FACULTY OF BIOSCIENCE ENGINEERING

Blue Growth Research Lab

In silico tools for screening of environmental hazard early in the drug development process

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Prof. Colin Janssen and Prof. Jana Asselman

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BGRL

EPI Suite™ – Estimation Program Interface

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EPI Suite™ overview

US-EPA

EPI SUITE™

Estimation Program Interface

Physical/chemical properties

Environmental fate/transport

Ecotoxicity

Predictive computerized models

Environmental risk assessment of new chemicals

- Used as a screening level predictive tool
- Screening chemicals for persistence and exposure potential
- Applied for chemicals when the measured values are absent

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QSARs available

Physical and chemical properties

KOWWIN™ – logKow
KOCWIN™ – Koc
KOAWIN™ – octanol–air partition coefficient
AOPWIN™ – atmospheric oxidation potential (rate)
HENRYWIN™ – Henry's Law constant
MPBPWIN™ – Melting point, boiling point, and vapor pressure
WSKOWWIN™ – water solubility based on logKow and structural correlation factor
WATERNT™ – water solubility based on fragment approach

US-EPA

EPI SUITE™

Estimation Program Interface

Ecotoxicity

ECOSAR: Ecological Structure Activity Relationship

Acute/chronic data for aquatic organisms

Fate/Transport

AEROWIN™ – atmospheric aerosol formation
BioHCwin – Biodegradation half-life of HC
BCFBAF™ – bioconcentration
HYDROWIN™– hydrolysis rate
BIOWIN™ – aerobic and anaerobic biodegradability
WVOLWIN™ – rate of volatilization from water
STPWIN™ – removal of a chemical in a sewage treatment plant
LEV3EPI™–partitioning of chemicals between air, soil, sediment, and water

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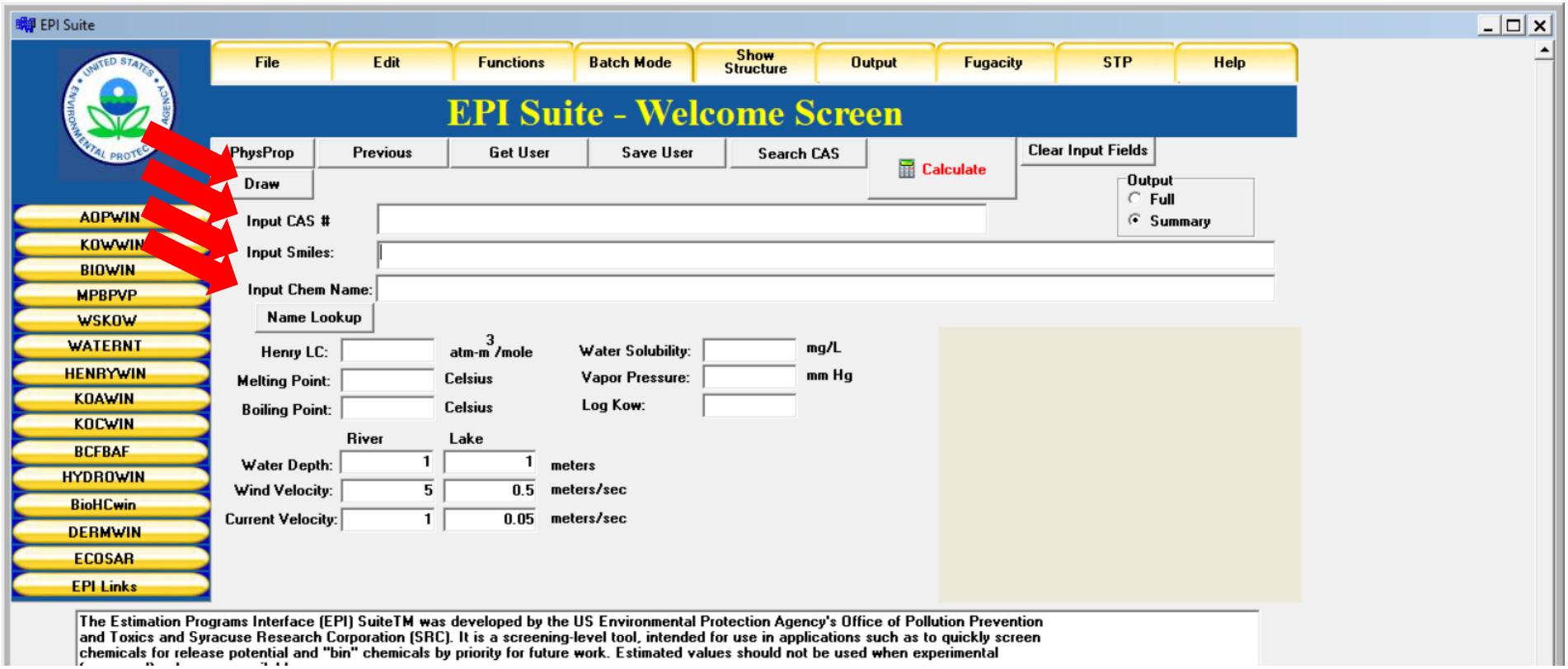
EPI Suite™ input



