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Development of a Tool for Integrating Traditional and New Approach Methodologies (NAMs) for Chemical Safety Decisions

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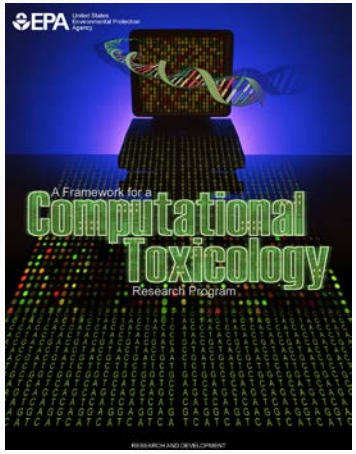
March 2018

ACS Spring Meeting, New Orleans

National Center for Computational Toxicology



- National Center for Computational Toxicology (NCCT) established in 2005 to integrate:
  - High-throughput and high-content technologies
  - Molecular biology
  - Data mining and statistical modeling
  - Computational biology and chemistry
- Outputs: a lot of data, models, algorithms and software applications
- Open Data – we want scientists to interrogate it, learn from it, develop understanding

Background

- EPA must designate a set of high-priority chemicals for detailed risk assessment.

- NCCT is building a web-based tool as *one* approach to help guide that selection

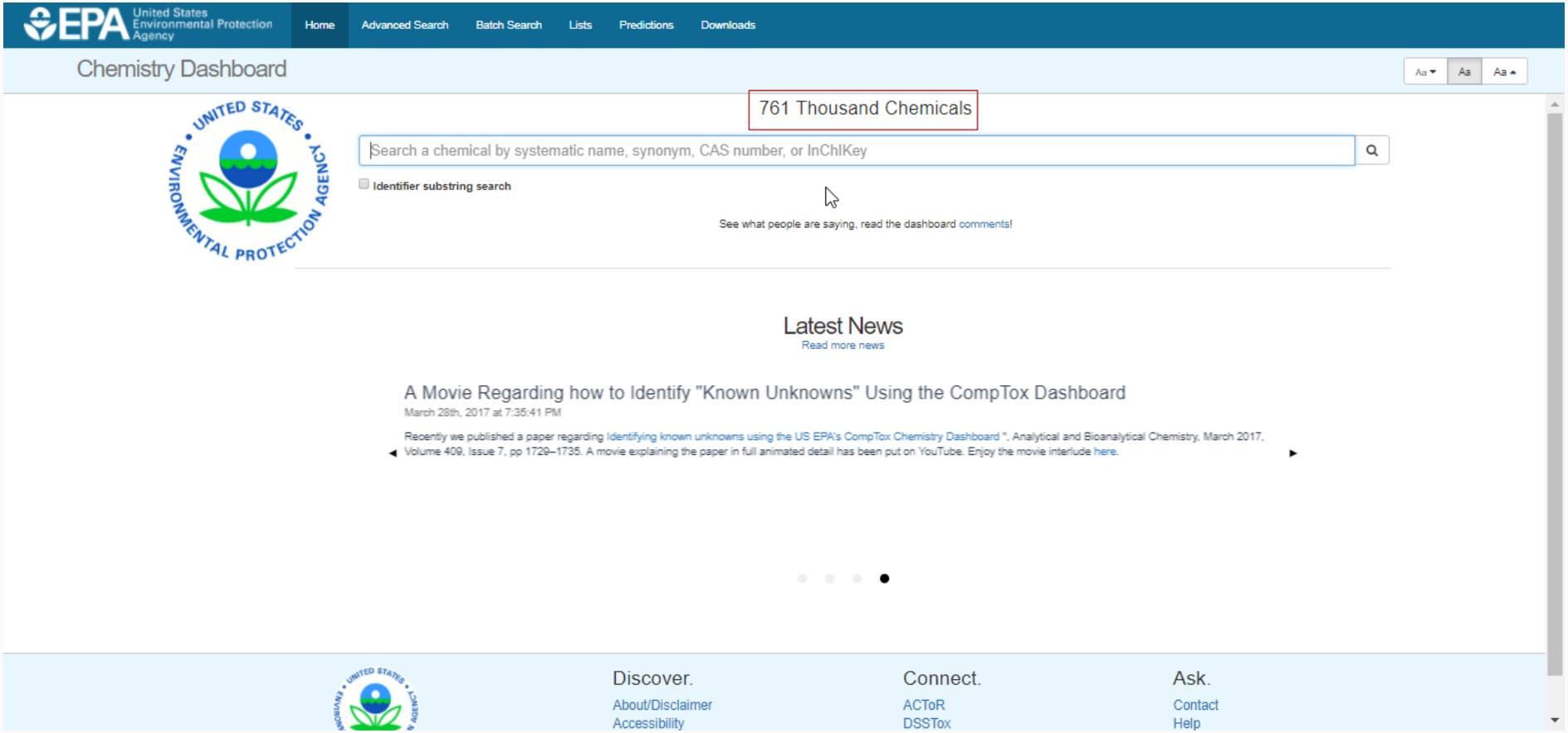
The CompTox Dashboard

- NCCT has lots of data to build relevant tools and approaches. The source data are available via the CompTox Dashboard

