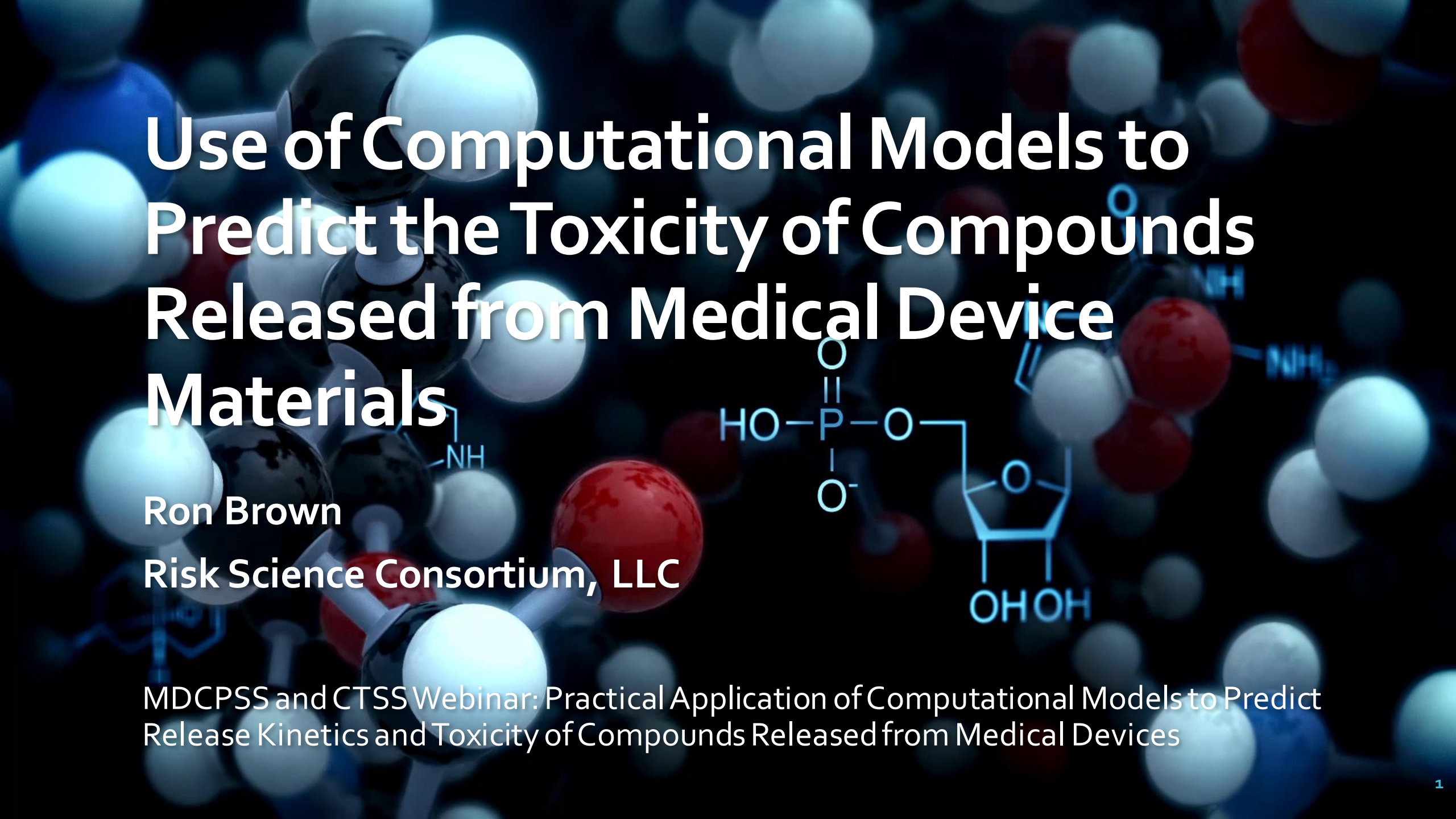
Use of Computational Models to Predict the Toxicity of Compounds Released from Medical Device Materials



Ron Brown

Risk Science Consortium, LLC

MDCPSS and CTSS Webinar: Practical Application of Computational Models to Predict Release Kinetics and Toxicity of Compounds Released from Medical Devices

Caveats

- Because of time restrictions, it's not possible to discuss all aspects of using computational models for toxicity assessment of medical devices.
- Goals of this presentation are:
  - mention some new and potentially useful programs that you may not be aware of
  - provide pointers to online resources to allow you to investigate these online tools in more detail at your convenience.
- Apologies to our friends from the CTSS, but the webinar will primarily focus on tools for the safety assessment of medical devices.

Overview

- Explore updates to open source comptox models
- Review the need for expert review of model-derived predictions
- Provide recommendations for additional training in the field
- Provide update on new sources of toxicity information

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Why do we need to use computational models?

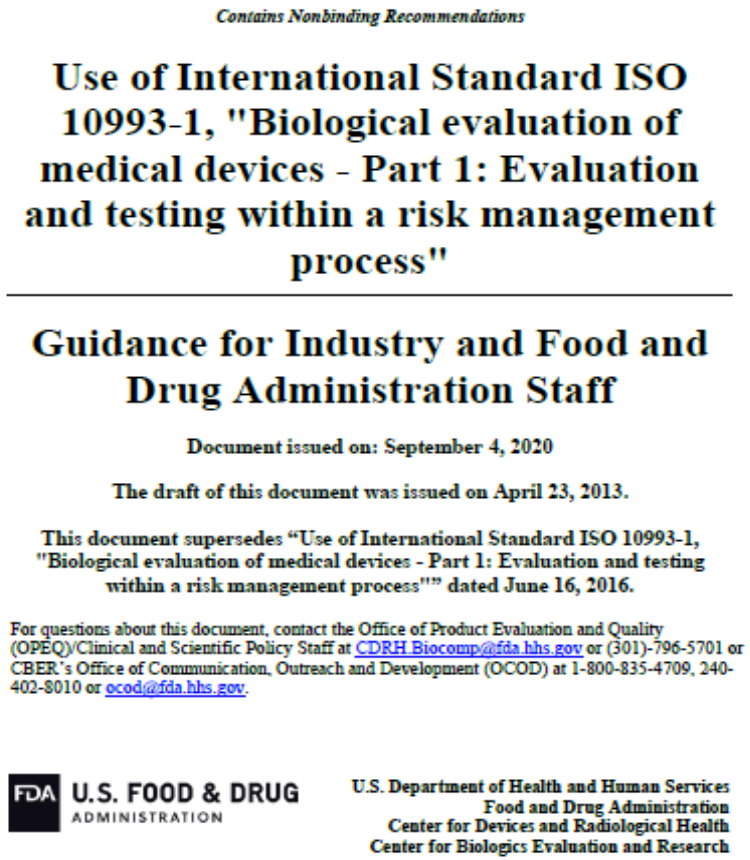
Have data

- Ideally have data to estimate exposure and derive Tolerable Intake (TI) values for compounds released from device materials.
- In reality, exposure and toxicity data are not available for many compounds released from device materials.

Don't have data

- Use conservative default assumptions (e.g., worst case exposure estimate, TTC as a default TI)
- Use computational models to estimate exposure and toxicity.

What does the CDRH Biocompatibility Guidance document say about the use of computational models?



Contains Nonbinding Recommendations

Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 4, 2020

The draft of this document was issued on April 23, 2013.

This document supersedes "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"" dated June 16, 2016.

For questions about this document, contact the Office of Product Evaluation and Quality (OPEQ)/Clinical and Scientific Policy Staff at CDRH.Biocomp@fda.hhs.gov or (301)-796-5701 or CBER's Office of Communication, Outreach and Development (OCOD) at 1-800-835-4709, 240-402-8010 or ocod@fda.hhs.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

G. Carcinogenicity

In the absence of experimentally derived carcinogenicity information, structure activity relationship (SAR) modeling for these materials may be needed regardless of the duration of contact, to better understand the carcinogenicity potential for these materials.

How do we typically use model-derived estimates of genotoxicity/ carcinogenicity?

Determine whether it is necessary to use a TTC value intended to be protective for carcinogenic effects or if it's possible to use a Cramer Class value as a default TI.

From ISO 21726:2019

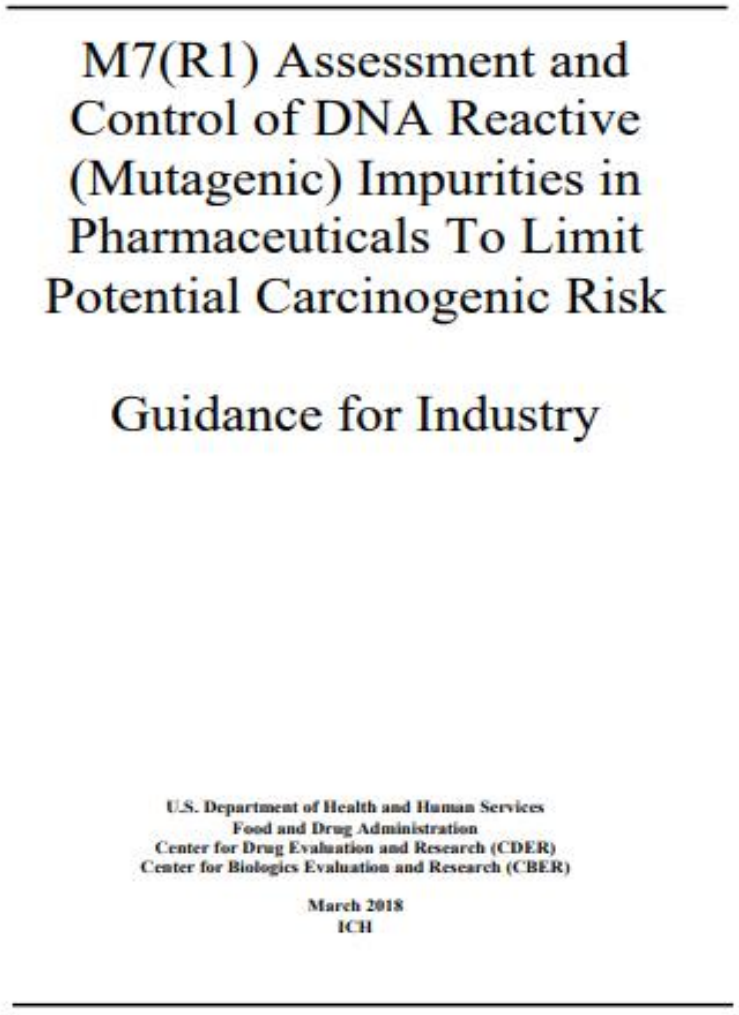
- ***When experimental data or model-derived predictions suggest that an identified constituent is not likely to have carcinogenic effects (e.g. negative mutagenicity data or negative results in at least two computational models that operate using different approaches; system-based and statistically based), then categorizing the constituent into its appropriate Cramer Class and use of the corresponding TTC value is recommended***

How do we use model-derived estimates of genotoxicity/carcinogenicity?

