

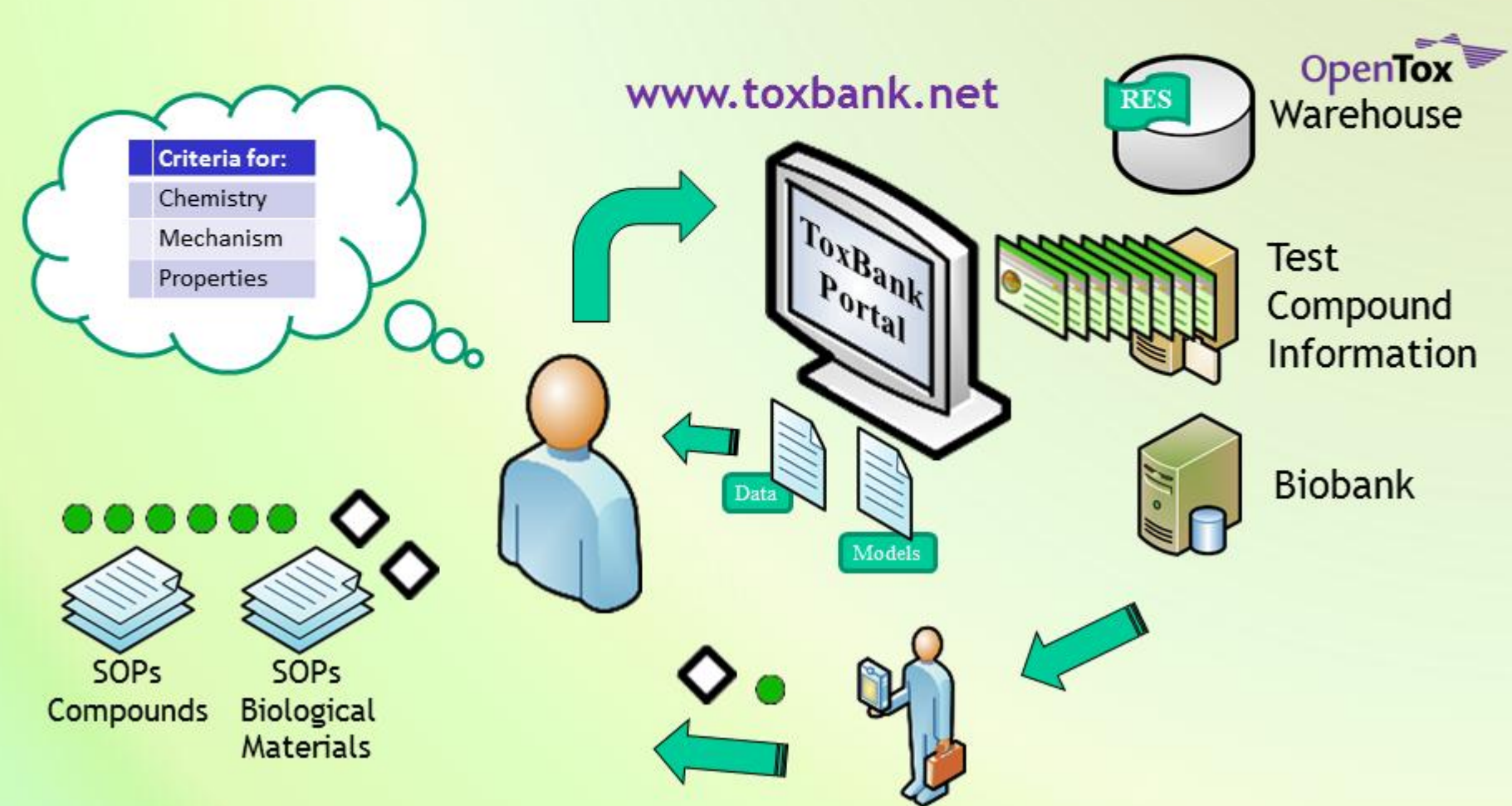
The ToxBank Compound Wiki was created to support the organisation and presentation of information on reference compounds to SEURAT-1 scientists. The selection of a semantic media wiki to develop this resource enables both the collaborative assembly, annotation and curation of information profiles on compounds and the structured capture of metadata such as on linked toxicological data or biochemical mechanisms.

The wiki provides an extensible high quality information resource servicing the selection and use of reference compounds by researchers during their experimental planning. Compound information pages are linked to sources of repeated-dose toxicity *in vivo* and *in vitro* data, physical and chemical property data, linked biological resources on genes and pathways, and whenever available, human adverse event and epidemiological data.

The wiki is extensible for further development as a critical SEURAT-1 cluster resource for the support of chemical and biological reagents evaluation, selection, quality control, distribution and use.