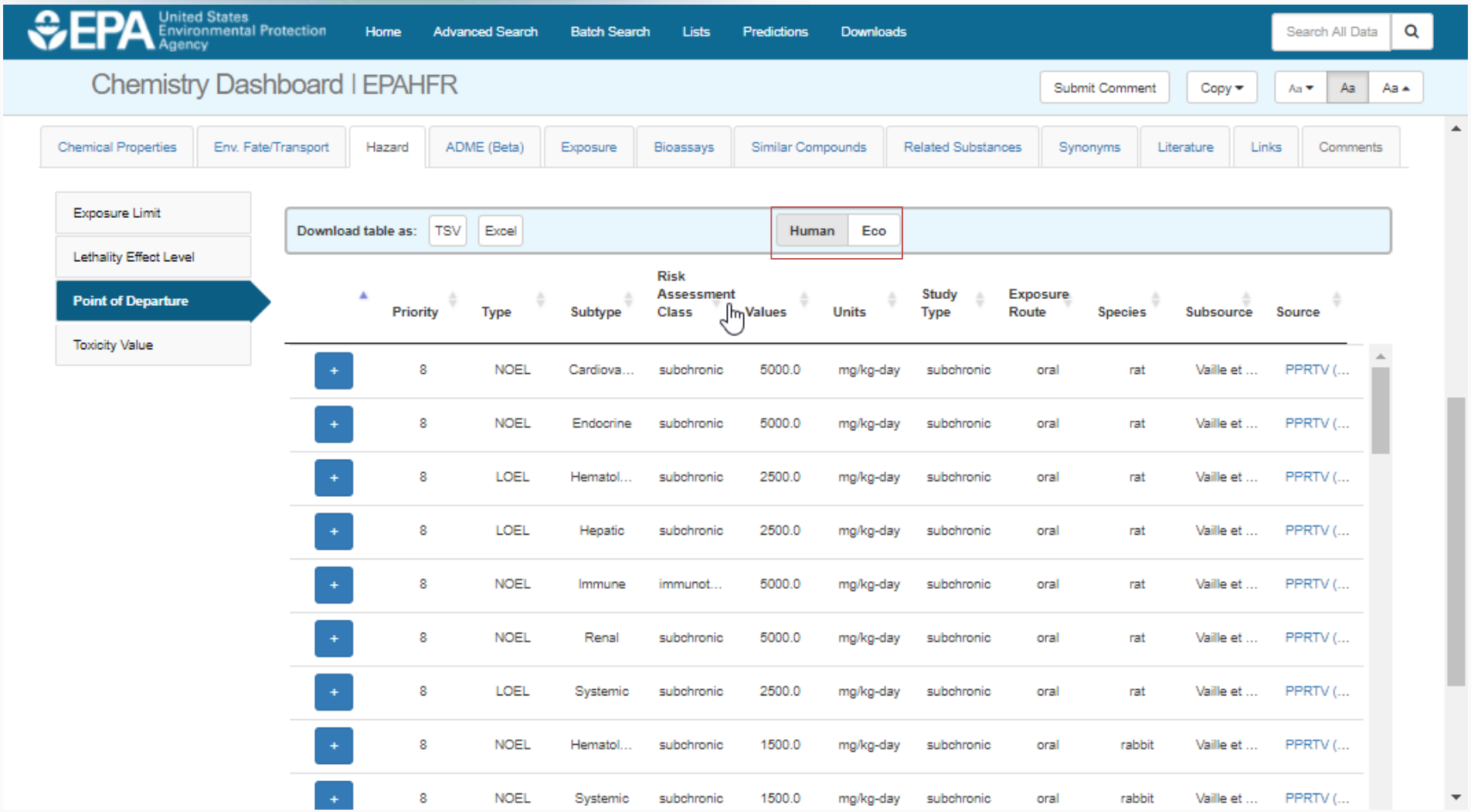
- A **publicly accessible website** delivering access:
  - ~760,000 chemicals with related property data
  - Experimental and predicted **physicochemical property data**
  - Integration to "**biological assay data**" for 1000s of chemicals
  - Data regarding **chemical exposure**
  - Links to other agency websites and public data resources
  - "Literature" searches for chemicals using public resources
  - "Batch searching" for thousands of chemicals

CompTox Dashboard

https://comptox.epa.gov/dashboard



Chemical Hazard Data



	Priority	Type	Subtype	Risk Assessment Class	Values	Units	Study Type	Exposure Route	Species	Subsource	Source
+	8	NOEL	Cardiova...	subchronic	5000.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	NOEL	Endocrine	subchronic	5000.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	LOEL	Hematol...	subchronic	2500.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	LOEL	Hepatic	subchronic	2500.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	NOEL	Immune	immunot...	5000.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	NOEL	Renal	subchronic	5000.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	LOEL	Systemic	subchronic	2500.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	NOEL	Hematol...	subchronic	1500.0	mg/kg-day	subchronic	oral	rabbit	Vaille et ...	PPRTV (...
+	8	NOEL	Systemic	subchronic	1500.0	mg/kg-day	subchronic	oral	rabbit	Vaille et ...	PPRTV (...

