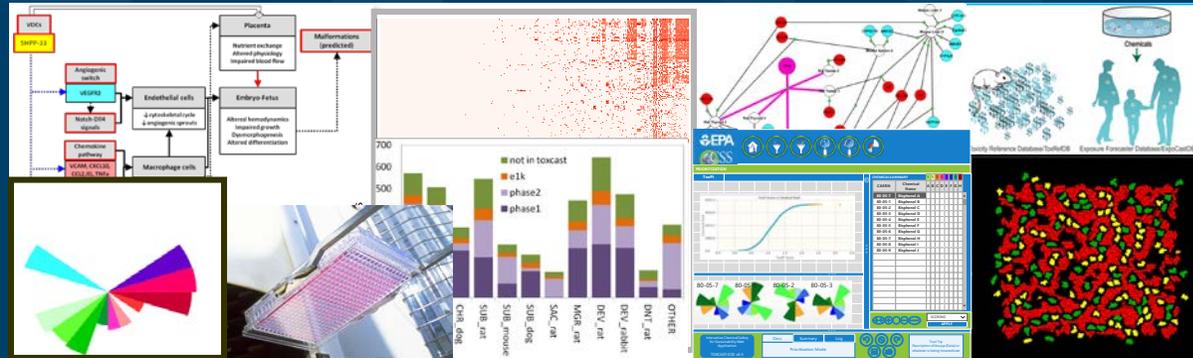


Toxicity Testing in the 21st Century and NexGen Risk Assessments



Grace Patlewicz
National Center for Computational Toxicology (NCCT), US EPA

Outline

- **Regulatory Drivers**
- **Integrated Approaches to Testing and Assessment (IATA) - definitions and Adverse Outcome Pathway (AOP) informed**
- **Decision contexts and their impact on the approaches applied**
- **Practical workflow - where and what approaches can be used**
 - **Using the US EPA Chemistry Dashboard**
- **Summary remarks**

Regulatory drivers

- Societal demands for safer and sustainable chemical products are stimulating changes in toxicity testing and assessment frameworks
- Chemical safety assessments are expected to be conducted faster and with fewer animals, yet the number of chemicals that require assessment is also rising with the number of different regulatory programmes worldwide.
- In the EU, the use of alternatives to animal testing is promoted.
- Animal testing is prohibited in some sectors e.g. cosmetics
- The European Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation lays out specific information requirements, based on tonnage level triggers. However, the regulation explicitly expresses the need to use New Approach Methodologies (NAM) to reduce the extent of experimental testing in animals.

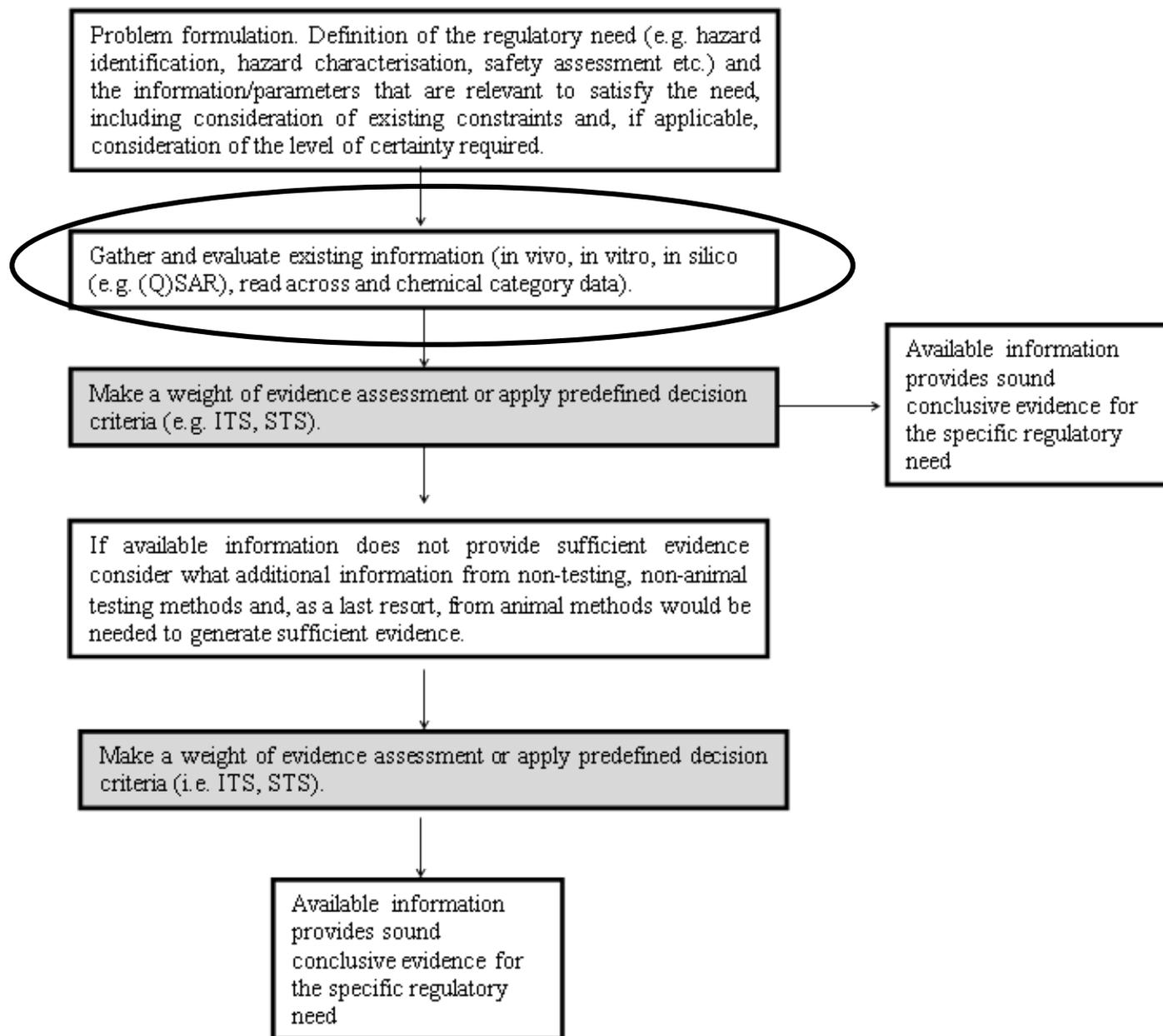
Regulatory drivers

- REACH-like schemes also have been established in China, South Korea, and Turkey.
- In the US, the new Frank Lautenberg Chemical Safety for the 21st Century Act (LCSEA) requires that a risk based prioritisation is conducted for all substances in commerce, some 80,000, many of which are lacking sufficient publicly available toxicity information.
- The LCSEA also suggests developing alternative methods to reduce/refine animal testing.
- Risk based prioritisation is also an important aspect of regulatory frameworks in Canada (the Domestic Substance List), Australia and the EU.
- NAM offer a means of facilitating the regulatory challenges in chemical safety assessment

Integrated Approaches to Testing and Assessment (IATA)

- A means of integrating existing data and non-testing data together, determining what new information needs to be generated in order to make a decision with sufficient confidence for the purpose in mind
- IATA can be likened to workflows depicting the steps of gathering information for a substance and evaluate its fitness for purpose for the decision required
- Some IATA are more complex than others but the generic building blocks of considering existing data, NAM (i.e. *in vitro* methods, non-testing approaches) BEFORE instigating new *in vivo* testing are the same
- NAM fit within the context of these IATA schemes and should not necessarily be considered *in vacuo*

General framework of an IATA



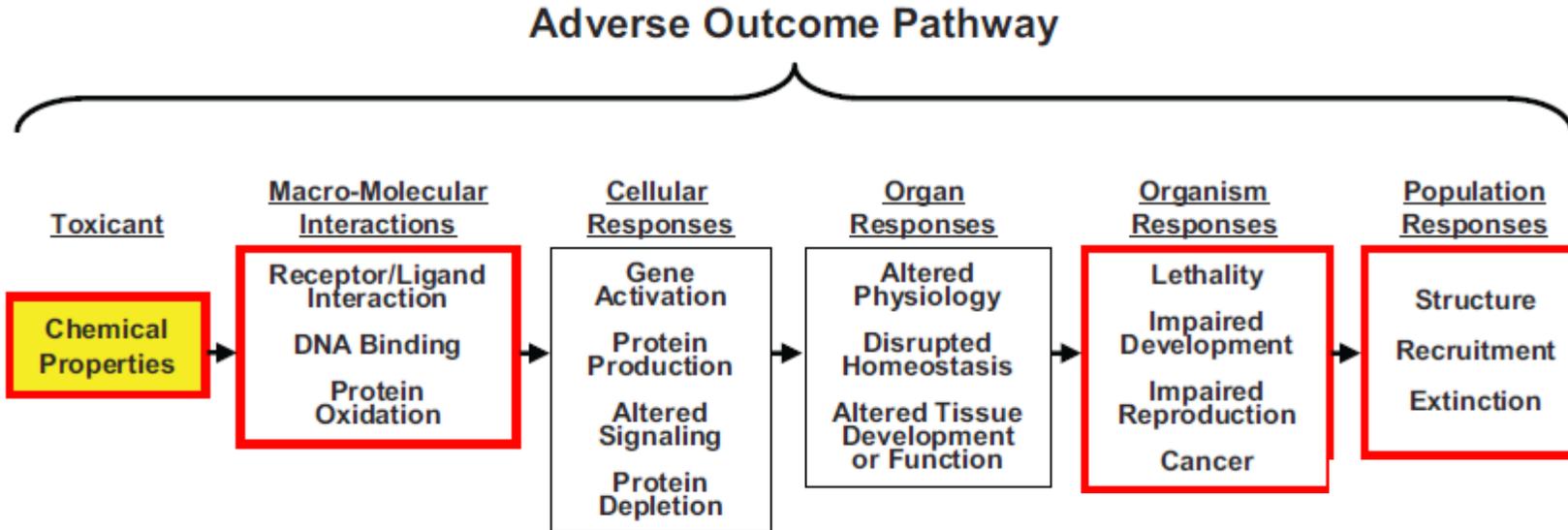
Typical Information within an IATA

- Historical information on the chemical of interest
- Non-standard *in vivo* tests
- Information from “similar” chemicals
- Predictions from other non-testing approaches such as (Q)SAR
- *In chemico* tests
- *In vitro* tests
- Molecular biology, -omics
- Exposure, (bio-)kinetics

