The Chemical Landscape of New Approach Methodologies for Exposure

Kristin Isaacs

Center for Computational Toxicology and Exposure
Office of Research and Development, United States Environmental Protection Agency
Disclaimer

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA
Triaging Chemical Exposure Data Needs and Tools for Advancing Next-Generation Risk Assessment

- Identify available New Approach Methodologies (NAMs) for exposure data streams
- Examine the landscape of exposure data (both traditional and NAMs) for an inventory of chemicals relevant to APCRA partners
- Identify key information or activities that would enable or enhance fit-for-purpose exposure estimates, predictions, or assessments
- Provide exposure metrics to support the APCRA inventory and hazard-focused case study activities
- Evaluate exposure NAMs against traditional methods to evaluate utility in different regulatory contexts
# Contributors

<table>
<thead>
<tr>
<th>US EPA Office of Research and Development Center for Computational Toxicology and Exposure</th>
<th>Health Canada</th>
<th>European Chemicals Agency</th>
</tr>
</thead>
</table>
| Kathie Dionisio  
Annette Guiseppi-Elie  
Kristin Isaacs  
Katherine Phillips  
Jon Sobus  
Elin Ulrich  
John Wambaugh  
Barbara Wetmore | Angelika Zidek | Andreas Ahrens |
Evaluating chemicals for risk to humans or the environment requires information on hazard and exposure potential.

Exposure potential quantifies the degree of contact between a chemical and a receptor.

Toxicokinetic information is required to bridge hazard and exposure (what real-world exposure is required to produce an internal concentration consistent with a potential hazard?)

Regulatory bodies are tasked with evaluating risks associated with 1000s of chemicals in commerce. For example, as of 2019 there were ~40,000 chemicals on EPA’s TSCA Active Inventory.
Critical Exposure-Relevant Domains

- **Chemical use and release.** Provides critical information for identifying chemical sources, exposure pathways, and relevant predictive models for a given chemical.

- **Media occurrence, environmental surveillance, and biomonitoring.** Provides exposure data for evaluating predictive models.

- **Exposure estimates.** Predictions of chemical intake in mg/kg/day that can be compared with hazard information to inform risk.

- **Toxicokinetics.** Provides real-world exposure context to *in vitro* high-throughput screening data and biological receptor monitoring information.
Classes of NAMs for Exposure

- **Chemical descriptors** that provide information on chemicals in an exposure context (e.g., how chemicals are used)
- **Machine-learning approaches** that use these descriptors to fill gaps in existing data
- **High-throughput exposure models** for various pathways
- **High-throughput measurements** to fill gaps in monitoring data
- New **evaluation frameworks** for integrating models and monitoring to provide consensus exposure predictions
- High-throughput approaches for measuring and predicting chemical **toxicokinetics**
- All these pieces together provide the tools for high-throughput **chemical prioritization**
Characterizing the Chemical Landscape for Exposure NAMs

- **“APCRA inventory” - case study chemical list**
  - 6621 chemical substances compiled by APCRA partners for potential use in retrospective or prospective case studies- primarily single component
  - Selected from regulatory lists from EPA, Health Canada, ECHA, EFSA, NICNAS

- Investigated the coverage of this inventory
  - “Traditional” exposure data
    - Regulatory reporting
    - Targeted monitoring data
    - Regulatory exposure assessments
    - *In-vivo* toxicokinetic information
  - Exposure NAMs across all four domains
Traditional and NAM Exposure Datasets

- Regulatory or agency data reporting of chemical use
  - New quantitative and qualitative chemical use descriptors from EPA’s Chemicals and Products Database (CPDat, Dionisio et al., 2018)
  - Machine learning models for chemical function (Phillips et al. 2017)

- NAM dataset

- Chemical Use and Release
  - Environmental Surveillance and Biomonitoring

- Toxicokinetics
  - IVIVE

- Exposure Estimates
Traditional and NAM Exposure Datasets

- Regulatory or agency data reporting of chemical use
- New quantitative and qualitative chemical use descriptors from EPA’s Chemicals and Products Database (CPDat, Dionisio et al., 2018)
- Machine learning models for chemical function (Phillips et al. 2017)

Traditional (targeted) monitoring data for various environmental media from publicly available monitoring databases


- Machine learning models for media occurrence

- Regulatory or agency data reporting of chemical use
- New quantitative and qualitative chemical use descriptors from EPA’s Chemicals and Products Database (CPDat, Dionisio et al., 2018)
- Machine learning models for chemical function (Phillips et al. 2017)

Traditional (targeted) monitoring data for various environmental media from publicly available monitoring databases


- Machine learning models for media occurrence
Traditional and NAM Exposure Datasets

**Regulatory or agency data reporting of chemical use**
- New quantitative and qualitative chemical use descriptors from EPA's Chemicals and Products Database (CPDat, Dionisio et al., 2018)
- Machine learning models for chemical function (Phillips et al. 2017)

**Traditional (targeted) monitoring data for various environmental media from publicly available monitoring databases**
- Machine learning models for media occurrence