In Vitro Bioassay Screening

ToxCast and Tox21

Sources of Exposure to Chemicals

- **Product & Use Categories**
- Chemical Weight Fraction
- Chemical Functional Use
- Monitoring Data
- Exposure Predictions
- Production Volume

osure | Bioassays | Similar Compounds | Related Substances | Synonyms | Literature | Links | Comments

Product & Use Categories (PUCs)

Categorization type	Number of Unique Products
PUC	288
PUC	206
PUC	117
PUC	107
PUC	107
PUC	101
PUC	101
PUC	90
PUC	89

Approach

- Use **available data** for *in vivo, in vitro*, exposure and chemical property data
- Develop **scoring schemes** to merge different types of data
- Develop methods to note or **fill data gaps**
- Make data, scores, prioritization ranking available in the **web-based tool**

Potential Data Sources

***In Vivo* Human Hazard:**

- Mammalian toxicity studies – guideline-like, use POD
- System-specific *in vivo* data (Cancer, developmental)
- Models (QSAR) to predict POD and organ-specific effects
- Genotoxicity
- *In vitro*-derived endocrine disruption and neurotoxicity models

***In Vivo* Eco Hazard**

- Aquatic *in vivo* studies – POD
- Models (QSAR) of POD

Potential Data Sources

EPA United States Environmental Protection Agency

Human Exposure

- Data on production volume and releases
- Quantitative biomonitoring data
- Predictions of oral and inhalation exposure

Eco Exposure

- Biomonitoring data
- Predictions of water concentrations

Physchem

- Persistence and Bioaccumulation models (OPERA)


Mansouri et al. J Cheminform (2018) 10:10
https://doi.org/10.1186/s13321-018-0263-1

Journal of Cheminformatics

RESEARCH ARTICLE Open Access

OPERA models for predicting physicochemical properties and environmental fate endpoints

Kamel Mansouri[1,2,3*], Chris M. Grulke[1], Richard S. Judson[1] and Antony J. Williams[1]

Aggregating Data

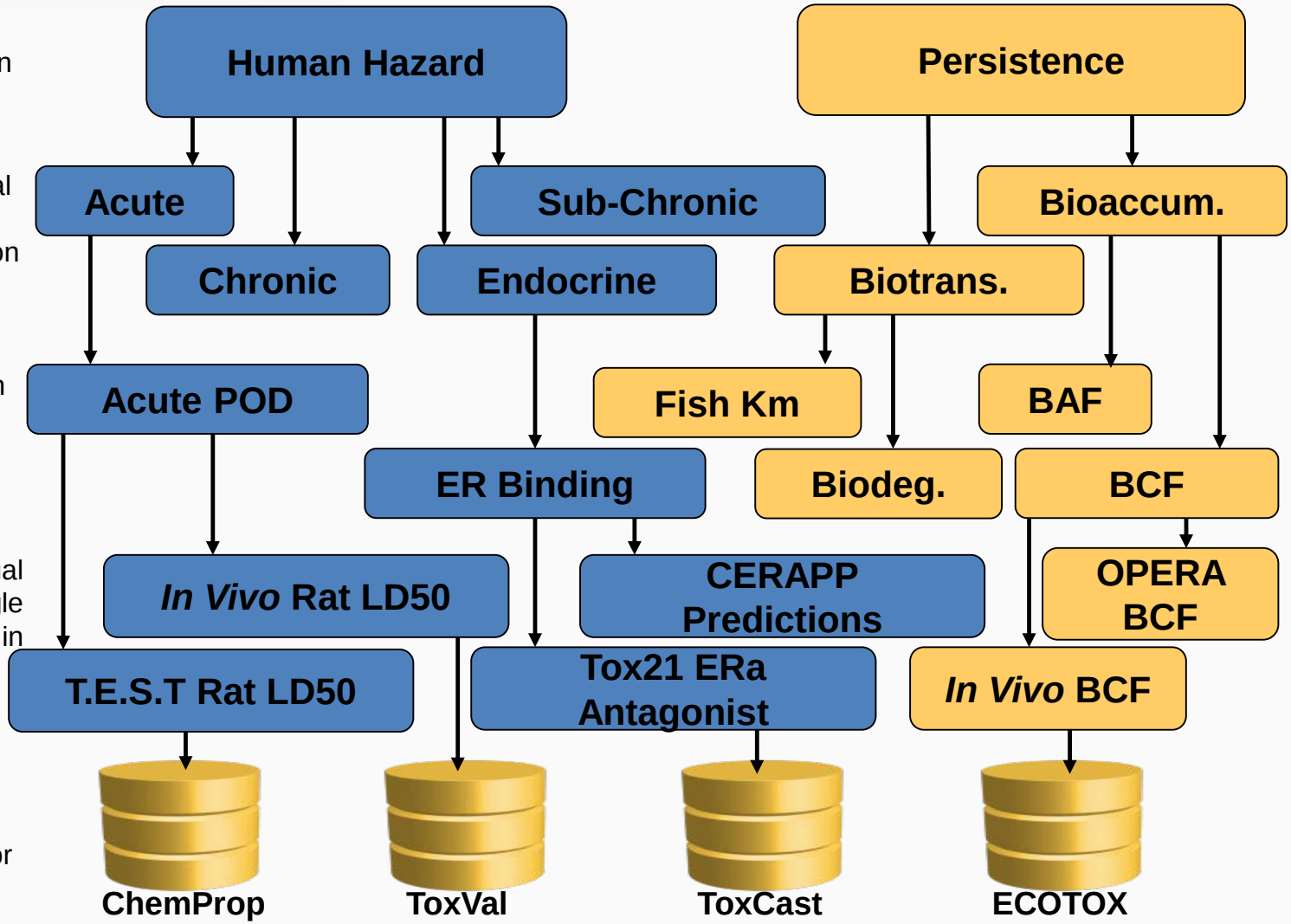
DOMAINS: Top level aggregation for reporting in the web-interface

