Automated workflows for data curation and standardization of chemical structures for QSAR modeling

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

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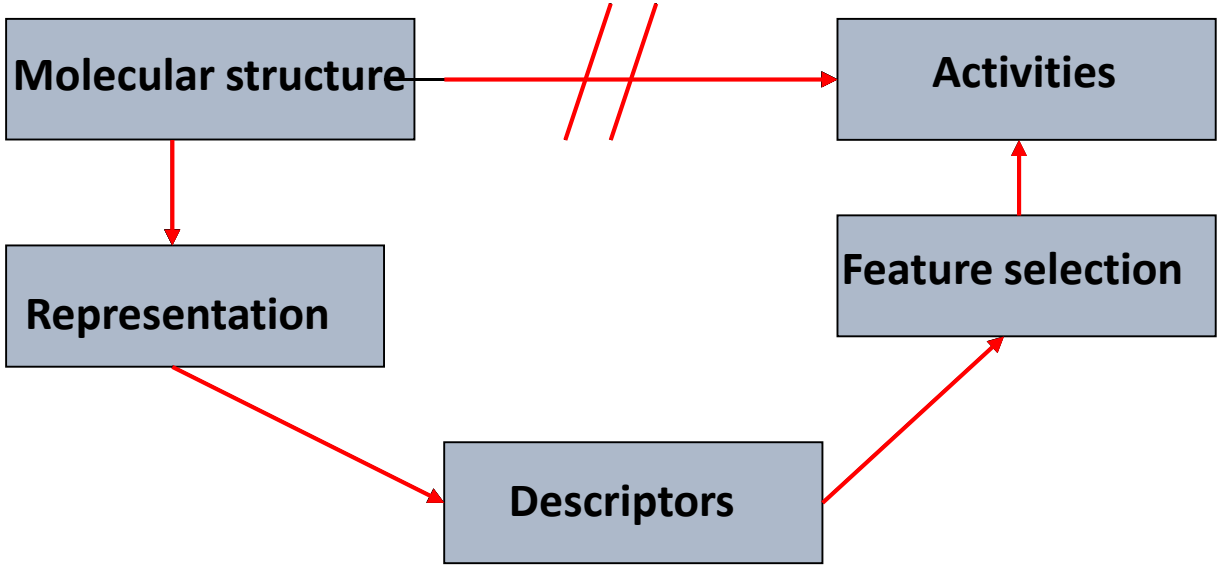
ScitoVation
INNOVATIVE CELL BASED SCIENCE
www.scitovation.com

Quantitative Structure Activity/Property Relationships (QSAR/QSPR)

QSARs correlate, within congeneric series of compounds, their chemical or biological activities, either with certain structural features or with atomic, group or molecular descriptors.

Katritzky, A. R.; Lobanov, V. S.; Karelson, M. Chem. Soc. Rev. ***1995****, 279-287*



Development of a QSAR model

- Curation of experimental data
- **Generation of QSAR-ready structures**
- Preparation of training and test sets
- Calculation of an initial set of descriptors
- Selection of a mathematical method
- Variable selection technique
- Validation of the model's predictive ability
- Define the Applicability Domain

Chemical structures online

ChemSpider
The free chemical database
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chemexper.com
Enter a name, molecular formula, cas number, InChI, InChIKey or SMILES
Search

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Revision 7464 by midnighter checked in on 2012-05-29 19:03:16. Built from
Online chemical database
with modeling environment
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PHYSPROP Data: Available from:

http://esc.syrres.com/interkow/EpiSuiteData.htm

EPI Suite Data

The downloaded files are provided in "zip" format ... the downloaded file must be "un-zipped" with common utility programs such as WinZip.

Basic Instructions:

(1) Download the zip file
(2) Un-Zip the file

WSKOWWIN Program Methodology & Validation Documents (includes Training & Validation datasets) - Download file is: WSKOWWIN_Datasets.zip (180 KB)

Click here to download WSKOWWIN_Datasets.zip

WATERNT (Water Solubility Fragment) Program Methodology & Validation Documents (includes Training & Validation datasets) - Download file is: WaterFragmentDataFiles.zip (511 KB)

Click here to download WaterFragmentDataFiles.zip

MPBPWIN (Melting Pt, Boiling Pt, Vapor Pressure) Program Test Sets - Download file is: MP-BP-VP-TestSets.zip (1983 KB)

Click here to download MP-BP-VP-TestSets.zip

BCFBAF Excel spreadsheets of BCF and kM data used in training & validation ... (includes the Jon Arnot Source BCF DB with multiple BCF values) - Download file is: Data_for_BCFBAF.zip (1.4 MB)

Click here to download Data_for_BCFBAF.zip

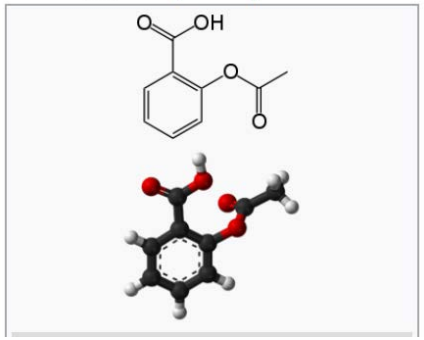
HENRYWIN Data files used in training & validation ... (includes Meylan and Howard (1991) Data document) - Download file is: HENRYWIN_Data_EPI.zip (531 K)

Click here to download HENRYWIN_Data_EPI.zip

- Water solubility
- Melting Point
- Boiling Point
- LogP (KOWWIN: Octanol-water partition coefficient)
- Atmospheric Hydroxylation Rate
- LogBCF (Bioconcentration Factor)
- Biodegradation Half-life
- Ready biodegradability
- Henry's Law Constant
- Fish Biotransformation Half-life
- LogKOA (Octanol/Air Partition Coefficient)
- LogKOC (Soil Adsorption Coefficient)
- Vapor Pressure

Chemical Identifiers

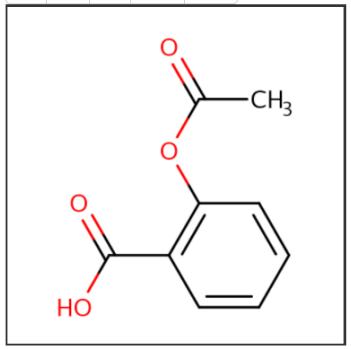
- CAS Registry Number
- Names:
  - IUPAC
  - Commercial
  - Synonyms…
- SMILES
- InChI
- InChI keys
- …



Identifiers		
IUPAC name		[show]
CAS Number	50-78-2 ✓	
PubChem CID	2244	
IUPHAR/BPS	4139	
DrugBank	DB00945 ✓	
ChemSpider	2157 ✓	
UNII	R16CO5Y76E	
KEGG	D00109 ✓	
ChEBI	CHEBI:15365 ✓	
ChEMBL	CHEMBL25 ✓	
PDB ligand	AIN (PDBe, RCSB PDB)	
ECHA InfoCard	100.000.059	

Aspirin
50-78-2 | DTXSID5020108

Searched by Approved Name: Found 1 result for 'Aspirin'.