**Publicly Available Traditional Assessments from Regulatory Bodies**
- High-Throughput Models for Various Pathways and Consensus Predictions from a Collaborative Modeling Study (Ring et al., 2019)

**Chemical Use and Release**
- Toxicokinetics
- Exposure Estimates
- IVIVE

**Environmental Surveillance and Biomonitoring**
- Cumulative Estimated Daily Intakes
- Chemicals Management Plan Environmental and Consumer Assessments
Traditional and NAM Exposure Datasets

- **Regulatory or agency data reporting of chemical use**
- **New quantitative and qualitative chemical use descriptors from EPA’s Chemicals and Products Database (CPDat, Dionisio et al., 2018)**
- **Machine learning models for chemical function (Phillips et al. 2017)**
  - *In-vivo* toxicokinetic parameters collected from the literature (Sayre et al., 2019)
- **Environmental Surveillance and Biomonitors**
- **Chemical Use and Release**
- **Toxicokinetics**
- **Exposure Estimates**
- **IVIVE**

**Traditional (targeted) monitoring data for various environmental media from publicly available monitoring databases**

- **Machine learning models for media occurrence**

**Publicly Available Traditional Assessments from Regulatory Bodies**

- **High-Throughput Models for Various Pathways and Consensus Predictions from a Collaborative Modeling Study (Ring et al., 2019)**

**New quantitative and qualitative chemical use descriptors from EPA’s Chemicals and Products Database (CPDat, Dionisio et al., 2018)**

**Machine learning models for chemical function (Phillips et al. 2017)**

**In-vivo toxicokinetic parameters collected from the literature (Sayre et al., 2019)**

**In-silico machine learning models for protein binding and clearance (Sipes et al. 2017, Ingle et al. 2018)**

**In-vitro protein binding and clearance (Wetmore et al. 2015, Pearce et al. 2017, Wambaugh et al 2019a.)**

**In-silico machine learning models for protein binding and clearance (Sipes et al. 2017, Ingle et al. 2018)**

**In-vitro protein binding and clearance (Wetmore et al. 2015, Pearce et al. 2017, Wambaugh et al 2019a.)**

**Package ‘httk’**

- **Version 2.0.0**
- **Date 2020-03-10**
- **Title High-Throughput Toxicokinetics**
The number of chemicals for which release data are available is still limited.
The number of chemicals for which release data are available is still limited.
Traditional Targeted Monitoring Data

Non-Targeted Studies in Several Media

Positive Prediction of Occurrence in Different Media from Machine Learning Models

APCRA Inventory

6621 Inventory Chemicals

- Traditional monitoring very limited
A limited number of non-targeted studies in media have provided data for many additional chemicals.
High-throughput exposure models covering different exposure pathway classes have generated exposure estimates for large numbers of chemicals compared to traditional assessments.
High-throughput exposure models covering different exposure pathway classes have generated exposure estimates for large numbers of chemicals compared to traditional assessments.
High throughput in vitro measurement of toxicokinetics has expanded the quantity and domain of chemicals with data, allowing for the development or refinement of in silico models.
In silico approaches have expanded the availability of HTTK parameters to nearly all chemicals tested for in vitro bioactivity (96% of Tox21 and 89% of ToxCast) allowing for in vitro to in vivo extrapolation of bioactive concentrations.

- High throughput in vitro measurement of toxicokinetics has expanded the quantity and domain of chemicals with data, allowing for the development or refinement of in silico models.
In all exposure-relevant domains, high-throughput NAMs have substantially increased the number of chemicals for which data are available and improved coverage of chemical inventories.

Methods for estimating chemical releases (quantitative estimates of emission into different environmental compartments) are needed; predictions for releases can reduce uncertainty in HT exposure models that currently rely on production volume as surrogates for emission rates.

Methods should be developed for addressing mixtures or UVCBs. Approaches are needed for identifying representative compositions or structures for multicomponent substances, and for making use of this information in *in silico* modeling (i.e., QSAR) frameworks.

Measurement NAMs (i.e., non-targeted approaches) have the potential to substantially increase the scope of evaluation datasets for predictive exposure models.

Continuing to develop and refine NAMs for exposure and toxicokinetic domains will improve the quality of and expand the scope of risk-based metrics available for chemical prioritization.
Ongoing Exposure NAM Evaluation Activities

- Will aid in assessing fit-for-use of exposure NAMs in various regulatory contexts (classification and labelling, prioritization, first-tier versus full assessments)

- Comparison of Quantitative Use Relationship (QSUR) models for chemical function with industry reported data
  - EPA’s Chemical Data Reporting for Industrial Uses (Public)
  - ECHA Plastics Additives Initiative (PLASI)
  - Health Canada Chemicals Management Plan Information Gathering

- Comparison of traditional exposure assessments (Health Canada Chemicals Management Plan) to high-throughput model predictions
  - Consumer Assessments
  - Environmental media (i.e., ambient/far-field)
References


