Development of a RapidTox Dashboard to Inform Risk Assessment

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Computational Toxicology Communities of Practice
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The views expressed in this presentation are those of the author and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

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Outline of this presentation

• Emergency Response and the U.S. EPA: brief overview
• Traditional Risk Assessment
  • Okay, Houston, we’ve had a problem here (Swigert, April 1970)
• CompTox Chemicals Dashboard
• RapidTox Prototype Workflow for Emergency Response
Decades of chemical production and use in product formulations
  • Pesticides, linear/(poly)cylic organics, complex materials (nano)
  • Consumer products, cosmetics, pharmaceuticals, textiles, etc. (e.g., CPSC, FDA)
Occurrence in soil, water, air (rarely singular chemicals; mixtures)
TSCA, FIFRA, CERCLA, SARA, RCRA
Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) and Superfund Amendments and Reauthorization Act (1986)
  • Superfund is an EPA program to clean up the most polluted sites in America
  • Sites are evaluated for risks to human health or the environment
  • Currently > 1300 NPL sites
Superfund is part of EPA’s Office of Land and Emergency Management (OLEM) which responds to a wide variety of environmental risks.

- **Emergency response**: Quick, reliable data to protect human health and the environment.
- **Superfund Cleanups**: Robust toxicity data that can hold up in court.
- **RCRA**: High quality hazard and physical properties data sufficient for regulations.
- **All programs**:• UVCBs• Mixtures• Exposure• Fate and Transport, PhysChem
Emergency Response and the U.S. EPA

• 1000’s of emergencies annually
  • Oil spills; release of chemical, biological, radiological, or nuclear contamination into the environment
• Scale of emergencies is diverse from localized/limited releases up to large-scale/national events
• Information needs for a given emergency scenario depends on the scope of the problem and the threat(s) involved (e.g., imminent threat to human health; intermediate phase(s); longer-term clean-up)
Emergency Response and the U.S. EPA

• Key reliance on existent health or toxicity values for exposure scenarios of concern (i.e., acute or short-term)

• Identification/use of values varies by response purview or condition (e.g., Regional Screening Level tables; AEGLs, CDC/NIOSH occupational values, NHSRC PALs, State-level values, etc.)

• No time to “come up” with health values for an emergency
  • Values available but for longer exposure duration(s)
  • No values at all; broad gradation of available toxicity data

• Option: wait for an assessment?? Can’t wait—livelihood depends on rapid decisions

• Option: integrate existent information and new approach methodologies-based data to inform decision-making?

• What is the fit-for-purpose? Priority ranking, screening, and/or assessment
Non-cancer Reference Values (RfD, RfC) = POD/UF_C

UF_C = composite uncertainty factor
  - UF_A = animal-to-human
  - UF_H = interindividual variability
  - UF_S = subchronic-to-chronic duration
  - UF_L = LOAEL-to-NOAEL
  - UF_D = database

Cancer Values (OSF, IUR) = increased cancer risk from a lifetime oral or inhalation exposure to a chemical. Usually expressed in units of proportion (of a population) affected per mg/kg-day (oral) or μg/m^3 (inhalation).
Okay Houston, we’ve “got” a problem

- Assessment timeline: Integrated Risk Information System (years), Provisional Peer-Reviewed Toxicity Values (months up to 2 years), ATSDR MRLs (years)

- Depending on who you talk to, there are anywhere from 20K to >80K chemicals currently in the environment/commerce

- Collectively, across our global community of toxicology and risk assessment practice, only a small fraction of those chemicals have been assessed for toxicity

*For problem formulations associated with protection of human health, in particular emergency response, higher throughput of qualitative and quantitative information for contaminants is paramount!

