New Approach Methodologies (NAMs) and Chemical Risk Assessment

April 24, 2020

EMAP 514: Introduction to Environmental Health Risk Assessment and Management
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The views presented are those of the author and do not necessarily reflect the views of the US EPA.
• Environmental Health and Chemical Risk Assessment
• Advancing Risk Assessment
• New Approach Methodologies (NAMs)
• EPA Specific Drivers
• Closing
Environmental Health and Chemical Risk Assessment – A long history

Risk assessment
- Dose-response assessment
- Hazard identification
- Exposure assessment

Risk characterization

Risk management
- Control options
- Legal considerations
- Risk management decisions
- Other economic and social factors

Source: EPA Office of Research and Development.

Chemical Risk Assessment

What are we really trying to do?
Regulatory Agencies Make a Broad Range of Decisions on Chemicals...

- Number of chemicals and combinations of chemicals is extremely large (>40,000 substances on active TSCA inventory)
- Traditional toxicity testing is expensive and time consuming
- Traditional animal-based testing has issues related to ethics and relevance
- Looking into new ways to address these problems.
EPA-Specific Drivers

USEPA Administrator Memo Prioritizing Efforts to Reduce Animal Testing, September 10, 2019

- EPA will reduce its requests for, and our funding of, mammal studies by 30 percent by 2025.
- EPA will eliminate all mammal study requests and funding by 2035. Any mammal studies requested or funded by the EPA after 2035 will require Administrator approval on a case-by-case basis.
- Form a working group of agency experts in this field who will provide a work plan within six months.
Letter to Stakeholders on OPP’s Goal to Reduce Animal Testing from Jack E. Housenger, Director

- [https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2016-0093-0003](https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2016-0093-0003)

- Working in partnership with other governmental entities, industry and non-governmental organizations (NGOs) and need continued robust participation and support to achieve our mutual goal.

- Activities fall under three main objectives
  - Critically evaluating which studies form the basis of OPP decisions;
  - Expanding acceptance of alternative methods and;
  - Reducing barriers such as challenges of data sharing among companies and international harmonization to adopting alternative methods in the U.S. and internationally.
The US Environmental Protection Agency’s (EPA) Endocrine Disrupting Screening Program (EDSP)

- established in response to Congressional mandates in the Federal Food Quality Protection and Safe Water Drinking Acts
- evaluating potential risk of endocrine disruption in humans and wildlife from exposure to pesticide chemicals and drinking water contaminants
- recommendations from an expert advisory committee established a two tiered system
  - Tier 1 screening for potential to interact with the estrogen, androgen or thyroid hormone systems
  - Tier 2 testing to verify interaction and quantify dose-response relationship
- In 2011, EPA began a multiyear transition to prioritize and screen thousands of EDSP chemicals using high-throughput in vitro assays and computational modeling approaches

https://www.epa.gov/endocrine-disruption
Use of High Throughput Assays and Computational Tools; Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment
EDSP “Pivot” Goals for Using Computational Toxicology Data

• Use computational tools and models in the EDSP framework to:
  ▪ Rapidly screen chemicals for endocrine bioactivity
  ▪ Contribute to the weight of evidence screening level determination of a chemical’s potential bioactivity
  ▪ Provide alternative data for specific endpoints in the EDSP Tier 1 battery

— Similar approaches are common to estrogen, androgen and thyroid pathways; however, estrogen agonist bioactivity is the most mature model and is used to demonstrate the proposed approach.
Toxic Substances Control Act (TSCA)

- The Toxic Substances Control Act (TSCA) regulates the introduction of new and existing chemicals.

- TSCA was amended by the Frank R. Launtenberg Chemical Safety for the 21st Century Act (June 22, 2016):
  - Large bipartisan support in both House and Senate;
  - Broad stakeholder support;
  - First major update to an environmental statute in about 20 years.

- Implementation of TSCA is the responsibility of the Office of Chemical Safety and Pollution Prevention (OCSPP), specifically, the Office of Pollution Prevention and Toxics (OPPT).

- EPA required to make determination if chemical substance presents an unreasonable risk of injury to human health or the environment. Determinations are risk-based.

https://www.epa.gov/chemicals-under-tsca
Under Lautenberg, EPA must identify 20 high- and 20 low-priority chemicals (TSCA Section 6).

EPA developed a document describing two approaches on how EPA may identify candidate chemicals to enter the prioritization process:

- Short-term approach may be used to identify high-priority chemicals (likely) from the TSCA 2014 Workplan and low-priority chemicals from the Safer Chemicals Ingredients List;
- Long-term approach proposed an approach to review chemicals in the TSCA active list (about 40K chemicals) based upon risk-related scoring and information availability.

On March 20, 2019, EPA initiated the prioritization process by issues a list of 40 chemical substances and began effort to designate 20 as high-priority and 20 low-priority substances.
Toxicology Moving to Embrace 21st Century Methods

Using 21st Century Science to Improve Risk-Related Evaluations

New Approach Methodologies (NAMs)

• Commonly defined to include *in silico* approaches, *in chemico* and *in vitro* assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard assessment.