Wikipedia

Intrinsic Properties

Structural Identifiers

IUPAC Name: 2-(Acetyloxy)benzoic acid

SMILES: CC(=O)OC1=C(C=CC=C1)C(O)=O

InChI String: InChI=1S/C9H8O4/c1-6(10)13-8-5-3-2-4-7(8)9(11)12/h2-5H,1H3,(H,11,12)

InChIKey: BSYNRYMUTXBXSQ-UHFFFAOYSA-N

Search Google for: Structural Skeleton | Full Structure

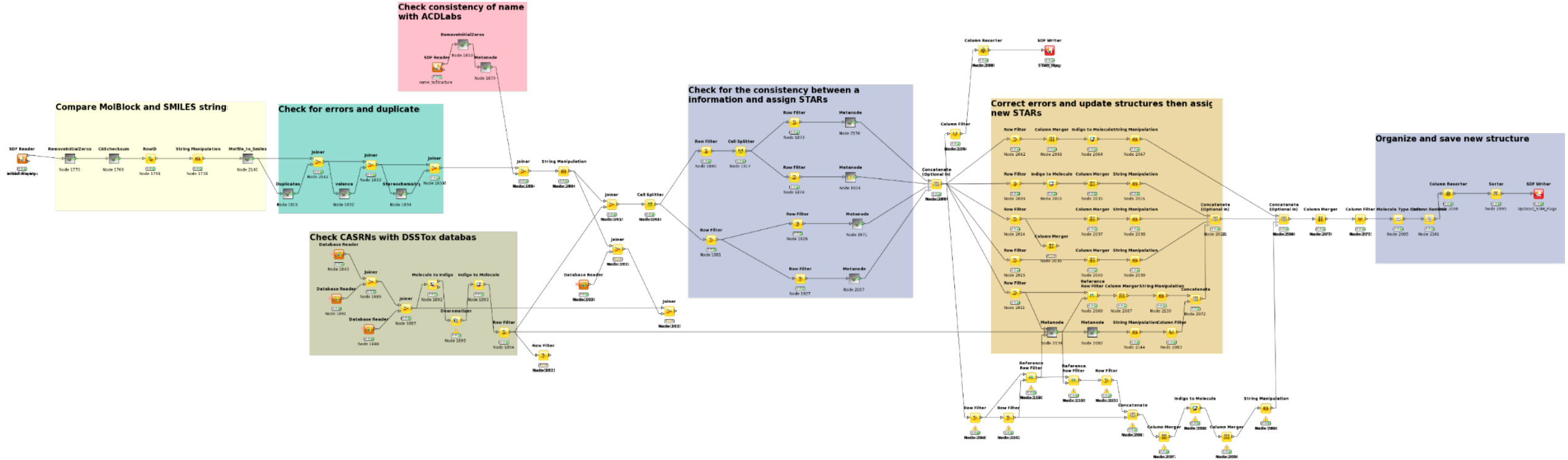
Copy All

The Approach

- To build models we need the set of chemicals and their property series

- Our curation process
  - Decide on the "chemical" by checking levels of consistency
  - We did NOT validate each measured property value
  - Perform initial analysis manually to understand how to clean the data (chemical structure and ID)
  - Automate the process (and test iteratively)
  - Process all datasets using final method

KNIME Workflow to Evaluate the Dataset



Mansouri et al. (https://www.tandfonline.com/doi/abs/10.1080/1062936X.2016.1253611)

The InChI Identifier

- Unique code managed by IUPAC: No variability as with SMILES
- InChI Strings can be reversed to structures: same as with SMILES
- Adopted by the community (databases, blogs, Wikipedia): good for searching the internet

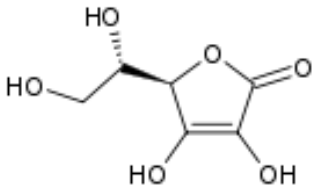
International Chemical Identifier

From Wikipedia, the free encyclopedia
(Redirected from InChI)

The **IUPAC International Chemical Identifier** (**InChI**, pronounced "INchee") is a textual identifier for chemical substances, designed to provide a standard and human-readable way to encode molecular information and to facilitate the search for such information in databases and on the web. Developed by IUPAC and NIST during 2000-2005, the format and algorithms are non-proprietary and the software is freely available under the open source LGPL license (though the term "InChI" is a trademark of IUPAC).[1]

CH_3CH_2OH
ethanol

`InChI=1/C2H6O/c1-2-3/h3H,2H2,1H3`



L-ascorbic acid

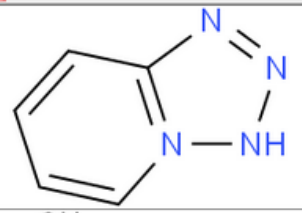
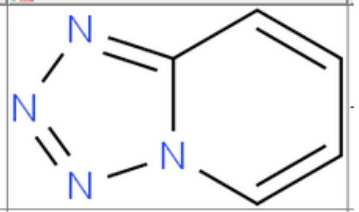
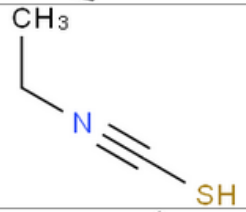
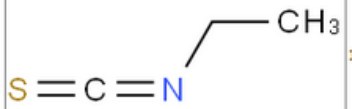
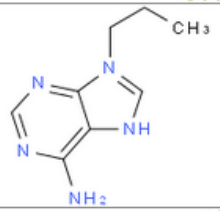
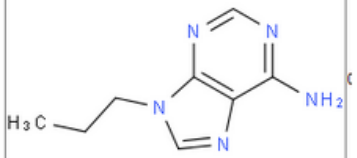
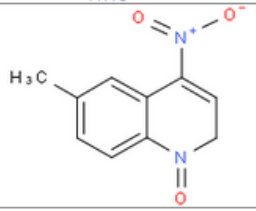
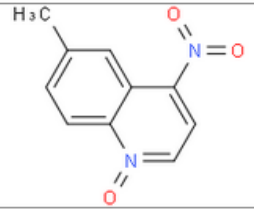
`InChI=1/C6H8O6/c7-1-2(8)5-3(9)4(10)6(11)12-5/h2,5,7-10H,1H2/t2-,5+/m0/s1`