Mechanistic based and AOP-informed IATA

- As noted earlier, there is a shift towards non animal alternatives as a response to regulatory drivers
- Integration of different non-animal approaches requires an organising framework to ensure that the different information sources are being interpreted in their appropriate context. This is particularly relevant for New Approach Methodologies (NAMs).
- AOPs serve to provide this organisational framework and hence play an important role in developing and applying IATA for different purposes as well as provide a roadmap for future QSAR development
- AOPs provide the linkage from chemistry, through the Molecular Initiating Event (MIE) to Adverse Effect

AOPs

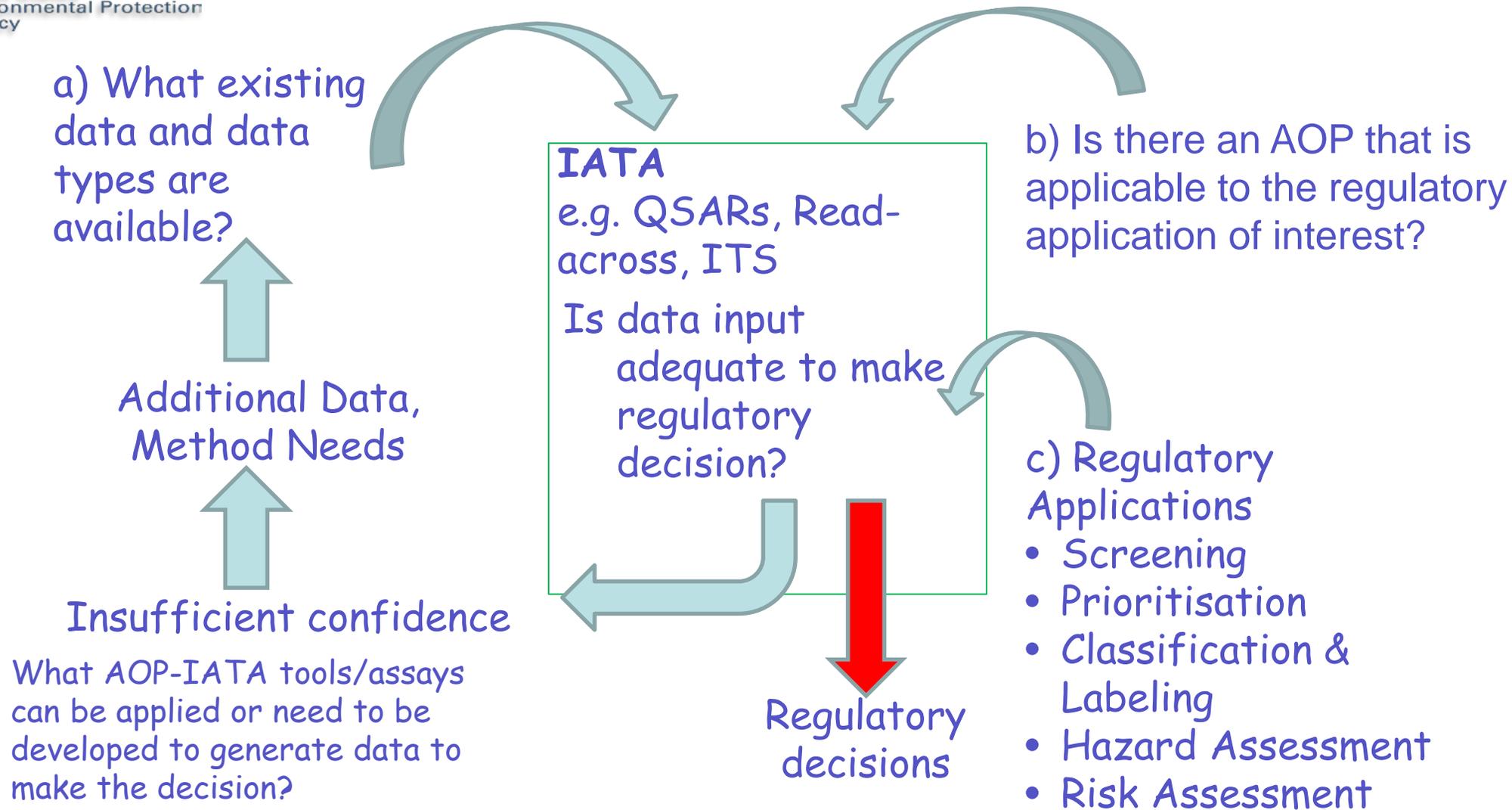


An AOP represents existing knowledge concerning the sequence of events and causal linkages between initial molecular events, ensuing key events and an adverse outcome at the individual or population level.

Establishing Scientific Confidence in the application of AOPs for IATA

1	Develop the AOP
2	Develop new (or map existing) specific assays to key events within the AOP
3	Conduct (or document) Analytical Validation of each assay
4	Develop new (or map existing) models that predict a specific key event from one or more pre-cursor key events. (The input data for the prediction models comes from the assays described in Steps 2 and 3 above.)
5	Conduct (or document) Qualification of the prediction models
6	Utilization: defining and documenting where there is sufficient scientific confidence to use one or more AOP-based prediction models for a specific purpose (e.g., priority setting, <i>chemical category formation, integrated testing, predicting in vivo responses, etc.</i>)
7	For regulatory acceptance and use, processes need to be agreed upon and utilized to ensure robust and transparent review and determination of fit-for-purpose uses of AOPs. This should include dissemination of all necessary datasets, model parameters, algorithms, etc., to enable stakeholder review and comment, fully independent verification and independent scientific peer review. Whilst these processes have yet to be defined globally, in time, these should evolve to enable credible and transparent use of AOPs with sufficient scientific confidence by all stakeholders.