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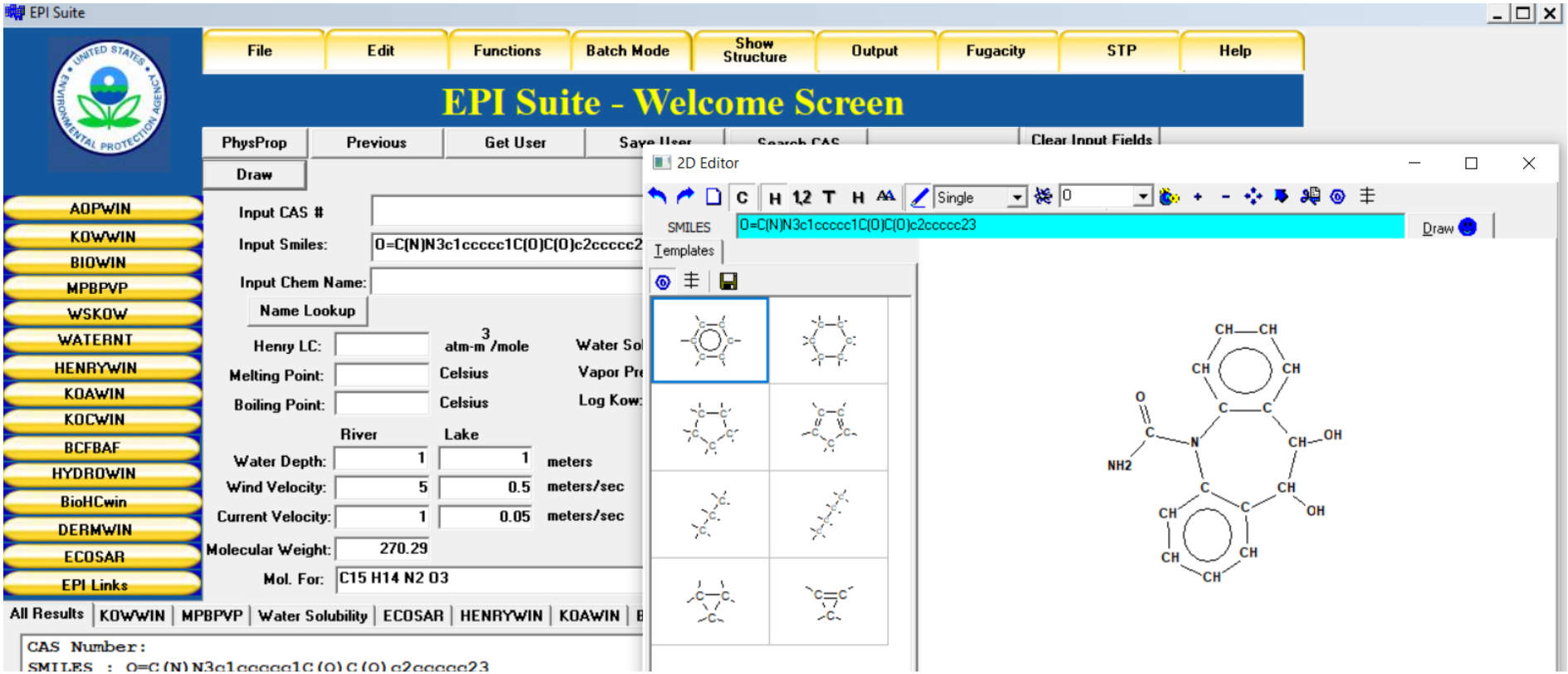
EPI Suite™ output