Very little guidance offered in the CDRH Biocompatibility Guidance document on which SAR models to use

Refer to ICH M7 "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m7r1-assessment-and-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential for information on use of the TTC and structure activity relationship (SAR) modeling to address genotoxicity and carcinogenicity issues within a risk management process.

Guidance in ICH M7 on which models to use


M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2018
ICH

A computational toxicology assessment should be performed using Quantitative Structure Activity Relationship ((Q)SAR) methodologies that predict the outcome of a bacterial mutagenicity assay (Ref. 6). Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based, and the second methodology should be statistical-based.

Examples of expert systems and statistically based models

Expert systems

- **Toxtree**
- **OECD Toolbox**
- **OncoLogic**
- **DEREK Nexus**

Statistically based models

- **Lazar**
- **TOPKAT**
- **Sarah Nexus**
- **VEGA**
- **EPA T.E.S.T**

Expert system and statistical modules

- CASE Ultra (available through Danish QSAR database)
- Leadscope (available through Danish QSAR database)

Toxtree

Version 3.1.0 includes Revised Cramer Decision Tree module

Example of Cramer Class designations for formaldehyde.

Inconsistent results are possible. Not clear that one approach is preferred by regulatory agencies over another.

Using Toxtree to assess carcinogenic potential of nongenotoxic carcinogens

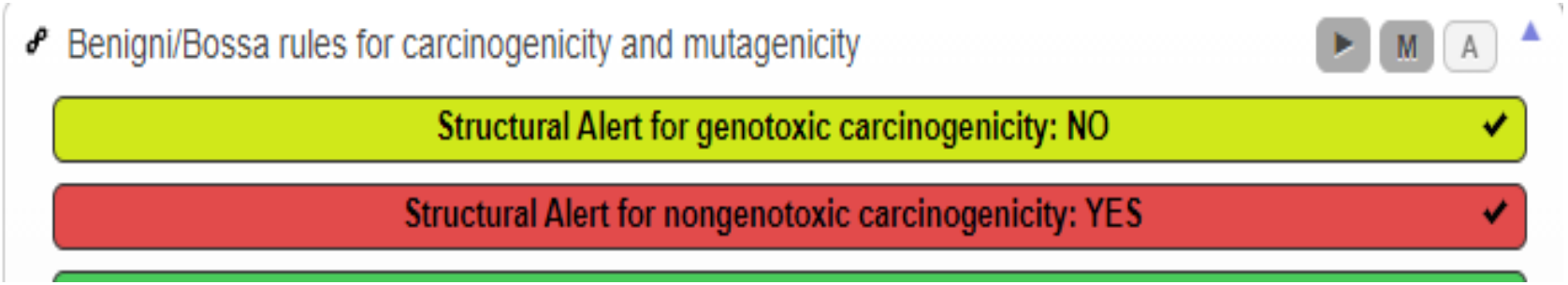
CDRH Biocompatibility Guidance

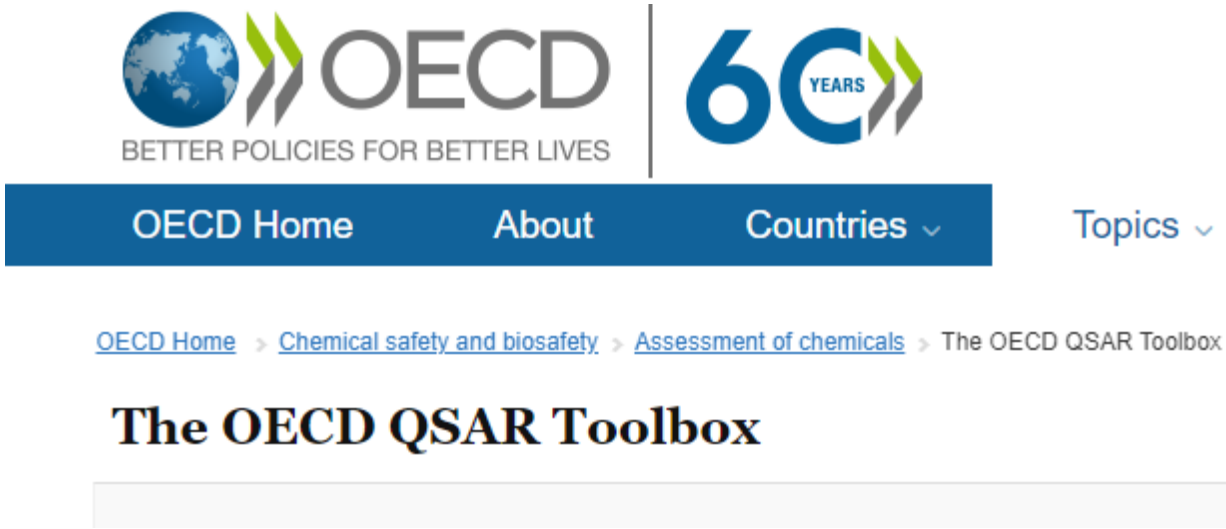
Because there are carcinogens that are not genotoxins and carcinogenesis is multifactorial, the assessment of carcinogenicity should not rely solely on genotoxicity information.

How should we assess the potential for carcinogenicity to occur by nongenotoxic mechanisms?

- **Conduct a search of the literature to determine potential for the compound to exert a carcinogenic effect via a nongenotoxic mechanism**
- **Toxtree can be used as a tool to help determine nongenotoxic carcinogens**

Example: carbon tetrachloride





Version 4.4 released in February, 2020; update 4.4.1 in April

<u>New features</u>

- New Simplified Toolbox interface
- Development of a Toolbox web repository where different modules which could be docked to Toolbox are stored
- Development of Toolbox repository client within the QSAR Toolbox which manages the docking of external modules via direct connection to web repository or uploading from the local computer
- Possibility to "unlock" the ECHA REACH database export in Toolbox which allows exporting of data after accepting the terms and condition for usage.

TUTORIALS

Webinar by OECD & ECHA: QSAR Toolbox Version 4.0 Features

WATCH VIDEO

OECD QSAR Toolbox training

WATCH VIDEO

Predicting SS by making use of read-across

DOWNLOAD PDF

New version of OncoLogic is available January, 2020

Examples of expert systems and statistically based models

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- **OncoLogic**
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Statistically based models

- **Lazar**
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Expert system and statistical modules

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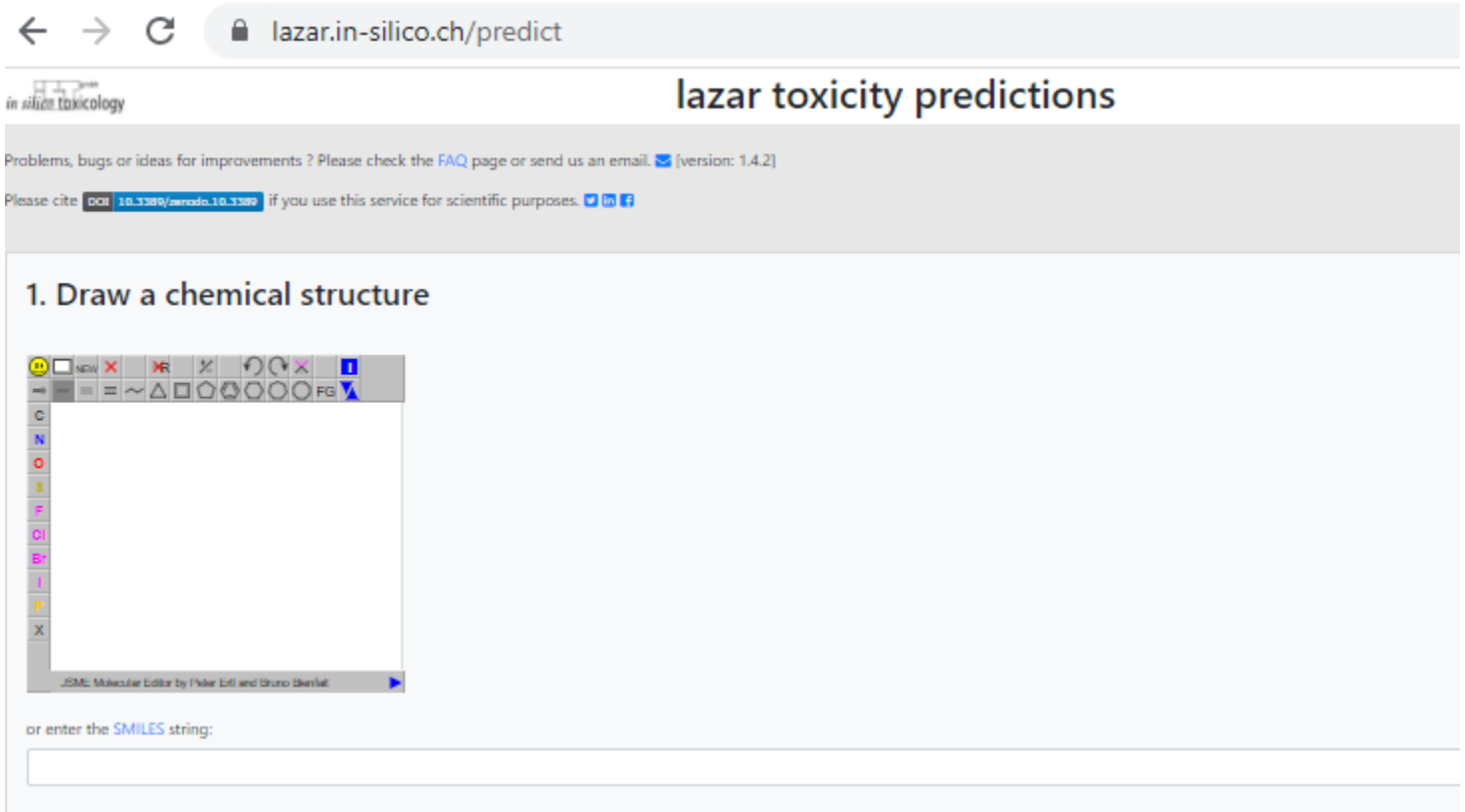
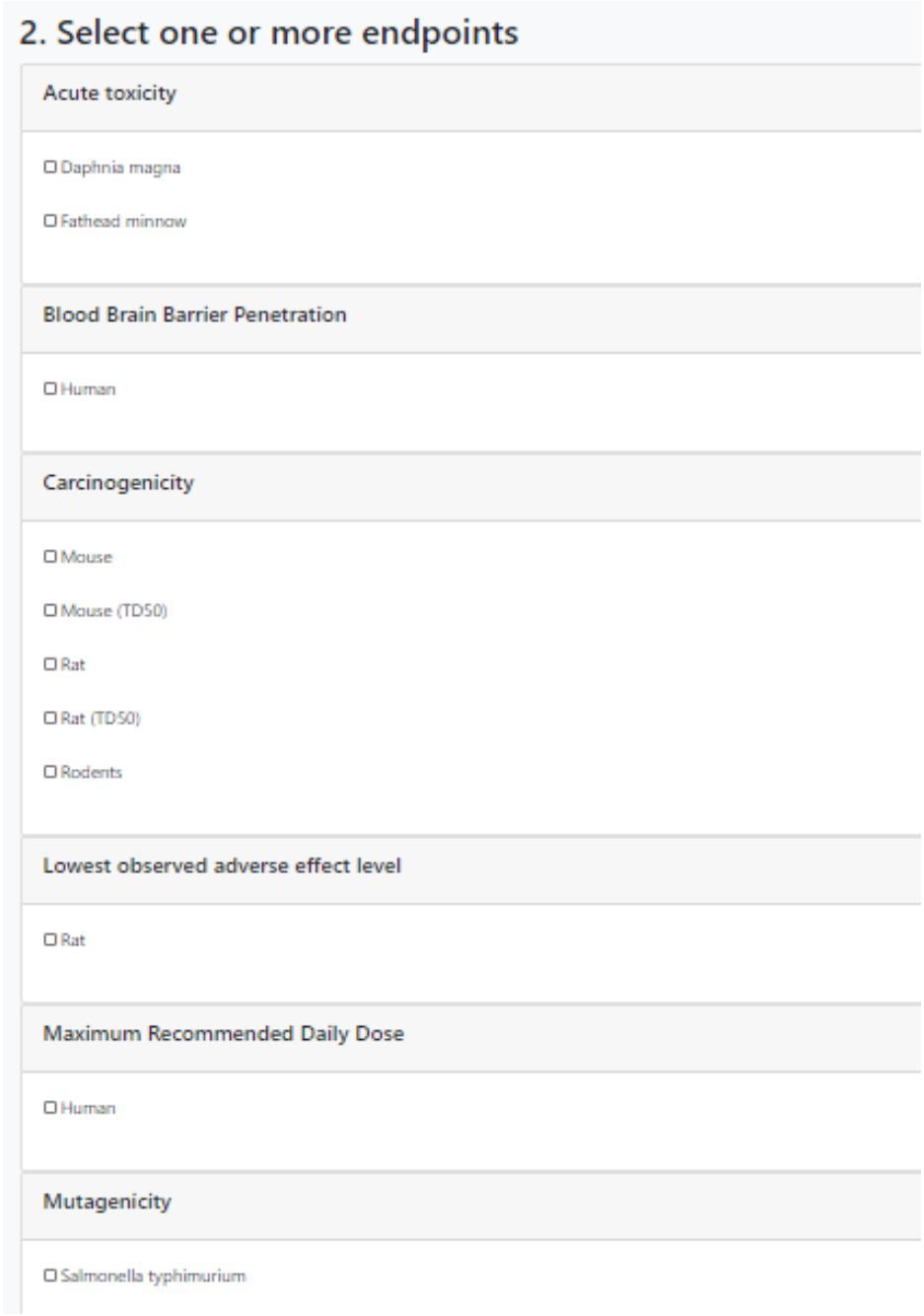
LAZAR *(Lazy Structure- Activity Relationships)* makes toxicity predictions for chemical structures. It uses an automated and reproducible *read across* algorithm and shows rationales for predictions, applicability domain estimations and validation results in a clear graphical interface