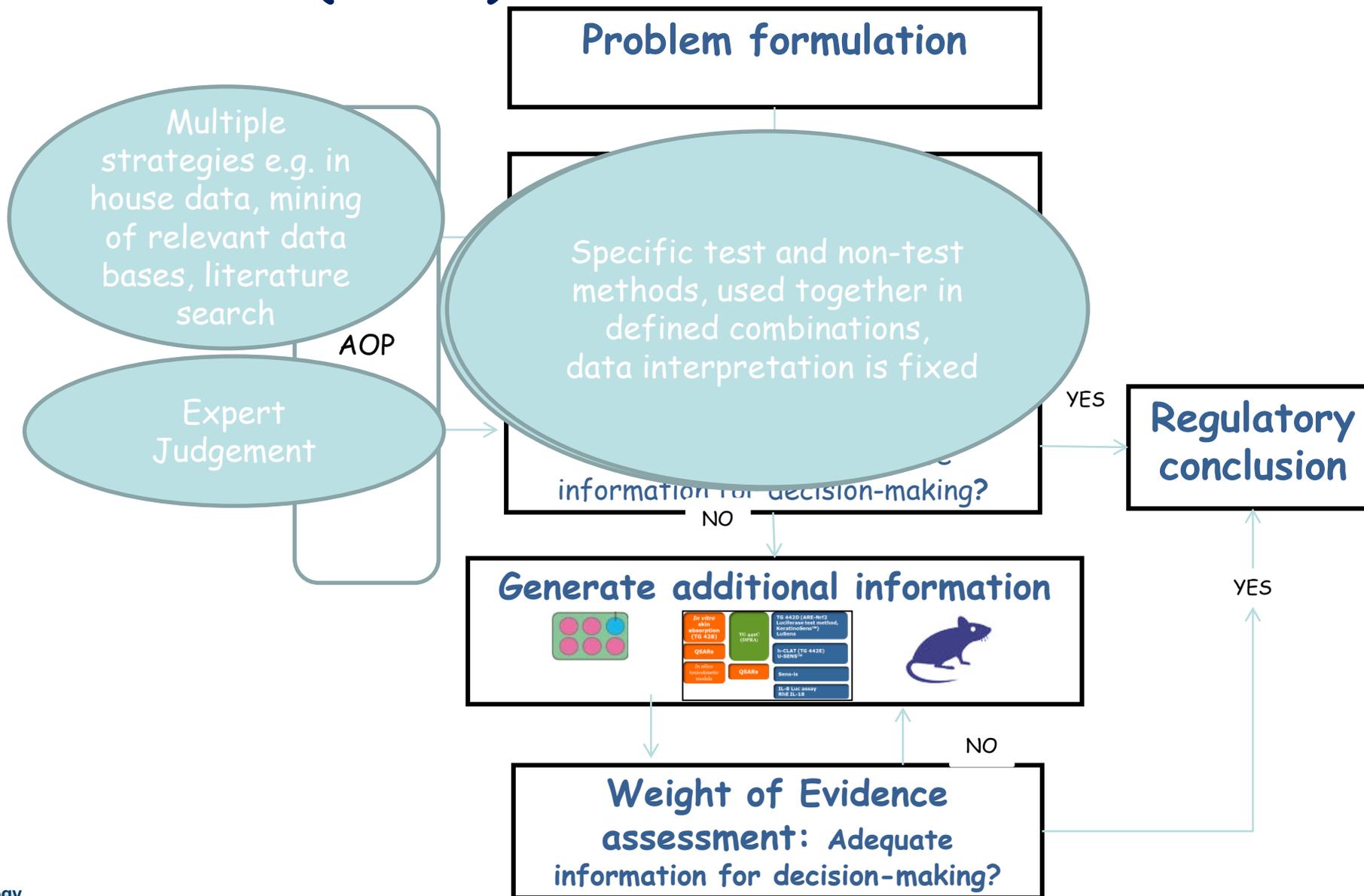
AOP-informed IATA



Scientific confidence considerations for IATA

- **Proposed validation principles:**
 - define the endpoint being assessed;
 - define the purpose/application for which the IATA is proposed;
 - describe the rationale underlying the construction of the IATA;
 - describe how the individual information sources constituting the IATA are integrated to derive the final prediction/assessment and,
 - describe the predictive capacity of the approach, the limitations in the application of the approach and the known uncertainties associated with the IATA application.

General workflow in Integrated Approaches to Testing and Assessment (IATA)



From OECD

Defined approaches within IATA

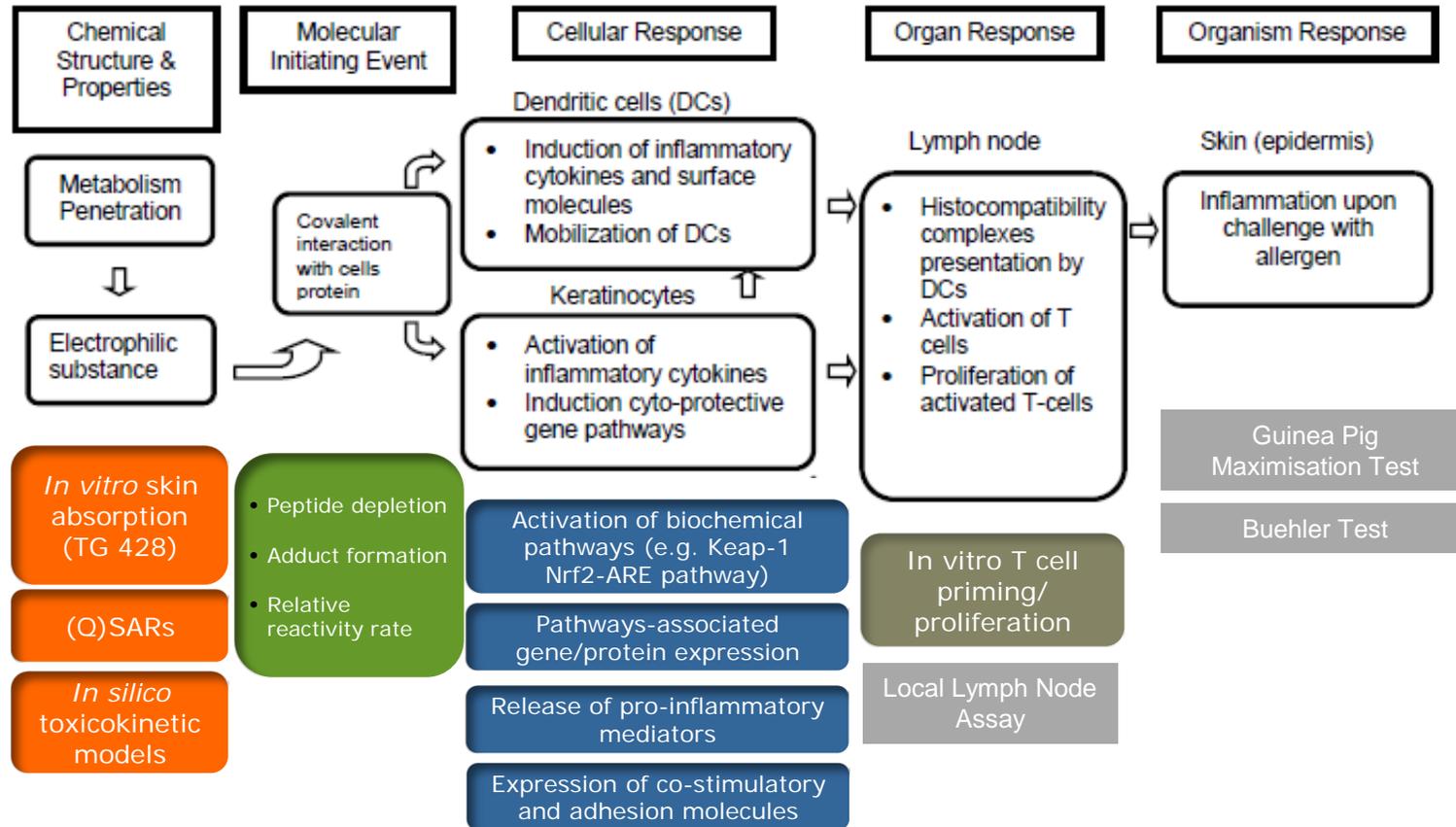
- A defined approach to testing and assessment consists of a fixed data interpretation procedure (DIP) used to interpret data generated with a defined set of information sources, that can either be used alone or together with other information sources, to satisfy a specific regulatory need.
- Guidance Document on the Reporting of Defined Approaches to be Used within Integrated Approaches to Testing and Assessment [ENV/JM/MONO\(2016\)28](#)
- Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be Used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation [ENV/JM/MONO\(2016\)](#)

Defined approaches within IATA

- Work currently underway within the OECD is aiming to establish Performance-based Defined Approaches for skin sensitisation
- Aims to substitute the need for animal testing for skin sensitisation based on a combination of methods which predict key endpoint responses in the AOP
- DA will be evaluated based on their performance using the same data sets/reference chemicals for the endpoint of interest

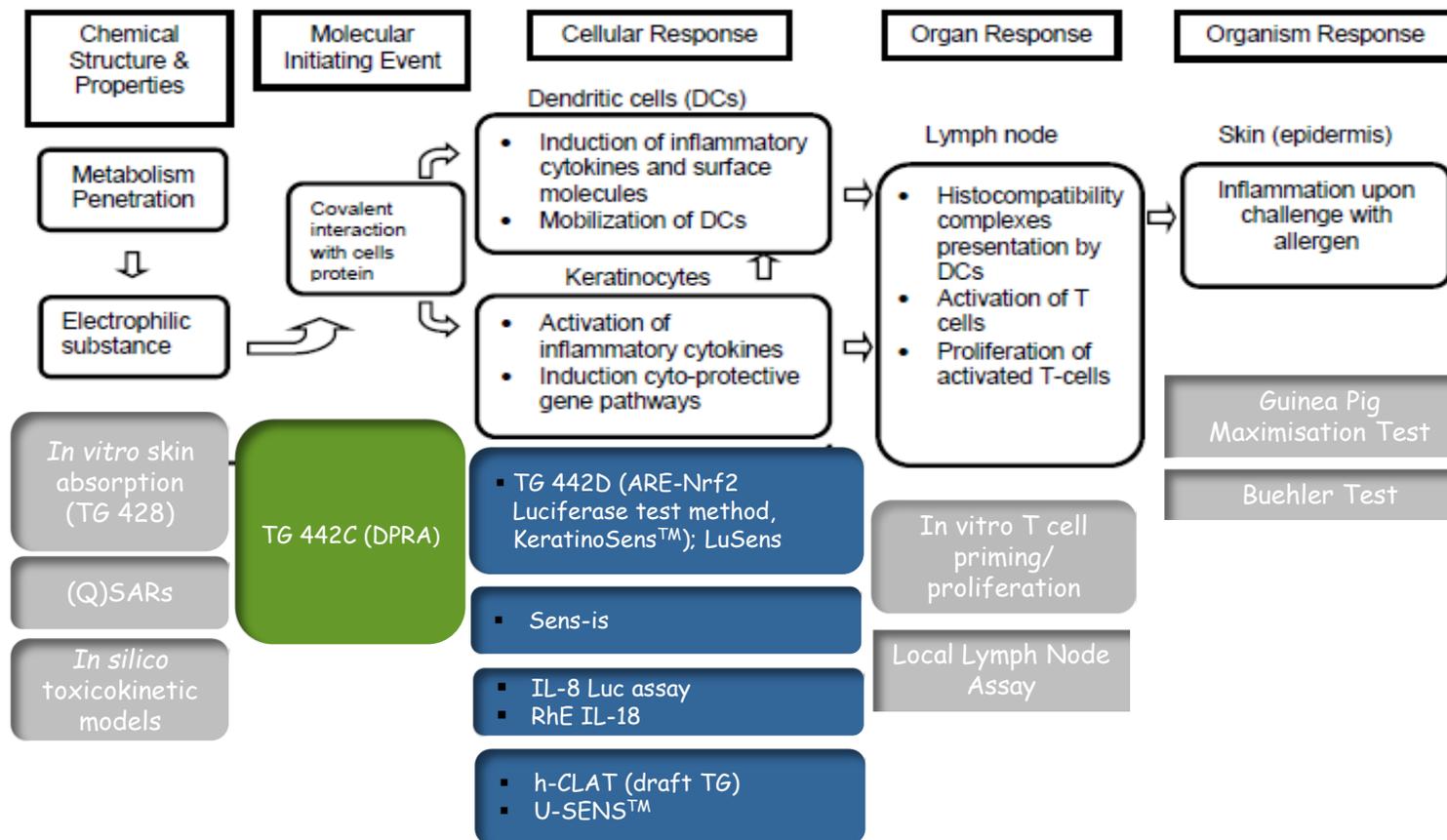
Defined approaches within IATA: Skin sensitisation

