 Total Production Volume</td>
<td>Sum total (kg/year) of production of the chemical from all sites that produced the chemical in quantities of 25,000 pounds or more per year. If information for a chemical is not available, it is assumed to be produced at &lt;25,000 pounds per year.</td>
<td>106</td>
</tr>
</tbody>
</table>
Calibrated Exposure Predictions for 7968 Chemicals

Wambaugh et al., 2014
We focus on the median and upper 95% predictions because the lower 95% is below the NHANES limits of detection (LoD).

Dotted lines indicate 25%, median, and 75% of the LoD distribution.
Calibrated Exposure Predictions for 7968 Chemicals

- Chemicals currently monitored by NHANES are distributed throughout the predictions.
- Chemicals with the first and ninth highest 95% limit are monitored by NHANES.

Wambaugh et al., 2014
The grey stripes indicate the 4182 chemicals with no use indicated by ACToR UseDB for any of the four use category heuristics.
• Bisphenol A was active at some concentration for 17 of 18 ER-related assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVS_NR_bER_ACC</td>
<td>0.19</td>
</tr>
<tr>
<td>NVS_NR_hER_ACC</td>
<td>0.20</td>
</tr>
<tr>
<td>NVS_NR_mERa_ACC</td>
<td>0.27</td>
</tr>
<tr>
<td>OT_ER_ERaERa_0480_ACC</td>
<td>1.27</td>
</tr>
<tr>
<td>OT_ER_ERaERa_1440_ACC</td>
<td>1.34</td>
</tr>
<tr>
<td>OT_ER_ERaERb_0480_ACC</td>
<td>0.23</td>
</tr>
<tr>
<td>OT_ER_ERaERb_1440_ACC</td>
<td>0.25</td>
</tr>
<tr>
<td>OT_ER_ERbERb_0480_ACC</td>
<td>0.23</td>
</tr>
<tr>
<td>OT_ER_EaERb_1440_ACC</td>
<td>0.19</td>
</tr>
<tr>
<td>OT_Ea_EaERGFP_0120_ACC</td>
<td>0.33</td>
</tr>
<tr>
<td>OT_Ea_EaERGFP_0480_ACC</td>
<td>0.52</td>
</tr>
<tr>
<td>ATG_Ea_TRANS_up_ACC</td>
<td>0.03</td>
</tr>
<tr>
<td>ATG_Ea_CIS_up_ACC</td>
<td>0.05</td>
</tr>
<tr>
<td>Tox21_Ea_BL_Agonist_ratio_ACC</td>
<td>1.88</td>
</tr>
<tr>
<td>Tox21_Ea_LUC_BG1_Agonist_ACC</td>
<td>0.14</td>
</tr>
<tr>
<td>ACEA_T47D_80hr_Positive_ACC</td>
<td>0.16</td>
</tr>
<tr>
<td>Tox21_Ea_BL_Antagonist_ratio_ACC</td>
<td>13.27</td>
</tr>
<tr>
<td>Tox21_Ea_LUC_BG1_Antagonist_ACC</td>
<td>1000000</td>
</tr>
</tbody>
</table>
Integrated Bioactivity: Exposure Ratio (IBER)

- A mathematical model was used to integrate all assays into a single predicted active concentration

Judson et al., in preparation
Integrated Bioactivity: Exposure Ratio (IBER)

- The error bar indicates the span between the median and the minimum plausible active concentration.

Judson et al., in preparation
Reverse dosimetry based on HTTK data was used to predict an oral equivalent dose that would cause the ACC in plasma for the 95-percentile, most sensitive adult.
Integrated Bioactivity: Exposure Ratio (IBER)

- Based on the ACToR UseDB descriptors and production volume, a median exposure for similar NHANES chemicals can be predicted.