LogP dataset: 15,809 chemicals (structures)

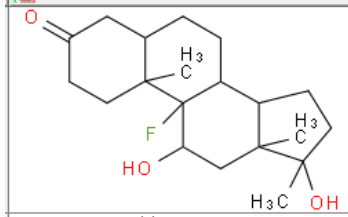
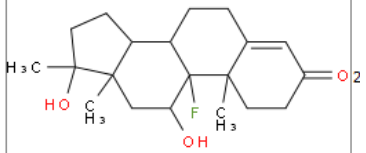
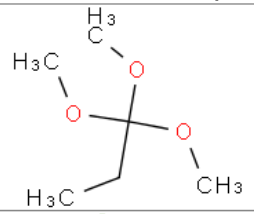
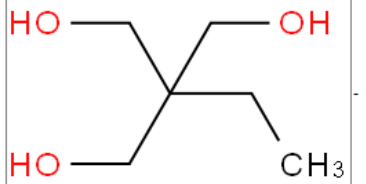
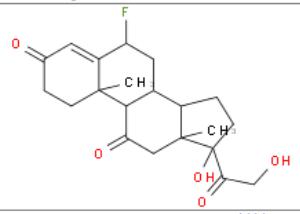
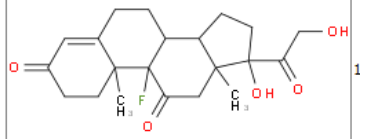
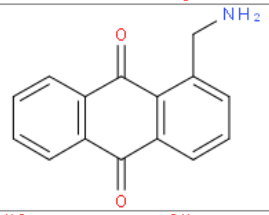
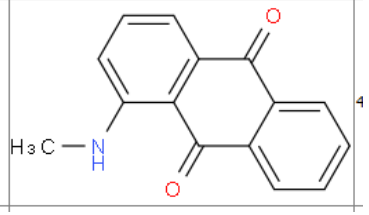
- CAS Checksum: 12163 valid, 3646 invalid **(>23%)**
- Invalid names: 555
- Invalid SMILES 133
- Valence errors: 322 Molfile, 3782 SMILES **(>24%)**
- Duplicates check:
  - 31 DUPLICATE MOLFILES
  - 626 DUPLICATE SMILES
  - 531 DUPLICATE NAMES
- SMILES vs. Molfiles (structure check)
  - 1279 differ in stereochemistry **(~8%)**
  - 362 “Covalent Halogens”
  - 191 differ as tautomers
  - 436 are different compounds **(~3%)**

Examples of Errors

Valence Errors

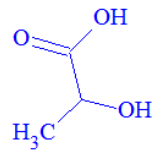
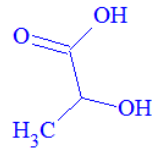
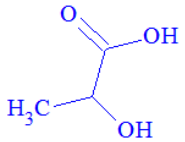
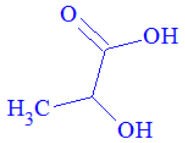
Mol Block	CAS	NAME	Smiles
	000274-87-3	TETRAZOLO[1,5-A]PYRIDINE	
	000542-85-8	ETHYL ISOTHIOCYANATE	
	000707-98-2	9-PROPYL ADENINE	
	000715-48-0	6-METHYL-4-NITROQUINOLINE-1-OXIDE	

Different Compounds

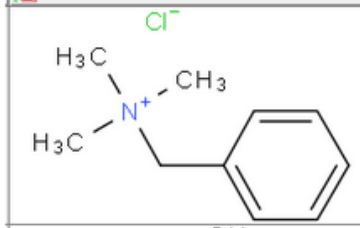
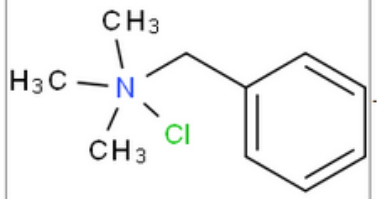
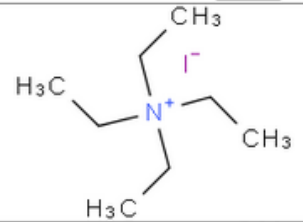
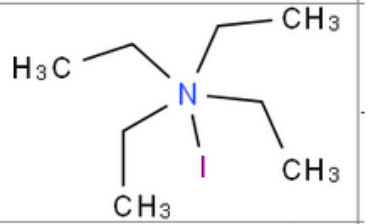
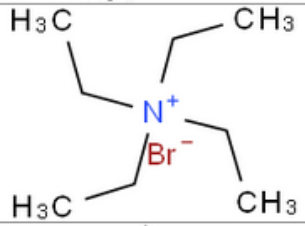
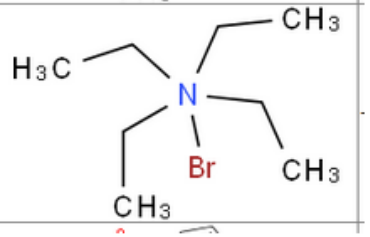
Mol Block	CAS	NAME	Smiles
	000076-43-7	FLUOXYMESTERONE	
	000077-99-6	1,1,1-TRIS(HYDROXYMETHYL)PROPANE	
	000079-60-7	CORTISONE-9A-FLUORO	
	000082-38-2	DISPERSE RED 9	

Examples of Errors

Duplicate Structures

Structure	Formula	FW	CAS	NAME	MP	EstMP	ErrorMP
	$C_3H_6O_3$	90.0779	000050-21-5	LACTIC ACID	1.6800000000000000e+001	2.2660000000000000e+001	5.8600000000000000e+000
	$C_3H_6O_3$	90.0779	000079-33-4	L-LACTIC ACID	5.3000000000000000e+001	2.2660000000000000e+001	-3.034000000000000e+001
	$C_3H_6O_3$	90.0779	000598-82-3	A-HYDROXYPROPIONIC ACID	1.8000000000000000e+001	2.2660000000000000e+001	4.6600000000000000e+000
	$C_3H_6O_3$	90.0779	010326-41-7	D-LACTIC ACID	5.2800000000000000e+001	2.2660000000000000e+001	-3.014000000000000e+001