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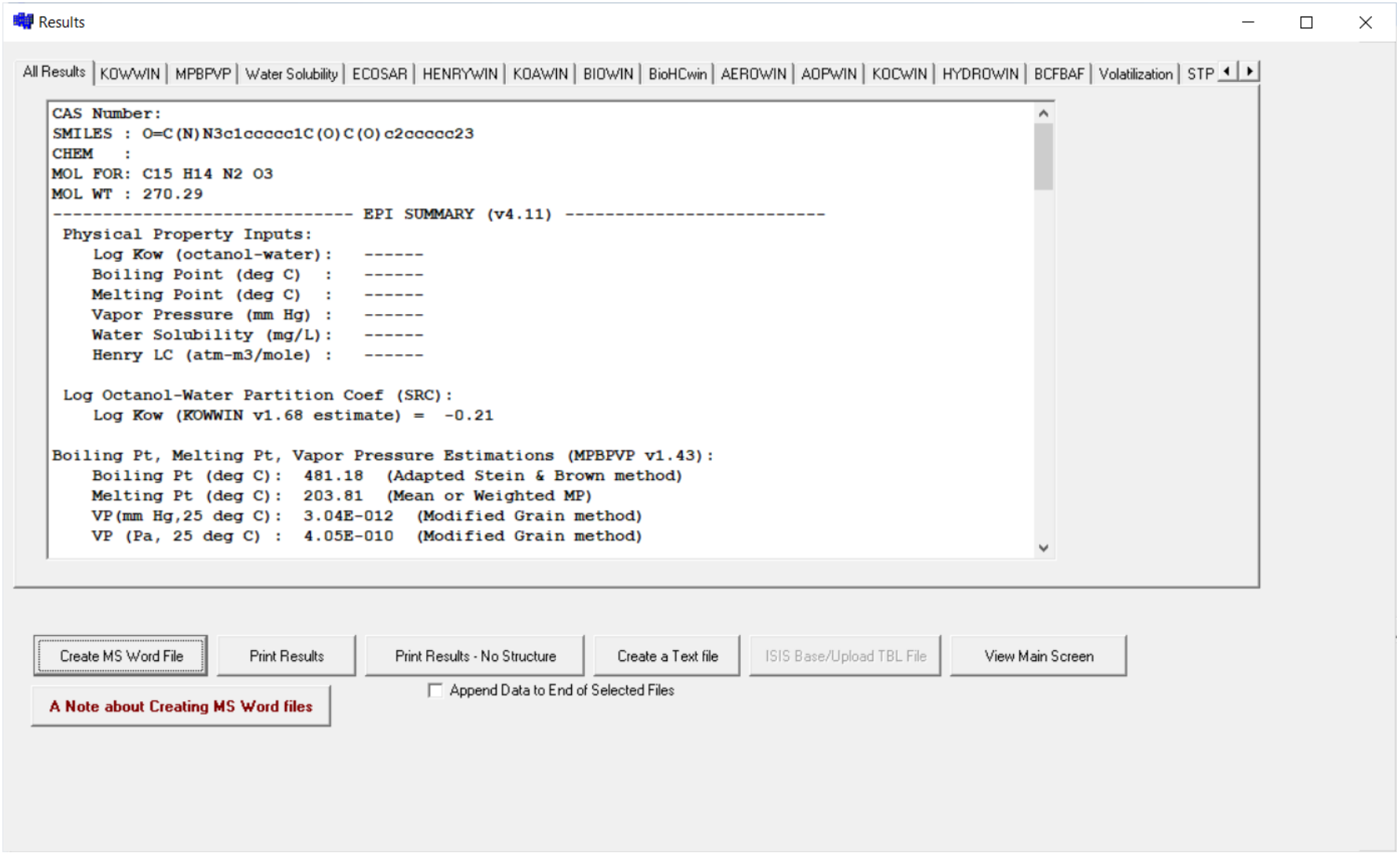
EPI Suite™ output