Not secure | qsar.food.dtu.dk

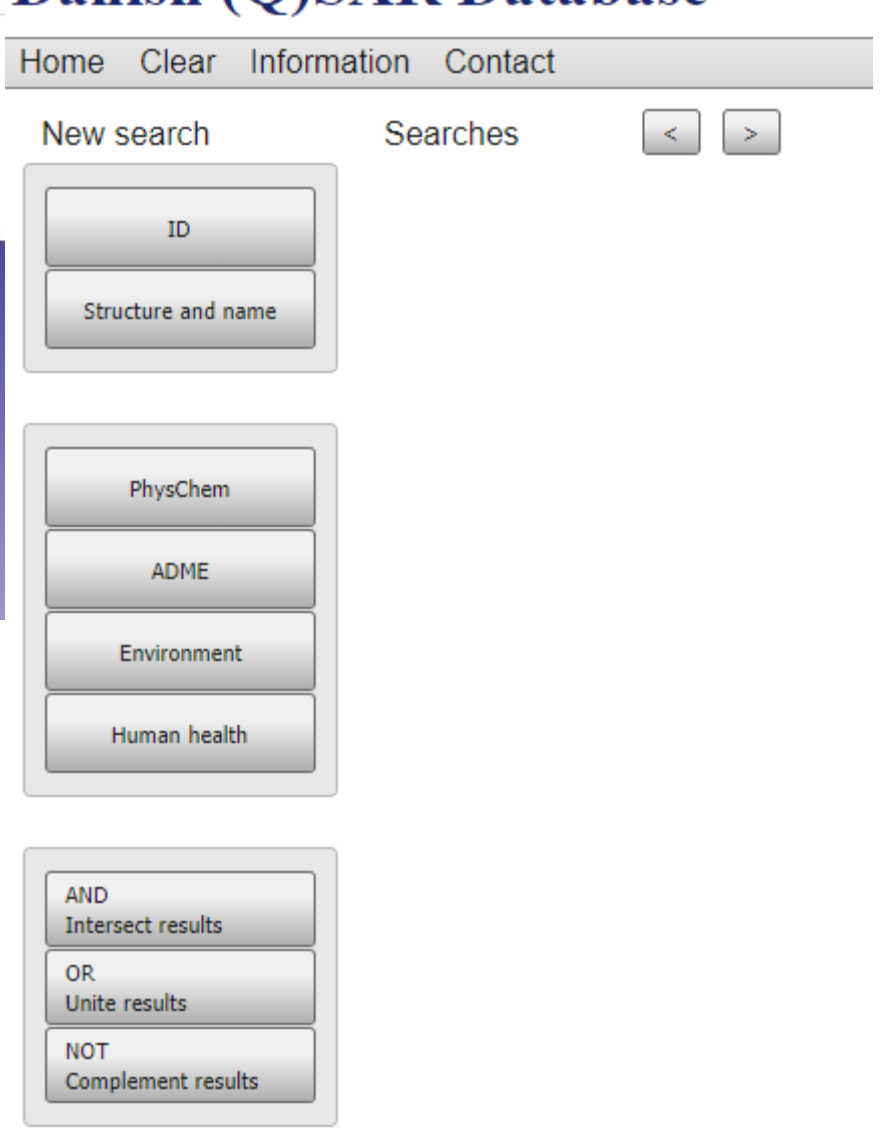
Nordic Council of Ministers

EUROPEAN CHEMICALS AGENCY

Ministry of Environment and Food of Denmark
Environmental Protection Agency

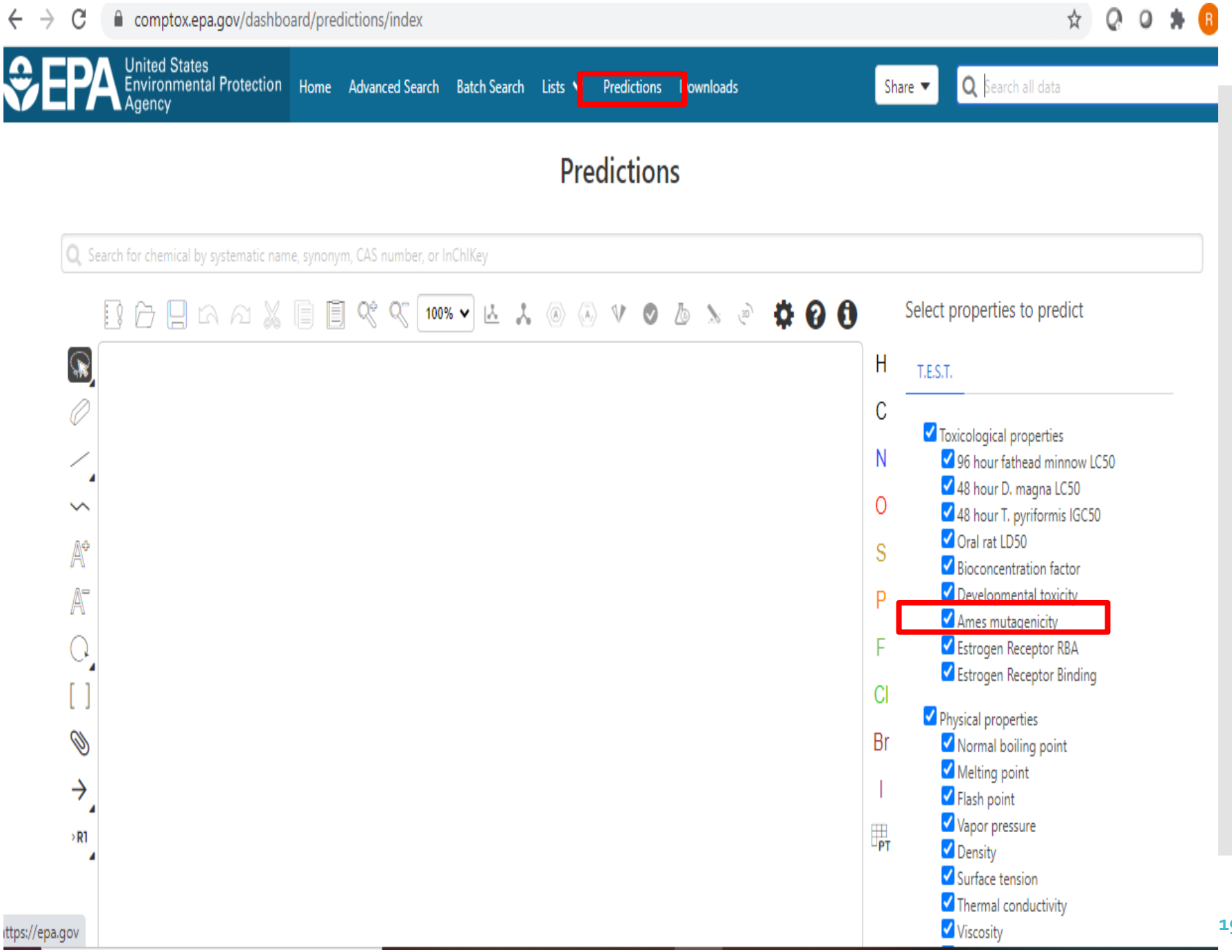
DTU Food
National Food Institute

Danish (Q)SAR Database



qsar.food.dtu.dk/

EPA T.E.S.T. is available through CompTox Chemicals Dashboard



CDRH Biocompatibility Guidance (2020)

The use of computational models alone for the assessment of potential carcinogenicity may not be sufficient

Evaluate the genotoxicity and carcinogenicity potential of the chemicals, including:

- ***a thorough literature review with identified search terms,***
- ***assessment of any evidence of carcinogenicity from long-term in vivo animal studies (e.g. inflammation, pre-neoplastic lesions, or tumor findings in animal studies),***
- ***the relevance of animal data to assess risks in humans, and***
- ***assessment of human data from epidemiological studies if available or any other relevant long-term clinical study findings, including susceptible population and life stages, and device implant site and propensity of the site to develop local tumors.57,58***

Use of QSAR models to predict the genotoxicity/ carcinogenicity of tentatively or partially identified compounds

Nontargeted analysis of extracts of medical devices often results in tentatively or partially identified compounds.