SUB-DOMAINS: Additional aggregation layer(s) to support flexible aggregation workflows

ENDPOINTS: Aggregation of data streams that are intended to estimate the same value

DATA STREAMS: Individual values coming from a single source that are of interest in prioritization.

DATABASES: Active database projects at US EPA can act as sources for data streams



Scoring approaches

- For each chemical, each domain receives a score of 1 (Low), 2 (Moderate), or 3 (High) concern
- **Hazard score** = maximum of human and eco hazard scores
- **Exposure score** = maximum of human and eco exposure scores
- **Total score** = hazard score + exposure score + physchem score
- If no data is available for a domain, it is given the "missing data score", currently 1 (Low)
- Scoring can include or exclude NAM

Implemented Scoring Methods

Method 1

- Maximum score from human and eco hazard: 1 – 3
- Maximum score from human and eco exposure: 1 – 3
- Maximum score from persistence/ bioaccumulation (P/B): 1 – 3
- No NAM
- Add hazard, exposure, and P/B
- Categorical bins
    - High: 7-9
    - Moderate: 5-6
    - Low: 3-4

Method 2: NAM Equal

- Same as Method 1 except NAM is incorporated with equal weighting in all domains
- Add hazard, exposure, and P/B
- Categorical bins
    - High: 7-9
    - Moderate: 5-6
    - Low: 3-4

Method 3: NAM Deferential

- Same as Method 1 except human hazard NAM is incorporated in the absence of traditional *in vivo* studies
- In other domains, NAM is given equal weight.
- Add hazard, exposure, and P/B
- Categorical bins
    - High: 7-9
    - Moderate: 5-6
    - Low: 3-4

Method 4: Sum of Scores

- Sum all components (incl. NAM) from human and eco hazard
- Sum all components (incl. NAM) from human and eco exposure
- Sum all components (incl. NAM) from persistence/ bioaccumulation
- Add hazard, exposure, and P/B
- Categorical bins
    - High: >30
    - Medium: 10-30
    - Low: ≤10

Method 5: H/BER*

- Ratio of the minimum effect level from *in vivo* toxicity studies or the quantitative human hazard NAM data divided by the maximum oral exposure
- Categorical bins
    - High: $\leq 10^4$
    - Medium: $10^4 – 10^6$
    - Low: $\geq 10^6$

*Hazard/Bioactivity Exposure Ratio

Overall Scoring Page

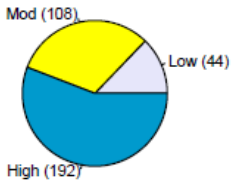
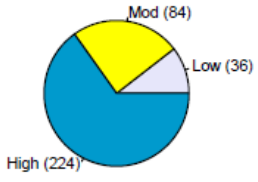
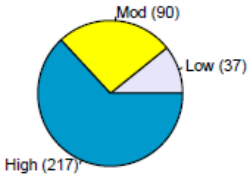
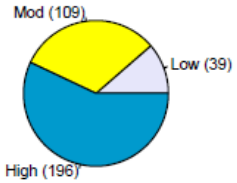
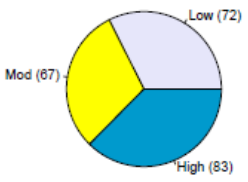
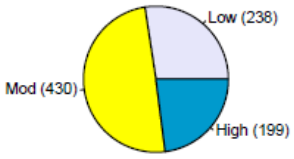
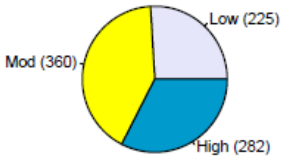
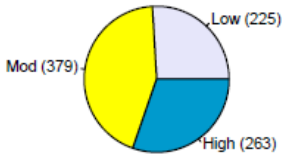
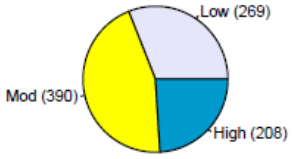
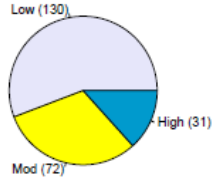
Cutoffs | Domain Help | Human Hazard Prioritization | Eco Hazard Prioritization | Human Exposure Prioritization | Eco Exposure Prioritization