Covalent Halogens

Mol Block	CAS	NAME	Smiles
	000056-93-9	BENZYL TRIMETHYL AMMONIUM CHLORIDE	
	000068-05-3	TETRAETHYL AMMONIUM IODIDE	
	000071-91-0	TETRAETHYL AMMONIUM BROMIDE	

Other issues

Invalid CASRNs

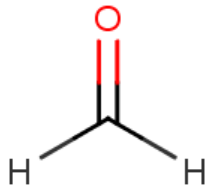
Truncated names

Missing SMILES

SRC000-02-7	Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propen
SRC000-04-3	Guanidine, N-hydroxy-N''-[4-(methylthio)benzeneme
SRC000-04-4	Hydrazinecarboximidamide, N'-[4-(methylthio)benz
SRC000-04-5	NNN5-TeMe-N-(3FuranMe),ammon Br
SRC000-04-6	Benzenamine, 4-bromo-N,N-bis(2,2,2-trifluoroethy
SRC000-04-7	2-Propenoic acid, 3-(2-chlorophenoxy)-, methyl e
SRC000-05-1	9H-Purine-9-acetaldehyde, a-(1-formyl-2-hydroxye
SRC000-05-2	N1-Pr-N2-CN-N3-Me guanidine
SRC000-05-3	1-(2-OHEt)-2-Me imidazoline HCL
SRC000-06-3	Propanoic acid, 3-[[(4-cyanophenyl)methyl]seleno

Data Files & Quality flags

- The data files have **FOUR** representations of a chemical, plus the property value.

SDF Molecule	Mol Mol Block	S Smiles	S CAS	S NAME	D Kow
-ISIS- 09141018452D 4 3 0 0 0 0 0 0 0 0999 V2000 2.4667 -0.0833 0.0000 O 0 0 ... 2.4667 -0.9125 0.0000 C 0 0 ... 1.7500 -1.3292 0.0000 H 0 0 ... 3.1833 -1.3292 0.0000 H 0 0 ... 2 1 2 0 0 0 0 3 2 1 0 0 0 0 4 2 1 0 0 0 0 M END > <CAS> (000050-00-0) 000050-00-0 > <NAME> (000050-00-0) FORMALDEHYDE > <Kow> (000050-00-0) 3.500000000000000e-001		O=C	000050-00-0	FORMALDEHYDE	0.35

4 levels of consistency exists among:

- The Molblock
- The SMILES string
- The chemical name (based on ACD/Labs dictionary)
- The CAS Number (based on a DSSTox lookup)

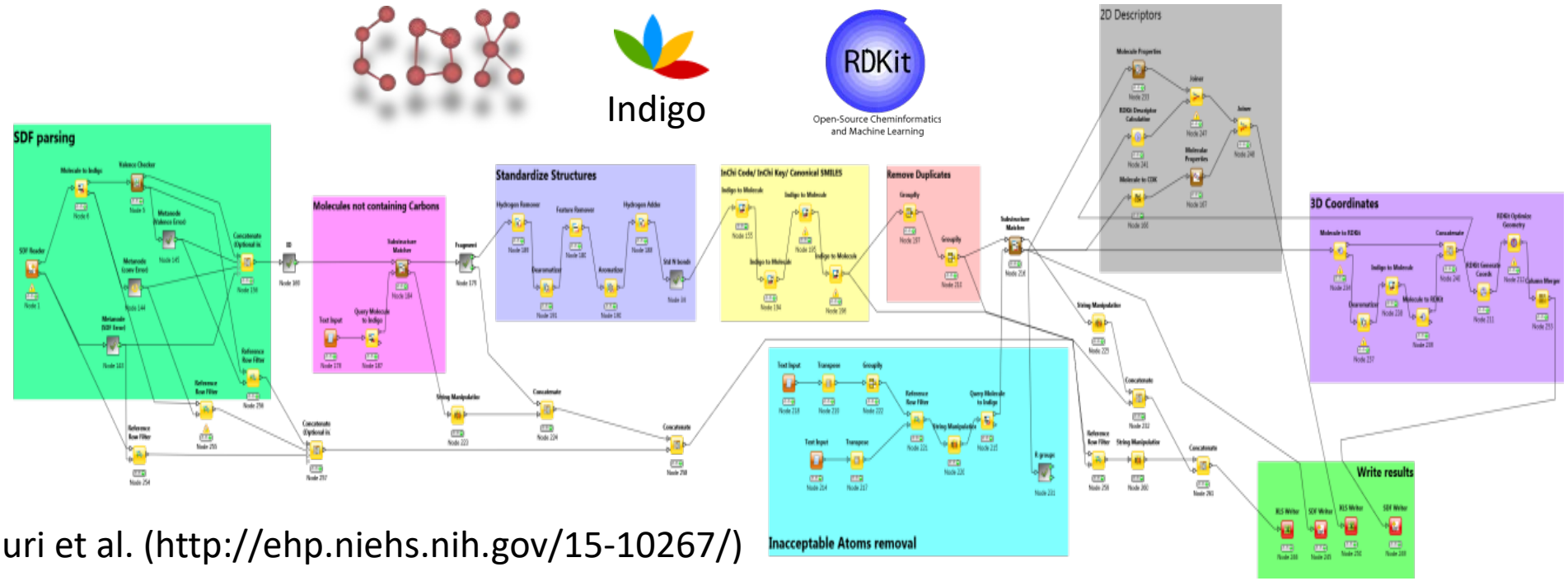
http://esc.syrres.com/interkow/EpiSuiteData.htm

Quality FLAGS and curated structures

QSAR-ready KNIME workflow

Aim of the workflow:

- Combine standardization procedures
- Minimize the differences between the structures used for prediction
- Produce a flexible free and open source workflow to be shared

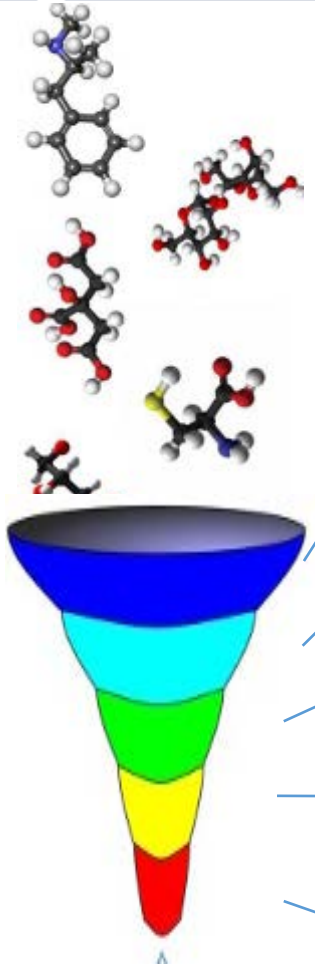


Mansouri et al. (http://ehp.niehs.nih.gov/15-10267/)