Toxbank Support of SEURAT-1 Experiments

Researchers access information on compounds, biological materials, data and models for experimental planning and integrated analysis of experimental results



During experimental planning researchers need to carefully consider the selection of chemical and biological materials for their *in vitro* experiments, including all available information on physical and chemical properties, biological mechanism or existing toxicity data. ToxBank is developing such curated information so as to enable future delivery to researchers of adequate data, models, chemical and biological materials, and all associated protocols or standard operating procedures (SOPs). The ToxBank Compound Wiki is a significant initiative in this resource creation as it assembles all relevant available information for the important test compounds of the SEURAT-1 program. These compounds will be used to evaluate the merit of all developed assays on the program supporting an integrated data analysis.

All information is made available at the cluster level through wiki pages available after logging in to wiki.toxbank.net

Compound Selection

Human Toxicity
Compound causes one or more of the following:

- cholestatic
- hepatic
- phospholipidosis
- fibrosis
- cell death

Accepted and/or confirmed as *in vitro* mechanism underlying one of these toxicities:

- mitochondrial disruption
- inhibition of lipid transport or metabolism
- nuclear receptor modulation
- compromised phospholipid

Toxicity occurs via one or more of the following mechanism:

- metabolic activation
- direct interaction
- immune-mediated

Therapeutic target:

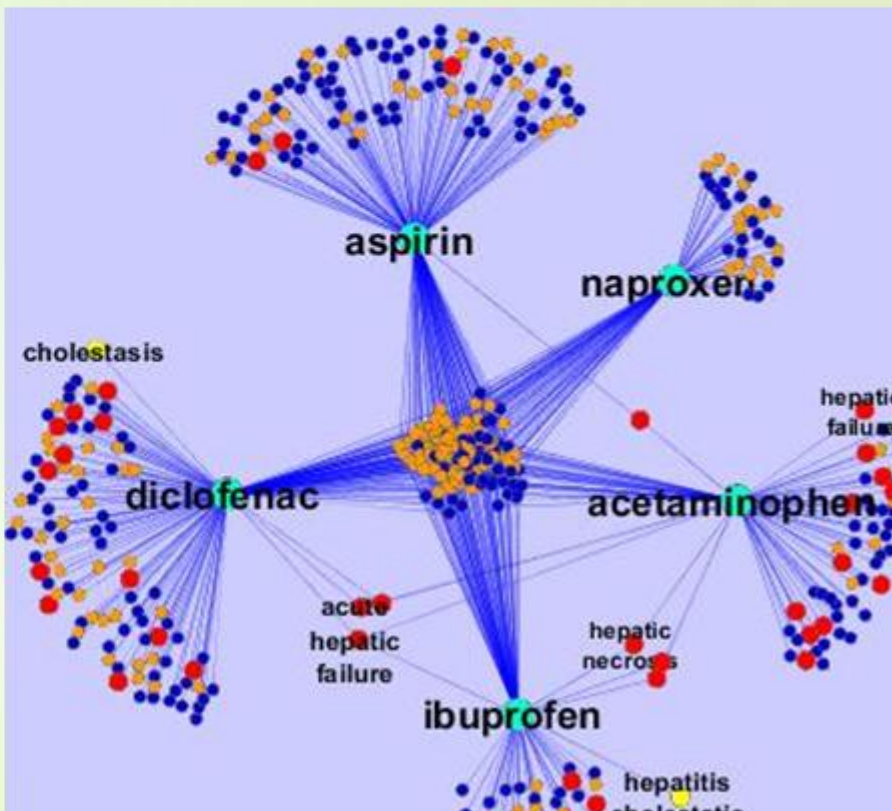
- Accepted and/or confirmed as *in vitro* mechanism underlying one of these toxicities:
- metabolic activation
- direct interaction
- immune-mediated

Physicochemical Properties:

- Accepted and/or confirmed as *in vitro* mechanism underlying one of these toxicities:
- metabolic activation
- direct interaction
- immune-mediated

Adverse Events Analysis (below)
Red – hepatic; Orange – gastric; Blue – other

Acetaminophen toxicity is distinguishable from NSAID pharmacology shared with other drugs



The general compound selection criteria (shown on left) were developed by the SEURAT-1 Gold Compound Working Group (GCWG) established at the very start of the program. During 2011 these criteria were elaborated further to take into account the emerging strategic goal of the SEURAT-1 cluster to develop a Mechanism of Action (MoA)-based approach to toxicity assessment. This includes evaluation of both on- and off-target effects of compounds, e.g. for marketed NSAID drugs (shown on right),

Information related to the selection criteria on compounds has been organised on the ToxBank wiki for work-in-progress on candidate compounds. When a compound has been approved by the GCWG, the page is published for access by all researchers at the cluster level.