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EPI Suite™ - ECOSAR

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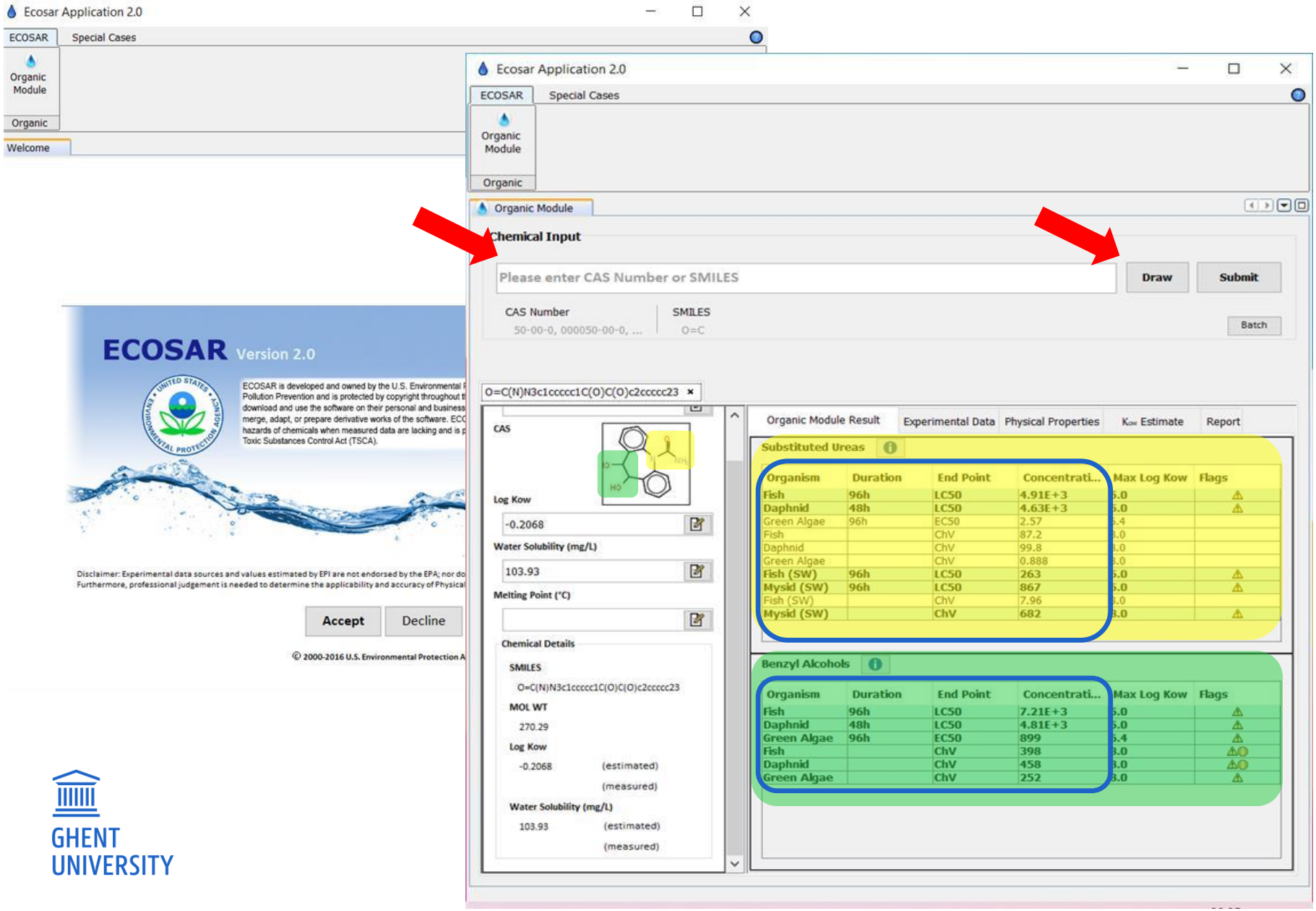
ECOSAR version 2.0