Standardization steps

Initial structures

Structure standardization



QSAR-ready structures

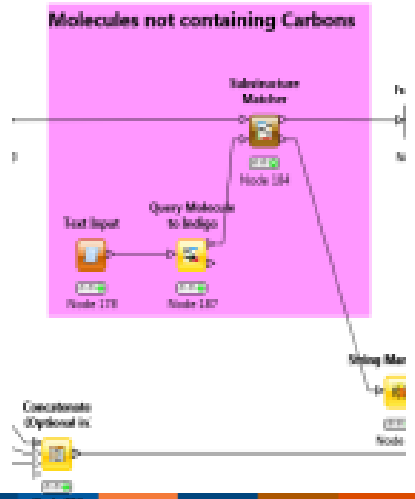
- Removal of inorganics and mixtures
- Cleaning salts and counter ions
- Normalization of tautomers
- Removal of duplicates
- Final inspection

Parsing and 1st filter

SDF Parser: original structures

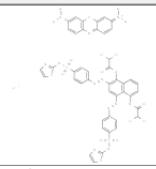
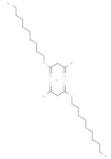
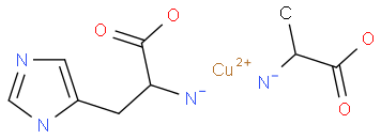
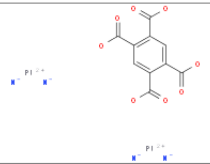
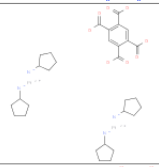
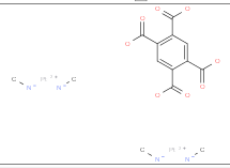
(Webservices: Pubchem, Chemspider)

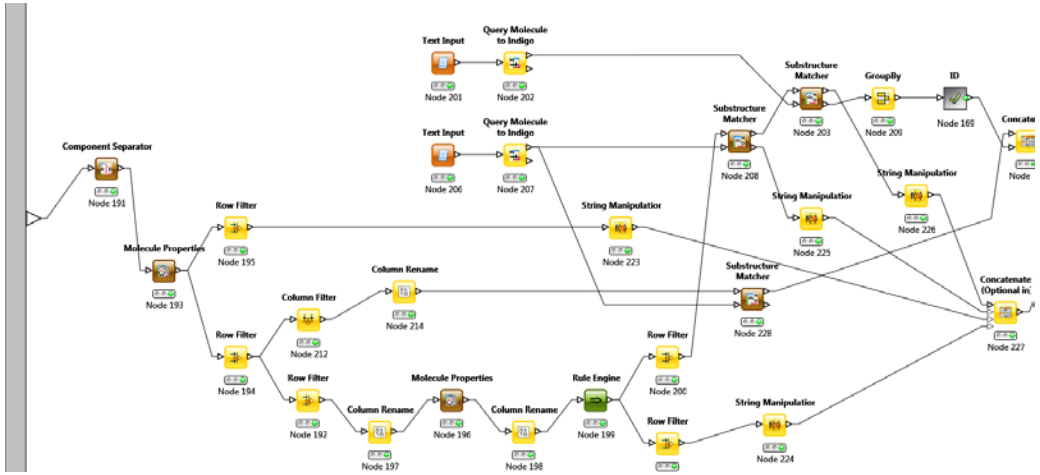
parsed compounds
Unique IDs



Errors reported

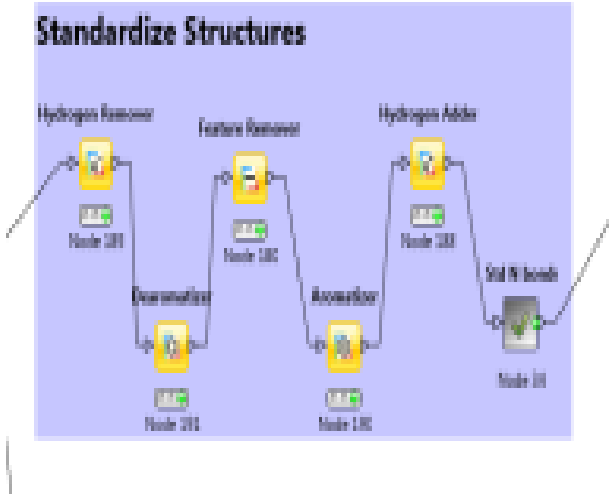
Unconnected structures (salts, solvents, mixtures)

Mol Block	gsid	dsstox_subs...	casrn	preferred_name
	639220	DTXSID70639220	74352-04-8	7-(Dimethylamino)...
	639221	DTXSID30639221	22757-23-9	PUBCHEM_24198890
	639250	DTXSID20639250	73655-89-7	Copper(2+) 1-carb...
	639266	DTXSID30639266	82422-15-9	Platinum(2+) azani...
	639267	DTXSID90639267	82422-14-8	Platinum(2+) cyclo...
	639268	DTXSID50639268	82422-13-7	Platinum(2+) meth...