Compound Profile Information Page

Acetaminophen

Executive Summary Information

Compound	Acetaminophen (Paracetamol)
Toxicities	Cell Death
Mechanism	Oxidation to the quinine imine NAPIQ metabolite, which traps cellular thiol, both protein and GSH, by formation of covalent adducts. Studies of quinine imine analogues suggest additional depletion of thiol by redox cycling.
Comments	
Recommended as Standard	Yes

Gold Compound Evaluation and Comments

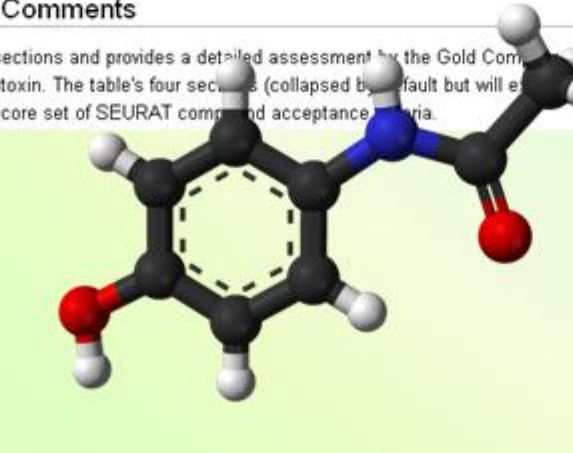
The following table is organized into four main sections and provides a detailed assessment of the Gold Compound Working Group for the use of this compound as a standard hepatotoxicant. The table's four sections are: General Information, the "color" bar (or click) contains detailed information for the core set of SEURAT-1 compounds.

Acetaminophen

Category: Hepatotoxic Compounds

Identifiers

Leadscope ID	103-90-2
DrugBank	DB00311
ChemSpider	1905
UNII	362000130



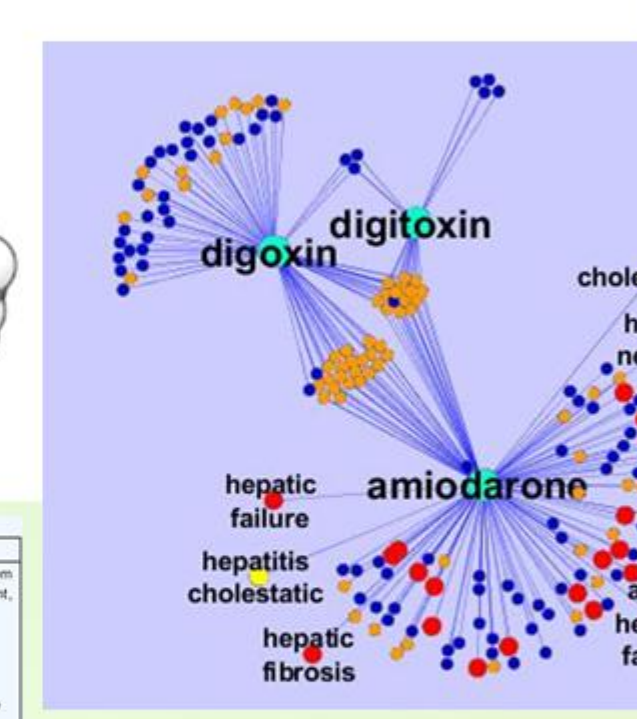
Each compound has an associated information profile page on the wiki which contains a summary of all relevant information discovered on that compound. This includes a summary of available knowledge in the literature, calculated and experimental properties, and compound-specific links to many other linked resources providing useful chemical, biological or toxicological information.

in vitro and *in vivo* Data Gathered on Compound

Human Adverse Events

The following data table has been mined from the **Adverse Events Reporting System (AERS)** of the US FDA. Significant human liver events. The first column ("# Reports") is the number of reports found for the corresponding adverse event reported in the third column ("Adverse Event"). The second column ("Report Baseline Ratio") is ratio calculated from the number of reports ("# Reports") divided by a calculated expected statistical baseline number of reports.

# Reports/Report:Baseline Ratio	Adverse Event
3 6.8103	cholestatic liver injury
12 4.84951	coma hepatic
37 3.19478	hepatic cirrhosis
23 3.26991	hepatitis acute
5 3.30262	hepatocellular injury
41 3.16351	hepatotoxicity
6 3.60446	ischemic hepatitis
2 21.1762	malignant neoplasm of ampulla of Vater
22 2.2907	edema due to hepatic disease



Adverse Events Analysis
Red – hepatic Orange – cardiac Blue – other

Amiodarone shows compound-specific hepatotoxicities cf. other β -oxidation enzyme class members

The wiki provides information available on a compound from previous *in vitro* and *in vivo* experiments (bottom left), including for example omics datasets on the compound, animal experiments or human adverse events data (top left).

