The CompTox Dashboard & Emerging Contaminants in the Superfund Program

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US EPA Office of Land and Emergency Management (Superfund)

US EPA Office of Research and Development

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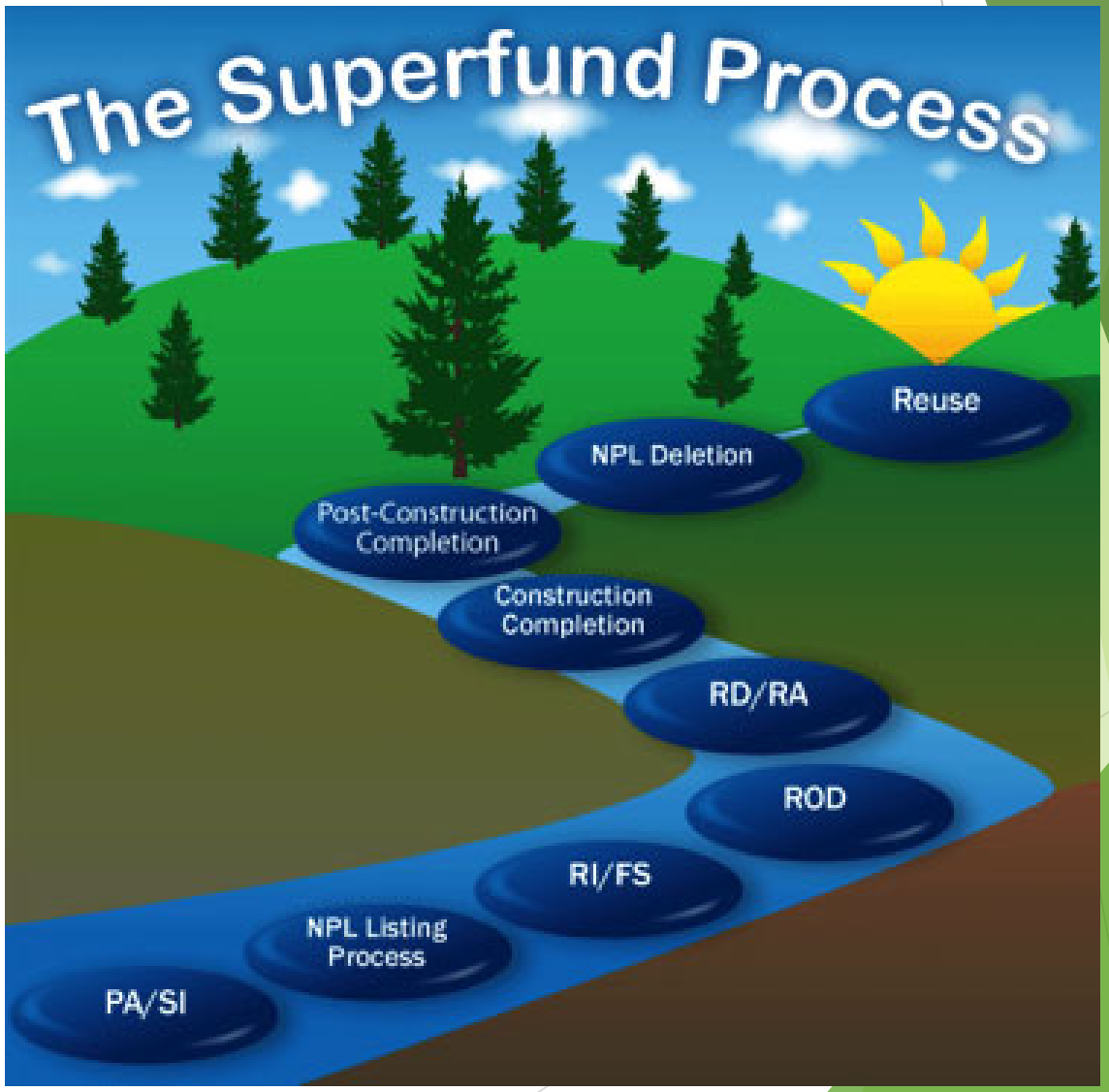
The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.

Background

- Superfund is an EPA program to clean up the most polluted sites in America that no other environmental program can successfully address
  - Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (**CERCLA**) and SARA (1986)
  - Sites are evaluated for risks to human health or the environment
  - Currently 1336 NPL sites + 393 deleted sites
  - Sites may take years to address



42 U.S. Code § 9604 - Response authorities

(a)REMOVAL AND OTHER REMEDIAL ACTION BY PRESIDENT; APPLICABILITY OF NATIONAL CONTINGENCY PLAN; RESPONSE BY POTENTIALLY RESPONSIBLE PARTIES; PUBLIC HEALTH THREATS; LIMITATIONS ON RESPONSE; EXCEPTION

(1) Whenever (A) any hazardous substance is released or there is a substantial threat of such a release into the environment, or (B) there is a release or substantial threat of release into the environment of any pollutant or contaminant which may present an imminent and substantial danger to the public health or welfare, the President is authorized to act, consistent with the national contingency plan, to remove or arrange for the removal of, and provide for remedial action relating to such hazardous substance, pollutant, or contaminant at any time (including its removal from any contaminated natural resource), or take any other response measure consistent with the national contingency plan which the President deems necessary to protect the public health or welfare or the environment.

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42 U.S. Code § 9601 - Definitions