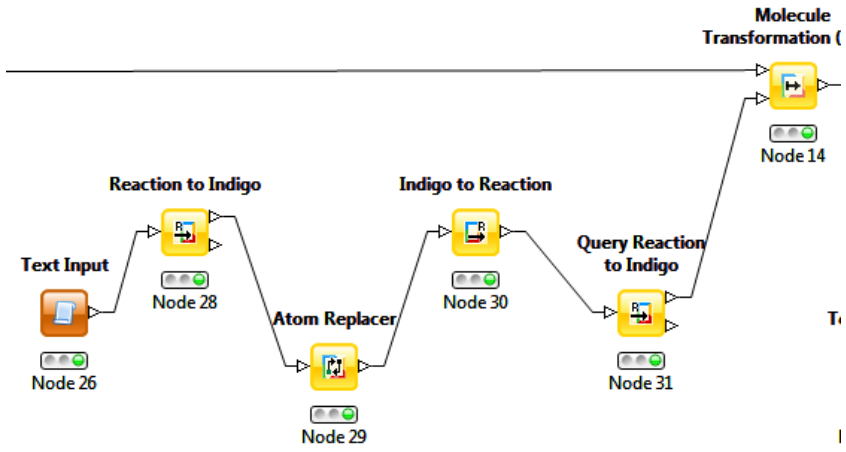
Standardization of structures

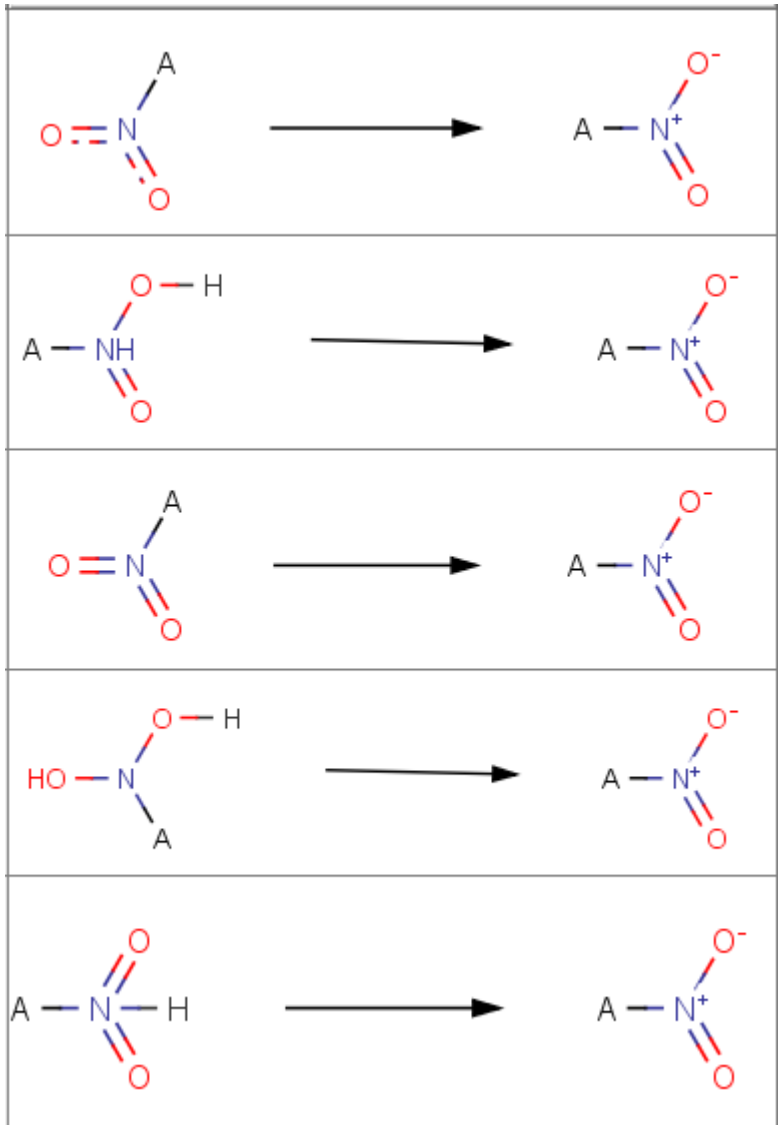
- Explicit hydrogen removed
- Dearomatization
- Removal of chirality/stereochemistry info, isotopes and pseudo-atoms
- Aromatization + add explicit hydrogen atoms
- Standardize Nitro groups
- Other: tautomerize/mesomerize
- Neutralize (when possible)