AOP and available toolbox of non-animal methods

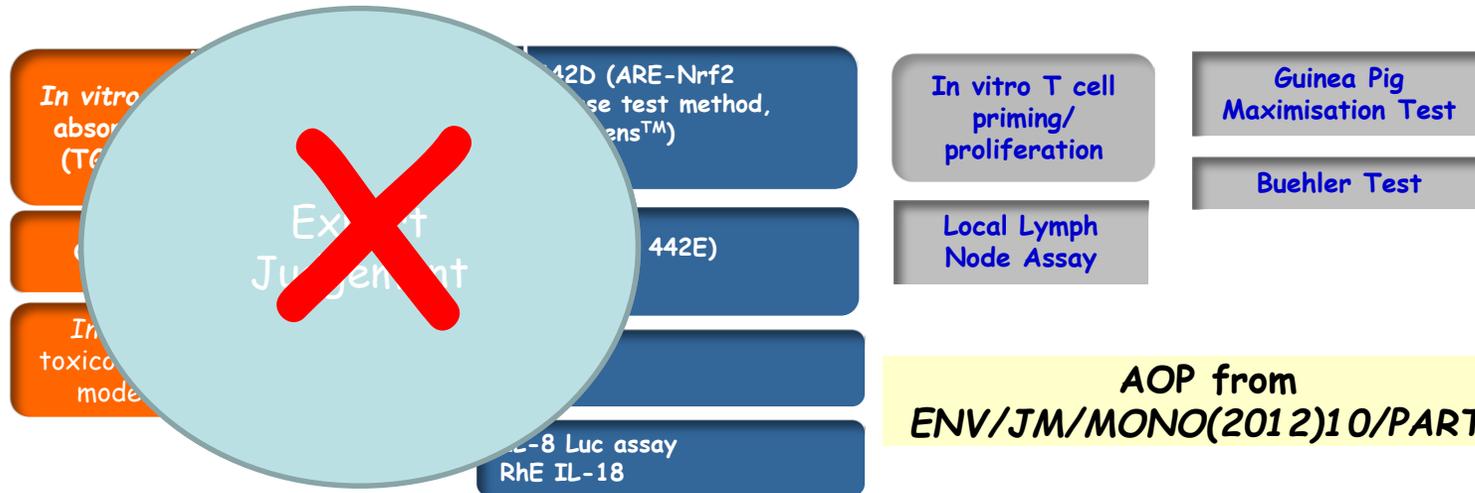
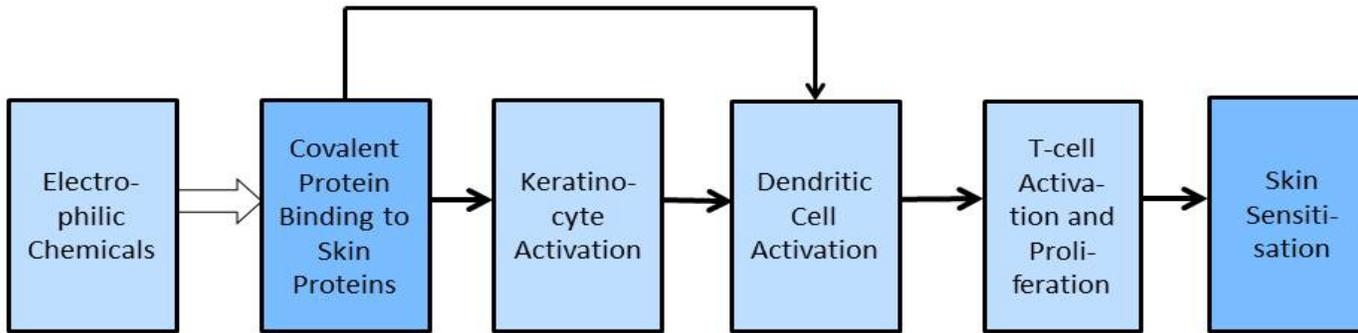
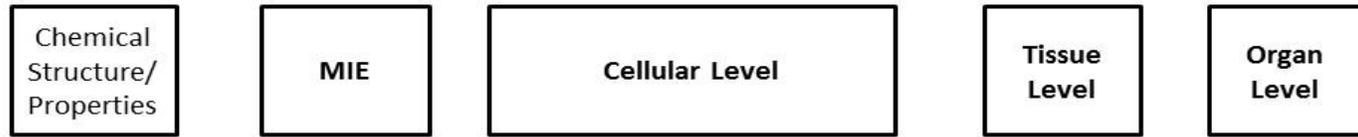


Presented by S Casati, JRC

Defined approaches within IATA: Skin sensitisation (SS)



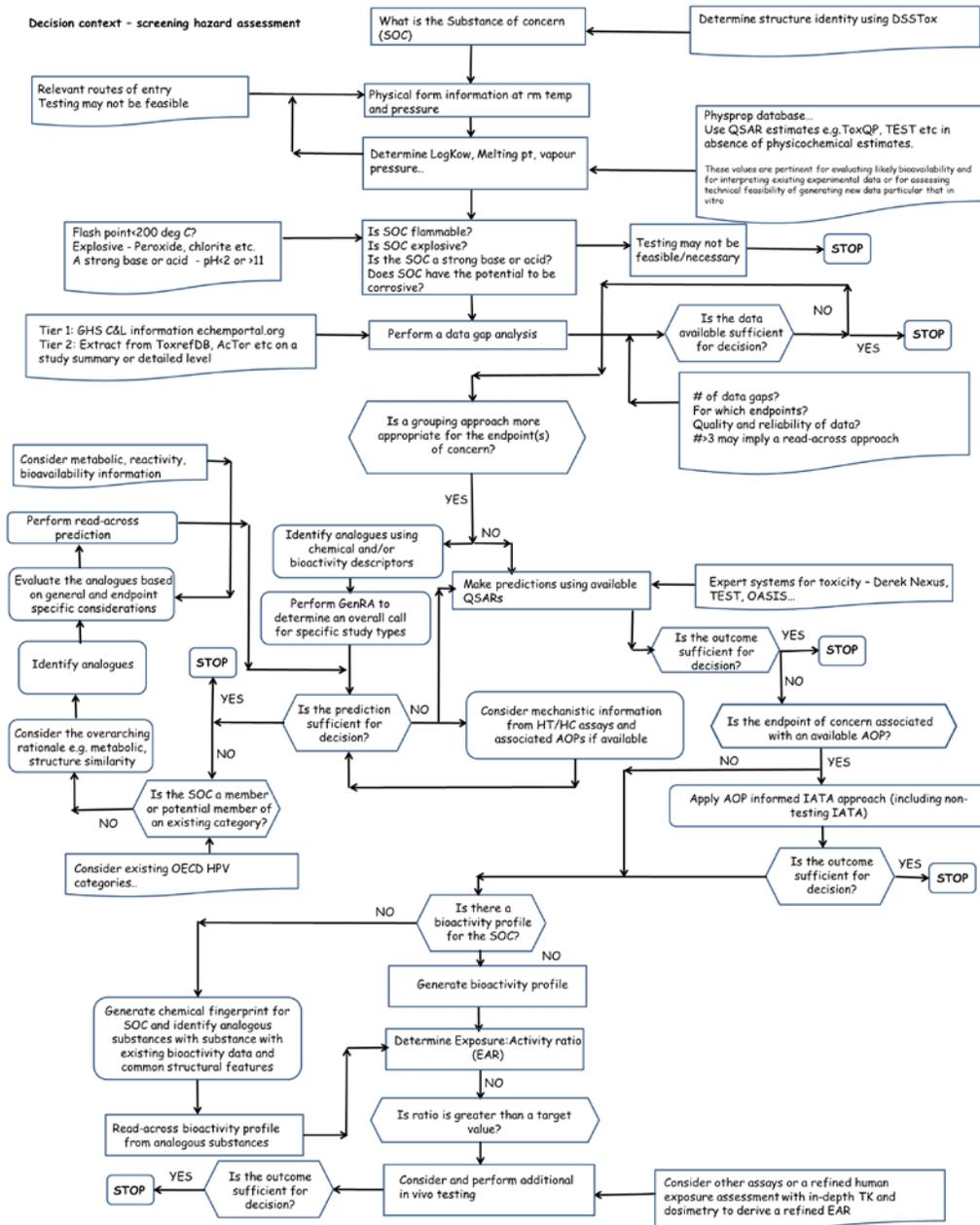
Defined approaches within IATA-SS



IATA in practice

- What is the Substance of concern (SOC)?
- What is already known about the SOC?
- What is the Decision context?

An Assessment workflow



An Assessment workflow

Data gap analysis

Strategies for filling the data gaps using read-across

Strategies for filling data using QSARs, AOP-informed DA etc.

