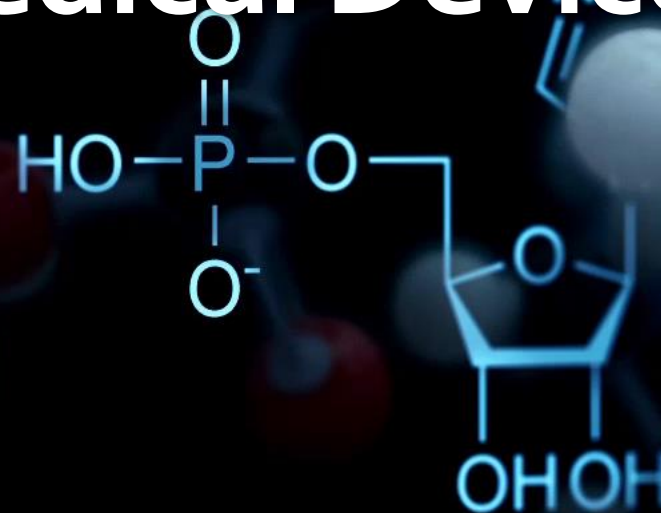


Use of Computational Models to Predict the Toxicity of Compounds Released from Medical Device Materials

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**

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

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.

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/car-
cinogenicity?

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.

Toxtree modules (0/15) select expand run

Cramer rules ▶ M A ▲

Intermediate (Class II)
Low (Class I) ✓
High (Class III)

1. Normal constituent of the body **Yes** Class Low (Class I)

Extended Cramer rules ▶ M A ▲

Intermediate (Class II)
Low (Class I) ✓
High (Class III)

1. Normal constituent of the body **Yes** Class Low (Class I)

Revised Cramer Decision Tree ▶ M A ▲

Intermediate (Class II)
Low (Class I)
High (Class III) ✓

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

Benigni/Bossa rules for carcinogenicity and mutagenicity

Structural Alert for genotoxic carcinogenicity: NO ✓

Structural Alert for nongenotoxic carcinogenicity: YES ✓

The OECD QSAR Toolbox

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

New features

- 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

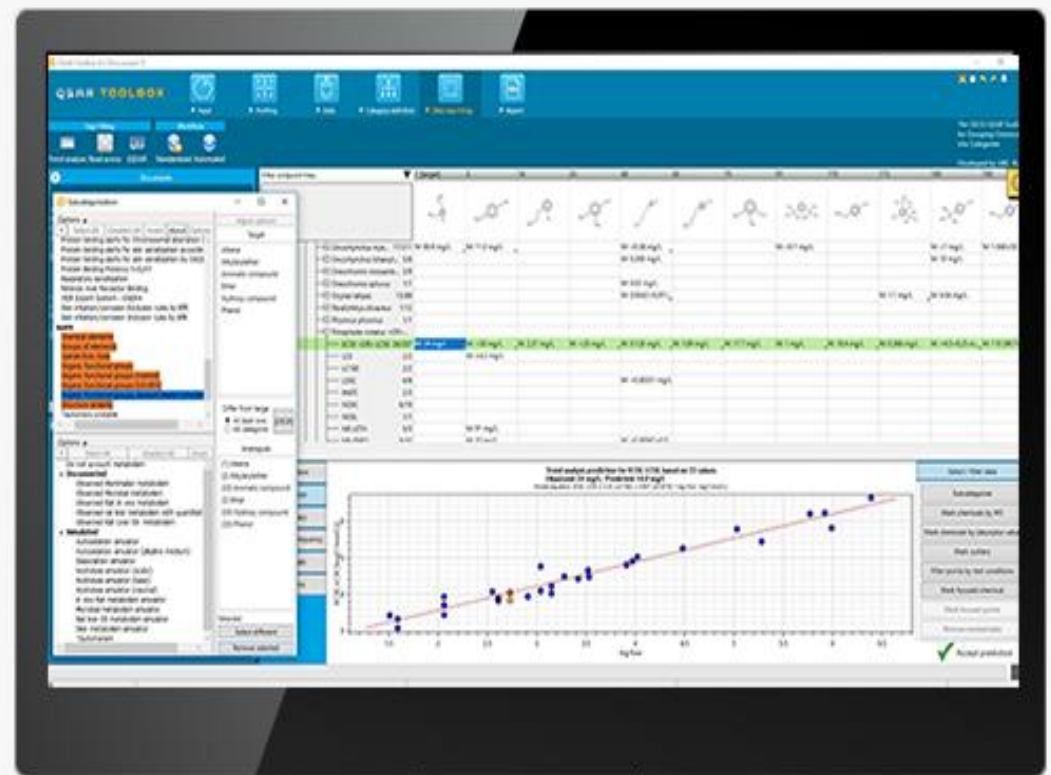
Webinar by OECD & ECHA: QSAR Toolbox Version 4.0 Features

[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



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Related Topics: [Predictive Models and Tools for Assessing Chemicals under the Toxic Substances Control Act \(TSCA\)](#)

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OncoLogic™ – An Expert System to Evaluate the Carcinogenic Potential of Chemicals

The OncoLogic™ model is an expert system that mimics the judgment of human experts by following sets of knowledge rules based on studies of how chemicals cause cancer in animals and humans. OncoLogic™ asks for chemical and use information from the user, and following the knowledge rules incorporated into the system, uses the responses to construct an estimation of the carcinogenicity potential of the chemical.