Standardize Nitro mesomers

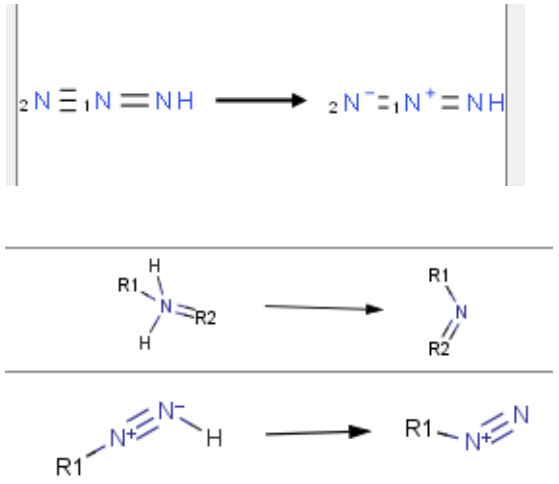
SMARTS query to reaction

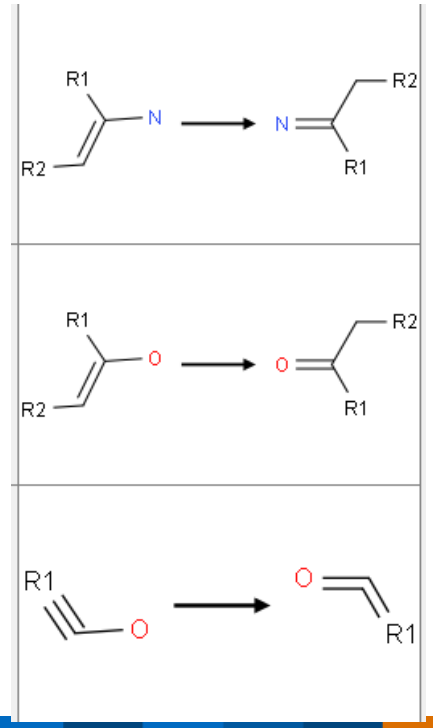


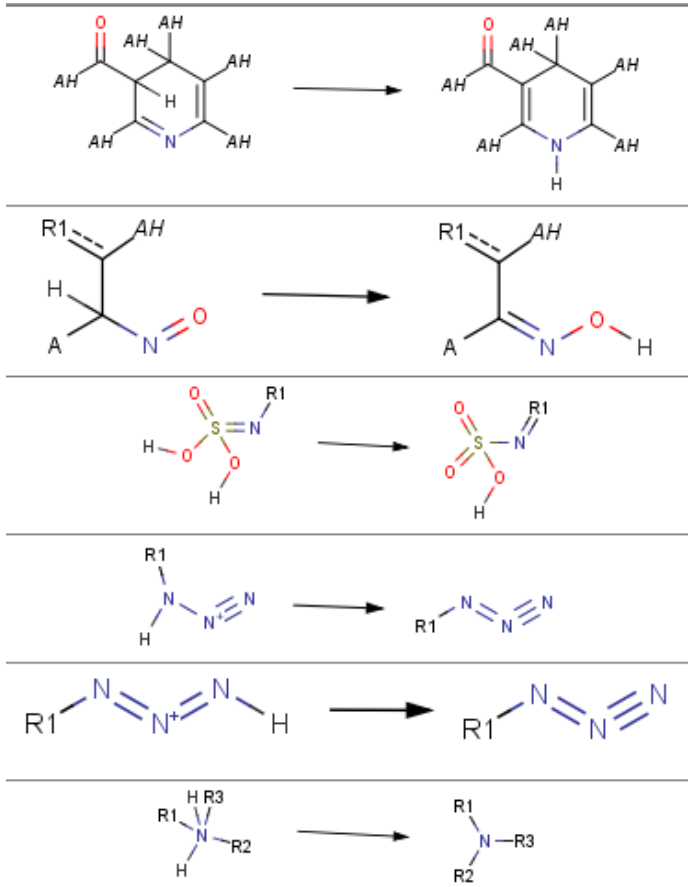


Mesomerization/tautomerization

- Azide mesomers
- Exo-enol tautomers
- Enamine-Imine tautomers
- Ynol-ketene tautomers
- ....



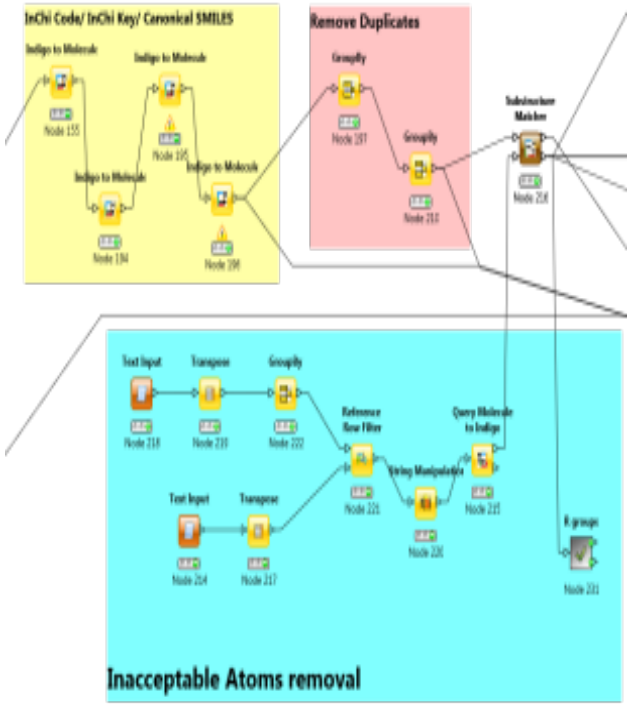




Neutralize Structures

Filter metalorganics

- Generate InChI, InChI Key and Canonical Smiles.
- Remove duplicates (InChIs & canonical SMI)
- Remove molecules with atoms. Other then:
  H, C, N, O, P, S, Se, F, Cl, Br, I, Li, Na, K, B, Si

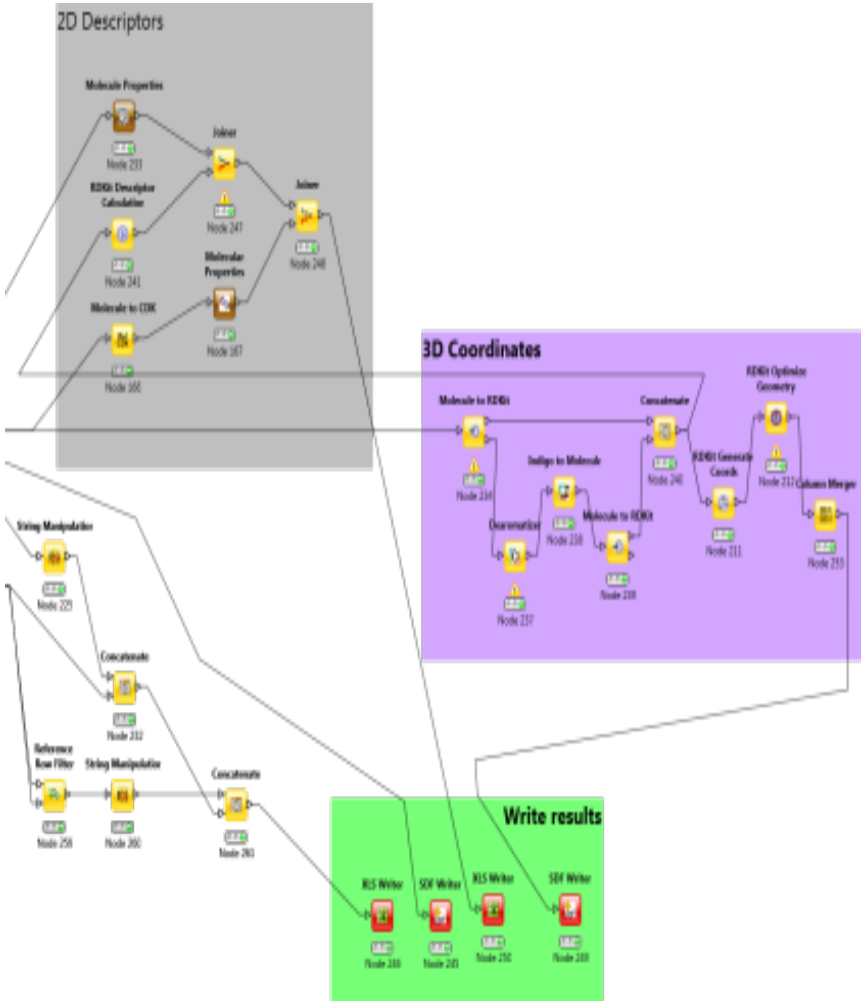


Write results

- Calculate 2D descriptors (Indigo, CDK, RDKit)
- Generate 3D conformers
- Optimize geometry (MMFF94S)