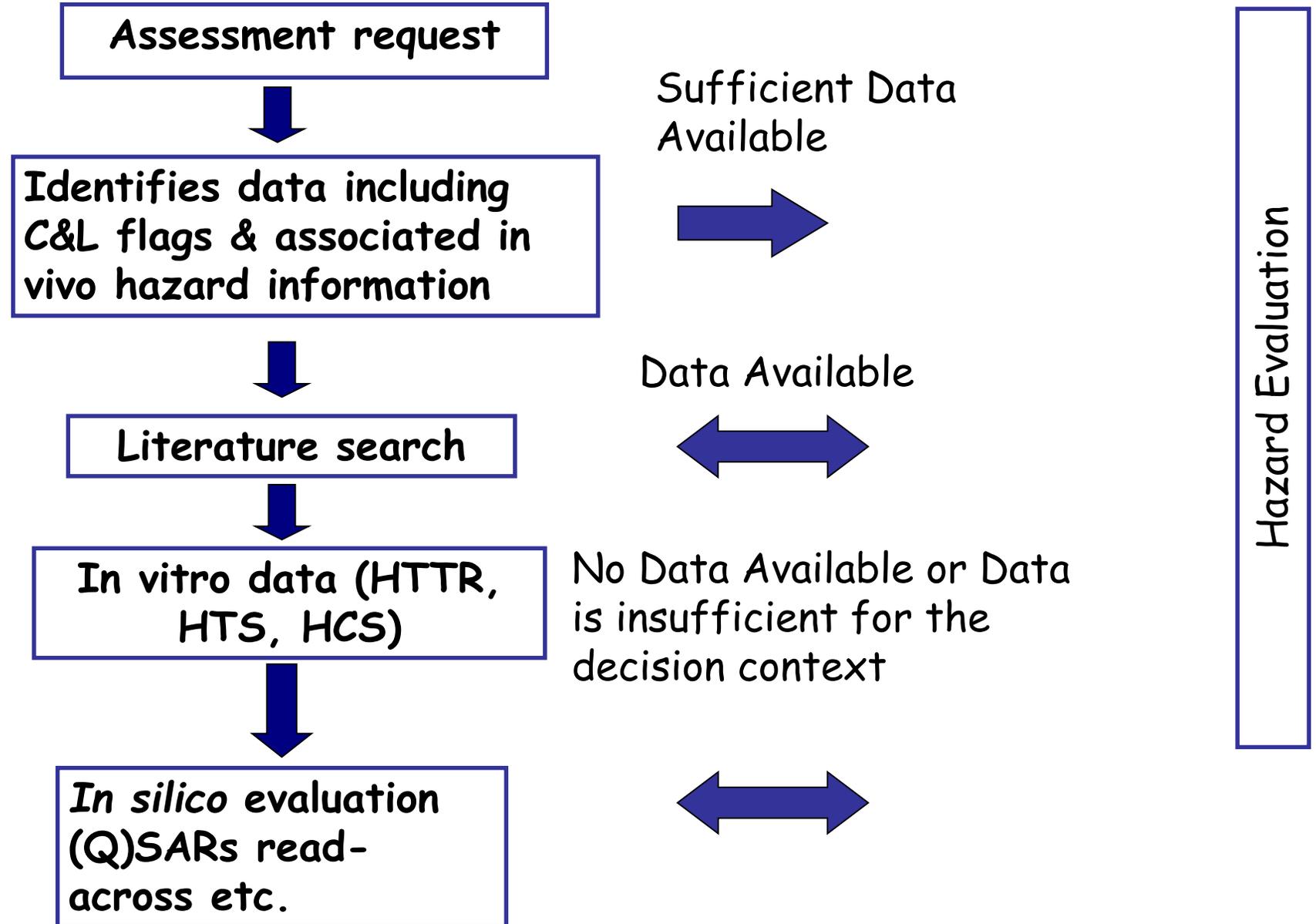
Strategies for filling data using bioactivity information

Decision contexts

- **Prioritisation** What do we know about
- **Screening** our substance of
- **Risk Assessment** interest..

A Data gap analysis is typically the first step

Data gap analysis



The CompTox Chemistry Dashboard

- **A publicly accessible website** delivering access:
 - ~760,000 chemicals with related property data
 - Experimental and predicted physicochemical property data
 - Integration to “biological assay data” for 1000s of chemicals
 - Information regarding consumer products containing chemicals
 - Links to other agency websites and public data resources
 - “Literature” searches for chemicals using public resources
 - “Batch searching” for thousands of chemicals
 - **DOWNLOADABLE** Open Data for reuse and repurposing

CompTox Chemistry Dashboard

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



United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Chemistry Dashboard

761 Thousand Chemicals

Search a chemical by systematic name, synonym, CAS number, or InChIKey

Identifier substring search

See what people are saying, read the dashboard comments!

Latest News

[Read more news](#)

A Movie Regarding how to Identify "Known Unknowns" Using the CompTox Dashboard
 March 28th, 2017 at 7:35:41 PM

Recently we published a paper regarding [Identifying known unknowns using the US EPA's CompTox Chemistry Dashboard](#). Analytical and Bioanalytical Chemistry, March 2017, Volume 409, Issue 7, pp 1729–1735. A movie explaining the paper in full animated detail has been put on YouTube. Enjoy the movie interlude [here](#).

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 United States Environmental Protection Agency

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Search All Data

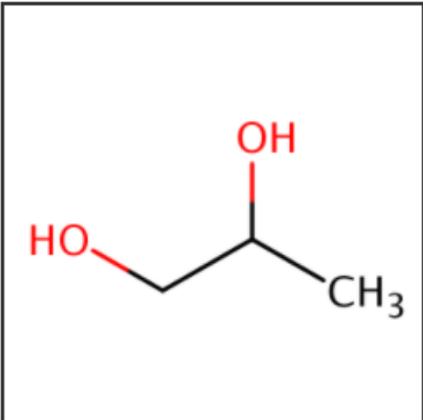
Chemistry Dashboard | EPAHFR

Submit Comment Copy Aa Aa Aa

1,2-Propylene glycol

57-55-6 | DTXSID0021206

© Searched by DSSTox_Substance_Id: Found 1 result for 'DTXSID0021206'.



Wikipedia

Propylene glycol (IUPAC name: propane-1,2-diol) is a synthetic organic compound with the chemical formula C₃H₈O₂. It is a viscous colorless liquid which is nearly odorless but possesses a faintly sweet taste. Chemically it is classed as a diol and is miscible with a broad range of solvents, including water, acetone, and chloroform. It is produced on a large scale and is primarily used in the production of polymers, but also sees use in food...[Read more](#)

Intrinsic Properties

Structural Identifiers

Linked Substances

Presence in Lists

Record Information

Quality Control Notes

Chemical Properties Env. Fate/Transport Hazard ADME (Beta) Exposure Bioassays Similar Compounds Related Substances Synonyms Literature Links Comments

Access to Chemical Hazard Data

EPA United States Environmental Protection Agency

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Search All Data

Chemistry Dashboard | EPAHFR

Submit Comment Copy Aa Aa Aa

Chemical Properties Env. Fate/Transport Hazard ADME (Beta) Exposure Bioassays Similar Compounds Related Substances Synonyms Literature Links Comments

Exposure Limit

Lethality Effect Level

Point of Departure

Toxicity Value

Download table as: TSV Excel **Human** Eco

	Priority	Type	Subtype	Risk Assessment Class	Values	Units	Study Type	Exposure Route	Species	Subsource	Source
+	8	NOEL	Cardiova...	subchronic	5000.0	mg/kg-day	subchronic	oral	rat	Vaile et ...	PPRTV (...)
+	8	NOEL	Endocrine	subchronic	5000.0	mg/kg-day	subchronic	oral	rat	Vaile et ...	PPRTV (...)
+	8	LOEL	Hematol...	subchronic	2500.0	mg/kg-day	subchronic	oral	rat	Vaile et ...	PPRTV (...)
+	8	LOEL	Hepatic	subchronic	2500.0	mg/kg-day	subchronic	oral	rat	Vaile et ...	PPRTV (...)
+	8	NOEL	Immune	immunot...	5000.0	mg/kg-day	subchronic	oral	rat	Vaile et ...	PPRTV (...)
+	8	NOEL	Renal	subchronic	5000.0	mg/kg-day	subchronic	oral	rat	Vaile et ...	PPRTV (...)
+	8	LOEL	Systemic	subchronic	2500.0	mg/kg-day	subchronic	oral	rat	Vaile et ...	PPRTV (...)
+	8	NOEL	Hematol...	subchronic	1500.0	mg/kg-day	subchronic	oral	rabbit	Vaile et ...	PPRTV (...)
+	8	NOEL	Systemic	subchronic	1500.0	mg/kg-day	subchronic	oral	rabbit	Vaile et ...	PPRTV (...)

