

# Toxicity Testing in the 21<sup>st</sup> Century and NexGen Risk Assessments



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- 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.

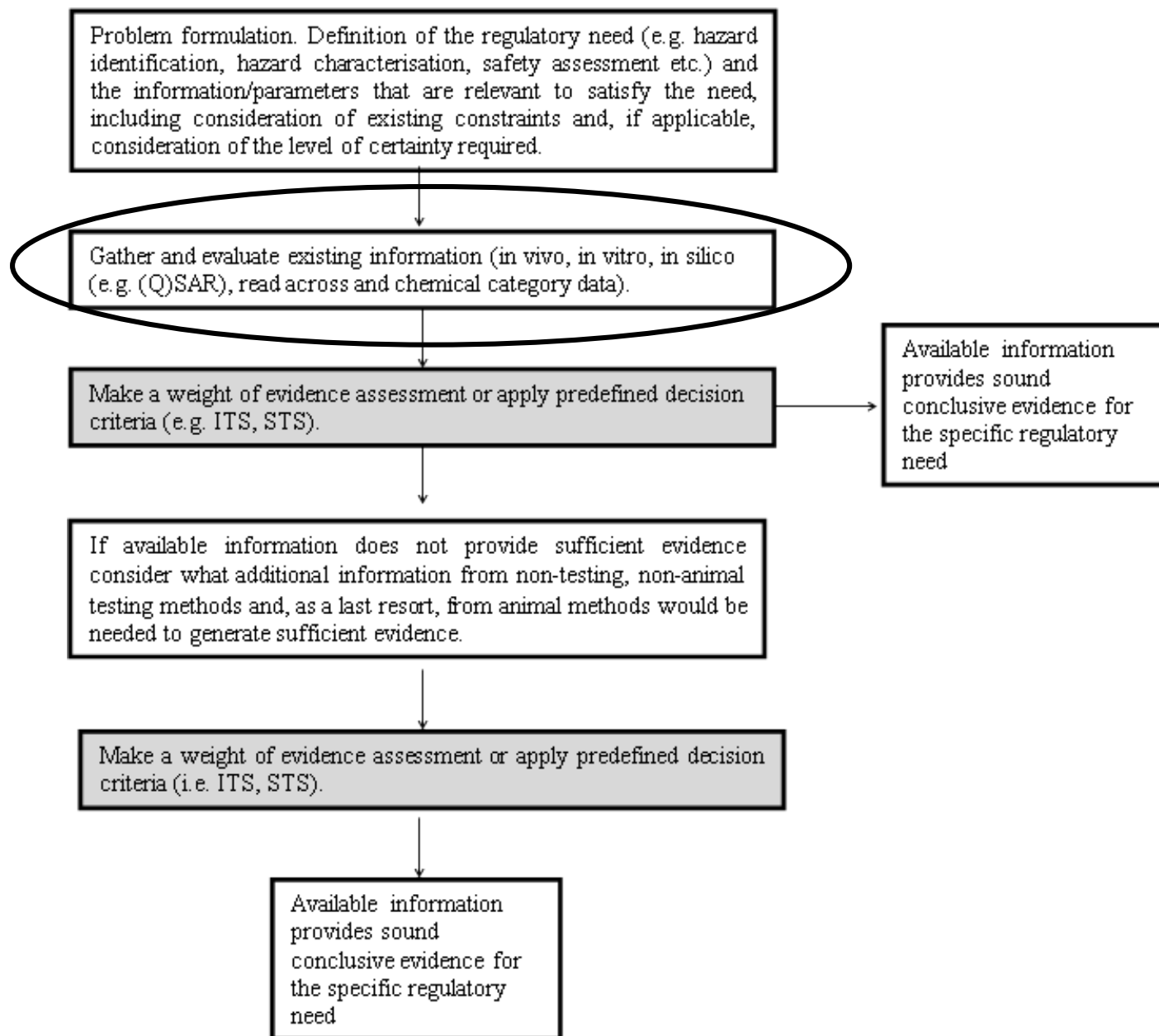
# Regulatory drivers

- REACH-like schemes also have been established in China, South Korea, and Turkey.
- In the US, the new Frank Lautenberg Chemical Safety for the 21<sup>st</sup> Century Act (LCSA) 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 LCSA 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 Substances 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