Examples of expert systems and statistically based models

Expert systems

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- OncoLogic
- DEREK Nexus

Statistically based models

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

Expert system and statistical modules

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- Leadscope (available through Danish QSAR database)

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

← → ↻ lazar.in-silico.ch/predict

 **lazar toxicity predictions**

Problems, bugs or ideas for improvements ? Please check the [FAQ](#) page or send us an email. [✉](#) [version: 1.4.2]

Please cite: DOI [10.3389/toxics.10.3389](https://doi.org/10.3389/toxics.10.3389) if you use this service for scientific purposes. [📄](#) [📱](#) [🌐](#)

1. Draw a chemical structure



JSMOL Molecular Editor by Peter Ertl and Bruno Glenz

or enter the [SMILES](#) string:

2. Select one or more endpoints

Acute toxicity

- ☐ Daphnia magna
- ☐ Fathead minnow

Blood Brain Barrier Penetration

- ☐ Human

Carcinogenicity

- ☐ Mouse
- ☐ Mouse (TD50)
- ☐ Rat
- ☐ Rat (TD50)
- ☐ Rodents

Lowest observed adverse effect level

- ☐ Rat

Maximum Recommended Daily Dose

- ☐ Human

Mutagenicity

- ☐ Salmonella typhimurium



norden
Nordic Council of Ministers



Ministry of Environment and Food of Denmark
Environmental Protection Agency

DTU FOOD
National Food
Institute

Danish (Q)SAR Database

Home Clear Information Contact

New search

Searches



ID

Structure and name

PhysChem

ADME

Environment

Human health

AND
Intersect results

OR
Unite results

NOT
Complement results

ID Search

Single ID

ID List

Affiliation

More

☒ Registry Number

☐ EC Number

☐ PubChem CID

Search

Cancel

qsar.food.dtu.dk/

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

The screenshot shows the EPA Comptox Dashboard Predictions page. The page has a blue header with the EPA logo and navigation links: Home, Advanced Search, Batch Search, Lists, Predictions (highlighted with a red box), and Downloads. A search bar is located in the top right corner. Below the header, the main content area is titled 'Predictions'. There is a search bar for chemical names, synonyms, CAS numbers, or InChIKeys. A toolbar with various icons is visible, including a 100% zoom dropdown. On the right side, there is a section titled 'Select properties to predict' with a list of properties. The 'Ames mutagenicity' property is highlighted with a red box. The list of properties includes:

- ☒ Toxicological properties
 - ☒ 96 hour fathead minnow LC50
 - ☒ 48 hour D. magna LC50
 - ☒ 48 hour T. pyriformis IGC50
 - ☒ Oral rat LD50
 - ☒ Bioconcentration factor
 - ☒ Developmental toxicity
 - ☒ Ames mutagenicity
 - ☒ Estrogen Receptor RBA
 - ☒ Estrogen Receptor Binding
- ☒ Physical properties
 - ☒ Normal boiling point
 - ☒ Melting point
 - ☒ Flash point
 - ☒ Vapor pressure
 - ☒ Density
 - ☒ Surface tension
 - ☒ Thermal conductivity
 - ☒ Viscosity