<table>
<thead>
<tr>
<th>Heuristic</th>
<th>Bisphenol A</th>
</tr>
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<tbody>
<tr>
<td>Consumer &amp; Industrial Use</td>
<td>Yes</td>
</tr>
<tr>
<td>Industrial Use Only</td>
<td>No</td>
</tr>
<tr>
<td>Pesticide Inert</td>
<td>No</td>
</tr>
<tr>
<td>Pesticide Active</td>
<td>No</td>
</tr>
<tr>
<td>Production Volume</td>
<td>&gt; 1 billion lbs/year</td>
</tr>
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</table>
Due to the large uncertainty, the upper 95% limit of the exposure estimate credible interval is used.

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</tbody>
</table>
Integrated Bioactivity: Exposure Ratio (IBER)

- ANSES (2013) BPA Receipts, 200 ng/kg BW/d (Workers) and 10 ng/kg BW/d (Consumers)
- LaKind and Naiman (2011) Estimated Exposure to BPA from NHANES data in ng/kgBW/day:

<table>
<thead>
<tr>
<th>Demographic</th>
<th>LaKind and Naiman (2011)</th>
<th>ExpoCast Geometric Mean Median</th>
<th>ExpoCast Geometric Mean Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>35.1</td>
<td>25.0</td>
<td>2193</td>
</tr>
<tr>
<td>Age 6-11y</td>
<td>54</td>
<td>63</td>
<td>4984</td>
</tr>
<tr>
<td>Age 12-19y</td>
<td>48</td>
<td>59</td>
<td>5169</td>
</tr>
<tr>
<td>Age 20-39y*</td>
<td>38.5</td>
<td>57</td>
<td>6056</td>
</tr>
<tr>
<td>Age 40-59y*</td>
<td>28.9</td>
<td>57</td>
<td>6056</td>
</tr>
<tr>
<td>Age &gt;=60y</td>
<td>27.3</td>
<td>66</td>
<td>84221</td>
</tr>
<tr>
<td>Male</td>
<td>39.6</td>
<td>38</td>
<td>3132</td>
</tr>
<tr>
<td>Female</td>
<td>31.2</td>
<td>12</td>
<td>1125</td>
</tr>
</tbody>
</table>

*ExpoCast makes single prediction for Age 20-59y*
December, 2015 Panel: “Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening”

• The grey stripes indicate the 4182 chemicals with no use indicated by ACToR UseDB for any of the four use category heuristics.
Gas-Phase Concentration Model

- 73 total chemicals in model including SVOCs\(^1\) reported from Wilke et al. (2004)

- 4 chemicals reported from Little et al. (2012)

- 1 main physicochemical property that model data (VP). Other predictors include formulation descriptors.

Acronyms:
- SVOCs = Semivolatile Organic Compounds
- FRs = Flame Retardants
- VP = Vapor Pressure
- \(Y^\circ\) = Gas-phase concentration

\(^1\) SVOCs = Semivolatile Organic Compounds
Refined Models and Better Data: SHEDS-HT

Chemical to Chemical Variability of NHANES Biomonitoring

~10% Far field (Industrial) Releases
Wambaugh et al. (2013)

~50% Indoor / Consumer Use
Wambaugh et al. (2014)

Model for Screening-Level Assessr Exposure to Neutral Organic Chemicals
Xianming Zhang, W. Graham Glen, Daniel Vallero, Raina Brooks, Christopher M. Gurke, Haluk Özkan

ABSTRACT: Screening organic chemicals for hazard and risk to human health requires near-field human exposure models that can be parameterised with available data. The integration of a model for exposure, uptake, and bioaccumulation into an indoor mass balance framework provides a quantitative framework linking emissions in indoor environments to intakes of substances. This framework is then used to estimate intakes from exposure to chemicals from various sources and to prioritize chemicals of concern.

SHEDS-HT: An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources
Kristin K. Isacs, W. Graham Glen, Peter Egeghy, Michael-Rock Goldsmith, Luther Smith, Daniel Vallero, Raina Brooks, Christopher M. Gurke, Haluk Özkan

ABSTRACT: SHEDS-HT is a probabilistic exposure model that is integrated with data on dietary sources to provide an estimate of the probability of exposure to chemicals in the near field and the probability of exposure to dietary sources. The model is used to prioritize chemicals of concern based on their potential for exposure and their potential for dietary intake.