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ToxCast database

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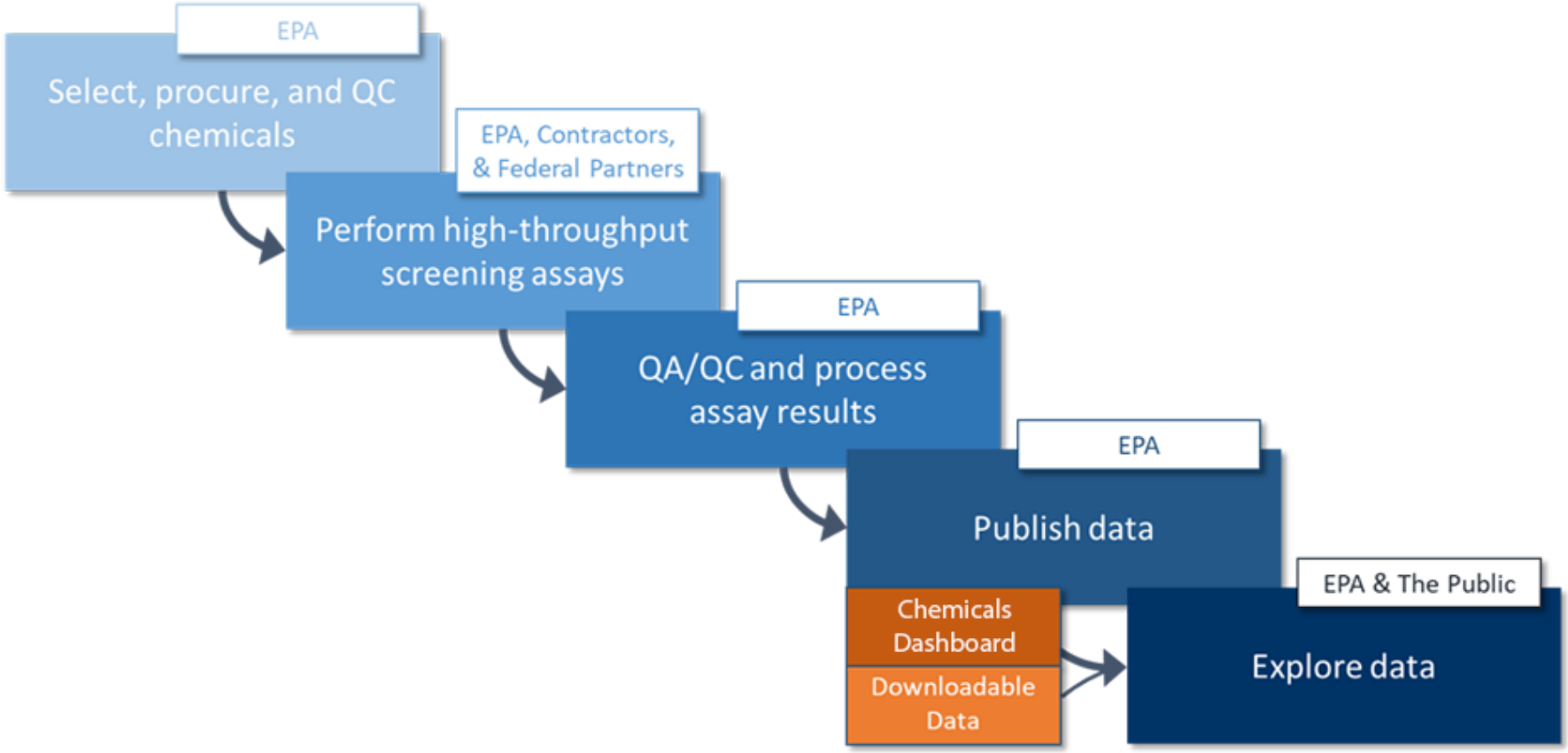
ToxCast high-throughput database