- Over the past decade, several reports, books, resource documents, etc. have been published regarding the use of New Approach Methods (NAM) across the human health risk assessment paradigm (i.e., shifting the paradigm)

- Numerous labs, centers, workgroups, and initiatives across federal, private, and academic institutions have been formed to advance NAM and Computational Toxicology platforms
• **Data-mining**: comprehensive collection and collation of extant hazard and exposure data – (Martin et al. 2009. Environ Health Perspect 117: 392-399)


• **Adverse Outcome Pathway (AOP)**: expert-driven identification of signal transduction pathways along the exposure to outcome continuum. – (Edwards et al. 2015. J Pharmacol Exp Ther. epub ahead of print: http://jpet.aspetjournals.org/content/early/2015/11/04/jpet.115.228239.long)
EPA’s CompTox Chemicals Dashboard

Data
Predictive Models
Chemical Structures
Web-Based Dashboard
Agency Scientists
Front Line Staff
Public

CompTox Chemicals Dashboard Overview

Data Availability

• Chemical Properties
• Environmental Fate and Transport
• Hazard (*in vivo, in vitro, in silico*)
• ADME
• Exposure
• Bioactivity
• Similar Compounds
• Literature

Data Interpretability/Application

• Key components:
  • Collects known health/tox/exposure values into one place
  • Readily surface hazard/D-R information (e.g., PODs)
  • Facilitates identification of analogue(s)
  • Can inform uncertainty(ies)
  • Fill information gaps
  • Linkable data streams

Current Public Dashboard: [https://comptox.epa.gov/dashboard](https://comptox.epa.gov/dashboard)
• RapidTox is a suite of workflows that facilitate the application of data surfaced in the CompTox dashboard in diverse assessment decision context.
Hypothetical Emergency Response Scenario

• Multiple rail cars transporting semi-volatile organic materials involved in accident near major source waterway for local utility

• Seven compromised cars spill over 200,000 gallons of Hexadecanoic acid (CASRN 57-10-3), also known as palmitic acid, down an embankment into the waterway

• No RSL values; no IRIS, PPRTV, CalEPA, ATSDR or other known human health assessment/toxicity value

• Municipal and State governments issue call for support in dealing with the emergency; water utility intake shut down; information on hexadecanoic acid needed within 12 hrs
Acute or Short-term Human Health values

Additional Options Available

Acute or Short-term Ecotoxicology values

Existent Points-of-Departure (all species)

Physicochemical Properties

Fate and Transport

Emergency Response: Pre-populated Outputs and Additional User-defined Options

(e.g., PAL, EL, MEG, TLV)

Additional Options Available

Pre-selected)

Literature Survey Heat Map

ToxCast/ToxPi profile

GenRA predictions

QSAR predictions

Emergency Response-Phase 1 Outputs

(Pre-selected)

Acute or Short-term Human Health values

Acute or Short-term Ecotoxicology values

Subchronic or Chronic Human Health values

Subchronic or Chronic Ecotoxicology values

Existent Points-of-Departure (all species)

Physicochemical Properties

Fate and Transport

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### Data Landscape for Output Generation - Emergency Response

#### Acute

- **Points-of-Departure (in vivo)**
  - Information Availability
  - Evaluate Information
  - Review
  - Remove

#### Subchronic

- Fate and Transport
  - Information Availability
  - Evaluate Information
  - Review
  - Remove

#### Chronic

- **Information Availability**
  - Evaluate Information
  - Review
  - Remove

#### Information Availability

<table>
<thead>
<tr>
<th>ToxVal type</th>
<th>Value</th>
<th>Units</th>
<th>Exposure route</th>
<th>Duration</th>
<th>Species</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air quality standard (background)</td>
<td>10</td>
<td>mg/m&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Inhalation</td>
<td>Chronic</td>
<td>-</td>
<td>DE AGOF Dust</td>
</tr>
<tr>
<td>Air quality standard (normal)</td>
<td>650</td>
<td>mg/m&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Inhalation</td>
<td>Chronic</td>
<td>-</td>
<td>DE AGOF Dust</td>
</tr>
<tr>
<td>Air quality standard (attention value)</td>
<td>1500</td>
<td>mg/m&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Inhalation</td>
<td>Chronic</td>
<td>-</td>
<td>DE AGOF Dust</td>
</tr>
<tr>
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<td>Inhalation</td>
<td>Chronic</td>
<td>-</td>
<td>DE AGOF SVOCs</td>
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<tr>
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<td>650</td>
<td>mg/m&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Air quality standard (attention value)</td>
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<td>mg/m&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Inhalation</td>
<td>Chronic</td>
<td>-</td>
<td>DE AGOF SVOCs</td>
</tr>
</tbody>
</table>