Consumer product database and two new near field models
Exposure Screening Tools for Accelerated Chemical Prioritization (ExpoCast)

- Solicitation posted May 22, 2013

- Two awardees:
  - Battelle Memorial Institute (Columbus, OH) and
  - Southwest Research Institute (San Antonio, TX)

- The EPA is interested in building models to quantitatively predict potential exposure for thousands of chemicals in commerce. Results will be used in the ExpoCast project to evaluate, calibrate and reduce uncertainty in exposure model predictions and for prioritizing compounds for more in-depth testing and risk assessment. To support computational models three kinds of exposure measurement data are required:
  1. key physical-chemical properties
  2. chemical emissions from consumer products used indoors
  3. chemical occurrence in product, environmental, and biological media.
SEEM Evolution – Human Exposure

Model and Predictors

- USEtox
- RAIDAR
  - Near Field / Far Field
  - Production Volume

Calibration/Evaluation Data

- NHANES Urine Data

SEEM Conclusion

- Existing complex fate and transport models have low correlation to measured exposures
  - Near field factor most important

1st Gen

2nd Gen

- Use Categories
- Production Volume
- Phys-Chem Properties

- NHANES Urine Data

- Simple, readily available data
- Better correlation to measured exposures
- Similar predictions across demographics

2nd Gen

3rd Gen

- SHEDS-HT
- Literature Models
  - CPcat Database

- NHANES Urine + Blood Data

- Analysis ongoing

Office of Research and Development
SEEM Evolution – Far-field Water Eco (fish) and Human Exposure

Model and Predictors
- USEtox
- RAIDAR
- HT EXAMS-KABAM-BASS
- SHEDS-HT Down the drain
- Production Volume

Calibration/Evaluation Data
- EPA/USGS water monitoring data and fish conc. data

SEEM Conclusion
- Analysis ongoing
Conclusions

• High throughput risk prioritization relies on three components – high throughput hazard characterization, high throughput exposure forecasts, and high throughput pharmacokinetics

• Characterize uncertainty in chemical exposures by examining the predictive ability of models and the coverage (or lack thereof) of critical pathways

• Upcoming analysis:
  – Augment heuristics with calibrations of new mechanistic HT models for exposure from consumer use and indoor environment (e.g., SHEDS-HT)
  – Develop new data sources with additional chemical descriptors (e.g., CPcatDB)
  – Should help decrease uncertainties and increase confidence in extrapolation
  – Perform similar analysis for water concentrations
Collaborators

Chemical Safety for Sustainability (CSS) Rapid Exposure and Dosimetry (RED) Project

NCCT
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Richard Judson
Thomas Knudsen
Chantel Nicolas*
Robert Pearce*
James Rabinowitz
Caroline Ring*
Woody Setzer
Imran Shah
Rusty Thomas
John Wambaugh

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NHEERL
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NERL
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Derya Biryol*
Dalizza Colon
Kathie Dionisio*
Peter Egeghy
Kim Gaetz
Kristin Isaacs
Julia Rager*
Mark Strynar
Jon Sobus
Mike Tornero-Velez
Dan Vallero

*Trainees

Arnot Research and Consulting
Jon Arnot
Chemical Computing Group
Rocky Goldsmith
Environmental Protection Agency
Alicia Frame
Hamner Institutes
Barbara Wetmore
Cory Strope
Indiana University
James Sluka
Michigan State University
Jade Mitchell
National Institute for Environmental Health Sciences (NIEHS)
Mike Devito
Nisha Sipes
Kyla Taylor
Kristina Thayer
Netherlands Organisation for Applied Scientific Research (TNO)
Sieto Bosgra
North Carolina State University
Anran Wang*
Research Triangle Institute
Timothy Fennell
Silent Spring Institute
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Deborah Bennett
University of Michigan
Olivier Jolliet
University of North Carolina, Chapel Hill
Alex Sedykh
Alex Tropsha

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