Potential applications include

- Indication of toxicity range - using similar chemicals
- Identification of most suitable assays
- Prioritization of chemicals for further testing

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ToxCast chemical selection criteria

Relevance

- Exposure potential
- Regulatory interest

Practical constrains

- Commercial availability
- DMSO solubility
- Volatility
- Chemical stability

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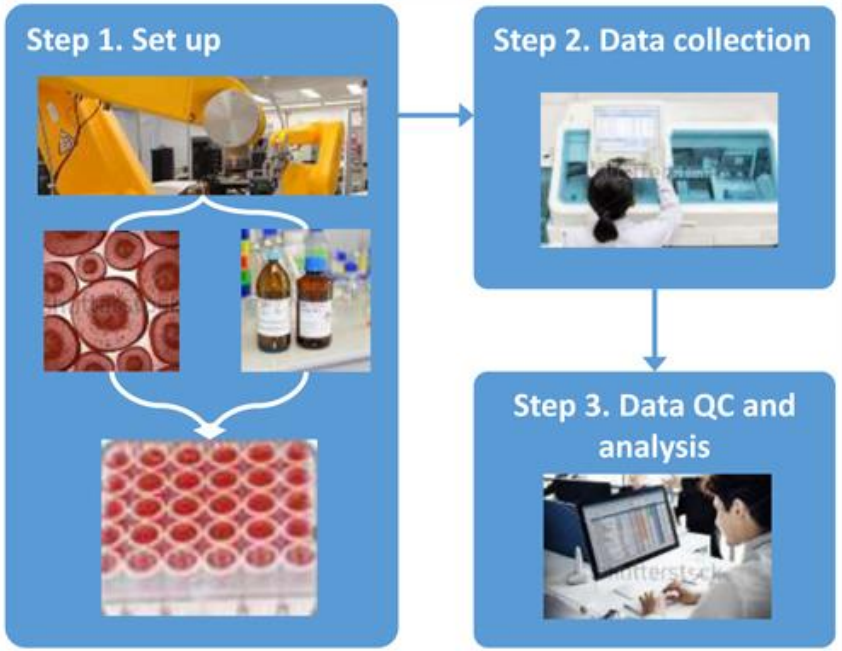
Generating ToxCast data



Step 1.
High-throughput technology set-up assays into plates with numerous wells (e.g. 384 well-plate)

Step 2.
Incubation, assay performance and data compilation

Step 3.
Quality control, normalization, analysis and formatting

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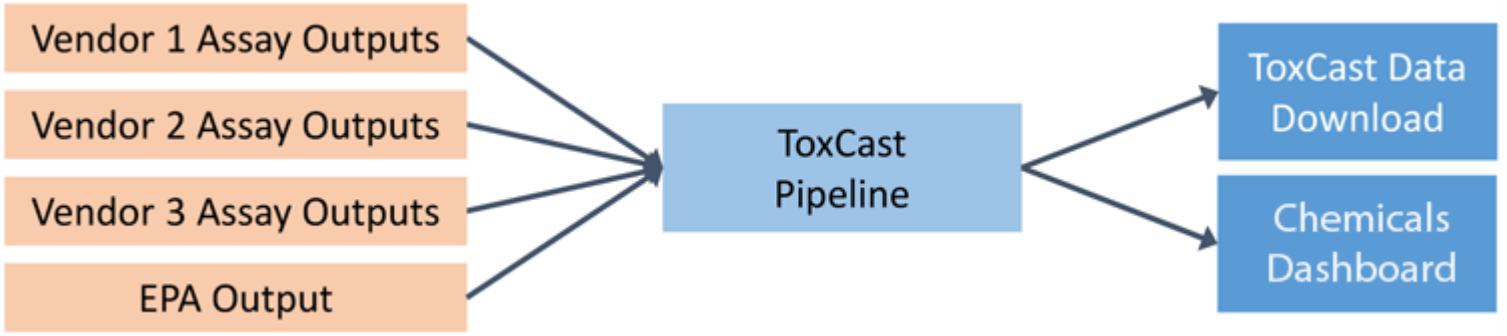
Data processing and analysis