Physchem Prioritization | Overall Prioritization | Data Coverage Summary | Distribution Graphs

Show 25 entries Search:

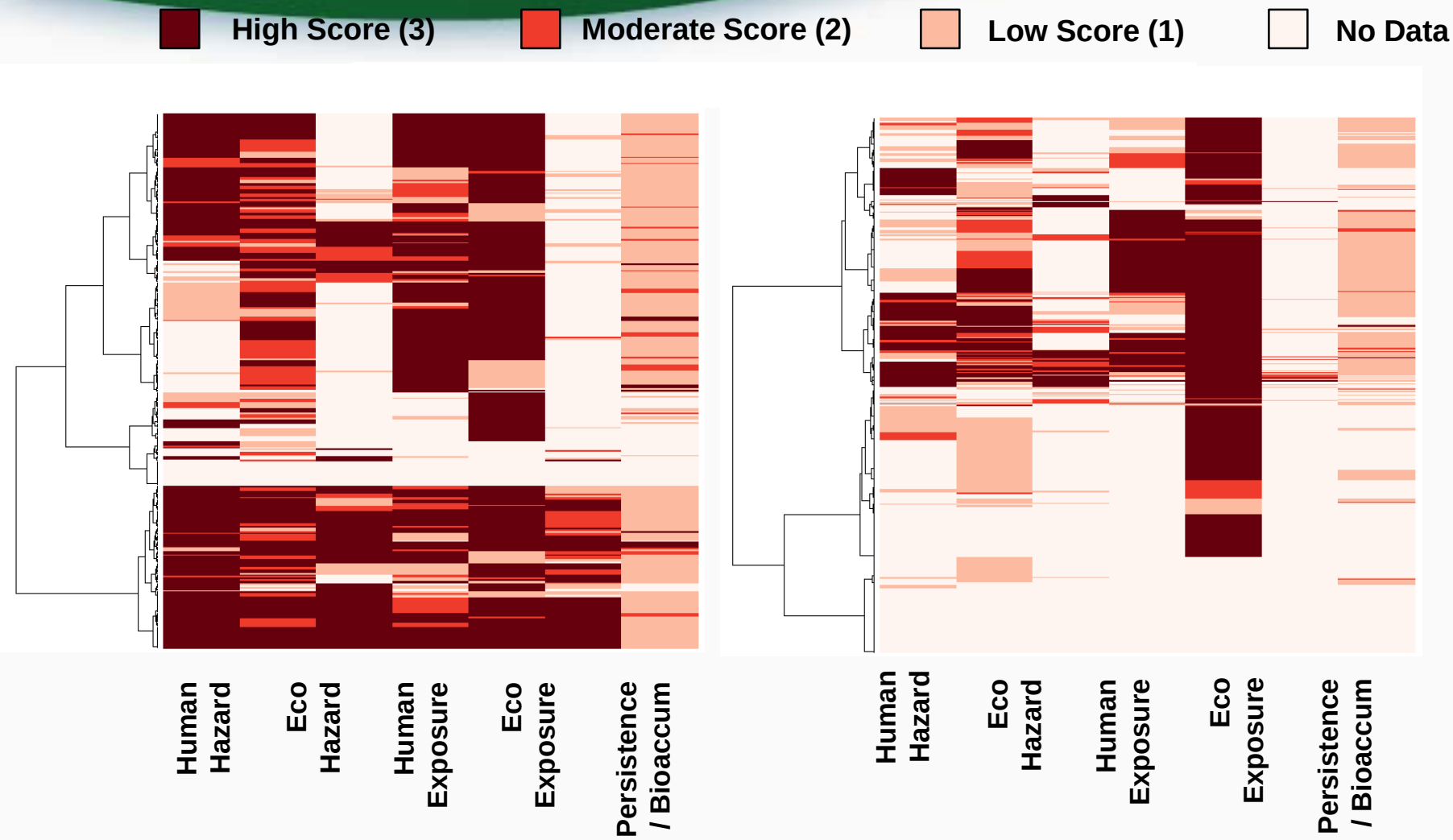
DSSTox_ID	CASRN	Name	Method 1 score	Method 1 bin	Method 2 score	Method 2 bin	Method 3 score	Method 3 bin	Method 4 score	Method 4 bin
DTXSID124356	1234-56-7	Name1	5	Moderate (ExeHzeHzh)	6	Moderate (ExeHzeHzh)	6	Moderate (ExeHzeHzh)	25	Moderate (ExeHzeHzh)
DTXSID124357	1234-56-8	Name2	5	Moderate (PbExeHzeHzh)	7	High (PbExeHzeHzh)	7	High (PbExeHzeHzh)	24	Moderate (PbExeHzeHzh)
DTXSID124358	1234-56-9	Name3	5	Moderate (ExeHzeHzh)	6	Moderate (ExeHzeHzh)	6	Moderate (ExeHzeHzh)	41	High (ExeHzeHzh)
DTXSID124359	1234-56-10	Name4	5	Moderate (ExeHzeHzh)	5	Moderate (ExeHzeHzh)	5	Moderate (ExeHzeHzh)	13	Moderate (ExeHzeHzh)
DTXSID124360	1234-56-11	Name5	5	Moderate (PbExeHzeHzh)	5	Moderate (PbExeHzeHzh)	5	Moderate (PbExeHzeHzh)	20	Moderate (PbExeHzeHzh)
DTXSID124361	1234-56-12	Name6	5	Moderate (ExeHzeHzh)	5	Moderate (ExeHzeHzh)	5	Moderate (ExeHzeHzh)	35	High (ExeHzeHzh)
DTXSID124362	1234-56-13	Name7	5	Moderate (PbExeHze)	5	Moderate (PbExeHze)	5	Moderate (PbExeHze)	21	Moderate (PbExeHze)
DTXSID124363	1234-56-14	Name8	6	Moderate (PbExeHze)	6	Moderate (PbExeHze)	6	Moderate (PbExeHze)	16	Moderate (PbExeHze)
DTXSID124364	1234-56-15	Name9	5	Moderate (PbExeHze)	5	Moderate (PbExeHze)	5	Moderate (PbExeHze)	26	Moderate (PbExeHze)
DTXSID124365	1234-56-16	Name10	6	Moderate (PbExeHze)	6	Moderate (PbExeHze)	6	Moderate (PbExeHze)	23	Moderate (PbExeHze)
DTXSID124366	1234-56-17	Name11	5	Moderate	5	Moderate	5	Moderate	17	Moderate