#### Existent Toxicity Values

- **ToxVal**
  - **Value**
  - **Units**
  - **Exposure route**
  - **Duration**
  - **Species**
  - **Source**

<table>
<thead>
<tr>
<th>Value</th>
<th>Units</th>
<th>Exposure route</th>
<th>Duration</th>
<th>Species</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>10000 mg/kg Oral</td>
<td>Acute</td>
<td>Rat</td>
<td>Tox</td>
<td>Acute Tox</td>
</tr>
<tr>
<td>PAC-1</td>
<td>2 mg/m&lt;sup&gt;3&lt;/sup&gt; Inhalation</td>
<td>Acute</td>
<td>DOE</td>
<td>Air quality standard</td>
<td>air quality standard</td>
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<td>PAC-2</td>
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<td>Acute</td>
<td>DOE</td>
<td>Air quality standard</td>
<td>air quality standard</td>
</tr>
<tr>
<td>PAC-3</td>
<td>12 mg/m&lt;sup&gt;3&lt;/sup&gt; Inhalation</td>
<td>Acute</td>
<td>DOE</td>
<td>Air quality standard</td>
<td>air quality standard</td>
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<tr>
<td>MEG</td>
<td>50 mg/m&lt;sup&gt;3&lt;/sup&gt; Inhalation</td>
<td>Subchronic</td>
<td>DOE</td>
<td>Air quality standard</td>
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<tr>
<td>Air quality standard</td>
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<td>Chronic</td>
<td>DOE</td>
<td>Air quality standard</td>
<td>air quality standard</td>
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<td>Air quality standard</td>
<td>650 mg/m&lt;sup&gt;3&lt;/sup&gt; Inhalation</td>
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<td>DOE</td>
<td>Air quality standard</td>
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<td>Chronic</td>
<td>DOE</td>
<td>Air quality standard</td>
<td>air quality standard</td>
</tr>
</tbody>
</table>

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Acute or Short-term Human Health Values

Hexadecanoic acid
57-10-3 | DTXSID2021602
Search by DSSTox

Subchronic or Chronic Human Health values (7)

Existent Points-of-Departure (in vivo all species)

Physicochemical Properties

Fate and Transport

Acute or Short-term Human Health Values

Hexadecanoic acid
57-10-3 | DTXSID2021602

Acute Oral Value(s):
Rat LD50 = 10,000 mg/kg

Inhalation Value(s):
Protective Action Criteria-1 = 2 mg/m³
Protective Action Criteria-2 = 12 mg/m³

Existent Point-of-departure:

Fate and Transport:

Physicochemical Properties:

PLEASE DO NOT DISTRIBUTE FURTHER
Hexadecanoic acid
57-10-3 | DTXSID2021602
Searched by DSSTox
Substance Id.

Data Landscape for Output Generation-Emergency Response

Step Three: Data Availability Acquisition

Existent Toxicity Values

Information Availability | Evaluate Information
------------------------|------------------------

Points-of-Departure (in vivo)

Information Availability | Evaluate Information
------------------------|------------------------

Environmental Chemistry

- PhysChem
- Fate and Transport

Ecotoxicology Values

Information Availability
- Acute/Short-term
- Subchronic/Chronic

New Approach Methods

Information Availability
- Automated lit search
- ToxCast / Tox21 (in vitro)
- GenRA

Generate Pre-Report
Automated Literature search

New Approach Methods

- Information Availability
  - Automated lit search
  - ToxCast / Tox21 (in vitro)
  - GenRA