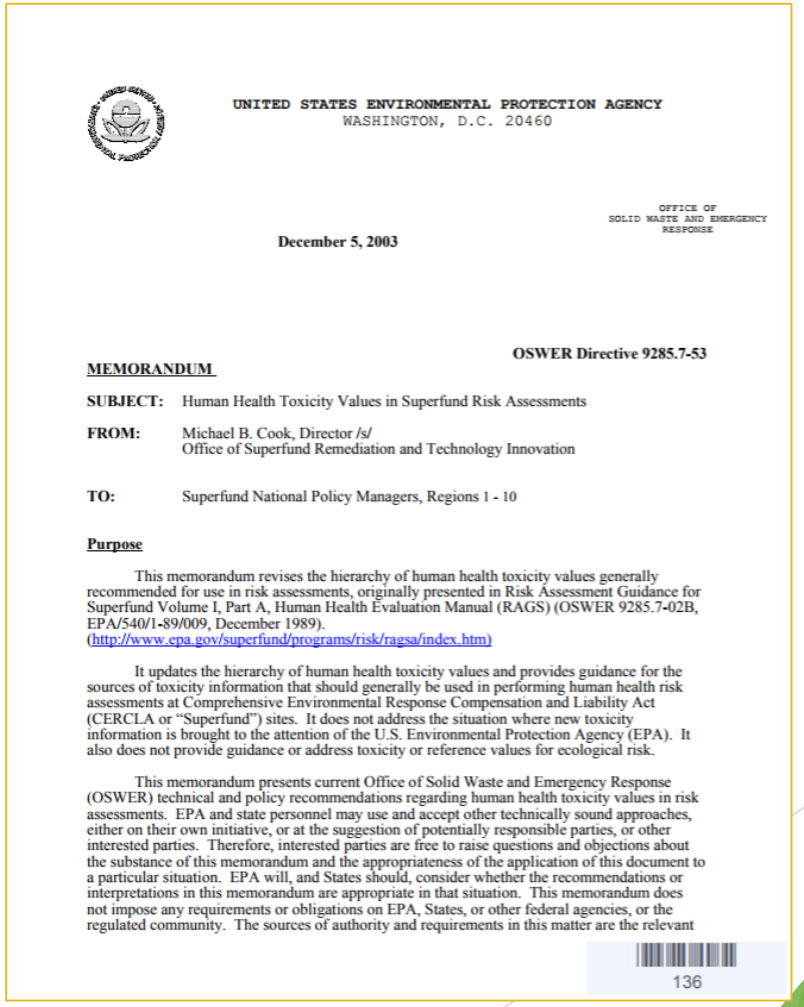
The term "**hazardous substance**" means (A) any substance designated pursuant to section 311(b)(2)(A) of the Federal Water Pollution Control Act [33 U.S.C. 1321(b)(2)(A)], (B) any element, compound, mixture, solution, or substance designated pursuant to section 9602 of this title, (C) any hazardous waste having the characteristics identified under or listed pursuant to section 3001 of the Solid Waste Disposal Act [42 U.S.C. 6921] (but not including any waste the regulation of which under the Solid Waste Disposal Act [42 U.S.C. 6901 et seq.] has been suspended by Act of Congress), (D) any toxic pollutant listed under section 307(a) of the Federal Water Pollution Control Act [33 U.S.C. 1317(a)], (E) any hazardous air pollutant listed under section 112 of the Clean Air Act [42 U.S.C. 7412], and (F) any imminently hazardous chemical substance or mixture with respect to which the Administrator has taken action pursuant to section 7 of the Toxic Substances Control Act [15 U.S.C. 2606].

42 U.S. Code § 9601 - Definitions

The term "pollutant or contaminant" shall include, but not be limited to, any element, substance, compound, or mixture, including disease-causing agents, which after release into the environment and upon exposure, ingestion, inhalation, or assimilation into any organism, either directly from the environment or indirectly by ingestion through food chains, will or may reasonably be anticipated to cause death, disease, behavioral abnormalities, cancer, genetic mutation, physiological malfunctions (including malfunctions in reproduction) or physical deformations, in such organisms or their offspring …

Data Sources for Pollutants and Contaminants

- Primary data sources:
  1. Integrated Risk Information System (IRIS) Assessments
  2. Provisional Peer Review Toxicity Values (PPRTVs)
  3. Other – other federal, state, international values, published studies
- Translate Point-of-Departure (POD) data to Reference Doses (RfDs)
- Risk Assessment Guidance for Superfund (RAGS) provides equations to translate toxicity and exposure into risks to human health



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
SOLID WASTE AND EMERGENCY
RESPONSE

December 5, 2003

OSWER Directive 9285.7-53

MEMORANDUM

SUBJECT: Human Health Toxicity Values in Superfund Risk Assessments

FROM: Michael B. Cook, Director /s/
Office of Superfund Remediation and Technology Innovation

TO: Superfund National Policy Managers, Regions 1 - 10

Purpose

This memorandum revises the hierarchy of human health toxicity values generally recommended for use in risk assessments, originally presented in Risk Assessment Guidance for Superfund Volume I, Part A, Human Health Evaluation Manual (RAGS) (OSWER 9285.7-02B, EPA/540/1-89/009, December 1989). (http://www.epa.gov/superfund/programs/risk/ragsa/index.htm)

It updates the hierarchy of human health toxicity values and provides guidance for the sources of toxicity information that should generally be used in performing human health risk assessments at Comprehensive Environmental Response Compensation and Liability Act (CERCLA or "Superfund") sites. It does not address the situation where new toxicity information is brought to the attention of the U.S. Environmental Protection Agency (EPA). It also does not provide guidance or address toxicity or reference values for ecological risk.

This memorandum presents current Office of Solid Waste and Emergency Response (OSWER) technical and policy recommendations regarding human health toxicity values in risk assessments. EPA and state personnel may use and accept other technically sound approaches, either on their own initiative, or at the suggestion of potentially responsible parties, or other interested parties. Therefore, interested parties are free to raise questions and objections about the substance of this memorandum and the appropriateness of the application of this document to a particular situation. EPA will, and States should, consider whether the recommendations or interpretations in this memorandum are appropriate in that situation. This memorandum does not impose any requirements or obligations on EPA, States, or other federal agencies, or the regulated community. The sources of authority and requirements in this matter are the relevant

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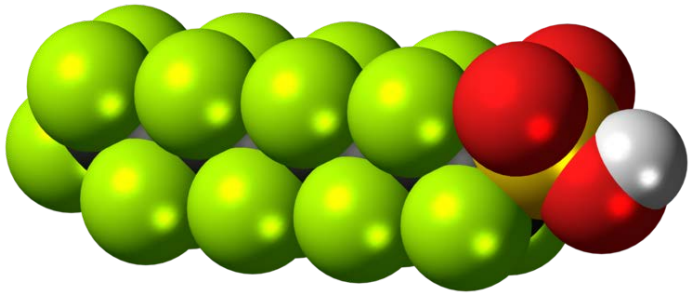
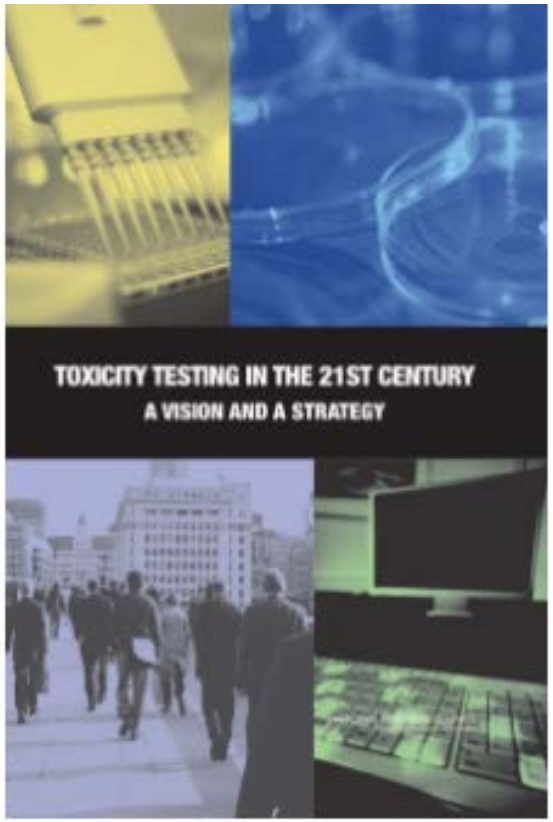
Emerging Contaminants