Fraction of chemicals in each bin

	General	NAM Equal	NAM Differential	Sum of Scores	H/BER
Set 1 (344)					 (222/344)
Set 2 (867)					 (233/867)

High Pre-Priority Moderate Pre-Priority Low Pre-Priority

Heat Maps



Heatmaps showing the domain-specific scores for chemical sets.

Registration and Curation of Chemicals

- Consolidation and registration of the original chemical lists into the underlying database (DSSTox)
- Careful (and time-consuming) curation
  - Confirming mappings of chemical names and CASRNs

Names to CASRN Mappings

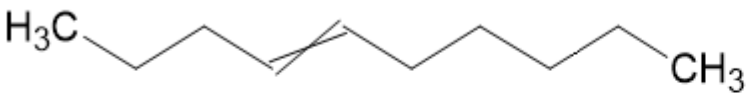
Substance Mapping

(1 of 66) 1 2 3 4 5 6 7 8 9 10 25

Source Casrn	Source Name	Hit Substance_ID	Hit Casrn	Hit Name	
19398-89-1	4-Decene	DTXSID50876156	19689-18-0	4-Decene	Remove Validation
112926-00-8	silica gel, cryst. -free	DTXSID9029851	112926-00-8	Hydrated silica	Remove Validation
124-28-7	1-Octadecanamine, N,N-dimethyl-	DTXSID4027026	124-28-7	N,N-Dimethyl-1-octadecanamine	Remove Validation
1330-43-4	Boron sodium oxide	DTXSID2034388	1330-43-4	Sodium tetraborate	Remove Validation
13492-26-7	Mono- and di-potassium salts of phosphorous acid	DTXSID9035961	13492-26-7	Phosphonic acid, potassium salt (1:2)	Remove Validation
135-37-5	Glycine, N-(carboxymethyl)-N-(2-hydroxyethyl)-, disodium salt	DTXSID8042008	135-37-5	Ethanoldiglycine disodium salt	Remove Validation

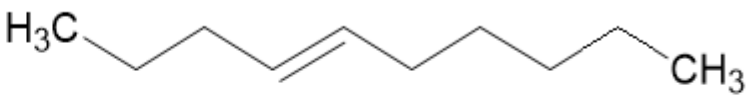
Subtleties

“4-Decene”



19398-89-1

E/Z-stereochemistry



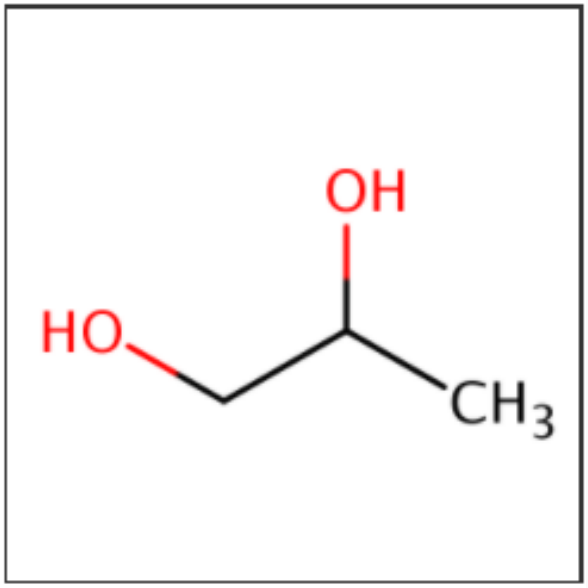
19689-18-0

E-stereochemistry

Registration and Curation

- Registration of the chemical list into the underlying database (DSSTox)
- Careful (and time-consuming) curation
  - Confirming mappings of chemical names and CASRNs
  - CASRN checking – Active, Alternate and Deleted