- Data compilation from different sources in unique formats
- Data upload into ToxCast Pipeline for processing, modeling, inspection and visualization
- Final data made available for download and in the Chemicals Dashboard

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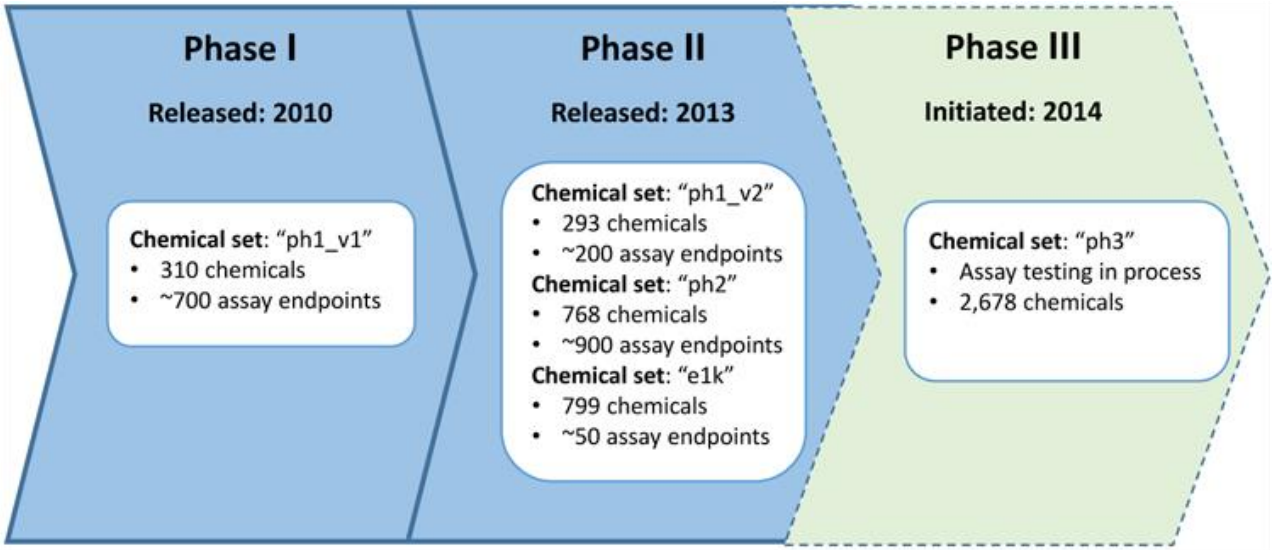
Publicly available data



- ToxCast has been developed in three distinct phases
- Currently data available for ~ 1800 chemicals and 700 assay endpoints
- Within Phase III 2678 more chemicals will be tested

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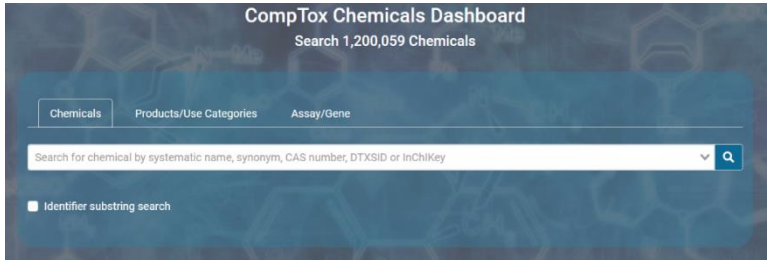
Accessing ToxCast data



https://comptox.epa.gov/dashboard/

https://epa.figshare.com/articles/dataset/ToxCast_Database_invitroDB_/6062623

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Accessing ToxCast data

Accession via

Chemical information

- systematic name
- synonym
- CASRN
- DTXSID – DSSTox substance identifier
- InChIKey – International Chemical Identifier