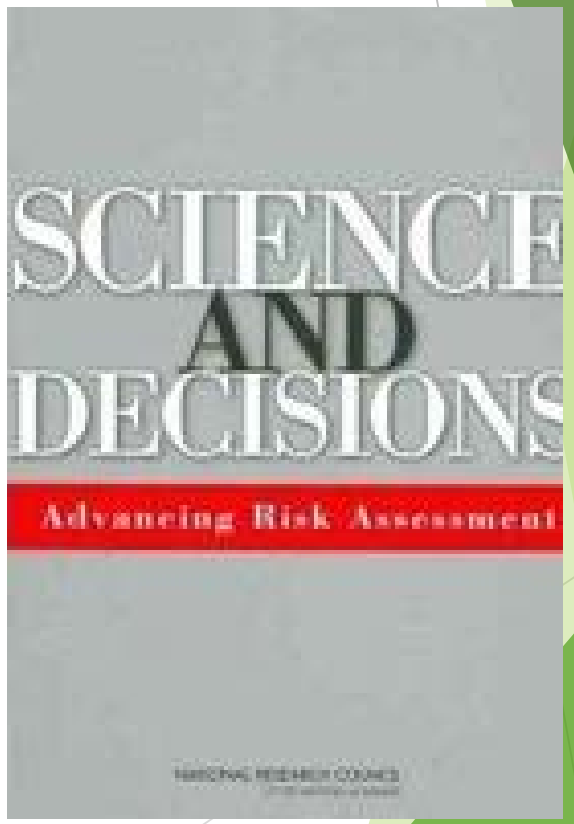
- New chemicals of concern with limited, or no, toxicity data
  - Perfluorinated compounds
  - Brominated flame retardants
  - Endocrine disruptors
  - Nanomaterials
- Current approach:
  - Hazardous substance designation
  - Wait for a PPRTV or IRIS assessment



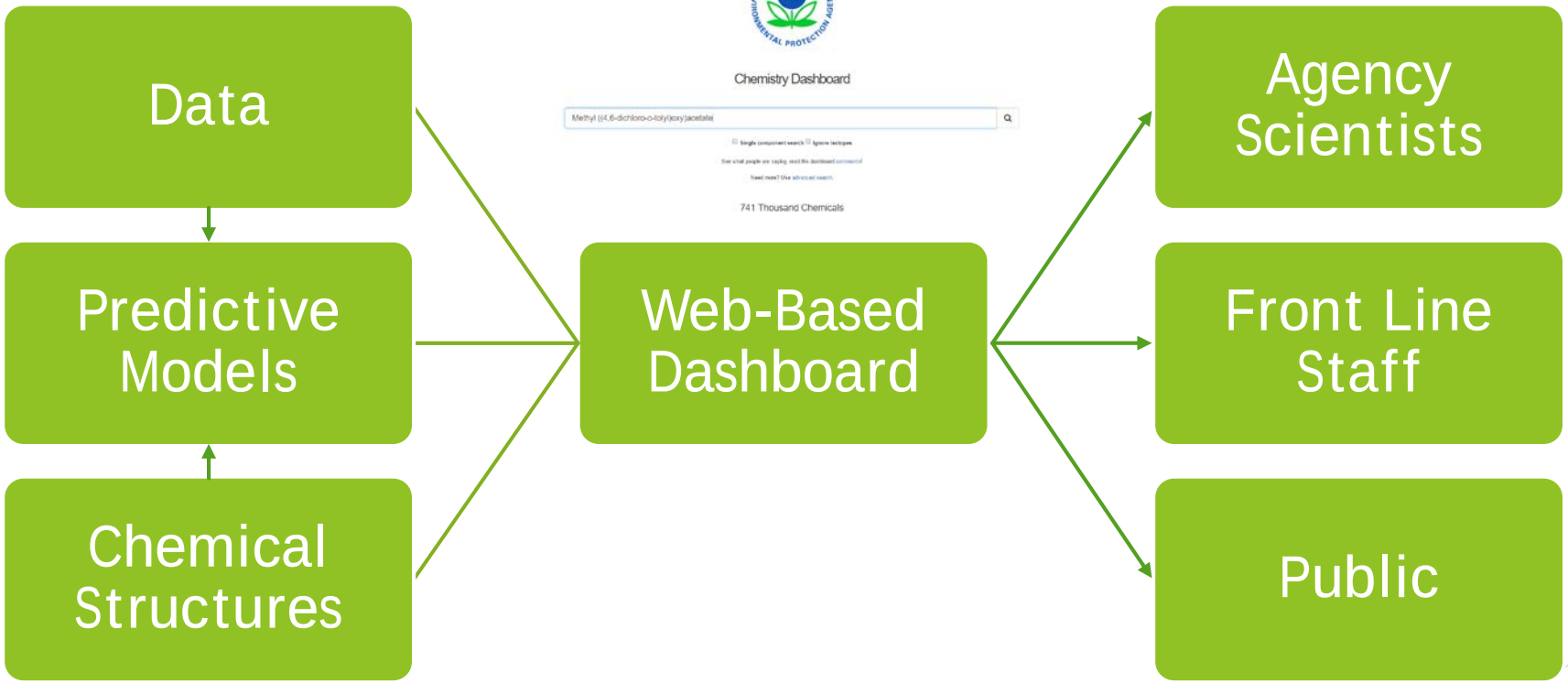
Motivation



- 2007 NAS Report: Toxicity Testing in the 21st Century
- Need to incorporate in vitro data, predictive models in risk assessments
- CompTox dashboard:
  - One-stop-shop for existing data
  - Easy to use tools to predict toxicity, physical properties