CAS Registry Numbers



1,2-Propylene glycol	Propylenglycol
Propane-1,2-diol	Sentry Propylene Glycol
1,2-Propanediol	Trimethyl glycol
57-55-6 Active CAS-RN	Ucar 35
alpha-Propylene glycol	a-Propylene glycol
(+/-) 1,2-Propanediol	alpha-propyleneglycol
(RS)-1,2-Propanediol	methyl glycol
dl-Propylene glycol	methylethyl glycol
3-01-00-02142 Beilstein Registry Number	1194046-20-2 Deleted CAS-RN
1,2-Propanediol	190913-75-8 Deleted CAS-RN
(.+-.)-1,2-Propanediol	4254-16-4 Deleted CAS-RN
(.+-.)-Propylene glycol	63625-56-9 Deleted CAS-RN

Registration and Curation

- Registration of the chemical list into the underlying database (DSSTox)
- Careful (and time-consuming) curation
  - Confirming mappings of chemical names and CASRNs
  - CASRN checking – Active, Alternate and Deleted
  - Misspellings, alternative synonyms, misassociations

Alternative Synonyms

Substance Mapping

(1 of 66) 1 2 3 4 5 6 7 8 9 10 25

Source Casrn	Source Name	Hit Substance_ID	Hit Casrn	Hit Name	
19398-89-1	4-Decene	DTXSID50876156	19689-18-0	4-Decene	Remove Validation
112926-00-8	silica gel, cryst. - free	DTXSID9029851	112926-00-8	Hydrated silica	Remove Validation
124-28-7	1-Octadecanamine, N,N-dimethyl-	DTXSID4027026	124-28-7	N,N-Dimethyl-1-octadecanamine	Remove Validation
1330-43-4	Boron sodium oxide	DTXSID2034388	1330-43-4	Sodium tetraborate	Remove Validation
13492-26-7	Mono- and di-potassium salts of phosphorous acid	DTXSID9035961	13492-26-7	Phosphonic acid, potassium salt (1:2)	Remove Validation
135-37-5	Glycine, N-(carboxymethyl)-N-(2-hydroxyethyl)-, disodium salt	DTXSID8042008	135-37-5	Ethanoldiglycine disodium salt	Remove Validation

UVCB Chemicals

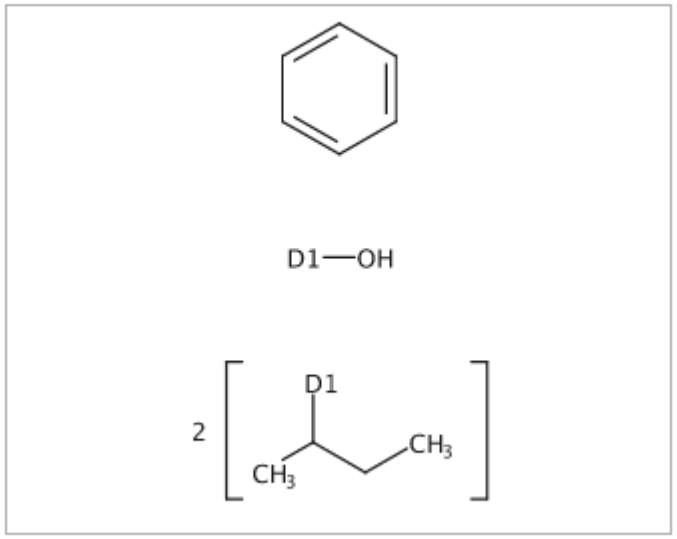
- UVCBs are chemical substances of unknown or variable composition, complex reaction products and biological materials
  - Surfactants (C11-14 linear alkyl sulfonates)
  - Reaction mass of p-t-butylphenyldiphenyl phosphate and bis(p-t-butylphenyl)phenyl phosphate and triphenyl phosphate
  - Almond Oil