• Recently defined in the EPA’s TSCA Alternative Toxicity Strategy as:
  • a broadly descriptive reference to any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals.


New Approach Methodologies (NAMs)

In silico (e.g. QSAR and Read-across)
Estimate effects and doses

In vitro assays
  - Broad / screening (transcriptomics, cell painting)
  - Targeted (receptors, enzymes)

In vitro PODs, modes / mechanisms of action

In vitro Toxicokinetics
  - Allow conversion of an in vitro POD to in vivo (IVIVE)

Computer models
  - Integrate multiple in silico and in vitro data streams

Databases of existing traditional toxicology data
  - Enables training and validation of NMA models
Computational Chemistry

• Curated chemical structure database of >800,000 unique substances with QC flags to link chemical structure with names and identifiers

• Comprehensive physical-chemical property database (experimental and predicted) to harmonize properties across the Agency

• Consensus QSAR models for a range of physical chemical properties, environmental fate, and hazard characteristics

• Curation of reference chemical lists

https://comptox.epa.gov/
ToxCast and Tox21: Adding the High-Throughput Hazard Screening Component

### ToxCast
- **Set**: ToxCast Phase I
  - Chemicals: 293
  - Assays: ~600
  - Completion: 2011
- **Set**: ToxCast Phase II
  - Chemicals: 767
  - Assays: ~600
  - Completion: 2013
- **Set**: ToxCast Phase III
  - Chemicals: 1001
  - Assays: ~100
  - Completion: Ongoing
- **Set**: E1K (endocrine)
  - Chemicals: 880
  - Assays: ~50
  - Completion: 2013
Application of High-Throughput Assays to Identify Potential Endocrine Disrupting Chemicals

18 In Vitro Assays Measure ER-Related Activity

- Use multiple assays per pathway
  - Different technologies
  - Different points in pathway
- No assay is perfect
  - Assay Interference
  - Noise
- Use model to integrate assays
- Model creates a composite dose-response curve for each chemical to summarize results from all assays

Judson et al., Tox Sci. 2015
Browne et al., ES&T. 2015
Kleinstreuer et al., EHP 2016
Beginning to Address Concerns for Increased Biological Coverage

**Gene Coverage**

- ToxCast
- Not in ToxCast

**Pathway Coverage***

*At least one gene from pathway represented

**Illustrations from Perkin Elmer**

~ 1300 endpoints (tcpl: “components”)
Beginning to Address Metabolic Competence

“Extracellular” Approach

- Chemicals metabolism in the media or buffer of cell-based and cell-free assays
- More closely models effects of hepatic metabolism and generation of circulating metabolites

“Intracellular” Approach

- Capable of metabolizing chemicals inside the cell in cell-based assays
- More closely models effects of target tissue metabolism

Integrated approach to model \textit{in vivo} metabolic bioactivation and detoxification

Collaboration with Unilever
Adding the High-Throughput Toxicokinetic Component

EPA ToxCast Phase I and II Chemicals

Human Liver Metabolism

Human Plasma Protein Binding

Population-Based IVIVE Model

In Vitro Potency Value

Administered Dose Required to Achieve Steady State Plasma Concentrations Equivalent to In Vitro Bioactivity

- Currently evaluated ~700 ToxCast Phase I and II chemicals
- Models available through “httk” R package (https://cran.r-project.org/web/packages/httk/)

Rotroff et al., Tox Sci., 2010
Wetmore et al., Tox Sci., 2012
Wetmore et al., Tox Sci., 2015

Upper 95th Percentile Css Among 100 Healthy Individuals of Both Sexes from 20 to 50 Yrs Old

EPA

Reverse Dosimetry

Plasma Concentration

Exposure Route

Human Liver

Exposure Route

Human Plasma

Protein Binding

Population-Based IVIVE Model

EPA ToxCast Phase I and II Chemicals

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**Linking Bioactivity and Exposure (i.e. Risk)**

- **High throughput risk characterization** relies on three components:
  1. High throughput **hazard** (i.e. bioactivity) characterization
  2. High throughput **exposure** forecasts
  3. High throughput **toxicocokinetics** (i.e. dosimetry)

ExpoCast: [http://www2.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research](http://www2.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research)
Enabling Risk-Based Prioritization

Wetmore et al., Tox Sci., 2015

Chemicals
Century Risk Assessment
Covering All the Components of a 21st Century Risk Assessment

Phys Chem

PODS

Hazard Expose

Uncertainty Risk Summary

Variability
What is needed to expand translation and implementation of NAMs?

• Integration of NAM data with traditional data
• Fit-for-purpose applications
• Build confidence and understanding
• Engage stakeholders
Incorporating new technologies and innovations in toxicology can more rapidly and inexpensively screen chemicals for potential adverse biological effects.

EPA has made great advances in the development of NAMs for filling information gaps for decision-making and integrating those tools and data streams into chemical risk assessment.

EPA has worked with other stakeholders to leverage resources and develop NAMs that can support different regulatory contexts.

Building confidence in the use of NAMs for regulatory decision-making is key to the increased implementation of these methods.