Evaluate Information

- Review
- Select

• Pre-loaded boolean strings but can be customized
## Bioactivity

### New Approach Methods

<table>
<thead>
<tr>
<th>Information Availability</th>
<th>Evaluate Information</th>
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<tbody>
<tr>
<td>Automated lit search</td>
<td>Review, Select</td>
</tr>
<tr>
<td>ToxCast / Tox21 (in vitro)</td>
<td>Review, Select</td>
</tr>
<tr>
<td>GenRA</td>
<td>Review, Select</td>
</tr>
</tbody>
</table>

![TOXCAST DATA Diagram]

### ToxCast / Tox21 (in vitro)
- **Acrylamide**
  - **Assay Endpoint Name**: Acrylamide Genotoxicity (in vitro)
  - **Assay Description**: Assays the genotoxicity of acrylamide in mammalian cells.
  - **Organism**: Human
  - **Biomarker**: DNA damage

<table>
<thead>
<tr>
<th>Target Name</th>
<th>GenBank Accession</th>
<th>AOP</th>
<th>Event</th>
<th>Hit Call</th>
<th>TopGg</th>
<th>TopGg Scaled</th>
<th>AC50</th>
<th>logAC50</th>
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<tr>
<td>_T47D_50nM_Negative</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>54.9</td>
<td>2.55</td>
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<tr>
<td>_T47D_50nM_Positive</td>
<td>NP_000116.2</td>
<td>ESR1</td>
<td>200</td>
<td>1151</td>
<td>ACTIVE</td>
<td>54.9</td>
<td>2.55</td>
<td></td>
</tr>
<tr>
<td>ERE_Cis_up</td>
<td>NP_000116.2</td>
<td>ESR1</td>
<td>200</td>
<td>1151</td>
<td>ACTIVE</td>
<td>29.1</td>
<td>1.19</td>
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<tr>
<td>PPARA_TRANS_up</td>
<td>NP_005027.2</td>
<td>PPARA</td>
<td>58</td>
<td>408</td>
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<td>1.80</td>
<td>1.52</td>
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<tr>
<td>RORa_TRANS_up</td>
<td>NP_005651.2</td>
<td>RORC</td>
<td>-</td>
<td>-</td>
<td>ACTIVE</td>
<td>1.40</td>
<td>1.18</td>
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<tr>
<td>XR_FXRNR1_L400</td>
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<td>61</td>
<td>479</td>
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<tr>
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<td>NRIH4</td>
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<td>479</td>
<td>ACTIVE</td>
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<td>2.29</td>
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<tr>
<td>ELa_LUC_BG1_Apopist</td>
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<td>ESR1</td>
<td>200</td>
<td>1151</td>
<td>ACTIVE</td>
<td>50.2</td>
<td>3.55</td>
<td></td>
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<tr>
<td>PGRE_CEB_dn</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>125</td>
<td>1.83</td>
</tr>
</tbody>
</table>

**AC50 (μM)**: 7.89
- **Scaled Top** 116
- **Gene Symbol**: ESR1
- **Intended Target Family**: Nuclear receptor
- **Tissue Derived**: Hepatocytes
- **Assay Format Type**: Cell-based
- **Biological Process Target**: Cell proliferation
- **Detection Technology**: RT-CES
- **Assay Description**: Data from the assay component Acrylamide Genotoxicity was analyzed into 2 assay endpoints. This assay endpoint Acrylamide Genotoxicity was analyzed into 2 assay endpoints.
Generalized read-across

New Approach Methods

Information Availability
- Automated lit search
- ToxCast / Tox21 (in vitro)
- GenRA

Evaluate Information
- Review
- Select

![Diagram showing data gap analysis and neighbors by chemical.]

Click on the image to view more details.
A Path Forward: Emergency Response and Beyond

- Early engagement with the end user community: define decision contexts from the beginning
- Iterative re-scoping of content and output structure based on end-user feedback
- Data producers, translators, and users work together
- Endgame: optimize workflow(s) and dashboard outputs


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• Questions?
  
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