Can we use QSAR models to predict the genotoxicity/carcinogenicity/toxicity of these compounds?

Topic of debate and discussion. This approach may not be accepted by CDRH in a regulatory submission.

Overview

- Explore some new and existing open source comptox models
- Review the need for expert review of model-derived predictions
- Provide recommendations for additional training in the field
- Provide update on new toxicity information sources

Example of Need for Expert Review

Don't rely solely on the output of QSAR models

Regulatory Toxicology and Pharmacology 77 (2016) 1–12

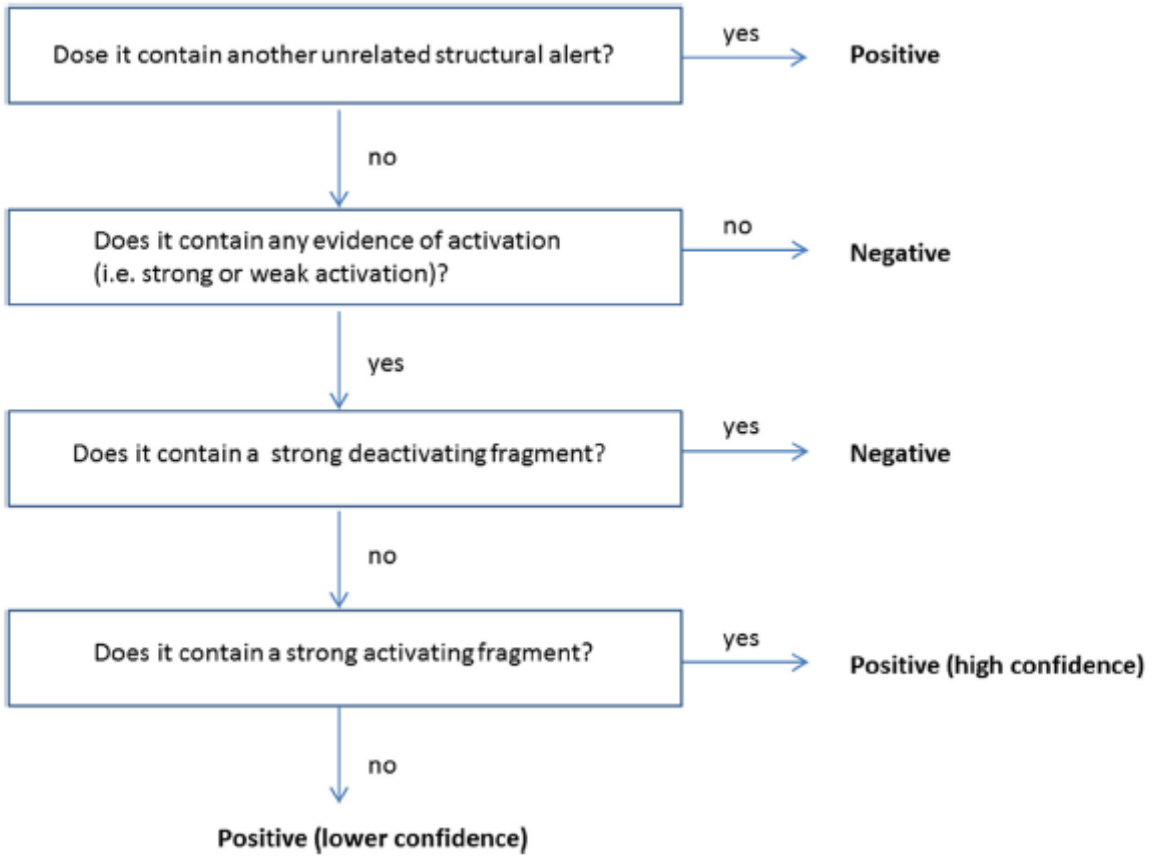
Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Extending (Q)SARs to incorporate proprietary knowledge for regulatory purposes: A case study using aromatic amine mutagenicity☆

Ernst Ahlberg [a], Alexander Amberg [b], Lisa D. Beilke [c], David Bower [d], Kevin P. Cross [d],



Need for expert review of model-derived predictions

Foster et al. Genes and Environment (2020) 42:27
https://doi.org/10.1186/s41021-020-00166-y

Genes and Environment

SHORT REPORT Open Access

The importance of expert review to clarify ambiguous situations for (Q)SAR predictions under ICH M7

Robert S. Foster*, Adrian Fowkes, Alex Cayley, Andrew Thresher, Anne-Laure D. Werner, Chris G. Barber, Grace Kocks, Rachael E. Tennant, Richard V. Williams, Steven Kane and Susanne A. Stalford

Regulatory Toxicology and Pharmacology 102 (2019) 53–64

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses☆

Alexander Amberg[a], Roxanne V. Andaya[b], Lennart T. Anger[a], Chris Barber[c], Lisa Beilke[d],

Take home messages on the use of QSAR models for the safety assessment of E&L compounds

- Updates are available for Toxtree, OECD Toolbox, Oncologic.
- Cramer Class modules in Toxtree can return differing results. Toxtree can be useful for the assessment of carcinogenicity by nongenotoxic effects.
- EPA TEST is available through the EPA CompTox Chemicals Dashboard.
- Don't accept the model-derived predictions without an expert review of the results; often needed when the resulting MoS is < 1 or when model-derived predictions of carcinogenicity are not convergent.
- Model-derived predictions of carcinogenicity alone are often not sufficient for the safety evaluation. Ideally, use experimentally derived data on genotoxicity along with model-derived predictions to inform decisions about potential carcinogenicity.

Advice on the Use of Read Across Approaches

There is no consensus approach for Read Across that has been recognized by CDRH in a standard or guidance document; however, CDRH may consider/accept this approach as a means to derive a PoD if it is supported with an adequate justification.

Recommendations

- **Use well established approaches; don't arbitrarily select a structural analog**
- **It's best to use multiple approaches to make your case**
- **Show your work, side-by-side comparison tables are useful.**
- **Establish toxicological equivalency between the data poor compound of interest and data rich structural analogs using both chemical and biological similarity**

Open source programs for Read Across and Chemical Grouping

Establish Chemical Similarity

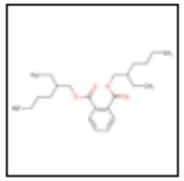
- GenRA
- NTP ICE
- ToxPrint Chemotyper
- ChemACE
- AIM
- PubChem
- ChemMine

Establishing Biological Similarity

- GenRA
- PubChem
- EPA CompTox Chemicals Dashboard – TOXCAST/Tox21
- OECD Toolbox
- QSAR models/expert systems

GenRA Tool in EPA CompTox Chemicals Dashboard

EPA United States Environmental Protection Agency | Home | Advanced Search | Batch Search | Lists | Predictions | Downloads | Copy | Share | Submit Comment | Search all data

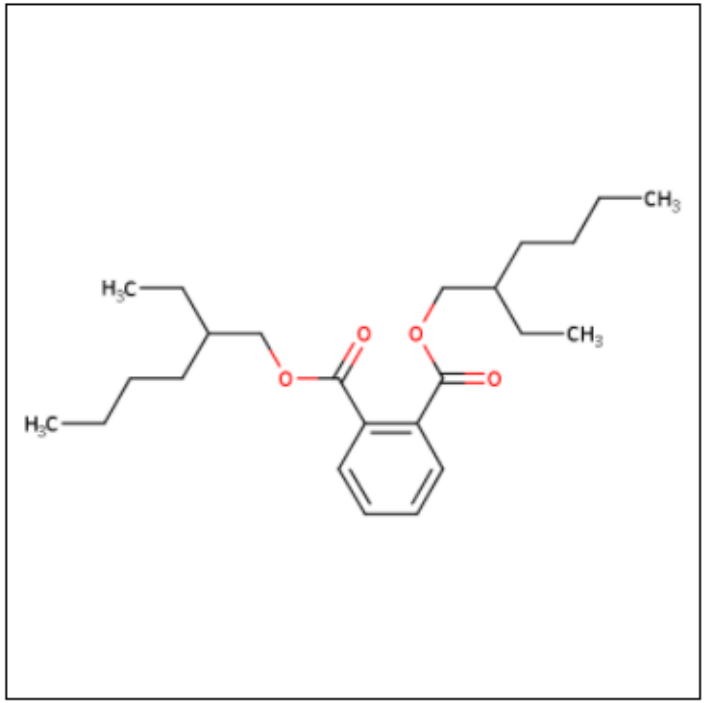


Di(2-ethylhexyl) phthalate

117-81-7 | DTXSID5020607

Searched by DSSTox Substance Id.

- DETAILS
- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- SAFETY
- ADME
- EXPOSURE
- BIOACTIVITY
- SIMILAR COMPOUNDS
- GENRA (BETA)
- RELATED SUBSTANCES



Wikipedia

Bis(2-ethylhexyl) phthalate (**di-2-ethylhexyl phthalate**, **diethylhexyl phthalate**, **DEHP**; **dioctyl phthalate**, **DOP**) is an organic compound with the formula $C_6H_4(CO_2C_8H_{17})_2$. DEHP is the most common member of the class of phthalates, which are used as plasticizers. It is the diester of phthalic acid and the branched-chain 2-ethylhexanol. This colorless viscous liquid is soluble in oil, but not

...