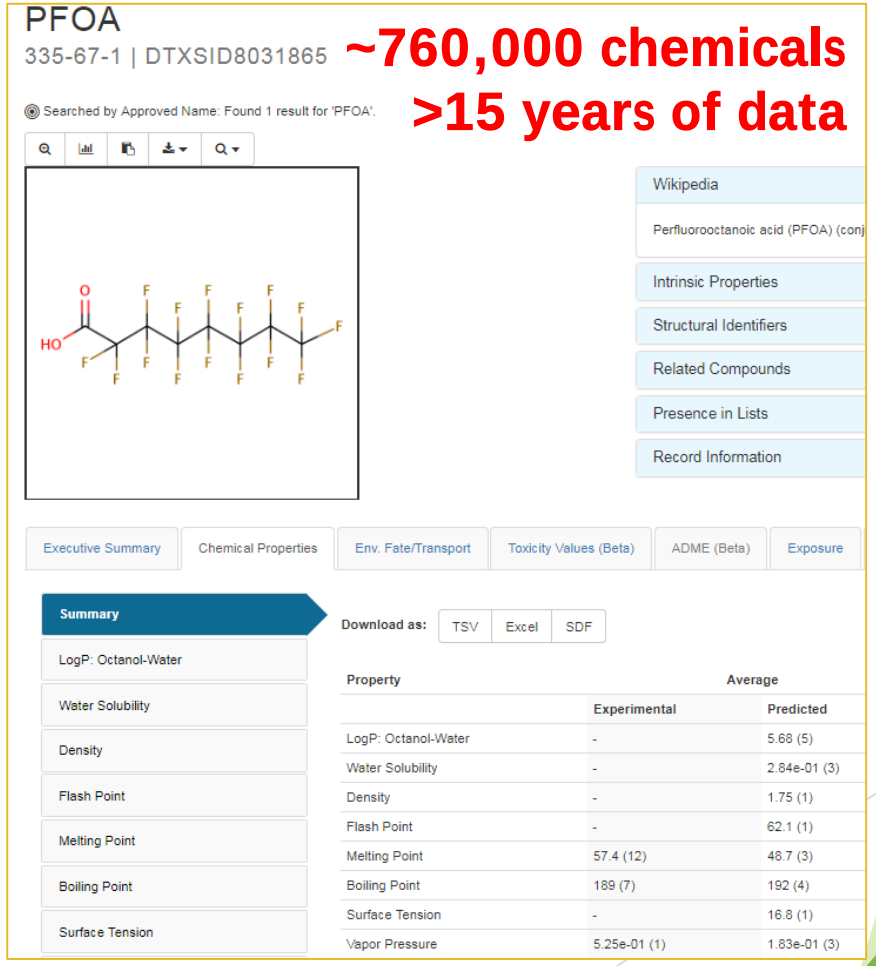
CompTox Dashboard



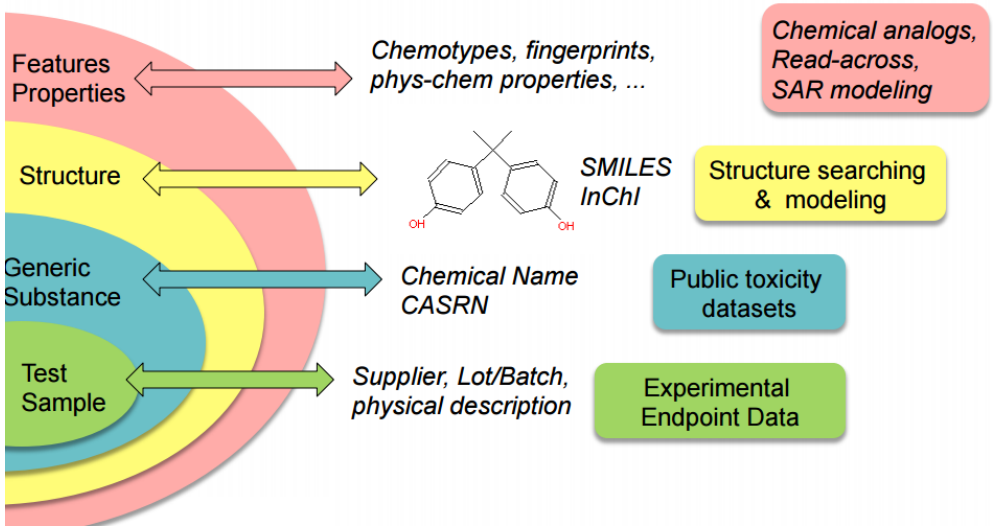
Current Public Dashboard: https://comptox.epa.gov/

Why CompTox?

- Coverage for information poor chemicals
- Single point of entry to data
  - Structure
  - Physical properties
  - Toxicity
  - Exposure
  - Regulatory data
- Access to robust, transparent, and defensible predictive models



Chemical Structures



- Chemical structures are essential:
  - How we identify unique chemicals
  - Used as inputs for predictive modelling
  - Often used to define regulatory and use classes
- Manually curated by chemists
- Currently integrating chemical mixtures
  - Some mixtures have fixed ratios
  - Some have variable or unknown ratios
  - Different frameworks for understanding mixture toxicity
  - Tackling how models can incorporate mixtures

Curated Data

- Toxicity data
  - In Vivo Chemical Toxicity Data:
    - Risk assessments for chemical registrations
    - EPA chemical evaluations
    - Literature
    - Publically available databases
  - In Vitro Toxicity Data – ToxCast
- Exposure: NHANES
- Regulatory data
  - State, Federal, International
  - Exposure limits, regulatory classes

Organized into an ontology

Data must be:

- Quality controlled
- Associated with chemical structures and unique sources
- Assigned a hierarchy score

Displayed as raw data in dashboard
Used as inputs for predictive models
Combined for risk assessments

Predictive Models

- Physical properties:
  - EPISUITE
  - NICEATM
  - ACD/Labs
  - T.E.S.T.
  - OPERA
- ADME properties – used for *in vivo in vitro* extrapolation
- Toxicity
  - Generalized read-across (GenRA)
  - Point-of-Departure predictions
- Exposure
  - Use categories
  - Far field exposure

Physical Properties

- Summary
- LogP: Octanol-Water
- Water Solubility
- Density
- Melting Point
- Boiling Point
- Surface Tension
- Vapor Pressure
- LogKoa: Octanol-Air
- Henry's Law
- Index of Refraction
- Molar Refractivity
- pKa Acidic Apparent