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

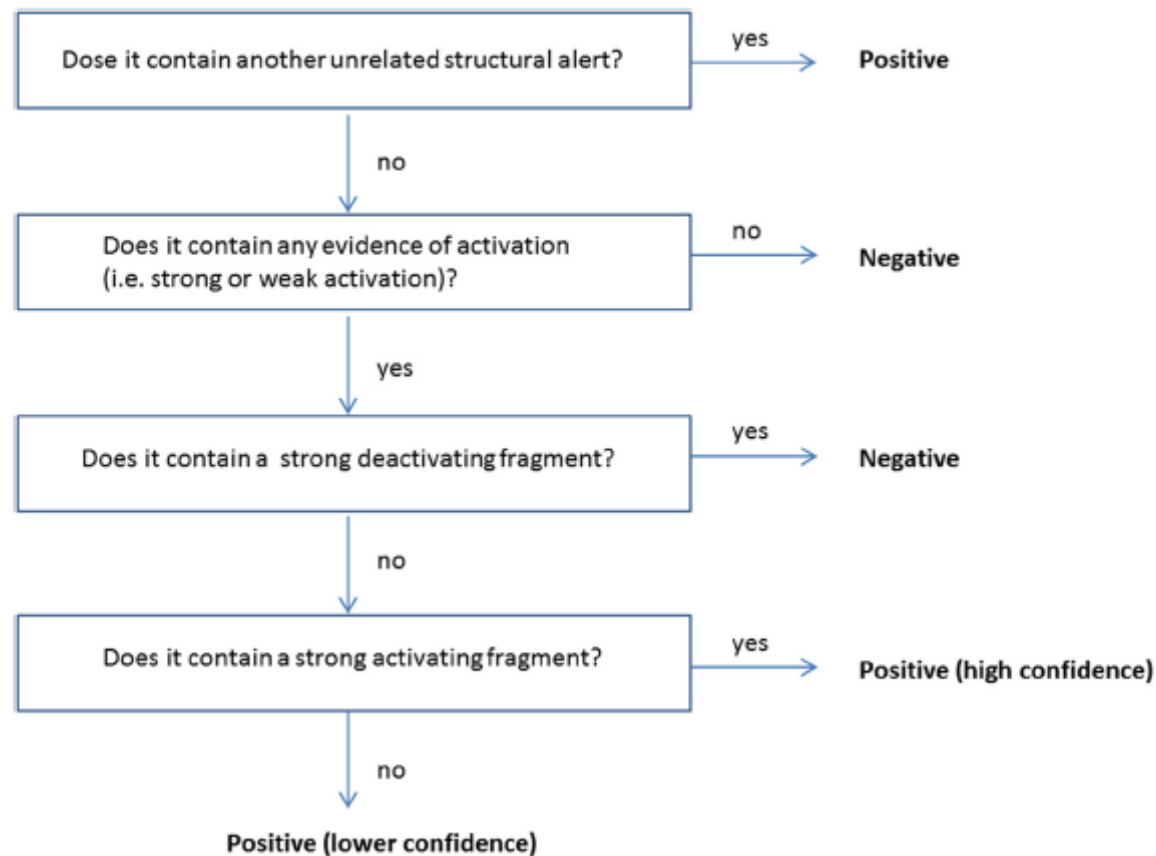
Example of Need for Expert Review

Don't rely
solely on the
output of
QSAR models



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

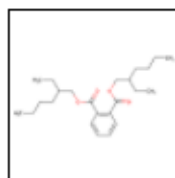
Establish Chemical Similarity

- 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

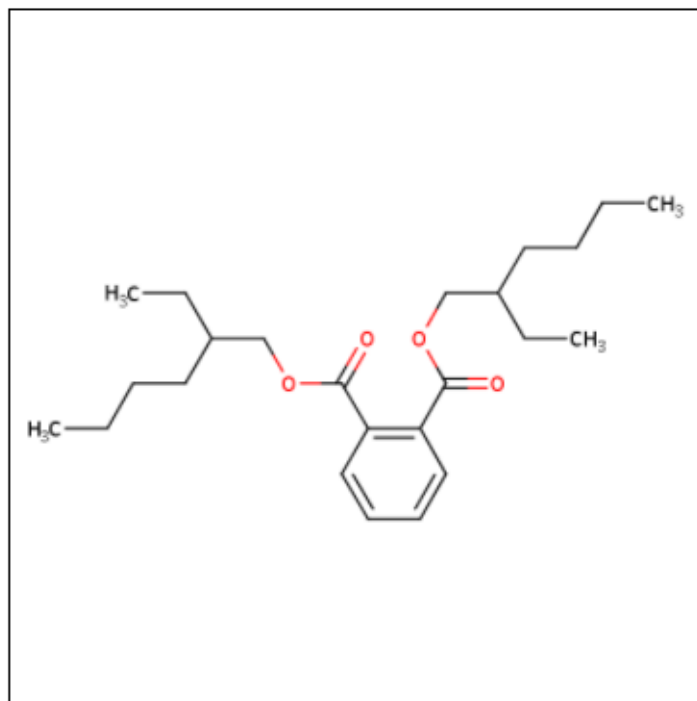
GenRA Tool in EPA CompTox Chemicals Dashboard



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

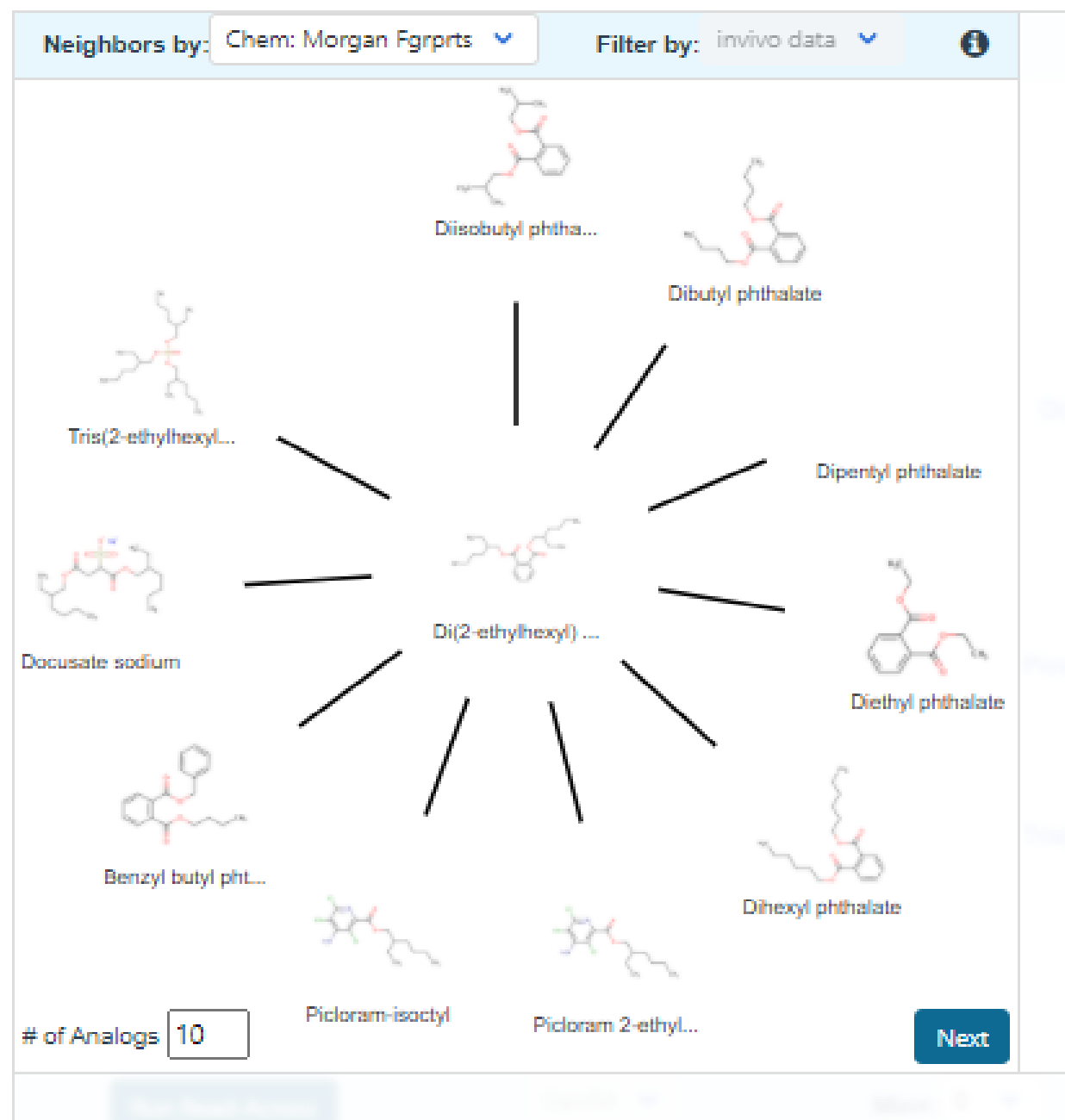
 **Molecular Formula:** $C_{24}H_{38}O_4$  [Mol File](#)  [Find All Chemicals](#)