Compound analysis includes research on the specificity and promiscuity of compounds with regards to their known pharmacology and toxicology. The analysis shown on right examines the specificity of the hepatotoxic mechanisms of amiodarone.

Physical and Chemical Properties

Calculated/Predicted Properties

Water Solubility Results

pH Sol, mg/mL

pH	2	3	4	5	6	7	8	9	10
Solubility	21.96	18.0	81.2	-	-	-	-	-	-

LogP Results

pH LogP

pH	2	3	4	5	6	7	8	9	10
LogP	0.25	0.34	0.34	0.34	0.34	0.34	0.34	0.34	0.34

Summary Solubility Data

Property	Value	Units	Source
Intrinsic Solubility, mg/mL	17.8454		SPARC v4.5
Intrinsic Solubility, logS, mol/L	0.3079		SPARC v4.5
Solubility in Pure Water, g/L	5.7	mg/mL	17.8454

Acetaminophen

Category: Hepatotoxic Compounds

Identifiers

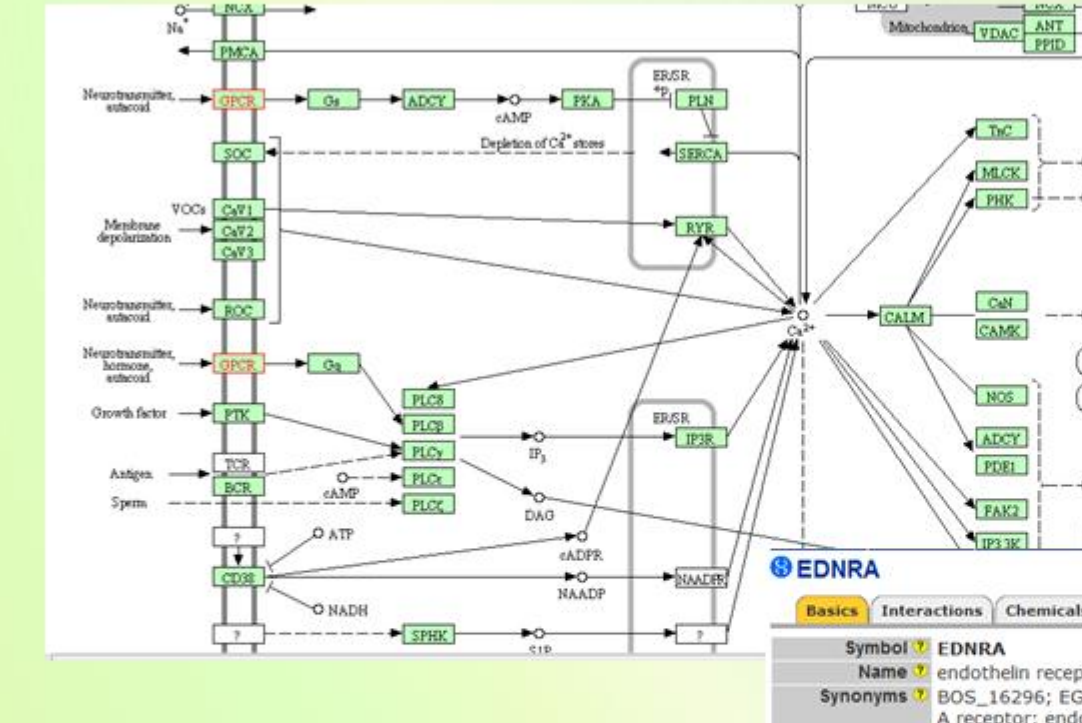
Leadscope ID	103-90-2
DrugBank	DB00311
ChemSpider	1905
UNII	362000130
CHEBI	116455

Pathway IDs

Pathway ID	Value	Units	Source
KEGG	000121		KEGG
PubChem CID	1903		PubChem
CHEBI	112		CHEBI

Experimental data and model predictions on physico-chemical properties such as solubility and partition coefficient are assembled for each compound.

Linked Biological Information Resources



EDNRA

Interactions

Chemicals

Proteins

Pathways

GO

References

Links

Top Interacting Chemicals

Chemical	Interactions
Acetaminophen	25
Paracetamol	20
Acetaminophen	15
Paracetamol	10
Acetaminophen	5
Paracetamol	5

Through using a linked resource approach the compound profiles can be linked to related key biological information available of interest e.g., on genes and pathways associated with the MoA probed by the test compound (Links to Comparative Toxicogenomics Database and Kegg pathways resources shown).

Authors

David Bower, Leadscope
Kevin Cross, Leadscope
Barry Hardy, Douglas Connect
Nina Jeliazkova, Ideaconult
Glenn Myatt, Leadscope
Silvia Maggioni, IRFMN
Michael Rautenberg, in silico toxicology
Egon Willighagen, Karolinska Institutet
Jeff Wiseman, Pharmatrope