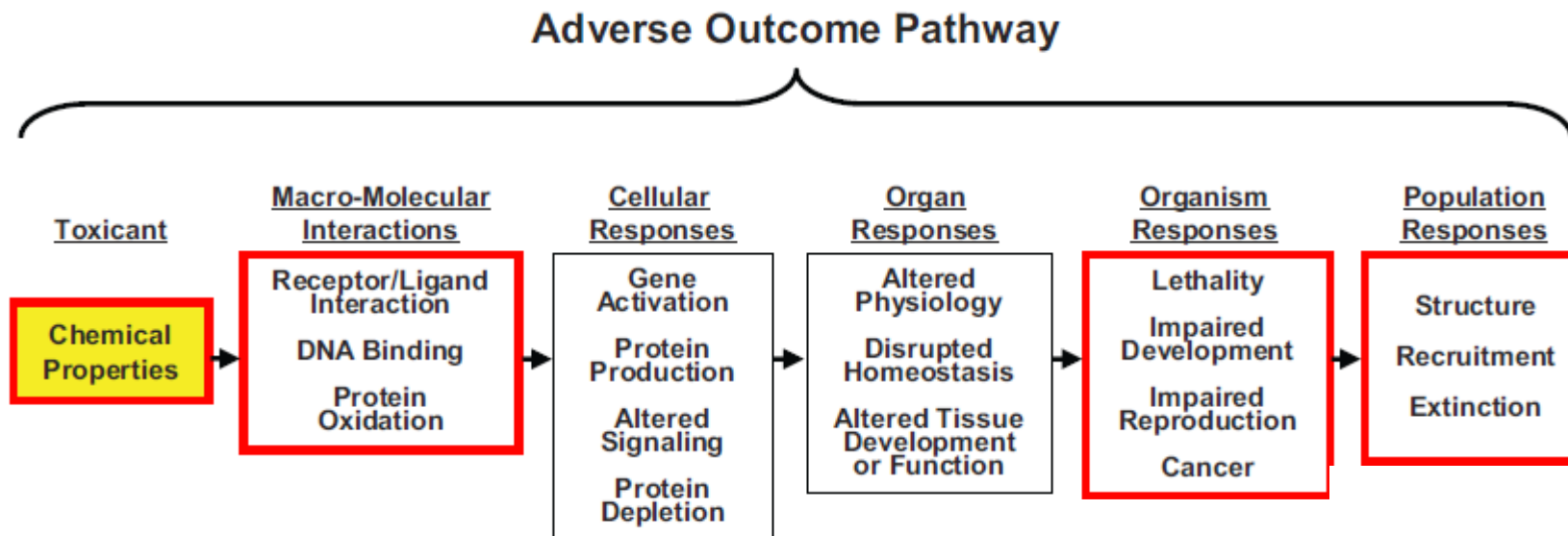


# Mechanistic based and AOP-informed IATA

- 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

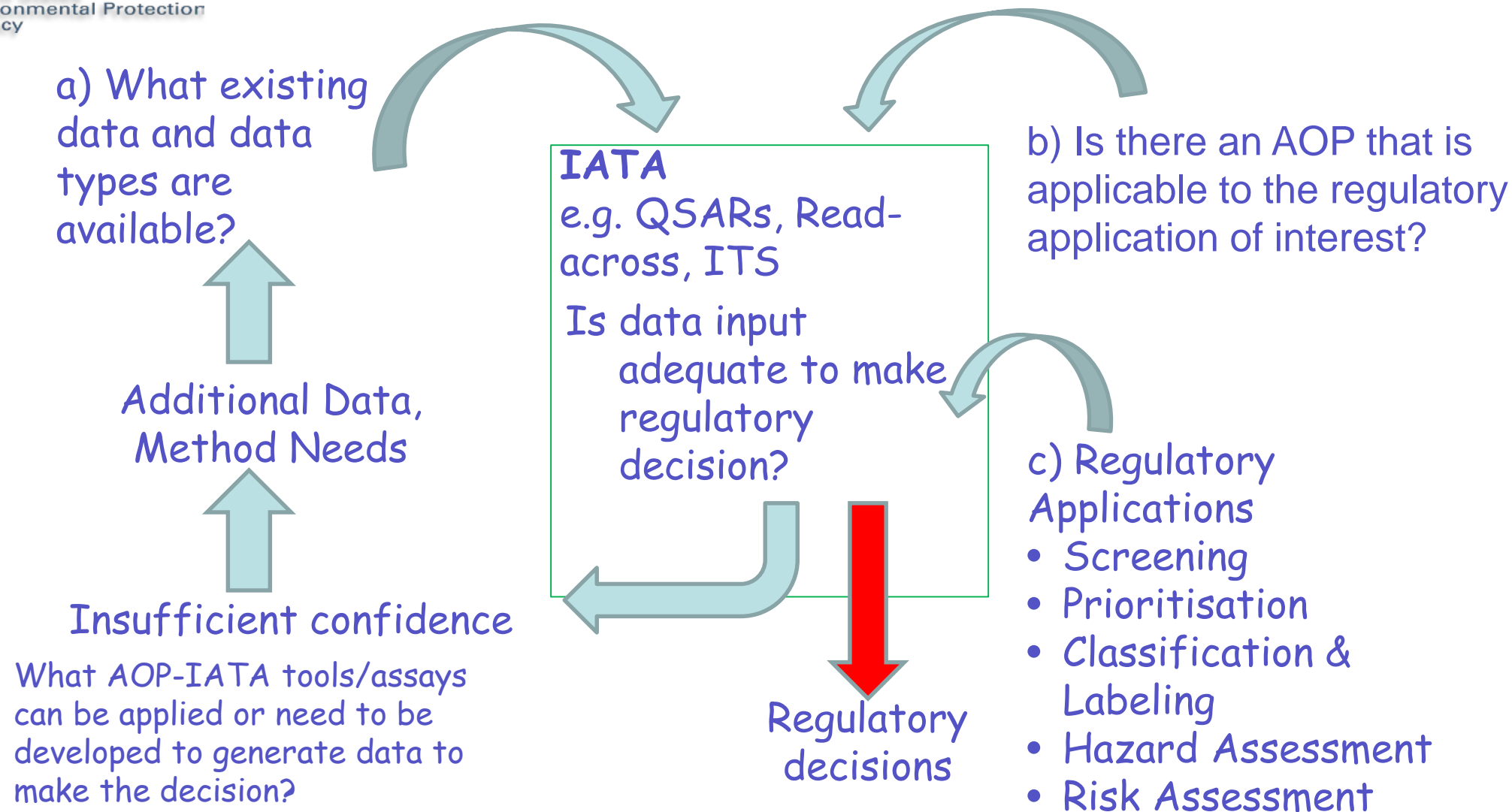


An AOP represents existing knowledge concerning the sequence of events and causal linkages between initial molecular events, ensuing key events and an adverse outcome at the individual or population level.

# 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) <b>Analytical Validation</b> 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) <b>Qualification</b> of the prediction models
6	<b>Utilization:</b> defining and documenting where there is sufficient scientific confidence to use one or more AOP-based prediction models <b>for a specific purpose</b> (e.g., priority setting, <i>chemical category formation, integrated testing</i> , predicting <i>in vivo</i> responses, etc.)
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.