 **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

EXECUTIVE SUMMARY

PROPERTIES

ENV. FATE/TRANSPORT

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BIOACTIVITY

TOXCAST: SUMMARY

EDSP21

TOXCAST/TOX21

PUBCHEM

TOXCAST: MODELS

[PUBCHEM](#) > [FORMALDEHYDE](#) > [BIOASSAY RESULTS](#)

BioAssay Results

466 items [View More Rows & Details](#)

[Download](#)

SORT BY [Activity Value](#)

Activity ?	Activity Value, μ M	Activity Type ?	Target Name	BioAssay Name	BioAssay AID	Substance SID
Inconclusive	28.6163	Potency		qHTS assay for small molecule disruptors of the mitochondrial membrane potential: Summary	720637	144212755
Inconclusive	28.6163	Potency		qHTS assay for small molecule disruptors of the mitochondrial membrane potential	720635	144212755
Inconclusive	71.8809	Potency		Human pregnane X receptor (PXR) small molecule agonists, qHTS cell viability counter screen	1346977	144212755
Active				DSSTox (CPDBAS) Carcinogenic Potency Database Salmonella Mutagenicity	1194	48413792
Active				DSSTox (CPDBAS) Carcinogenic Potency Database Summary Rat Bioassay Results	1208	48413792

1 2 3 ... 94 Next >

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 Shah², Antony J. Williams², Jeff Edwards², Jeremy Dunne² and Grace Patlewicz²

¹Oak Ridge Institute for Science and Education (ORISE), Oak Ridge, TN, USA; ²National 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 <i>Comput Toxicol.</i> 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

^aNational 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



Curve Surfer

PBPK

IVIVE

Chemical Characterization

Input

Results

Report an Issue



The Chemical Characterization tool allows you to view and compare one or two chemical lists based on their physicochemical properties. Comparisons are available in tabular format along with principal component analysis plots of list against subsets of the ICE chemical inventory.

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

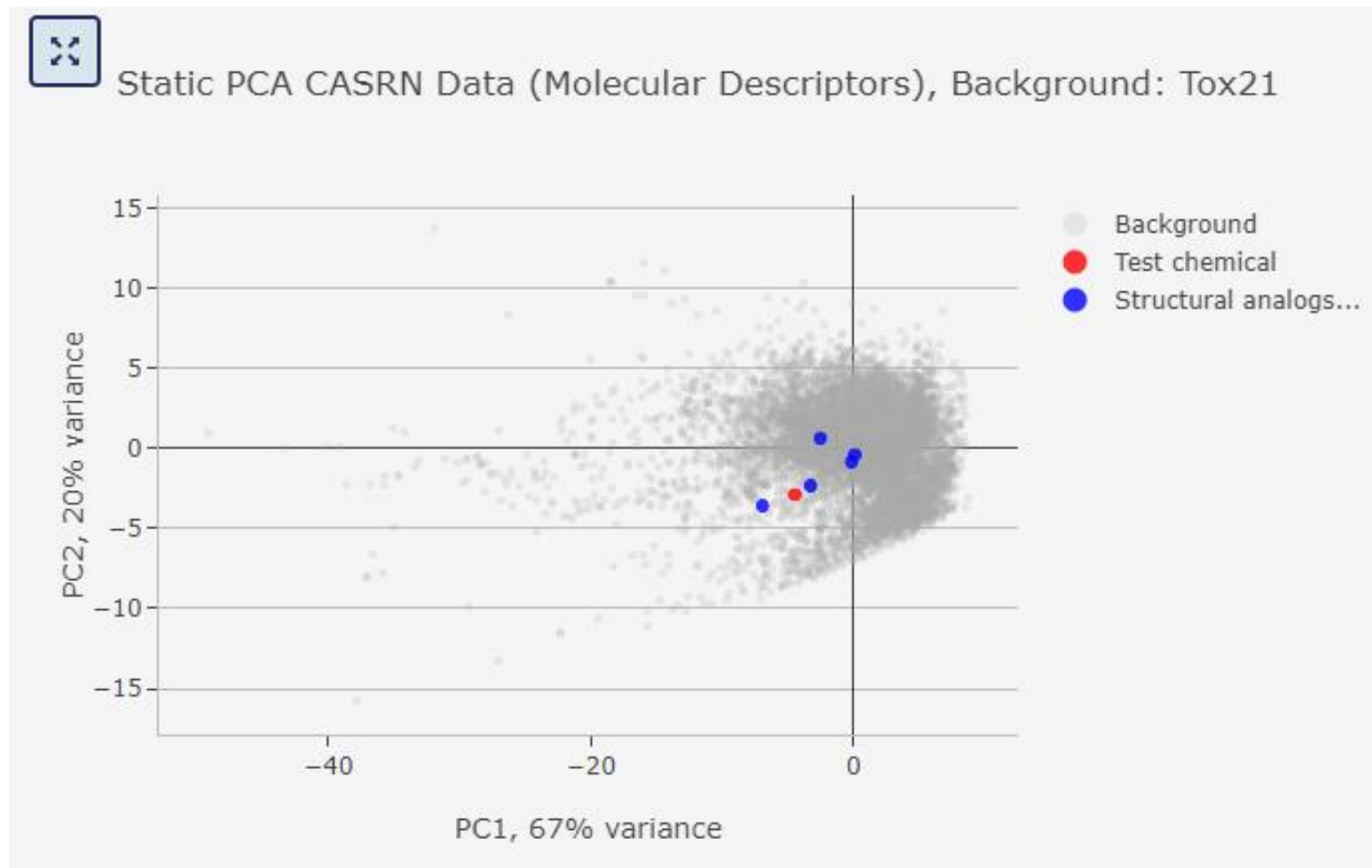
Shannon Bell ^a, Jaleh Abedini ^a, Patricia Ceger ^a, Xiaoqing Chang ^a, Bethany Cook ^a, Agnes L. Karmaus ^a, Isabel Lea ^{a,1}, Kamel Mansouri ^a, Jason Phillips ^b, Eric McAfee ^b, Ruhi Rai ^{a,2}, John Rooney ^a, Catherine Sprankle ^a, Arpit Tandon ^b, David Allen ^a, Warren Casey ^c, Nicole Kleinstreuer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