Read more

Quality Control Notes

Intrinsic Properties

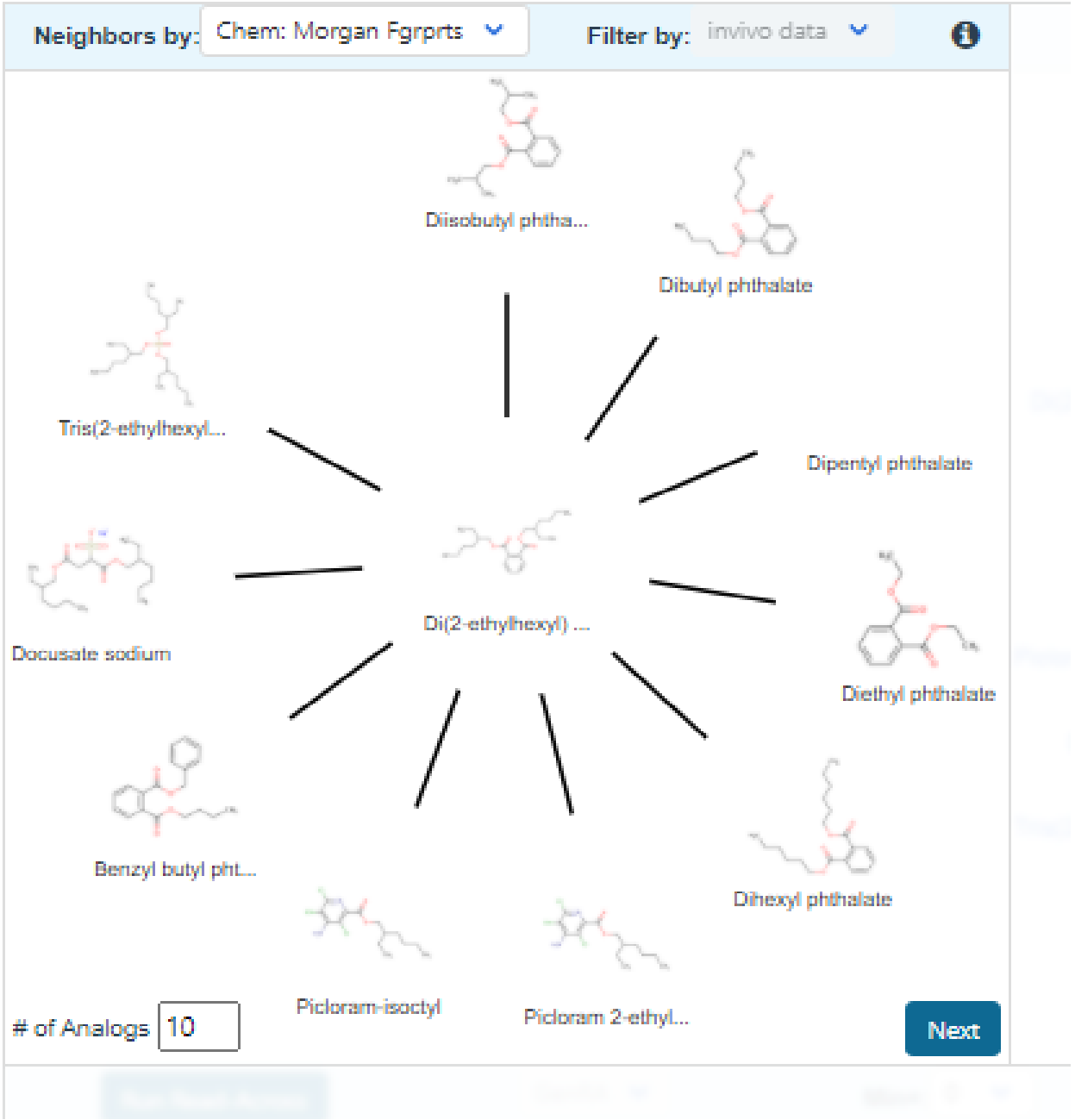
Molecular Formula: $C_{24}H_{38}O_4$ | Mol File | Find All Chemicals

Average Mass: 390.564 g/mol | Isotope Mass Distribution

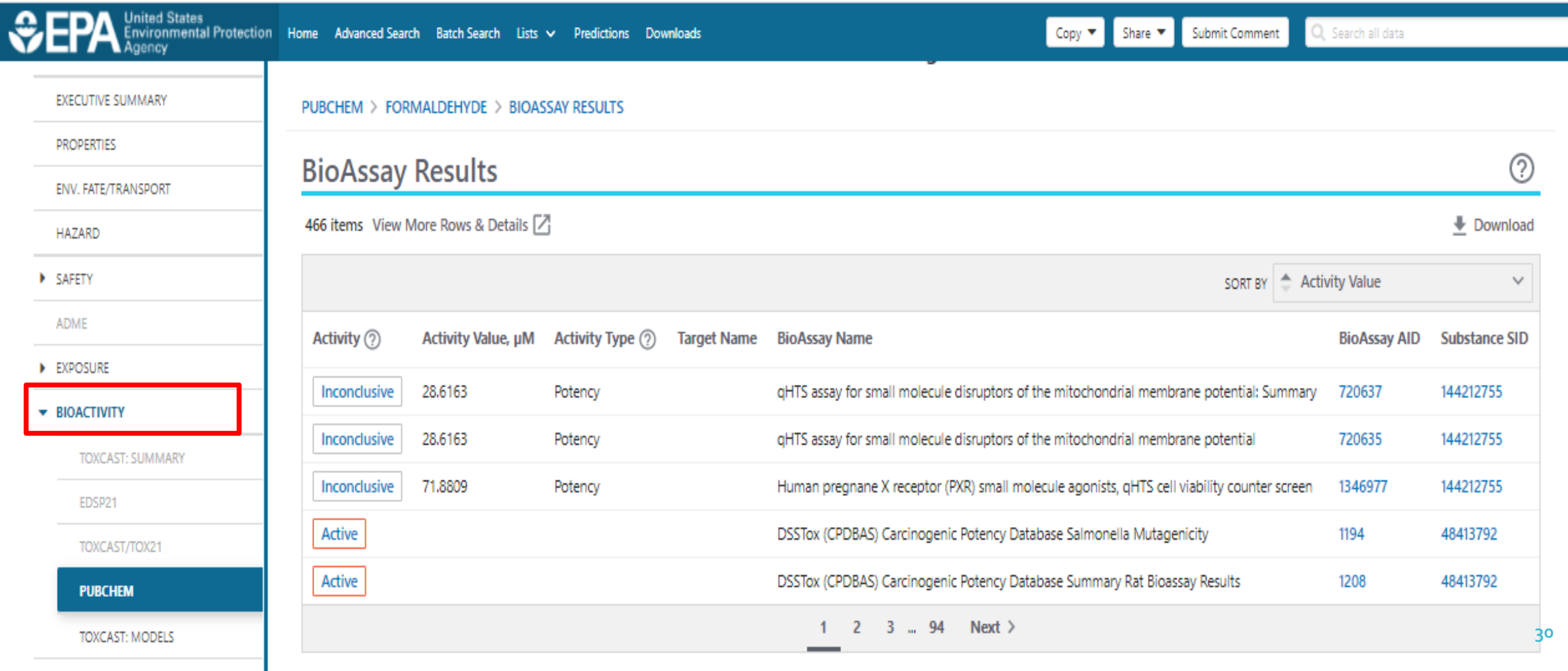
Monoisotopic Mass: 390.27701 g/mol

Structural Identifiers

GenRA will identify closest analogs based on structure or biological activity



Obtaining *in vitro* data from TOXCAST/Tox21 using EPA CompTox Chemicals Dashboard



Useful Open Source Papers on GenRA and Read Across

Short Communication

Generalized Read-Across (GenRA): A Workflow Implemented into the EPA CompTox Chemicals Dashboard

George Helman[1,2], *Imran Shah*[2], *Antony J. Williams*[2], *Jeff Edwards*[2], *Jeremy Dunne*[2] *and Grace Patlewicz*[2]

[1]Oak Ridge Institute for Science and Education (ORISE), Oak Ridge, TN, USA; [2]National Center for Computational Toxicology (NCCT), Office of Research and Development, US Environmental Protection Agency, Research Triangle Park (RTP), NC, USA

ALTEX. **2019;36(3):462-465.**

EPA Public Access

Author manuscript

Comput Toxicol. Author manuscript; available in PMC 2018 September 12.

About author manuscripts | Submit a manuscript

Published in final edited form as:

Comput Toxicol. 2017 August ; 3: 1–18. doi:10.1016/j.comtox.2017.05.003.

Navigating through the minefield of read-across tools: A review of in silico tools for grouping

Patlewicz Grace[a,*], **Helman George**[a,b], **Pradeep Prachi**[a,b], and **Shah Imran**[a]

[a]National Center for Computational Toxicology (NCCT), Office of Research and Development, US Environmental Protection Agency, 109 TW Alexander Dr, Research Triangle Park (RTP), NC 27711, USA

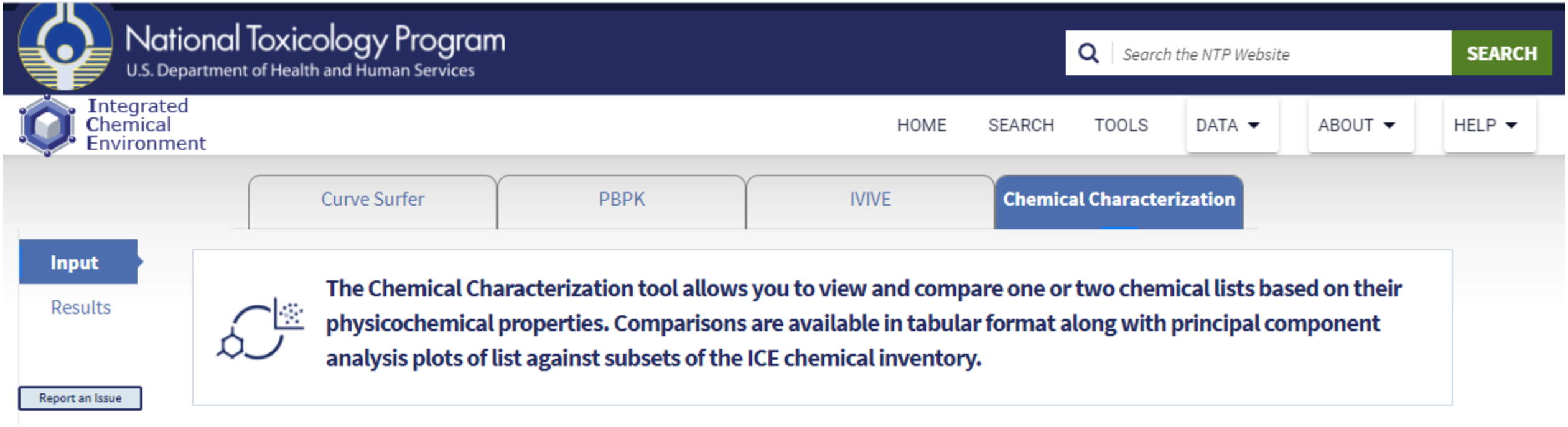
Open source programs for Read Across and Chemical Grouping

Establish Chemical Similarity

- GenRA
- NTP ICE
- ToxPrint Chemotyper
- ChemACE
- AIM
- PubChem
- ChemMine

Establishing Biological Similarity

- GenRA
- PubChem
- EPA CompTox Chemicals Dashboard – TOXCAST/Tox21
- OECD Toolbox
- QSAR models/expert systems



Use to establish similarity of compounds on the basis of molecular descriptors or physical-chemical properties