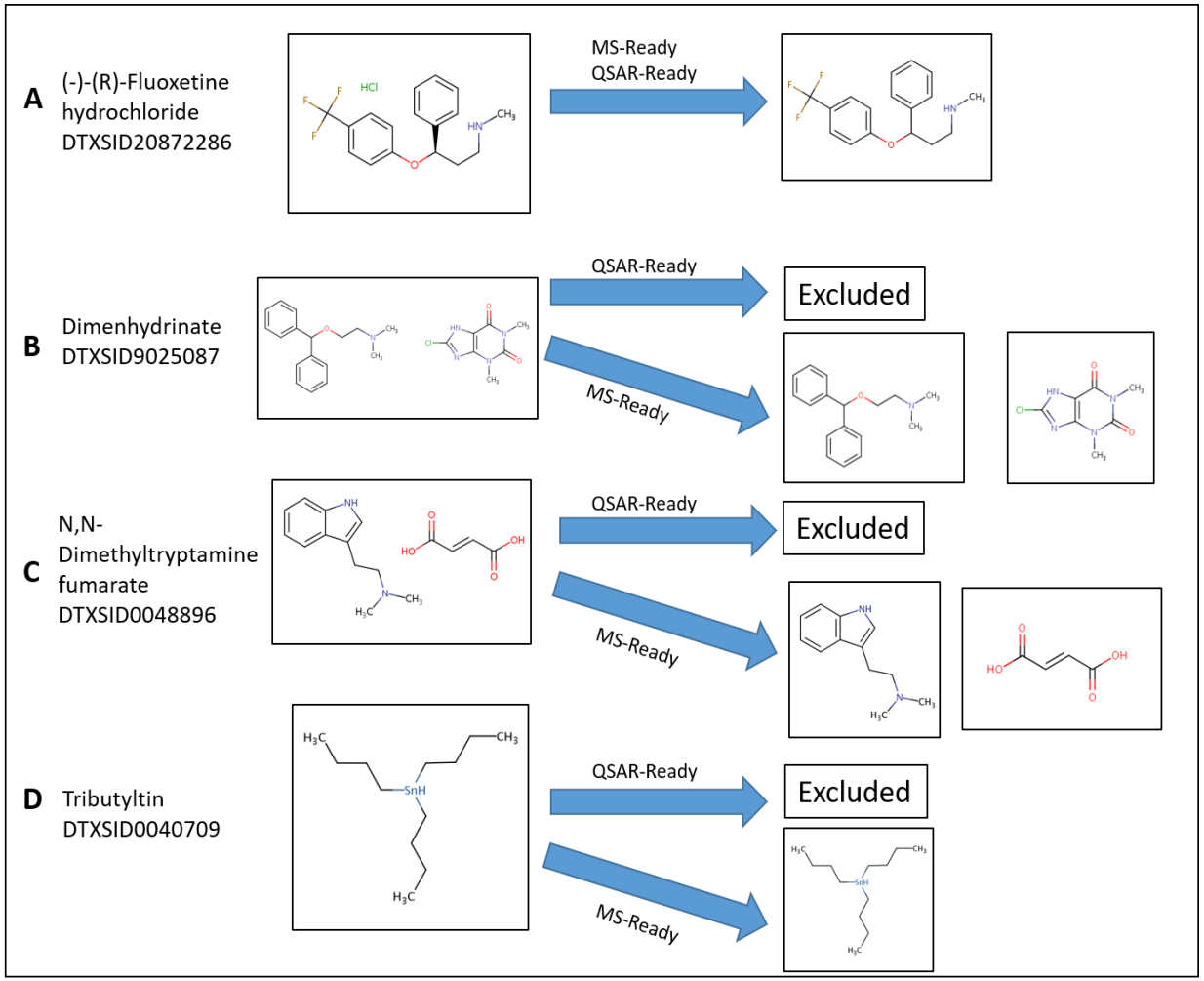
<u>Generated files:</u>

- Sdf file containing the 2D structures
- Excel file containing 2D descriptors
- Sdf file containing the 3D structures
- Excel file for error messages

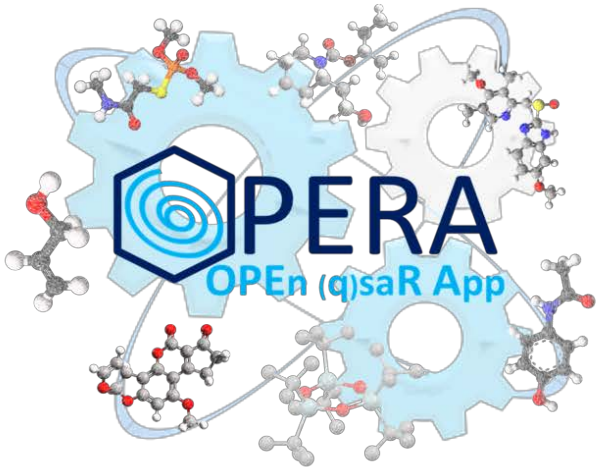


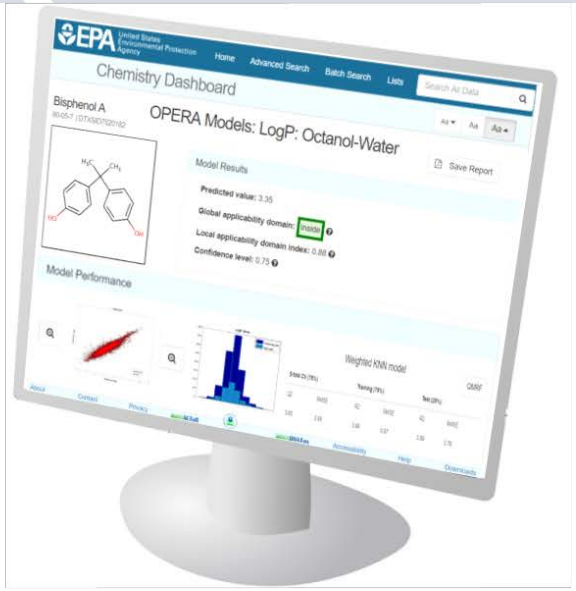
“MS-Ready” structures

- The related QSAR-Ready workflow was modified to produce an MS-ready workflow



Applications: OPERA models, Endocrine disruption screening…





Mansouri et al. OPERA models. (https://link.springer.com/article/10.1186/s13321-018-0263-1)

CERAPP

Collaborative Estrogen Receptor Activity Prediction Project

Mansouri et al. (http://ehp.niehs.nih.gov/15-10267/)

CoMPARA

Collaborative **M**odeling **P**roject for **A**ndrogen **R**eceptor **A**ctivity

Mansouri et al. (https://www.researchgate.net/profile/Mansouri_Kamel)

Thank you for your attention

Question OR Comment