Example of using NTP ICE to identify structural analogs

Test chemical – Butyl-2-ethylhexyl phthalate

Structural analogs – series of phthalate esters

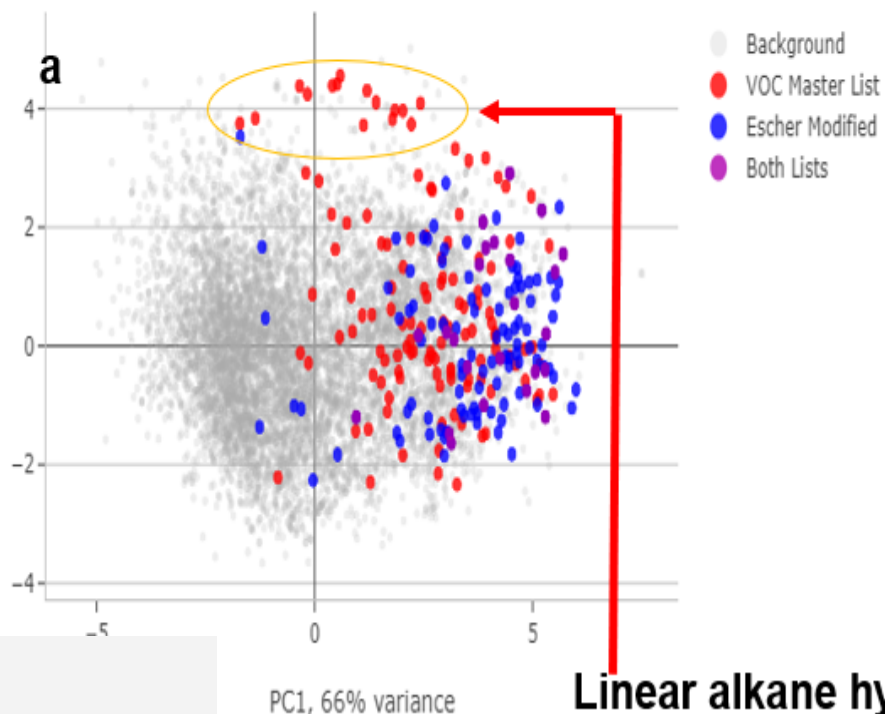
Use PCA feature in Chemical Characterization module to identify closest analogs on the basis of structure or physical-chemical properties



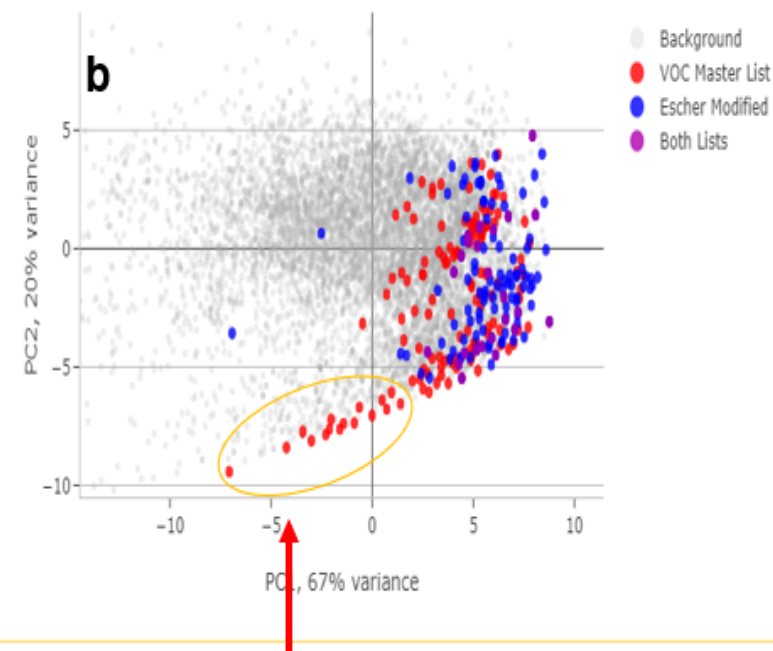
Use of NTP ICE to visually define chemical space

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

Returned CASRN PCA Data (Chemical Properties), Background: Tox21



Returned CASRN PCA Data (Molecular Descriptors), Background: Tox21



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



National Toxicology Program
U.S. Department of Health and Human Services

[Calendar & Events](#) | [News & Media](#) | [Get Involved](#) | [Support](#)

SEARCH



Integrated Chemical Environment

[HOME](#) | [SEARCH](#) | [TOOLS](#) | [DATA](#) ▾ | [ABOUT](#) ▾ | [HELP](#) ▾

News & Events

ICE v3.3 Release

ICE updates include:

New tools and expanded capabilities:

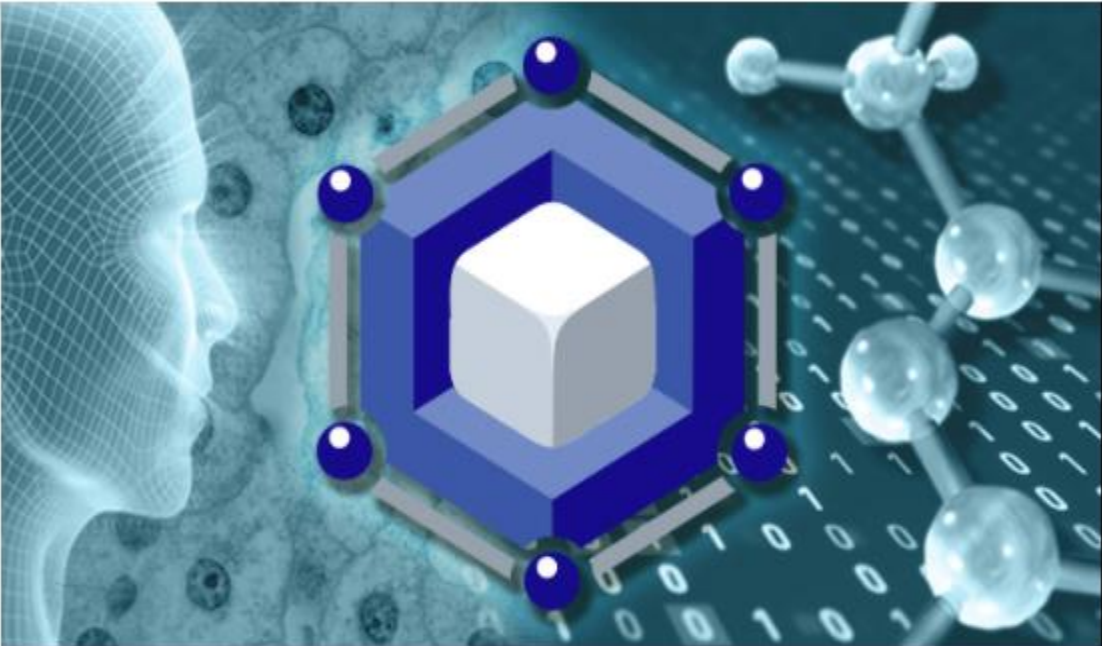
- Curve Surfer
- PBPK Modeling
- Consumer Use Explorer

Graphical visualizations of substance bioactivity in Search query results

User in vivo data upload in IVIVE tool

Learn about ICE updates

UPDATES



ICE provides data to support development of new approaches for chemical safety testing.

[Click here to learn more about ICE!](#)

PAUSE





Wiki

Backlogs

[Bug Backlog](#)

[Feature Requests](#)

Wiki

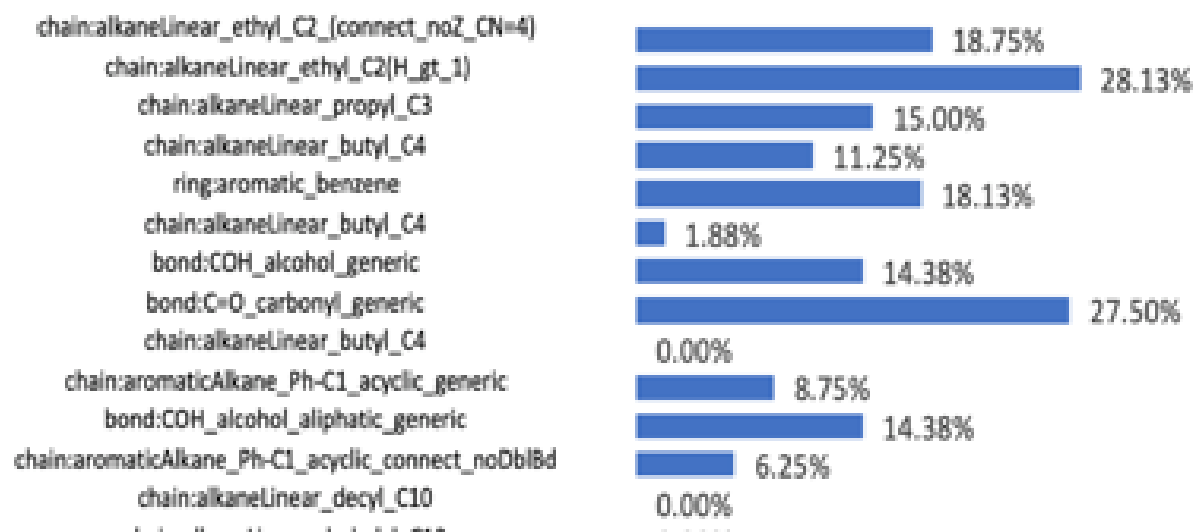
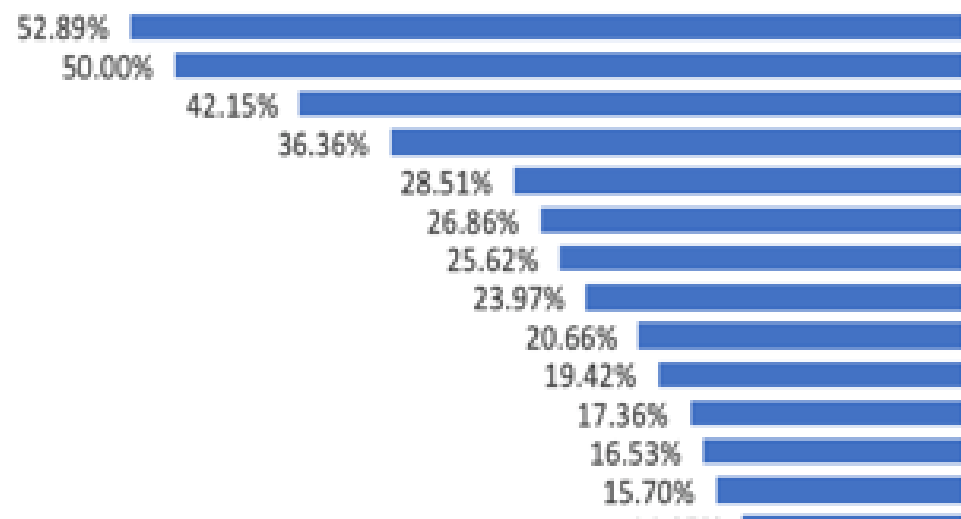
[Wiki Homepage](#)