Di-sec-butylphenol

CAS Representation

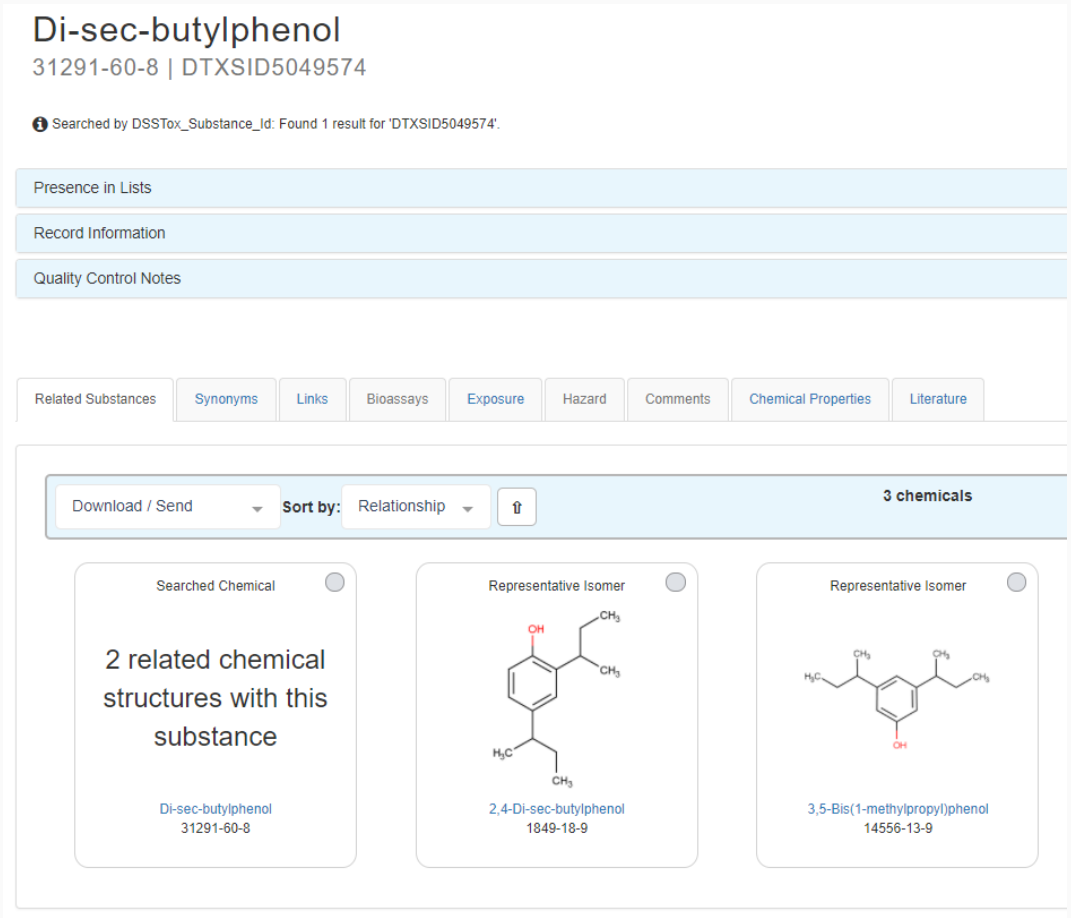
1. 31291-60-8

~31 ~4



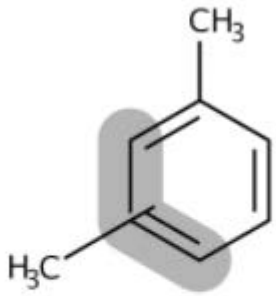
$C_{14}H_{22}O$
Phenol, bis(1-methylpropyl)-

Dashboard Representation

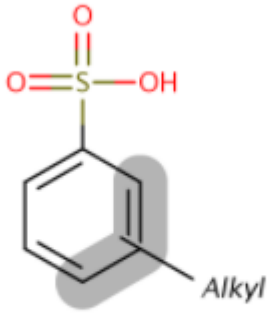


“Markush Structures”

https://en.wikipedia.org/wiki/Markush_structure

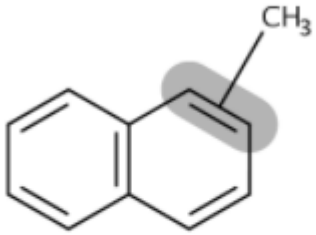


Xylenes
1330-20-7

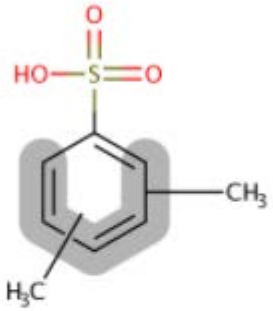


(C10-C16) Alkylbenzenesulfonic acid
68584-22-5

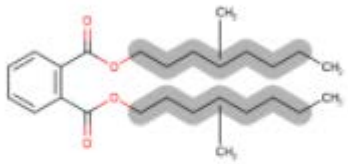
n-Nonylphenol
25154-52-3



Methylnaphthalene
1321-94-4



Sodium xylenesulfonate
1300-72-7



Diisononyl phthalate
28553-12-0

Summary

- RapidTox workflow enabled identification of data that contributed most to candidate selection
- Allowed flexible exploration of prioritization methods
- **Incorporation of NAM data** does result in changes for chemical test sets, either by adding data or by changing the overall bin (Low, Moderate, High)

Acknowledgments

- The NCCT CompTox Dashboard Development Team
- Kamel Mansouri – OPERA models
- Todd Martin – TEST predictions

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