In Vitro Bioassay Screening

ToxCast and Tox21

EPA United States Environmental Protection Agency

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Search All Data

Chemistry Dashboard | EPAHFR

Submit Comment Copy Aa Aa Aa

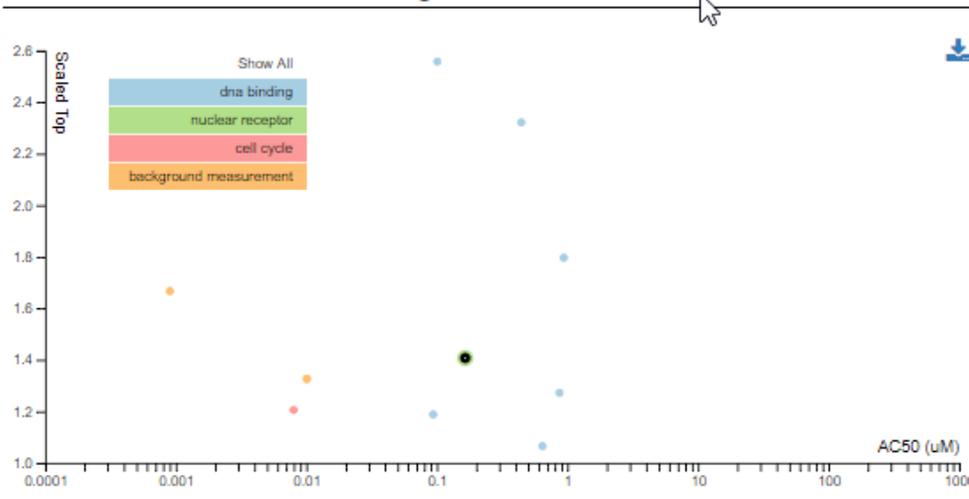
Chemical Properties Env. Fate/Transport Hazard ADME (Beta) Exposure Bioassays Similar Compounds Related Substances Synonyms Literature Links Comments

ToxCast: Summary

PubChem

Chemical Activity Summary **i**

ToxCast Data **i**



Download as: TSV Excel Show: Inactive Background

Assay Details **i**

AC50 (uM): 0.16
Scaled top: 1.41
Assay Name: NVS_NR_hFXR_Antagonist
Assay Description: 716
Gene Symbol: NR1H4
Organism: human
Tissue: NA
Assay Format Type: biochemical
Biological Process Target: receptor binding
Detection Technology: TR-FRET
Analysis Direction: positive
Intended Target Family: nuclear receptor
Description: Data from the assay component NVS_NR_hFXR_Antagonist was analyzed into 1 assay endpoint. This assay endpoint, NVS_NR_hFXR_Antagonist, was analyzed in the positive fitting direction relative to DMSO as the negative control and baseline of activity. Using a type of binding reporter, loss-of-signal activity can be used to understand changes in the binding as they relate to the gene NR1H4.

Assay Name Assa... **i** SeqA... AOP Link AOP Eve... **i** Hit Call **i** T... Scale... **i** ... log ... **i** Target Family

Sources of Exposure to Chemicals

- Chemical Properties
- Env. Fate/Transport
- Hazard
- ADME (Beta)
- Exposure
- Bioassays
- Similar Compounds
- Related Substances
- Synonyms
- Literature
- Links
- Comments

Product & Use Categories

- Chemical Weight Fraction
- Chemical Functional Use
- Monitoring Data
- Exposure Predictions
- Production Volume

Product & Use Categories (PUCs) ⓘ

<u>Categorization type</u>	<u>Number of Unique Products</u>
PUC	288
PUC	206
PUC	117
PUC	107
PUC	107
PUC	101
PUC	101
PUC	90
PUC	89

Identifiers to Support Searches

Chemical Properties Env. Fate/Transport Hazard ADME (Beta) Exposure Bioassays Similar Compounds Related Substances Synonyms

Found 78 synonyms

Legend: **Valid Synonyms** *Good Synonyms* *Other Synonyms*

 Copy all Synonyms

1,2-Propylene glycol

Propane-1,2-diol

1,2-Propanediol

57-55-6 Active CAS-RN

alpha-Propylene glycol

(+/-) 1,2-Propanediol

(RS)-1,2-Propanediol

dl-Propylene glycol

3-01-00-02142 Beilstein Registry Number

1,2-Propanediol

(+,-)-1,2-Propanediol

(+,-)-Propylene glycol

1,2-(RS)-Propanediol

1,2-DIHYDROXYPROPANE

1,2-PROPANDIOL

Literature Searches and Links

Google Scholar

PubMed Abstract Sifter

PubChem Articles

PubChem Patents

PPRTV

IRIS

Exposure Bioassays Similar Compounds Related Substances Synonyms Literature Links Comments

Click on the **Retrieve Articles** button. **1**

Optionally, edit the query before retrieving.

("57-55-8" OR "1,2-Propylene glycol" OR "Propylene Glycol") AND (NOAEL or NOEL OR LOEL or Rfd OR "reference dose" OR "reference concentration" OR "adverse effect level"[tiab] OR "cancer slope factor"[tiab])

13 of 13 articles loaded...

Click on the **Download Sifter for Excel** button. **1**

	Authors	Journal	Rev
garettes: a systematic review of available studies on hea...	Zulkifi; Abidin; Abidin; Amer Nordin; Praveena; Sye...	Reviews on environmental health	
l assessment of a prototype e-cigaret device and three fl...	Werley; Kirkpatrick; Oldham; Jerome; Langston; Lill...	Inhalation toxicology	
monitoring Equivalents for selected E- and P-series glyo...	Poet; Ball; Hays	International journal of hygiene and environmental h...	
mful health effects of inhaling nicotine-free shisha-pen v...	Kienhuis; Soeteman-Hernandez; Bos; Cremers; Kle...	Tobacco induced diseases	
le: Developmental and reproductive toxicity potential of ...	Glynn; Jo; Minowa; Sanada; Nejishima; Matsuuchi; ...	Reproductive toxicology (Elmsford, N.Y.)	
safety assessment of Efnazonazole Solution (10%) for o...	Jo; Glynn; Nejishima; Sanada; Minowa; Calvarese; ...	Regulatory toxicology and pharmacology : RTP	
ad formulations for intravenous mouse pharmacokinetic ...	Thackaberry; Wang; Schweiger; Messick; Valle; De...	Xenobiotica; the fate of foreign compounds in biolog...	
safety and pharmacokinetic evaluations of propylene gly...	Werley; McDonald; Lilly; Kirkpatrick; Wallery; Byron;...	Toxicology	
on the safety assessment of methoxyisopropanol and m...		International journal of toxicology	
logically-based pharmacokinetic modeling to address n...	Kiman; Sweeney; Corley; Gargas	Risk analysis : an official publication of the Society f...	
of 2-methoxypropionic acid formed from beta-propylene...	Carney; Pottenger; Johnson; Liberacki; Tormesi; Dry...	Toxicological sciences : an official journal of the Soc...	

External Links to Data and Services

Chemical Properties	Env. Fate/Transport	Hazard	ADME (Beta)	Exposure	Bioassays	Similar Compounds	Related Substances	Synonyms	Literature	Links
<p>General</p> <ul style="list-style-type: none"> EPA Substance Registry ... Household Products Data... PubChem CPCat DrugBank Wikipedia MSDS Lookup ChEMBL Chemical Vendors NIOSH Chemical Safety ... ToxPlanet ACS Reagent Chemicals Wikidata ChemHat: Hazards and A... Wolfram Alpha 	<p>Toxicology</p> <ul style="list-style-type: none"> ACToR DrugPortal CCRIS ChemView CTD eChemPortal Gene-Tox HSDB ToxCast Dashboard 2 LactMed International Toxicity Esti... ATSDR Toxic Substances... ACToR PDF Report CREST 	<p>Publications</p> <ul style="list-style-type: none"> Toxline Environmental Health Per... NIEHS National Toxicology Progr... Google Books Google Scholar Google Patents PPRTVWEB PubMed IRIS Assessments EPA HERO RSC Publications BioCaddie DataMed Springer Materials Federal Register 	<p>Analytical</p> <ul style="list-style-type: none"> RSC Analytical Abstracts Tox21 Analytical Data MONA: MassBank North ... NIST NIST IR Spectrum NIST NIST MS Spectrum 	<p>Prediction</p> <ul style="list-style-type: none"> 2D NMR HSQC/HMBC Pr... Carbon-13 NMR Prediction Proton NMR Prediction ChemRTP Predictor LSERD 						

Integrated Linkouts

Substance Registry ... ACToR Toxiline

use
Ch
Cat
igBa

eChemPortal provides free public access to information on properties of chemicals. Direct links to collections of chemical hazard and risk information prepared for government chemical review programmes at national, regional and international levels are obtained.

ikipedia
MSDS Lookup

eChemPortal
Gene-Tox

Google Scholar
Google Patents

MSDS Lookup Gene-Tox

The International Chemical Safety Cards (ICSC) summarize essential health and safety information on chemicals for their use at the

NIOSH Chemical Safety ... LactMed

International Toxicity Esti

Substance Registry ... ACToR Toxiline

el
Ch
at
Bank

Comparative Toxicogenomics Database is a robust, publicly available database that aims to advance understanding about how environmental exposures affect human health.

ikipedia
MSDS Lookup

CTD
eChemPortal

Google Books
Google Scholar

Integrated Linkouts

Comparative Toxicogenomics DB



illuminating how chemicals affect human health.

YOUR QUERIES | CONTACT US

Comparative Toxicogenomics Database

Home Search Analyze Download Help

Chemicals Name, CAS RN, ID Search

Propylene Glycol

Basics Gene Interactions Genes **Diseases** Phenotypes Comps Pathways GO Exposure Studies Exposure Details References

These diseases are associated with *Propylene Glycol* or its descendants. Each association is *curated* (M marker/mechanism and/or T therapeutic) and/or *inferred* (via a curated gene interaction).

Disease categories [\[Show chart\]](#)



Filter by	Disease category	Association type	Filter
	ALL	ALL	

1-50 of 240 results.