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



Related Topics: [Predictive Models and Tools for Assessing Chemicals under the Toxic Substances Control Act \(TSCA\)](#)[CONTACT US](#)

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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)

1 Structures

1.1 2D Structure

Find Similar Structures

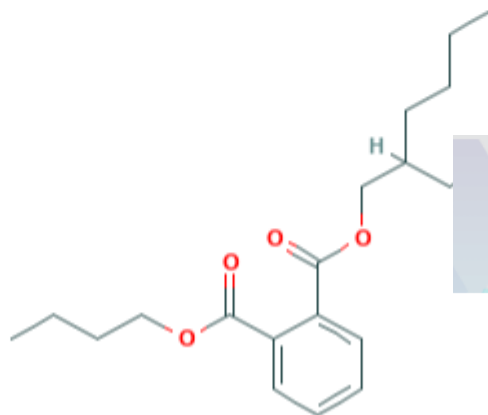


Get Image



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%.

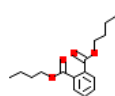
☐ Search All

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](#)

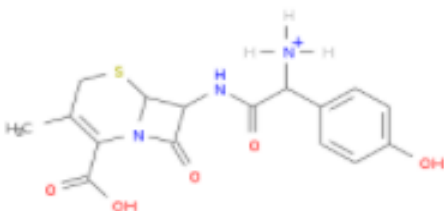
[Similarity Workbench](#)

Compound Similarity

Select two compounds to compare from the grid below.

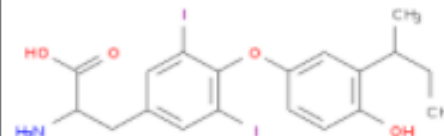
Selected Compounds

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 consider 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

Benchmark Dose Tools

CONTACT

BMDS 3.2 Released

Preview versions of the Bayesian continuous models -- plus user interface enhancements -- highlight this release. [Download](#) and [learn more](#) about this update.

 Bayesian BMD

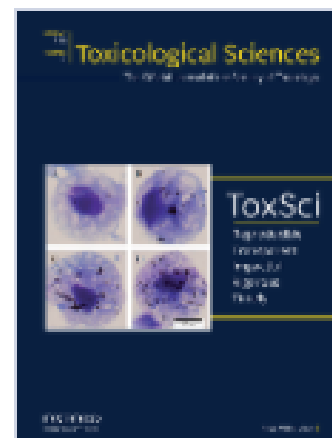
[Dashboard](#) [Help](#) [About](#) [Log In](#)



BAYESIAN BENCHMARK DOSE MODELING SYSTEM

Update to
BMD models

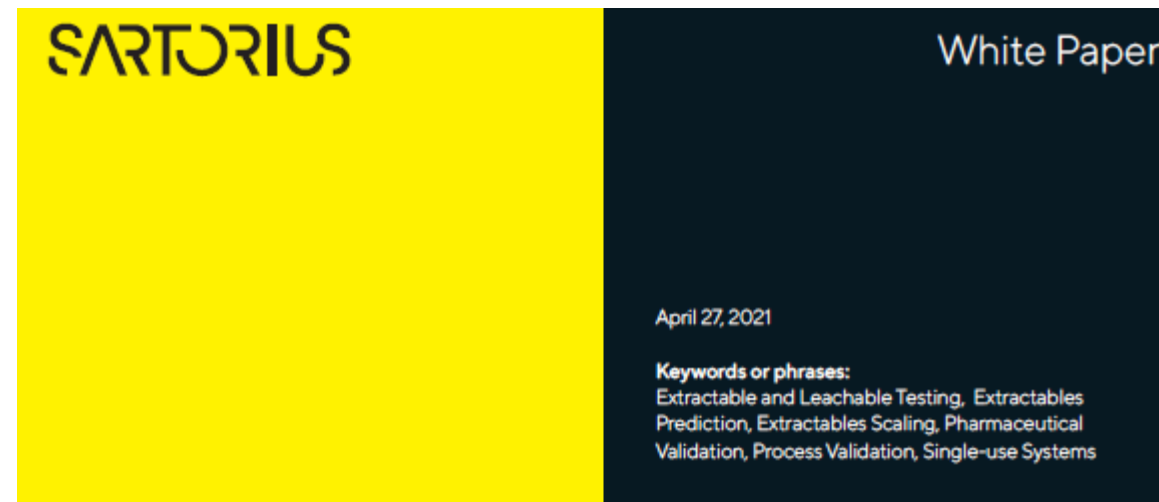
Exposure models



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,



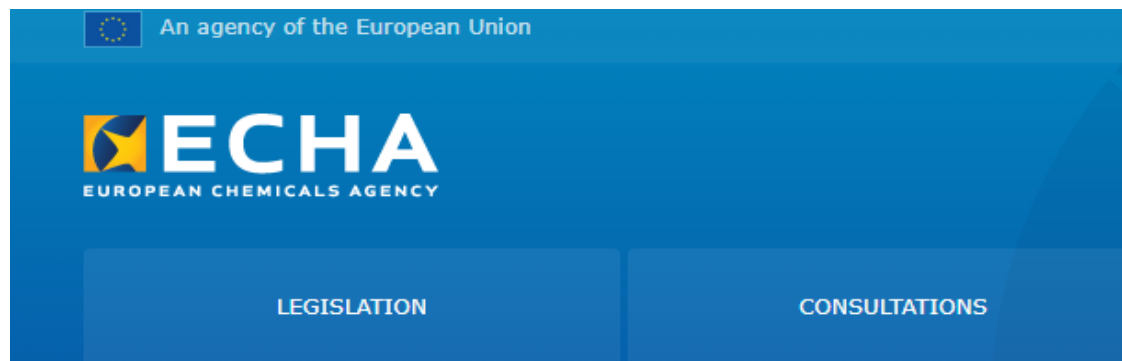
Sartorius Extractables Simulator: Simplifying E&L Through in-Silicio Modeling