Toxicology in Vitro
Volume 67, September 2020, 104916

An integrated chemical environment with tools for chemical safety testing

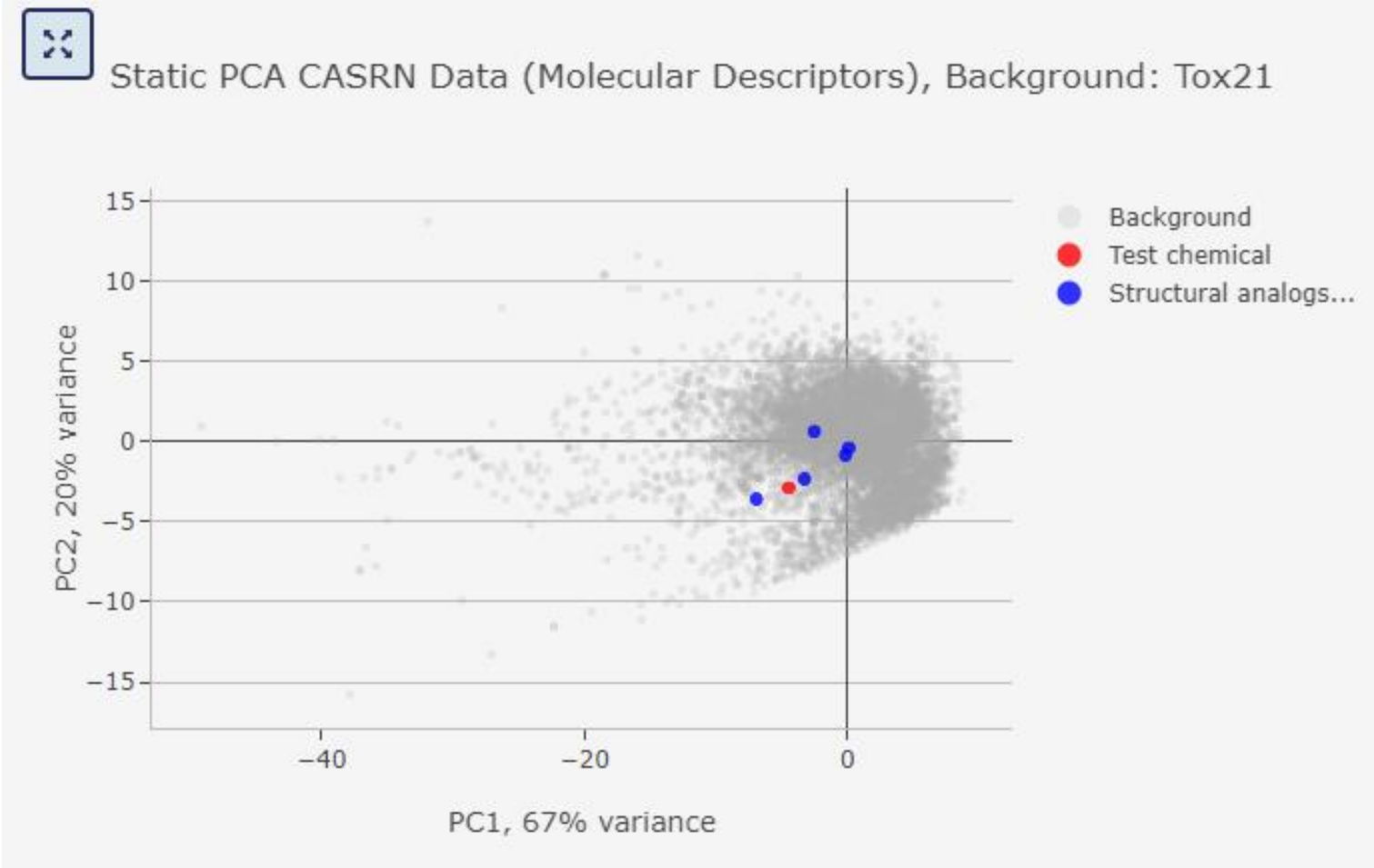
Shannon Bell [a], Jaleh Abedini [a], Patricia Ceger [a], Xiaoqing Chang [a], Bethany Cook [a], Agnes L. Karmaus [a], Isabel Lea [a, 1], Kamel Mansouri [a], Jason Phillips [b], Eric McAfee [b], Ruhi Rai [a, 2], John Rooney [a], Catherine Sprankle [a], Arpit Tandon [b], David Allen [a], Warren Casey [c], Nicole Kleinstreuer [c]

Example of using NTP ICE to identify structural analogs

Test chemical – Butyl-2-ethylhexyl phthalate

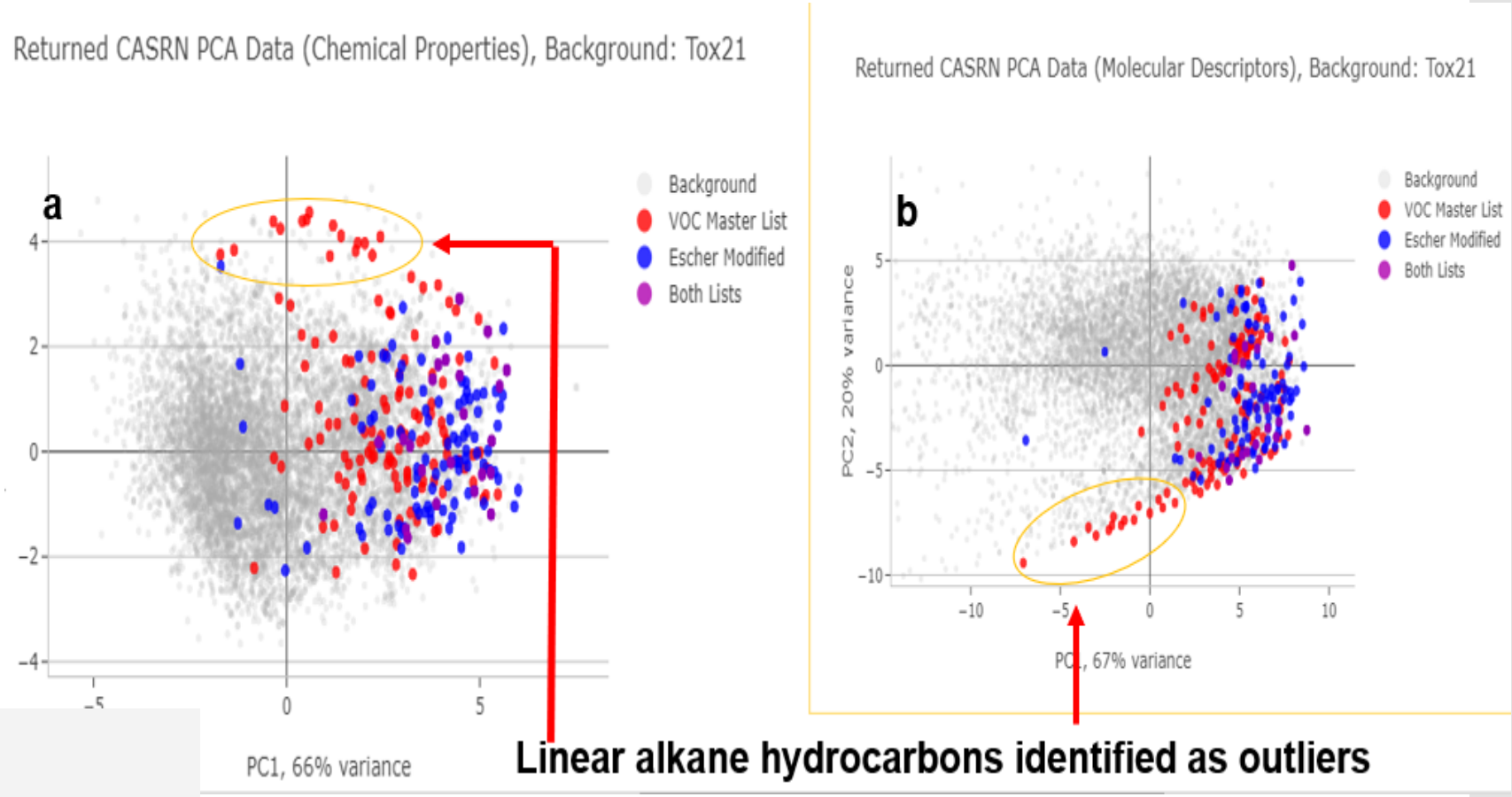
Structural analogs – series of phthalate esters

Use PCA feature in Chemical Characterization module to identify closest analogs on the basis of structure or physical-chemical properties



Use of NTP ICE to visually define chemical space

Example of using NTP ICE to compare chemical space of VOCs released from device materials and VOCs used to derive inhalation TTC value.



CTSS Webinar

Moving from One-Size-Fits-All to Fit-for Purpose TTC Values

Speaker(s):

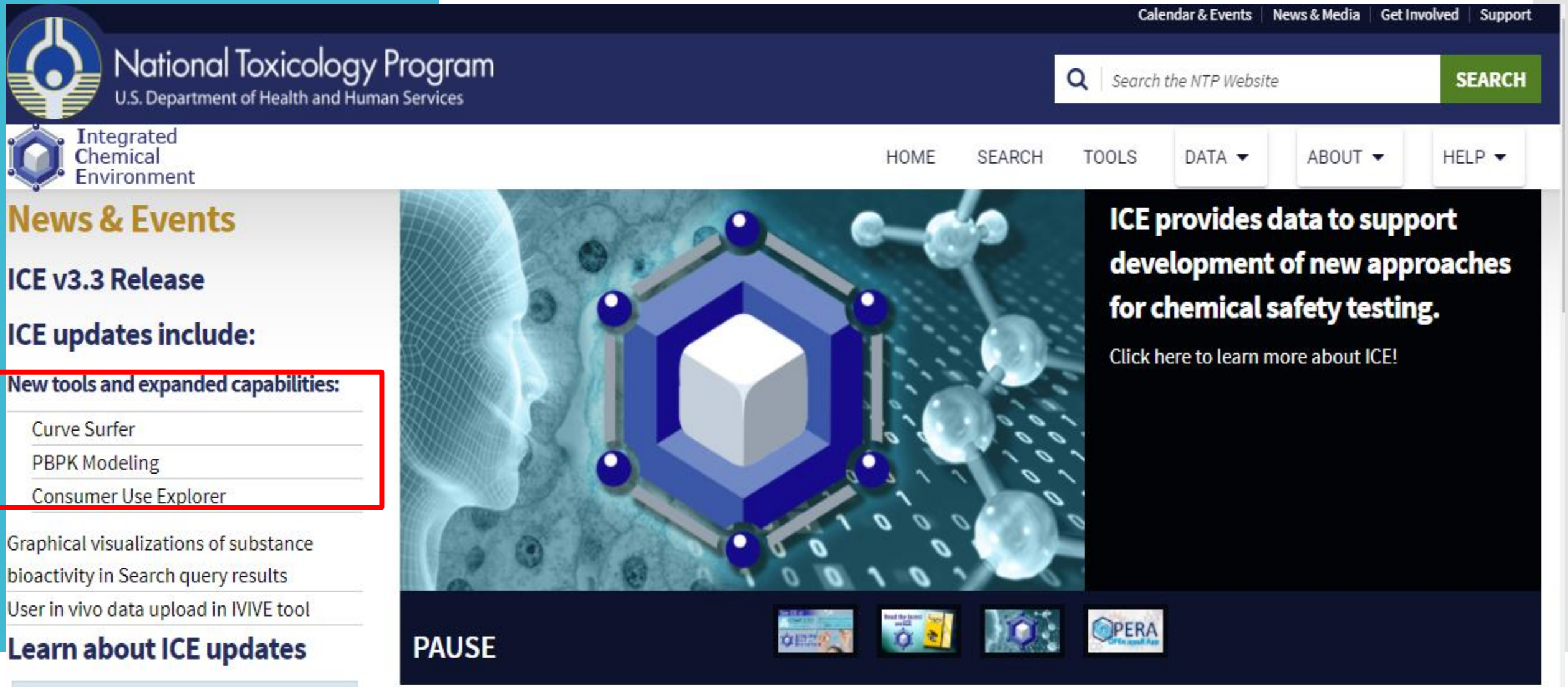
Ron Brown, PhD, Risk Sciences Consortium