First Previous 1 2 3 4 5 Next Last

	Chemical	Disease	Direct Evidence	Enrichment Analysis	Inference Network	Inference Score	References
1.	Propylene Glycol	Drug-Related Side Effects and Adverse Reactions	M	GO	2 genes: ABCC2 ABCC4	4.09	5
2.	Propylene Glycol	Acute Kidney Injury	M	GO	2 genes: IL6 TGFB1	3.78	3
3.	Propylene Glycol	Chemical and Drug Induced Liver Injury	M	GO	2 genes: ABCC2 IL6	2.82	5
4.	Propylene Glycol	Kidney Diseases	M		1 gene: TGFB1	2.54	4

Advanced Searches

Advanced Search

Mass Search

Min/Max

Mass Da \pm Error Da ppm

Molecular Formula Search

Molecular Formula

MS Ready Formula 
 Exact Formula 

Generate Molecular Formula(e)

Min/Max

Mass Da \pm Error Da ppm

Default Options: C[1-50] H[0-100] O[0-20] N[0-20] P[0-20] S[0-10]
Include Halogens: F[0-20] Cl[0-20] Br[0-20] I[0-20]

Options 

Advanced Searches

Mass Based Search

Mass Search

 ± Min/Max ▼ Da

±

Chemistry Dashboard

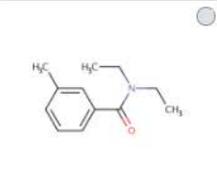
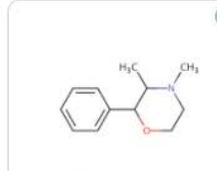
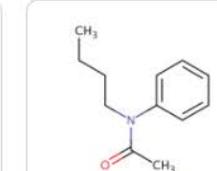
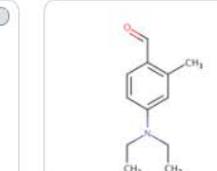
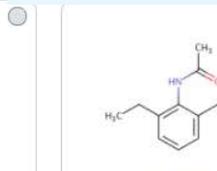
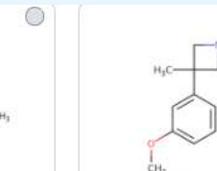
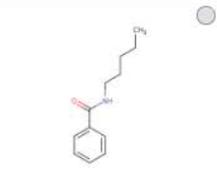
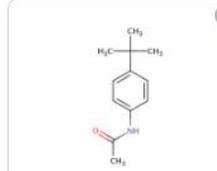
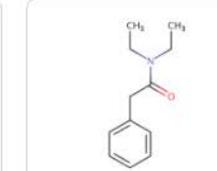
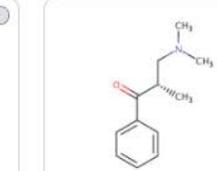
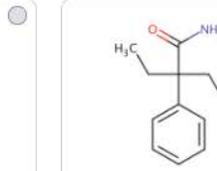
Search Results

Searched by Mass: '191.031 +/- 5 ppm'.

Download / Send Sort by: Mass Difference

298 of 298 chemicals visible

Hide: **Multicomponent Chemicals**

 <p>DEET 134-62-3</p>	 <p>Phendimetrazine 634-03-7</p>	 <p>N-Butylacetanilide 91-49-6</p>	 <p>Benzaldehyde, 4-(diethylamino)-... 92-14-8</p>	 <p>Acetanilide, 2',6'-diethyl- 16665-89-7</p>	 <p>Azetidine, 1,3-dimethyl-3-(m-met... 19832-26-9</p>
 <p>Benzamide, N-pentyl- 20308-43-4</p>	 <p>p-t-Butylacetanilide 20330-45-4</p>	 <p>N,N-Diethylphenylacetamide 2431-96-1</p>	 <p>3-(Dimethylamino)-2-methylpropi... 26171-50-6</p>	 <p>Butyramide, 2-ethyl-2-phenyl- 30568-39-9</p>	 <p>1-Heptanone, 1-(4-pyridyl)- 32941-30-3</p>

Batch Searches

Batch Search

Step One Step Two Step Three Step Four Step Five Step Six

Step One: Select Input

Select Input Type(s)

- Chemical Name 
- CASRN 
- InChIKey  Skeleton 
- DSSTox Substance ID 
- MS-Ready Formula(e) 
- Exact Formula(e) 
- Monoisotopic Mass

Enter Identifiers to Search (searches should be limited to <1000 identifiers)

Batch Search

Select Input Type(s)

- Chemical Name **i**
- CASRN **i**
- InChIKey **i** Skeleton **i**
- DSSTox Substance ID **i**
- MS-Ready Formula(e) **i**
- Exact Formula(e) **i**
- Monoisotopic Mass

Metadata

- Curation Level Details **i**
- Data Sources **i**
- Assay Hit Count **i**
- Include links to ACToR reports - SLOW! (BETA) **i**
- NHANES/Predicted Exposure **i**
- Include ToxVal Data Availability **i**
- Number of PubMed Articles **i**
- Abstract Sifter Input File (Beta) **i**
- MetFrag Input File(Beta)
- IRIS
- PPRTV
- PubChem Data Sources
- ToxPrint fingerprints **i**

Enter Identifiers to Search (searches should be limited to <1000 identifiers)

C6H12O3
C7H7N3
C8H11NO
C7H5NOS
C9H15NO
C11H12O
C9H8O3
C6H12O5
C9H15NO2

- NIOSH IDLH Values
- NIOSH International Chemical Safety Cards
- NIOSH Pocket Guide to Chemical Hazards
- NIOSH Skin Notation Profiles
- NORMAN Collaborative Trial 2015 Targets and Suspects
- Norman Network PFAS (KEMI Report)
- NORMAN Network Priority List
- NormaNEWS: Norman Early Warning System
- PFAS list provided by X.Trier et al
- Pharmaceutical List with EU, Swiss and US Consumption Data
- Provisional Peer Reviewed Toxicity Values
- Stockholm Convention on Organic Pollutants
- STOFF-IDENT Database of **Water**-Relevant Substances
- Superfund Chemical Data Matrix
- Surfactant List Screened in Swiss Wastewater (2014)

INPUT	FOUND_BY	DTXCID_IN	DATA_SQL	TOXVAL_D	TOXCAST	TOXCAST	NUMBER_C	PUBCHEM	STOFFIDEI
C6H12O3	MS Ready	DTXCID701	51	Y	0.36	2/562	24	83	Y
C6H12O3	MS Ready	DTXCID003	67	Y	0.36	1/276	376	80	Y
C6H12O3	MS Ready	DTXCID106	65	Y	4.42	5/113	6	77	Y
C6H12O3	MS Ready	DTXCID105	45	Y	0.0	0/163	3	94	-
C6H12O3	MS Ready	DTXCID901	38	Y	-	-	14	110	Y
C6H12O3	MS Ready	DTXCID402	34	Y	0.0	0/113	-	53	Y
C6H12O3	MS Ready	DTXCID202	31	Y	-	-	-	36	Y
C6H12O3	MS Ready	DTXCID202	30	-	2.54	7/276	-	54	-
C6H12O3	MS Ready	DTXCID109	26	Y	-	-	-	46	-
C6H12O3	MS Ready	DTXCID202	24	Y	0.0	0/113	-	47	-
C6H12O3	MS Ready	DTXCID303	22	Y	-	-	-	89	-
C6H12O3	MS Ready	DTXCID302	20	Y	-	-	2	25	Y
C6H12O3	MS Ready	DTXCID407	19	Y	-	-	12	62	-
C6H12O3	MS Ready	DTXCID704	17	Y	-	-	-	64	-
C6H12O3	MS Ready	DTXCID704	16	Y	-	-	3	49	-

The screenshot displays a software interface for predicting chemical properties. On the left, a chemical structure is shown in a central workspace. The structure is 1-(4-hydroxyphenyl)butan-1-ol, represented by the SMILES string CCCC(O)c1ccc(O)cc1. The interface includes a top toolbar with standard file and editing icons, a left sidebar with drawing tools, and a right sidebar titled "Select properties to predict". This sidebar features a "T.E.S.T. 18" indicator and two columns of checkboxes for "Toxicological properties" and "Physical properties". A "Calculate" button is located at the bottom right of the interface.

Select properties to predict

T.E.S.T. 18

<input checked="" type="checkbox"/> Toxicological properties	<input checked="" type="checkbox"/> Physical properties
<input checked="" type="checkbox"/> 96 hour fathead minnow LC50	<input checked="" type="checkbox"/> Normal boiling point
<input checked="" type="checkbox"/> 48 hour D. magna LC50	<input checked="" type="checkbox"/> Melting point
<input checked="" type="checkbox"/> 48 hour T. pyriformis IGC50	<input checked="" type="checkbox"/> Flash point
<input checked="" type="checkbox"/> Oral rat LD50	<input checked="" type="checkbox"/> Vapor pressure
<input checked="" type="checkbox"/> Bioaccumulation factor	<input checked="" type="checkbox"/> Density
<input checked="" type="checkbox"/> Developmental toxicity	<input checked="" type="checkbox"/> Surface tension
<input checked="" type="checkbox"/> Ames mutagenicity	<input checked="" type="checkbox"/> Thermal conductivity
<input checked="" type="checkbox"/> Estrogen Receptor RBA	<input checked="" type="checkbox"/> Viscosity
<input checked="" type="checkbox"/> Estrogen Receptor Binding	<input checked="" type="checkbox"/> Water solubility