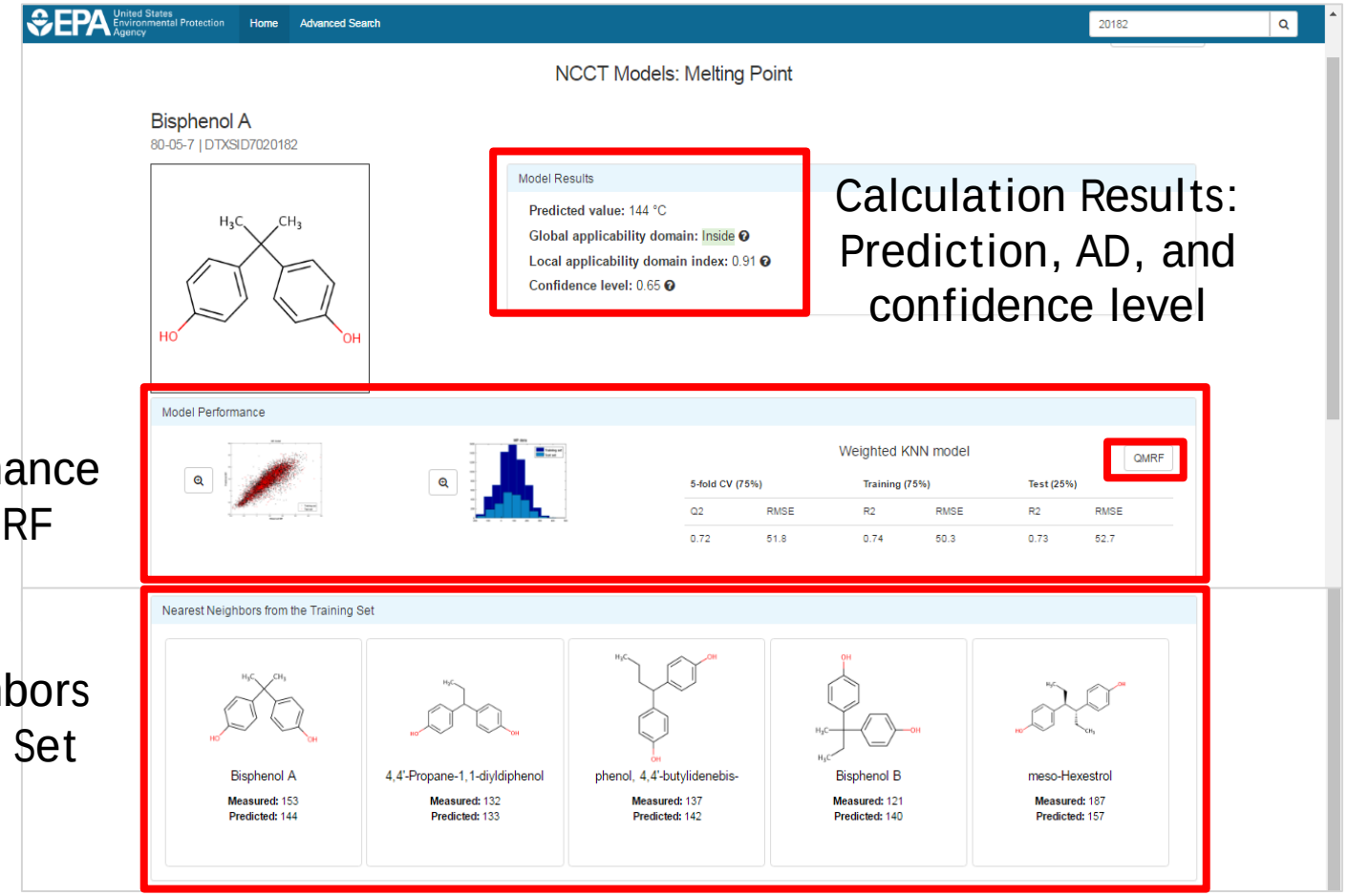
Download as: TSV | Excel | SDF

- Select/Deselect All
- LogP: Octanol-Water
- Water Solubility
- Density
- Melting Point
- Boiling Point
- Surface Tension
- Vapor Pressure
- LogKoa: Octanol-Air
- Henry's Law
- Index of Refraction
- Molar Refractivity
- pKa Acidic Apparent
- Molar Volume
- Polarizability

Download

Property			Median		Range		Unit
			Experimental	Predicted	Experimental	Predicted	
LogP: Octanol-Water			3.32	3.24	3.32	2.40 to 3.73	-
Water Solubility			5.26e-04	1.58e-03	5.26e-04	5.70e-04 to 3.68e-03	mol/L
Density			-	1.14	-	-	g/cm^3
Melting Point			156	144	153 to 158	132 to 157	°C
Boiling Point			200	349	200	334 to 364	°C
Surface Tension			-	46.0	-	-	dyn/cm
Vapor Pressure			-	2.52e-07	-	7.01e-08 to 5.34e-07	mmHg
LogKoa: Octanol-Air			-	8.38	-	-	-
Henry's Law			-	6.96e-07	-	-	atm-m3/mole
Index of Refraction			-	1.60	-	-	-
Molar Refractivity			-	68.2	-	-	cm^3
pKa Acidic Apparent	-	10.3 (1)	-	10.3	-	-	-
Molar Volume	-	200 (1)	-	200	-	-	cm^3
Polarizability	-	27.0 (1)	-	27.0	-	-	Å^3