Armin Hauk¹, Roberto Menzel¹, Ina Pahl¹, Sven Linz¹, Mehran Rafighi¹, Alexander Wildschütz², Stefan Baur²

¹Sartorius Stedim Biotech GmbH, August-Spindler-Strasse 11, 37079 Göttingen

²GWG | Max-Planck-Gesellschaft, Am Faßberg 11, 37077 Göttingen

Training Opportunities



[ECHA](#) > [Support](#) > [Webinars](#) > [All Webinars](#)

QSARs and their assessment under dossier evaluation

Webinar date

3 June 2021 11:00 - 12:30

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

<https://aim-hq.webex.com/recording/service/sites/aim-hq/recording/19dbaoa09ae11039bff800505681a6ea/playback>



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

TUTORIALS

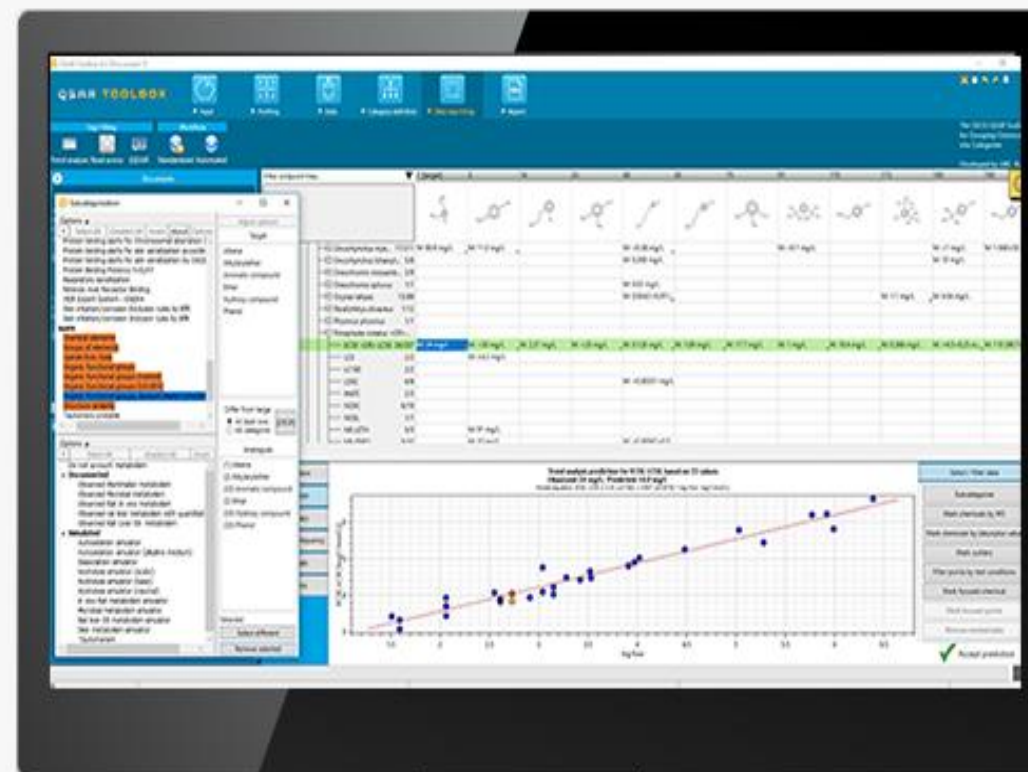
Webinar by OECD & ECHA: QSAR Toolbox Version 4.0 Features

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 2.1.3 (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

Chemical hazards data - OpenFoodTox

OpenFoodTox: chemical hazards database

an open-source database
of toxicological information



a "one-click" tool for risk assessors,
risk managers and stakeholders

OpenFoodTox provides chemical hazards data:



Use OpenFoodTox for



Looking up toxic
effects and safe levels
• from over 10,950 toxicity studies
• reference points
• reference values



information on chemical characterisation,
regulation, EFSA outputs, toxicity,
reference points (NOAEL, BMD, LD50, etc.) and
reference values (ADI, TDI, PNEC, etc.)*,
uncertainty factors, EFSA scientific outputs.



developing future methods and tools
as alternatives to animal testing

*reference points: No observed adverse effect level (NOAEL), benchmark dose (BMD), LD50, etc.
reference values: health-based guidance values such as acceptable/ tolerable daily intake (ADI/TDI), and environmental standards like predicted no effect concentration (PNEC)

Visit EFSA's Scientific Data Warehouse: <https://www.efsa.europa.eu/science/data>

 #efsaeuropa

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0000178-10-4444-000-10 | 04/11/2015/21/01 | TIR 02/2017/02/01/01



Computational Toxicology

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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

CARCINOGENICITY DATABASE



The Lhasa Carcinogenicity Database is a searchable repository of 7745 chronic-exposure carcinogenicity studies covering a total of 1726 chemicals. The database builds upon the work done between 1980 and 2005 by Lois Swirsky Gold and her team in creating the Carcinogenic Potency Database (CPDB). For further details, please see <https://files.toxplanet.com/cpdb/index.html>.

Some compounds from the CPDB dataset have been combined on inclusion in the Lhasa Carcinogenicity Database as they represent the same chemical active ingredient with differing formulations (for example at

I want to search by:

OTHER PARAMETERS

Chemical name, CAS, species, sex, Lhasa TD₅₀, tumour

Search on

Individual studies ▼

Type the chemical name or CAS number

Species

All species

Asian Musk Shrew

Bush Baby

Cynomolgus Monkey

Dog

Gerbil

Guinea Pig

Hamster

Mouse

Rabbit

Rat

Rhesus Monkey

Syrian Hamster

Tree Shrew

Sex

All

♀♂

Mixed

♀

Female

♂

Male

Lhasa TD₅₀ from

to

(mg/kg/day)

Tumour site

Tumour type



Datable

About

Select TTC Class (Raw SMILES)

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)



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}