Assay/Gene information

- endpoint name
- target gene name or symbol

Data available on

tested assays – including assay details
target protein ID – connection to SeqAPASS
target gene ID
connection to AOP-Wiki
toxicity data expressed as AC50 (µM) - 50% of maximum activity

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SeqAPASS – Sequence Alignment to Predict Across Species Susceptibility

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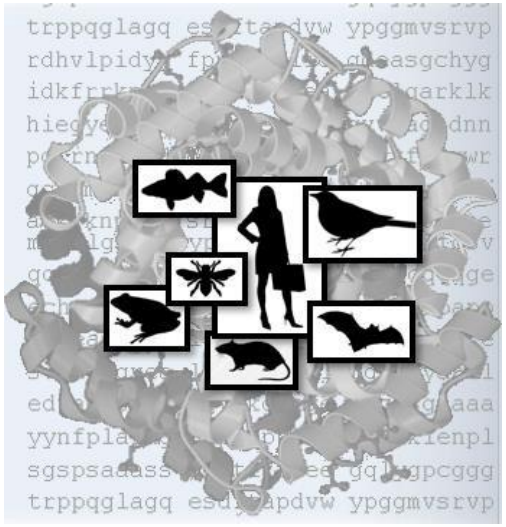
What is SeqAPASS?



Sequence **A**lignment to **P**redict **A**cross **S**pecies **S**usceptibility - **SeqAPASS**

Uses protein sequence alignment information

Evaluates sequence similarity across species

Predicts species susceptibility

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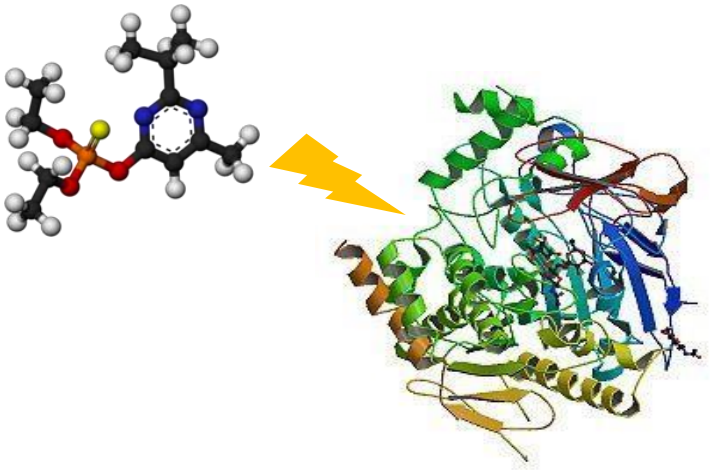
Required information



- Knowledge of sensitive or targeted species – targeted protein
- Protein sequence – e.g. NCBI

Sequence of chemical **molecular target** in **target species** → Compared to **millions of proteins** from **thousands of species**

Greater similarity = greater likelihood of chemical interaction

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Multi-level analysis

Level 1

Primary Amino Acid Sequence Alignments

Level 2

Conserved Functional Domain Alignments – e.g. DNA binding domain

Level 3

Critical Amino Acid Conservation

Gathers lines of evidence of protein conservation across species

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SeqAPASS output

- **Percent similarity** is quantified
- **Susceptibility cut-off** is estimated
- **Qualitative output (YES/NO)** based on protein conservation across different levels for various species

Common Name	Ortholog Candidate	Cut-off	Percent Similarity
Human	Y	33.15	100
Florida manatee	Y	33.15	98.8
Mallard	Y	33.15	82.29
Rock pigeon	Y	33.15	80.93
Green anole	Y	33.15	80.65
Pacific transparent sea squirt	Y	33.15	33.15
Yesso scallop	N	33.15	32.87
Purple sea urchin	N	33.15	26.05
Human whipworm	N	33.15	23.53
Bed bug	N	33.15	21.62

Lowest % Similarity that is still an ortholog

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Other interesting tools

- **OECD QSAR Toolbox - https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm**

- **VEGA QSAR - https://www.vegahub.eu/portfolio-item/vega-qsar/**

Both include human health hazard assessment

- **ECOdrug - https://ecodrug.org/**

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