Physical Properties: OPERA Models

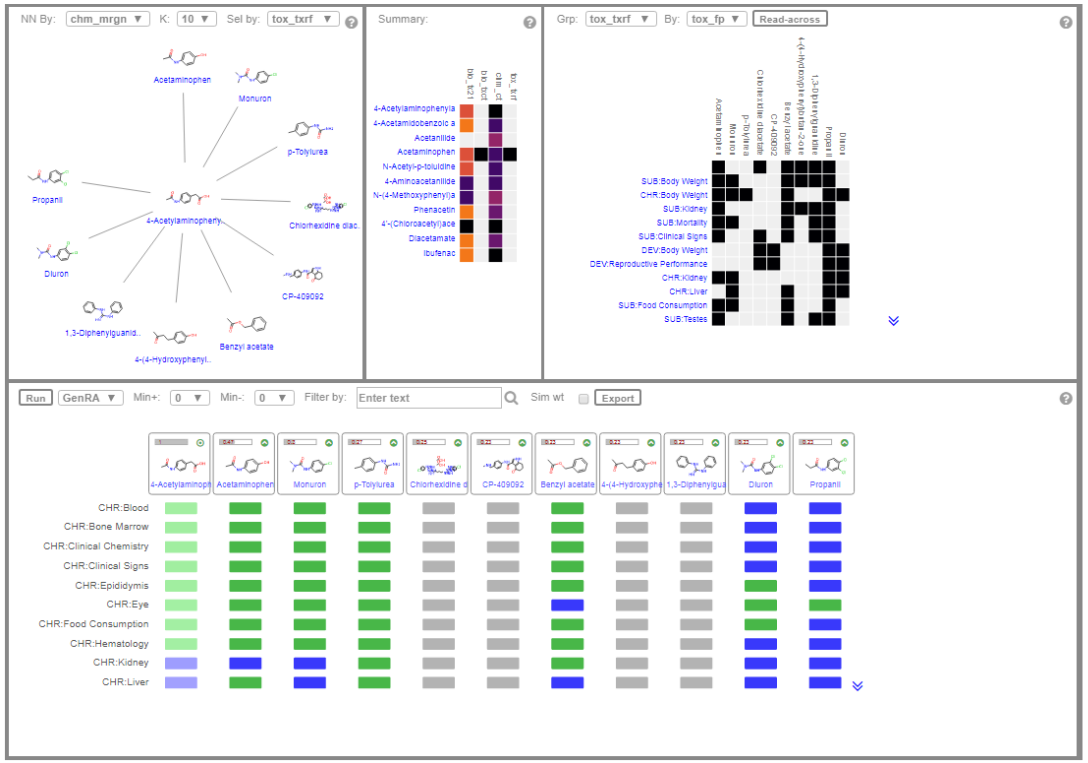


Calculation Results: Prediction, AD, and confidence level

Model Performance with full QMRF

Nearest Neighbors from Training Set

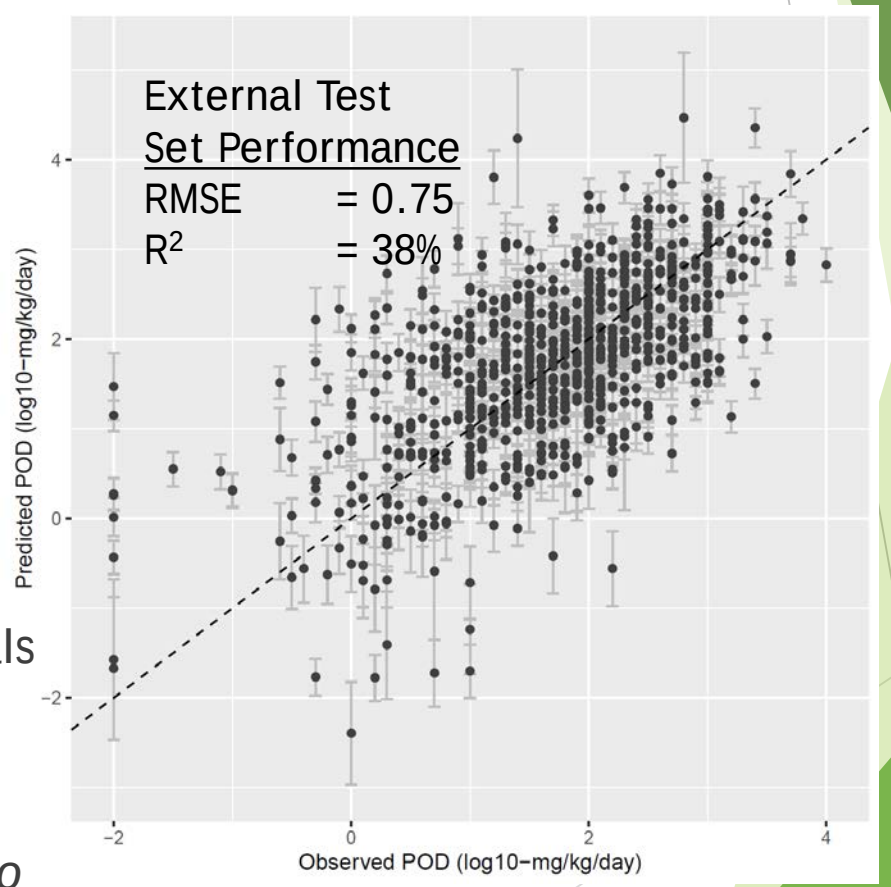
Toxicity: Categorical Predictions



- Generalized Read-Across – GenRA
- Internal “research” module
- Predictions using known activity classes of structurally similar chemicals
- Automated chemical read-across:
  - Identify most similar chemical neighbors
  - Calculate a similarity weighted toxicity score
  - Optimize number of neighbors and similarity cut off using ROC AUC

Toxicity: Quantitative Predictions

- Systematic Point-of-Departure (POD)
- Input data:
  - In-vitro toxicity tests
  - Chemical properties
  - ToxCast bioactivity data
  - Toxico-kinetic parameters
- Random Forest Regression Model
  - Training data: 3524 studies on 961 chemicals
  - 5 fold CV, 10x Bootstrapping
  - Predict a confidence interval for *lowest observed adverse effect level* (LOAEL) or *no observed adverse effect level* (NOAEL)



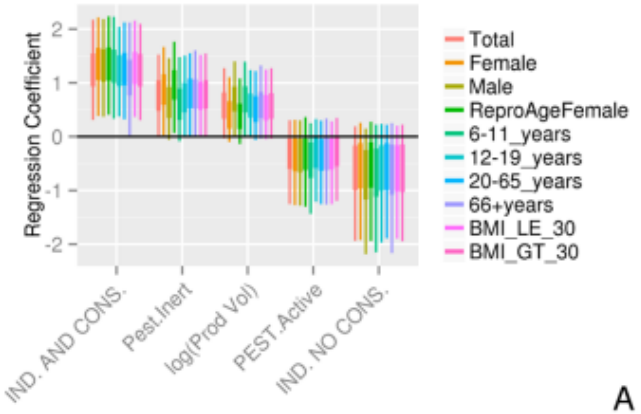
Exposure

Use Categories

- Existing use data
  - Regulatory classes
  - Product ingredient database
- Regression models to predict use if unknown
  - Structural and physical chemistry data

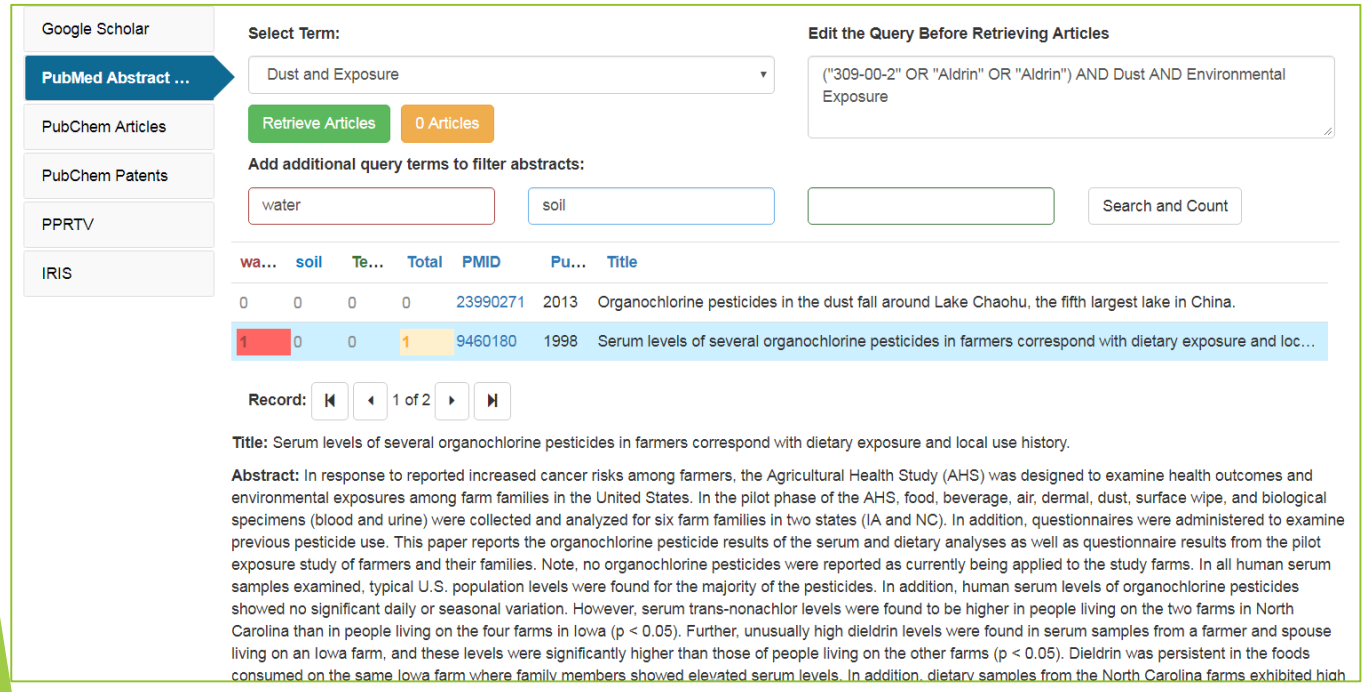
Exposure Predictions

- Wambaugh et al, 2014 – High throughput exposure model
- Linear regression based on physical properties, use data