Calculate

Real-Time Predictions

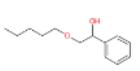
Property	Experimental Value	Prediction				
		Consensus	Hierarchical clustering	Single model	Group contribution	Nearest neighbor
96 hour fathead minnow LC50		4.477 -Log10(mol/L) 6.954 mg/L	4.195 -Log10(mol/L) 13.288 mg/L	3.994 -Log10(mol/L) 21.110 mg/L	3.478 -Log10(mol/L) 69.224 mg/L	6.238 -Log10(mol/L) 0.120 mg/L
48 hour D. magna LC50		4.398 -Log10(mol/L) 8.328 mg/L	3.877 -Log10(mol/L) 27.677 mg/L	4.039 -Log10(mol/L) 19.026 mg/L	4.084 -Log10(mol/L) 17.173 mg/L	5.593 -Log10(mol/L) 0.532 mg/L
48 hour T. pyriformis IGC50		4.063 -Log10(mol/L) 18.039 mg/L	3.731 -Log10(mol/L) 38.668 mg/L		3.386 -Log10(mol/L) 85.610 mg/L	5.070 -Log10(mol/L) 1.773 mg/L
Oral rat LD50		1.758 -Log10(mol/kg) 3640.950 mg/kg	1.982 -Log10(mol/kg) 2172.756 mg/kg			1.533 -Log10(mol/kg) 6101.245 mg/kg
Bioaccumulation factor		1.797 Log10 62.700	2.202 Log10 159.310	1.287 Log10 19.346	1.181 Log10 15.157	2.520 Log10 330.834
Developmental toxicity		false	false	false		true
Ames mutagenicity		false	false			false
Estrogen Receptor RBA		-3.075 Log10 8.418*10 ⁻⁴	-3.078 Log10 8.356*10 ⁻⁴	-3.720 Log10 1.907*10 ⁻⁴		-2.427 Log10 0.004
Estrogen Receptor Binding		true	true	true	false	true

Predicted Water solubility at 25°C for OC(C=1C=CC=CC1)COCCCCC from Consensus method

Prediction results

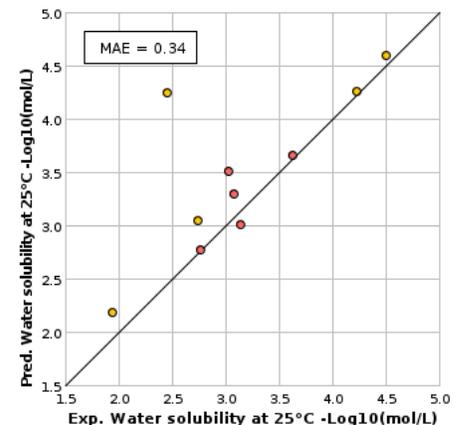
Endpoint	Experimental value	Predicted value
Water solubility at 25°C -Log10(mol/L)	N/A	2.46
Water solubility at 25°C mg/L	N/A	723.26

Individual Predictions	
Method	Predicted value -Log10(mol/L)
Hierarchical clustering	2.42
Group contribution	2.32
Nearest neighbor	2.64



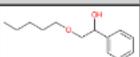
Predictions for the test chemical and for the most similar chemicals

Prediction results (colors defined in table below)



Chemicals	MAE*
Entire set	0.58
Similarity coefficient ≥ 0.5	0.34

*Mean absolute error in -Log10(mol/L)

CAS	Structure	Similarity Coefficient	Experimental value -Log10(mol/L)	Predicted value -Log10(mol/L)
<chem>OC(C=1C=CC=CC1)COCCCCC</chem> (test chemical)			N/A	2.46
104-40-5		0.68	4.50	4.60
1219-38-1		0.67	4.22	4.26

Chemistry Dashboard

Aa ▼ Aa Aa ▲

Downloads

[DSSTox Identifier to PubChem Identifier Mapping File](#)

Posted: 11/14/2016

The DSSTox to PubChem Identifiers mapping file is in TXT format and includes the PubChem SID, PubChem CID and DSSTox substance identifier (DTXSID).

SID	CID	DTXSID
316388891	20404	DTXSID30873143
316388890	10142816	DTXSID70873142
316388889	50742127	DTXSID40873139
316388888	19073841	DTXSID20873137
316388887	11505215	DTXSID00873135
316388886	25021861	DTXSID80873133
316388885	2784427	DTXSID60873131
316388884	6731	DTXSID00873130

[DSSTox identifiers mapped to CAS Numbers and Names File](#)

Posted: 11/14/2016

The DSSTox Identifiers file is in Excel format and includes the CAS Number, DSSTox substance identifier (DTXSID) and the Preferred Name.

1	casn	dssstox_substance_id	preferred_name
2	26148-68-5	DTXSID7020001	A-alpha-C
3	107-29-9	DTXSID2020004	Acetaldehyde oxime
4	60-35-5	DTXSID7020005	Acetamide
5	103-90-2	DTXSID2020006	Acetaminophen
6	968-81-0	DTXSID7020007	Acetohexamide
7	18523-69-8	DTXSID2020008	Acetone[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazone
8	75-05-8	DTXSID7020009	Acetonitrile
9	127-06-0	DTXSID6020010	Acetoxime
10	65734-38-5	DTXSID6020012	N'-Acetyl-4-(hydroxymethyl) phenylhydrazine

Step Two: Data Gap Analysis & Generate Data Matrix

Neighbors by: Chem: Morgan Fgrpts
Filter by: invivo data

Summary Data Gap Analysis

	bio tx27	bio txct	chm ct	tox txrf
Acrolein diethylacetal	14	0	4	0
Ethylene glycol diethyl e...	7	0	4	95
Ethion	20	674	4	345
Myrcene	22	714	8	311
Chlorethoxyfos	22	819	12	345
2-Ethoxyethyl acetate	0	714	8	95
bis(2-Chloro-1-methylet...	7	0	8	83
Methyleugenol	7	714	8	263
Fosamine ammonium	9	0	11	180
Ethoprop	2	819	6	402
Butanal oxime	5	187	6	85

Group: ToxRef
By: Tox Fingerprint
Run Read-Across

of Analogs: 10

	Acrolein diethylacetal	Ethylene glycol diethyl...	Ethion	Myrcene	Chlorethoxyfos	2-Ethoxyethyl acetate	bis(2-Chloro-1-methylet...	Methyleugenol	Fosamine ammonium	Ethoprop	Butanal oxime
CHR:Body Weight											
CHR:Bone Marrow											
CHR:Brain											
CHR:Clinical Chemistry											
CHR:Clinical Signs											
CHR:Food Consumption											
CHR:General											
CHR:Heart											
CHR:Hematology											
CHR:Kidney											
CHR:Liver											
CHR:Lung											

Next

Data gap analysis

GenRA

Step Three: Run GenRA Prediction

of Analogs: 10

Run

Next

Min+: 0

Min-:

Sim Wt:

Download: Filetype

Target

1

Source analogues

	Acrolein diethyl...	Ethylene glycol...	Ethion	Myrcene	Chlorethoxyfos	2-Ethoxyethyl a...	bis(2-Chloro-1-...	Methyleugenol	Fosamine amm...	Ethoprop	Butanal oxime
CHR:Abdominal Cavity											
CHR:Adrenal Gland											
CHR:Artery (General)											
CHR:Auditory Startle R...											
CHR:Bile duct											
CHR:Blood											
CHR:Blood vessel											
CHR:Body Weight											
CHR:Bone											

Run GenRA

Future Development Real Time OPERA Predictions

Mansouri et al. *J Cheminform* (2018) 10:10
<https://doi.org/10.1186/s13321-018-0263-1>

 Journal of Cheminformatics

RESEARCH ARTICLE

Open Access



OPERA models for predicting physicochemical properties and environmental fate endpoints

Kamel Mansouri^{1,2,3*} , Chris M. Grulke¹, Richard S. Judson¹ and Antony J. Williams¹

Select properties to predict

T.E.S.T. 18 **OPERA** Search

Toxicological properties + - **Physical properties** + -

96 hour fathead minnow LC50 Normal boiling point



United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Chemistry Dashboard

761 Thousand Chemicals

Search a chemical by systematic name, synonym, CAS number, or InChIKey

Chemical Assay Gene Product

Search Assay Endpoint Name

Identifier substring search

[Read more news](#)

An article regarding an Excel Version of the Abstract Sifter is published.
March 7th, 2018 at 9:21:27 AM

The abstract sifter that is integrated into the Dashboard (for example [here for Atrazine](#)) is available as an Excel add-in. Our recent article on the Abstract Sifter for Excel [has been published](#).

...●...

Summary remarks on the Dashboard

- **The CompTox Chemistry Dashboard provides access to data for ~760,000 chemicals**
- **High quality data from ongoing curation efforts**
- **An integration hub for multiple “modules”**
 - Experimental and predicted properties
 - Human and Ecological Hazard data
 - Exposure data - products, data in the environment
 - *In vitro* bioassay data - ToxCast/Tox21
 - Literature searching - Google Scholar and PubMed
 - Specialized searches - mass/formula for analytical support
 - Batch searching and Real Time Predictions
- **The primary architecture for NCCT data**

Take home messages

- **Outlined Regulatory Drivers**
- **What Integrated Approaches to Testing and Assessment (IATA) are and how they have evolved taking into account Adverse Outcome Pathways (AOPs)**
- **How different decision contexts impact the types of NAMs applied**
- **Practical workflow - where and what approaches (including NAMs) can be used with reference to the US EPA Chemistry Dashboard**

Acknowledgments

- The NCCT CompTox Chemistry Dashboard Development Team
- Ann Richard, Chris Grulke
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- Kamel Mansouri - OPERA models
- Todd Martin - TEST predictions
- Nancy Baker - Abstract Sifter
- George Helman, Imran Shah, Grace Patlewicz - GenRA

Dashboard Contact

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