Grace Patlewicz, PhD, US EPA

Thursday, August 5, 11 AM EDT

https://www.toxicology.org/groups/ss/ctss/events.asp

Additional source of information about NTP ICE



Wiki

Backlogs

Bug Backlog
Feature Requests

Wiki

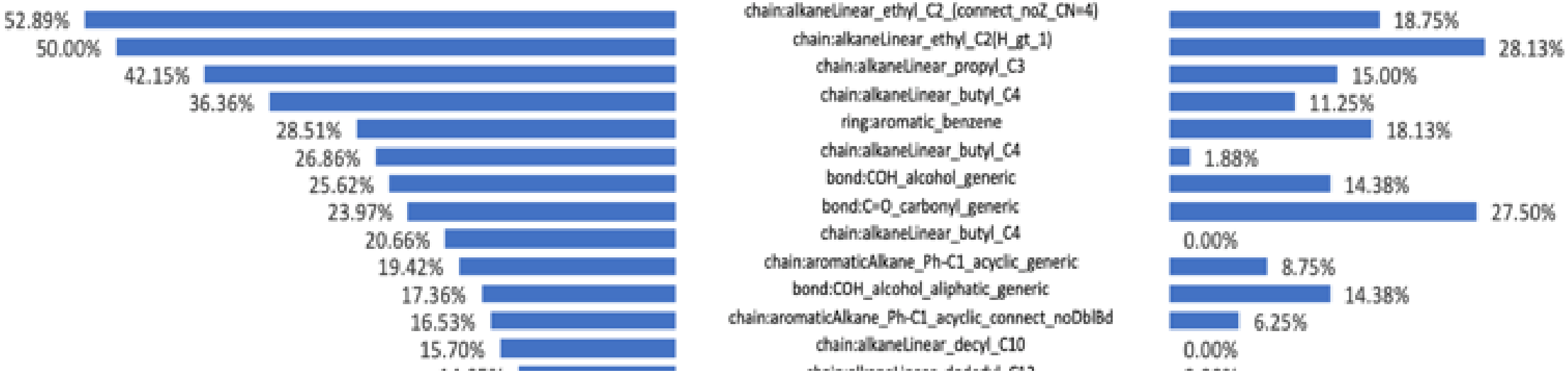
Wiki Homepage

Welcome to the ChemoTyper

The ChemoTyper application

The ChemoTyper application is a tool that allows for searching and highlighting chemical chemotypes (chemical substructures or subgraphs) in datasets of molecules. Typical applications are as following:

- searching for structural alerts for toxicity in chemical structure files
- filtering of chemical structures according to chemotypes
- visualization and inspection of chemotypes
- grouping of chemicals according to chemotypes, and
- fingerprinting of chemical structure sets against chemotypes



Analog Identification Methodology (AIM) Tool

The Analog Identification Methodology (AIM) is a downloadable software program that facilitates analog analysis and data identification in support of chemical assessment or read-across approaches to help scientists and chemical managers predict potential hazards of untested chemicals.

Key characteristics of the program include:

- Ability to conduct comprehensive structural analysis of chemicals using over 700 individual atoms, groups and super fragments indexed in a predefined database
- Uses structural analysis to match potential analogs from an inventory of over 86,000 chemicals with publicly available measured data and links to the data sources
- Ability to recode defined substitutions or exclusion rules for the refinement of analog search strategies

AIM software is available for free and is posted below as a downloadable software program without licensing requirements. Information on use and set-up is provided in the AIM User's Manual.

Analog Identification Methodology (AIM) Download (1 pg, 104 MB)

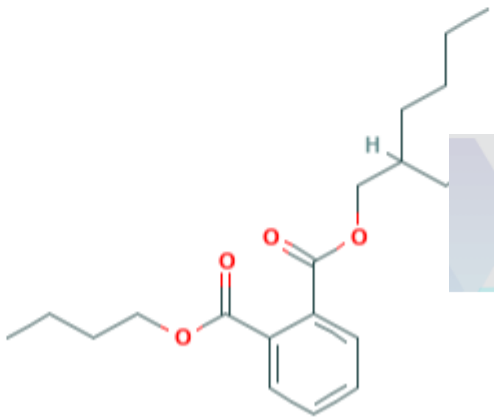
PubChem Butyl 2-ethylhexyl phthalate (Compound)

1 Structures

1.1 2D Structure

Find Similar Structures | Get Image | Download

Chemical Structure Depiction



CID6818 structure

Treating this as a structure search for CID 6818. Edit Structure Search for **CID6818 structure as text** instead.

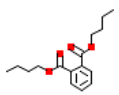
Identity (1)	Similarity (>1,000)	Substructure (>1,000)	Superstructure (>1,000)	3D Similarity (18)

Fingerprint Tanimoto-based 2-dimensional similarity search.

Percentage of the database searched: 9%.

Search All

1,000 results (incomplete) Filters SORT BY Relevance



Dibutyl Phthalate; 84-74-2; Di-N-Butyl Phthalate; N-Butyl Phthalate; Butyl Phthalate; ...

Compound CID: 3026

ACTIONS ON F

Compounds

Use ChemMine Tools to establish chemical similarity between compounds

ChemMine Tools About Help Downloads Optional:

WORKBENCH

My Compounds

Add Compounds

TOOLS

Past Jobs

Upload Numeric Data

Cluster

Physicochemical Properties

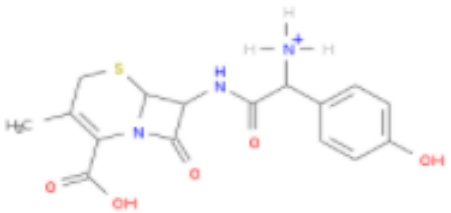
Similarity Workbench

Compound Similarity

Select two compounds to compare from the grid below.

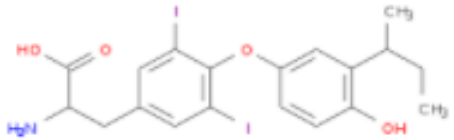
Selected Compounds

21680720



remove

13942129



remove

AP Tanimoto: 0.230315
MCS Tanimoto: 0.2439
MCS Size: 10
MCS Min: 0.4000
MCS Max: 0.3846
SMILES: C(Cc1ccc(cc1)O)N
21680720

Take home messages on the Use of Read Across Approaches

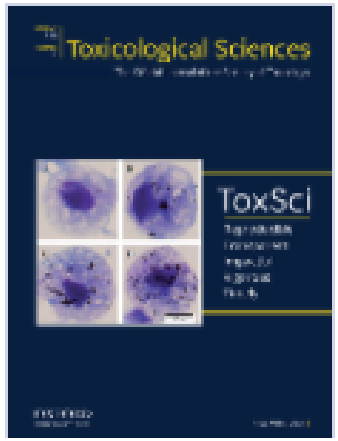
There is no consensus approach for Read Across that has been recognized by CDRH in a standard or guidance document; however, CDRH may considered this approach if it is supported based by scientific evidence.

Recommendations

- Use well established approaches; don't arbitrarily select a structural analog
- It's best to use multiple approaches to make your case
- Show your work, side-by-side comparison tables are useful.
- Establish toxicological equivalency between the data poor compound of interest and data rich structural analogs using both chemical and biological similarity

Update to BMD models

Exposure models



Leveraging Extraction Testing to Predict Patient Exposure to Polymeric Medical Device Leachables Using Physics-based Models

Paul Turner, Robert M Elder, Keaton Nahan, Anne Talley, Saloni Shah, Timothy V Duncan, Eric M Sussman, David M Saylor ✉

Toxicological Sciences, Volume 178, Issue 1, November 2020, Pages 201–211,

SARTORIUS

White Paper

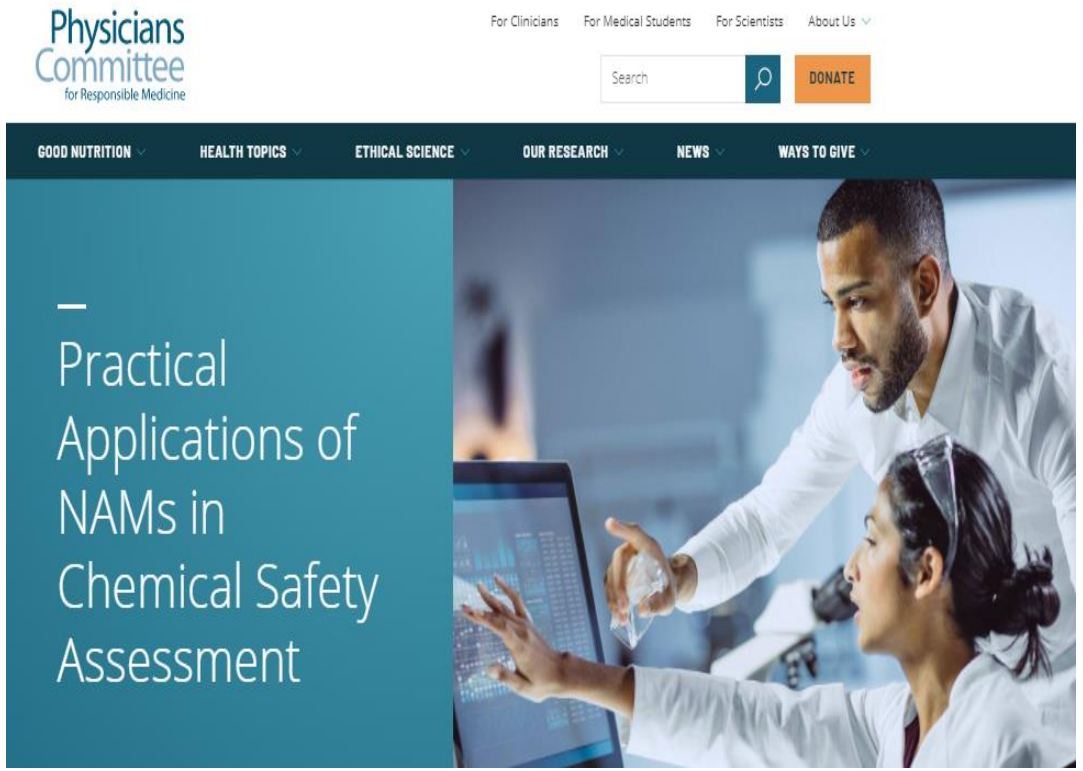
April 27, 2021

Keywords or phrases:
Extractable and Leachable Testing, Extractables Prediction, Extractables Scaling, Pharmaceutical Validation, Process Validation, Single-use Systems

Sartorius Extractables Simulator: Simplifying E&L Through in-Silicio Modeling

Armin Hauk[1], Roberto Menzel[1], Ina Pahl[1], Sven Linz*[1], Mehran Rafigh[1], Alexander Wildschütz[2], Stefan Baur[2]
[1]Sartorius Stedim Biotech GmbH, August-Spindler-Strasse 11, 37079 Goettingen
[2]GWDG | Max-Planck-Gesellschaft, Am Faßberg 11, 37077 Göttingen

Training Opportunities



IVAMSS and CTSS Webinar: State of the Science: QSAR Modeling of Skin Sensitization

https://aim-hq.webex.com/recordingservice/sites/aim-hq/recording/19dba0a09ae11039bff80050681a6ea/playback

Slides and recorded presentations can be found at: https://app.oxfordabstracts.com/events/1566/program-app/session/14962

TUTORIALS

Webinar by OECD & ECHA: QSAR Toolbox Version 4.0 Features

WATCH VIDEO

OECD QSAR Toolbox training

WATCH VIDEO

Predicting SS by making use of read-across

DOWNLOAD PDF

Questions

Send questions or comments to:

Ron Brown
Risk Science Consortium
riskscienceconsortium@gmail.com

Information resources

- Explore some new and existing open source comptox models
- Review the need for expert review of model-derived predictions
- Provide recommendations for additional training in the field
- Provide update on new toxicity information sources

Where do I find…?