A

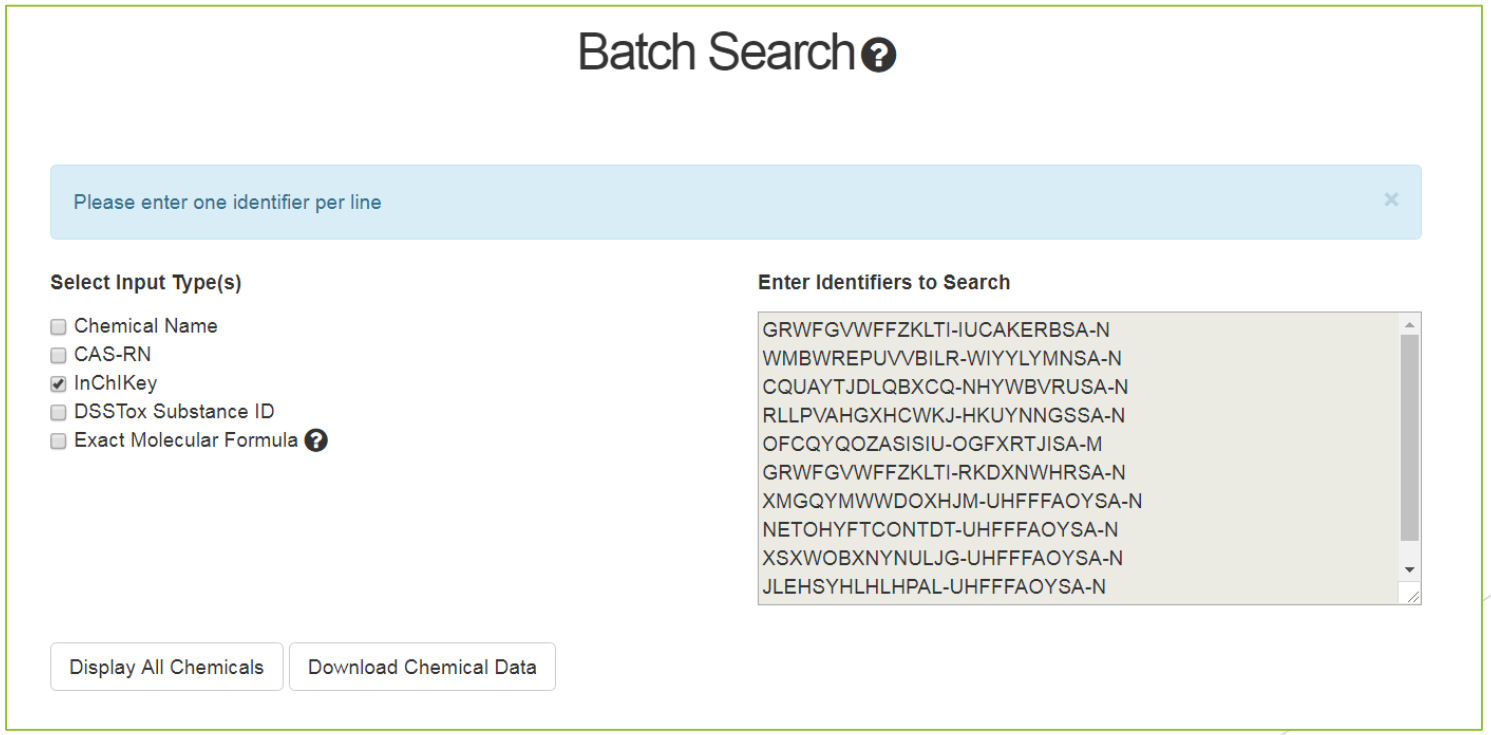
Literature



- Access to Google Scholar, PubMed, PubChem articles and patents, and IRIS assessments
- Abstract sifter lets users quickly search literature for pre-defined terms or add additional queries
- Sort and identify most relevant articles

Batch Searching

- Previous examples focused on reviewing one chemical at a time
- Batch search allows retrieval of data and model results for multiple chemicals



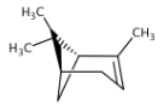
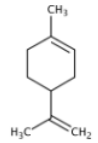
Batch Searching

- Previous examples focused on reviewing one chemical at a time
- Batch search allows retrieval of data and model results for multiple chemicals

Search Results

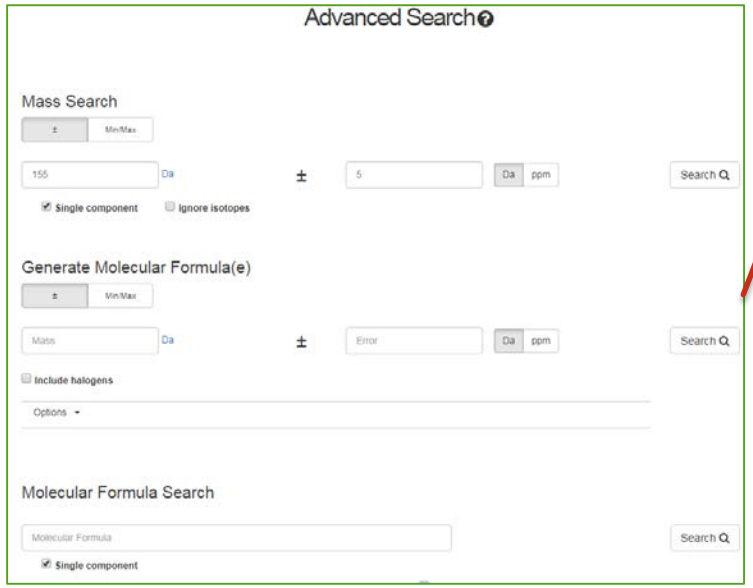
Searched by List: Found 10 results.

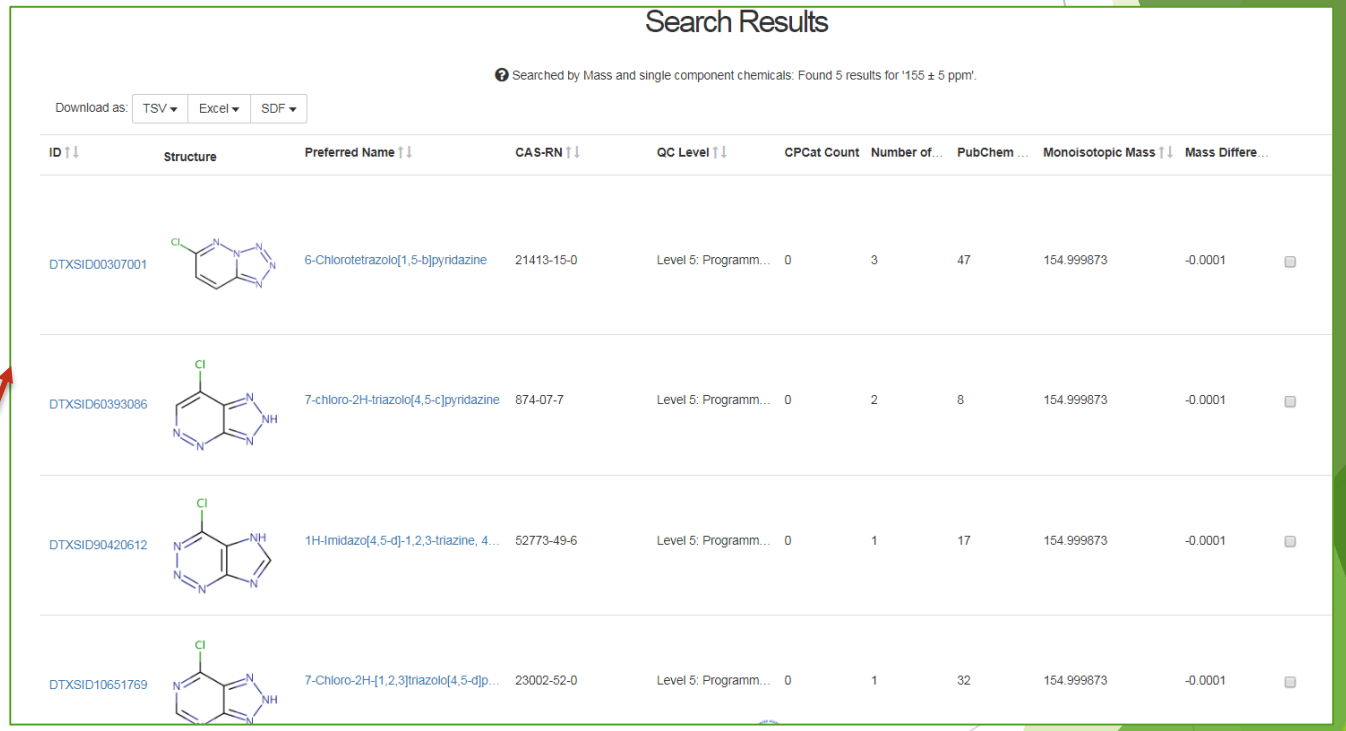
Download as: TSV Excel SDF

ID	Structure	Preferred Name	CAS-RN	QC Level	CPCat…	Numb…	PubC…	Monoisotopi…	
DTXSID202929 ToxCast™		(-)-alpha-Pinene	7785-26-4	Level 2: Exp…	1	42	61	136.125201	☐
DTXSID20296 ToxCast™		Limonene	138-86-3	Level 2: Exp…	189	68	123	136.125201	☐

Non-Targeted Analyses

- Supports high resolution mass spectrometry
- Mass and formula searching





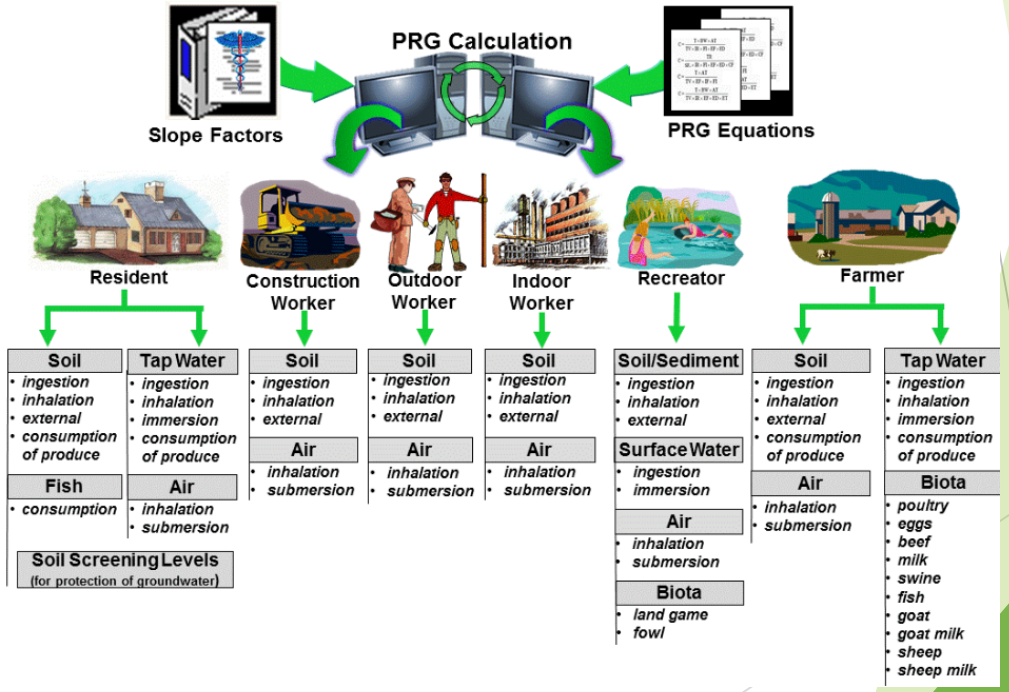
McEachran et al, 2017: "Identifying known unknowns using the US EPA's CompTox Chemistry Dashboard"

Dashboard


Data
Predictive Models
Chemical Structures
Chemistry Dashboard
741 Thousand Chemicals
Web-Based Dashboard
Agency Scientists
Front Line Staff
Public

Putting it all together…

- **Screening level calculations**:
  - Superfund specific policy
  - Toxicity used to calculate "reference doses" (RfDs)
  - RfDs are weighted with typical exposure assumptions
  - May be used to screen sites, assess risk to human health



Next Steps

- Public version of the dashboard: https://comptox.epa.gov/
- Superfund specific customizations planned for internal beta testing, fall 2017
  - Cross validation with existing toxicity assessments (for models)
  - Understand how novel data sources can be used in the context of Superfund policy
- Future Work:
  - Completion and integration of predictive toxicity models
  - Enhanced visualization and interpretation of *in vitro* bioassay data
  - Workflow to calculate human health risks (following RAGS)
  - Structure, substructure, and similarity searching

Acknowledgements

- EPA Office of Research and Development: Antony Williams, Richard Judson, Imran Shah, Chris Grulke, Grace Patlewicz, Ann Richard, Andrew McEachran, Jon Sobus, Jason Lambert, Scott Wesselkamper, Nancy Baker, Jeff Edwards
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- EPA Regional Risk Assessors: Wendy O'Brien, Kristen Keteles

- Questions?
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  - Antony Williams, ORD/NCCT – Williams.Antony@epa.gov
  - Richard Judson, ORD/NCCT – Judson.Richard@epa.gov

Thank you!!