- SMILES codes – PubChem
- Dose-Response data and existing HBEL values – EPA CompTox Chemicals Dashboard, EFSA OpenFoodTox, COSMOS NG
- TD50 values – Lhasa Carcinogenicity Database
- TTC values – TTC Data Mart

COMPOUND SUMMARY

Bis(2-ethylhexyl) phthalate

2.1.4 Canonical SMILES

CCCCC(CC)COC(=O)C1=CC=CC=C1C(=O)OCC(CC)CCCC

Computed by OEChem 2.1.5 (PubChem release 2019.06.18)

- PubChem

2.2 Molecular Formula

C24H38O4

C6H4(COOC8H17)2

- ILO International Chemical Safety Cards (ICSC)

C24H38O4

Computed by PubChem 2.1 (PubChem release 2019.06.18)

- PubChem

2.3 Other Identifiers

2.3.1 CAS

117-81-7

efsa
European Food Safety Authority

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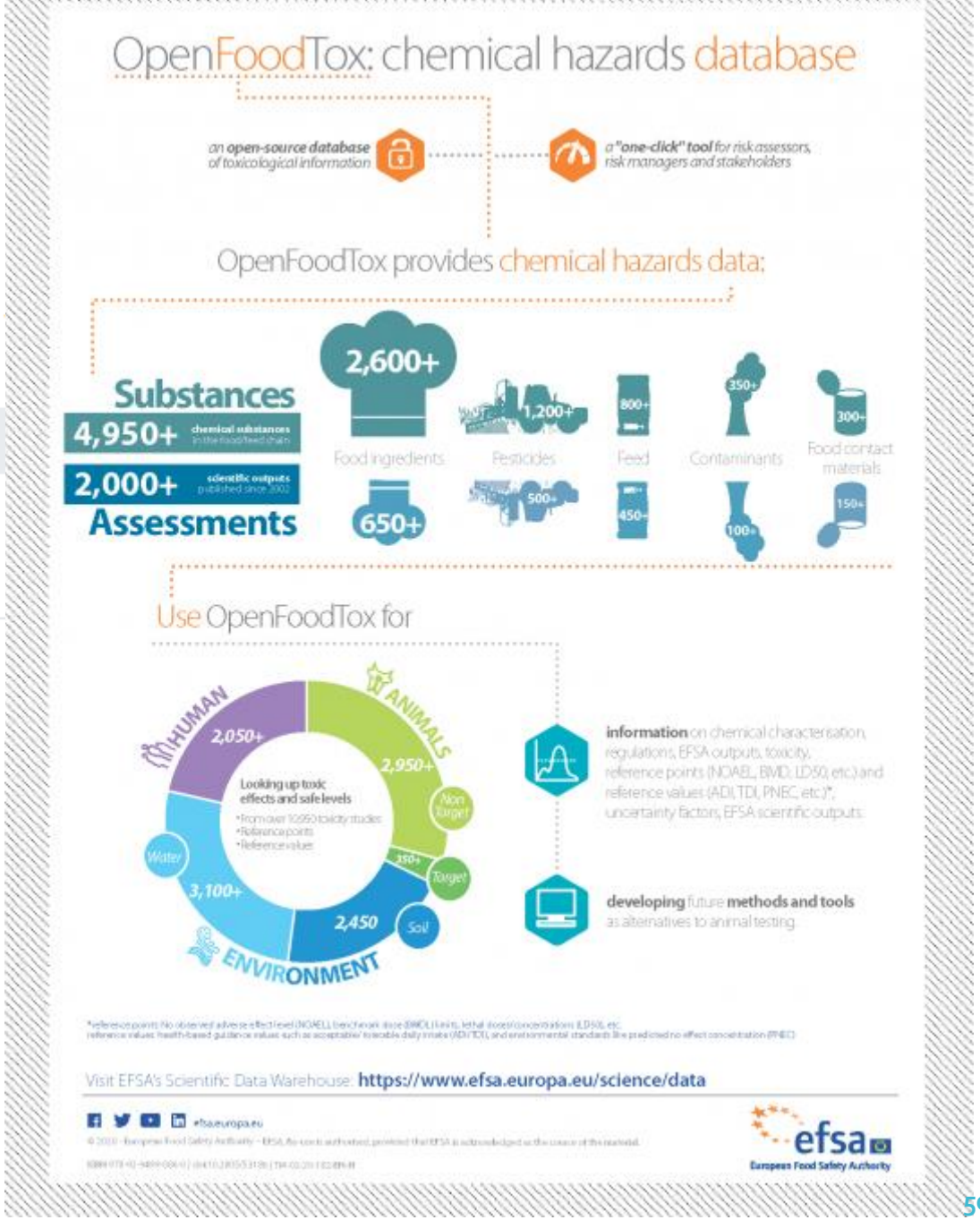
Chemical hazards data - OpenFoodTox



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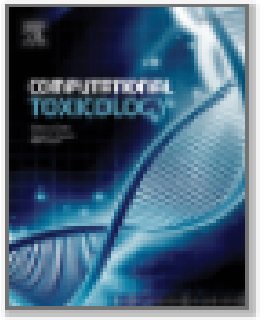
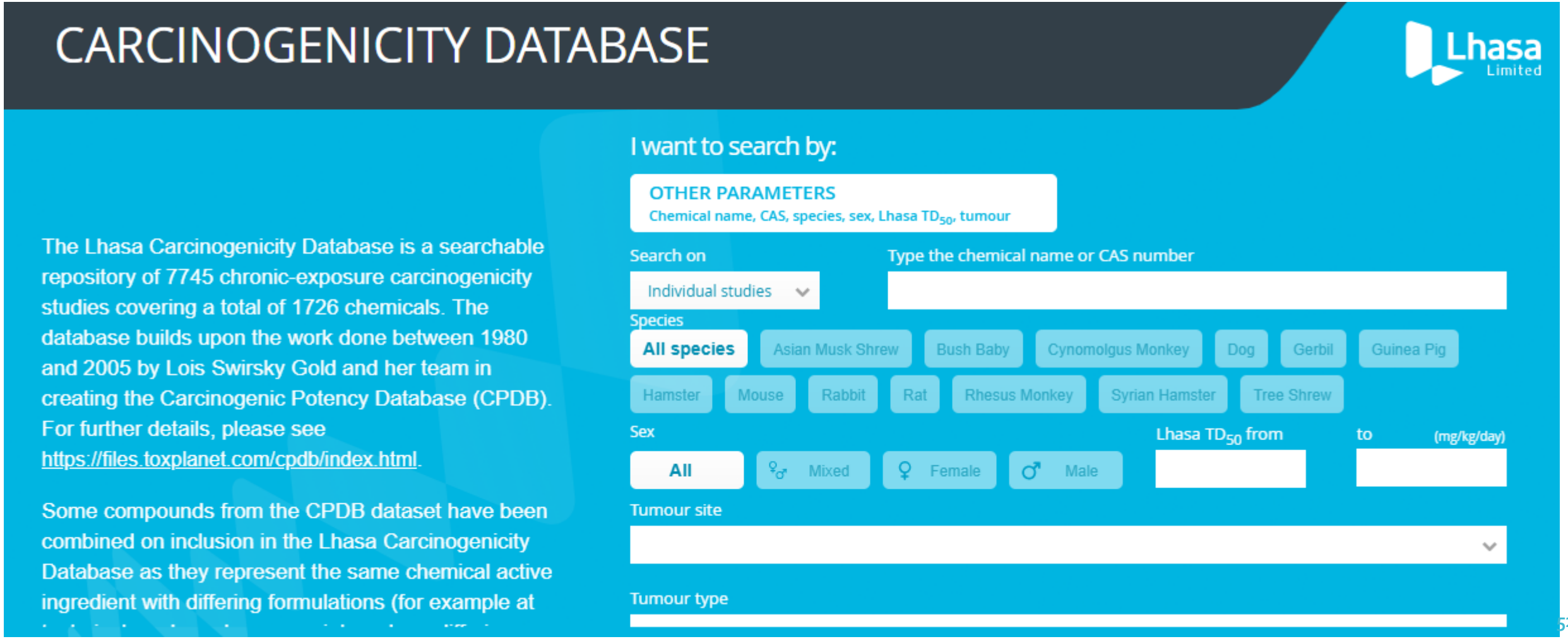
In Press, Journal Pre-proof



COSMOS Next Generation – a public knowledge base leveraging chemical and biological data to support the regulatory assessment of chemicals

C. Yang [a, b], M.T.D. Cronin [c], K.B. Arvidson [d], B. Bienfait [b], S.J. Enoch [c], B. Heldreth [e], B. Hobocienski [a], K. Muldoon-Jacobs [d], Y. Lan [f], J.C. Madden [c], T. Magdziarz [b], J. Marusczyk [b], A. Mostrag [a], M. Nelms [c], D. Neagu [f], K. Przybylak [c], J.F. Rathman [a, g], J. Park [a] ... A.P. Worth [i]

Lhasa Carcinogenicity Database



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6 classes selected

Upload list of chemicals to filter

Browse... | List of CAS numbers

Select Columns

7 of 25 columns selected

Show 15 entries

Search:

CASRN	DSSTox Substance ID	Name	SMILES (raw)	Cramer Decision (Raw SMILES)	TTC Value (mg/kg/d, Raw SMILES)	TTC Classification (Raw SMILES)

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Computational Toxicology
Volume 15, August 2020, 100128

The TTC Data Mart: An interactive browser for threshold of toxicological concern calculations

Chantel I. Nicolas [a], Kevin Bronson [a], Salil N. Pendse [a], Alina Efremenko [a], Jeremy M. Fitzpatrick [a], Melyssa S. Minto [a], Kamel Mansouri [b], Miyoung Yoon [a], Martin B. Phillips [a], Rebecca A. Clewell [c], Melvin E. Andersen [a], Harvey J. Clewell III [d, 1], Patrick D. McMullen [a, 1]