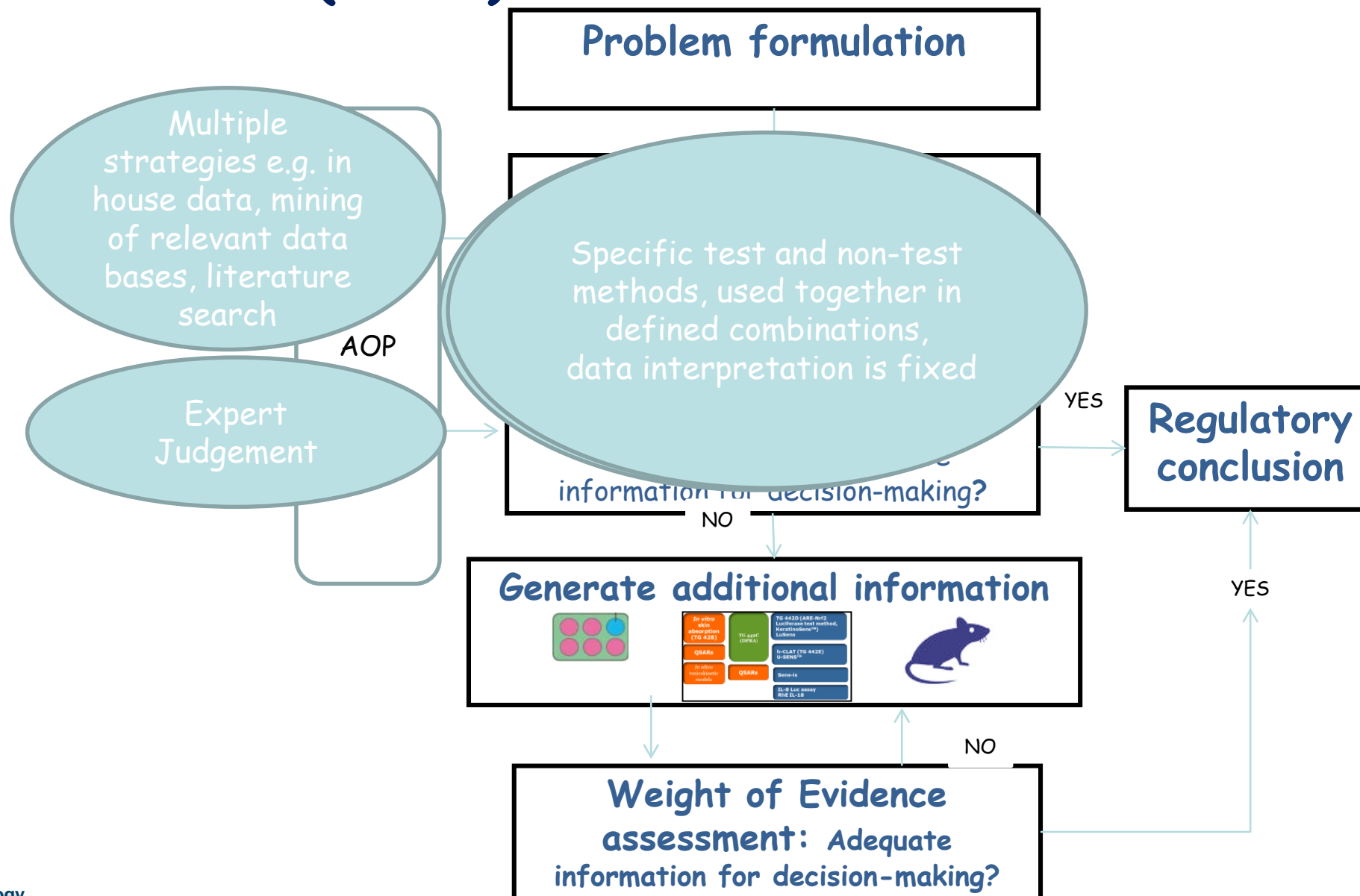
# AOP-informed IATA



# 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\(2016\)](#)

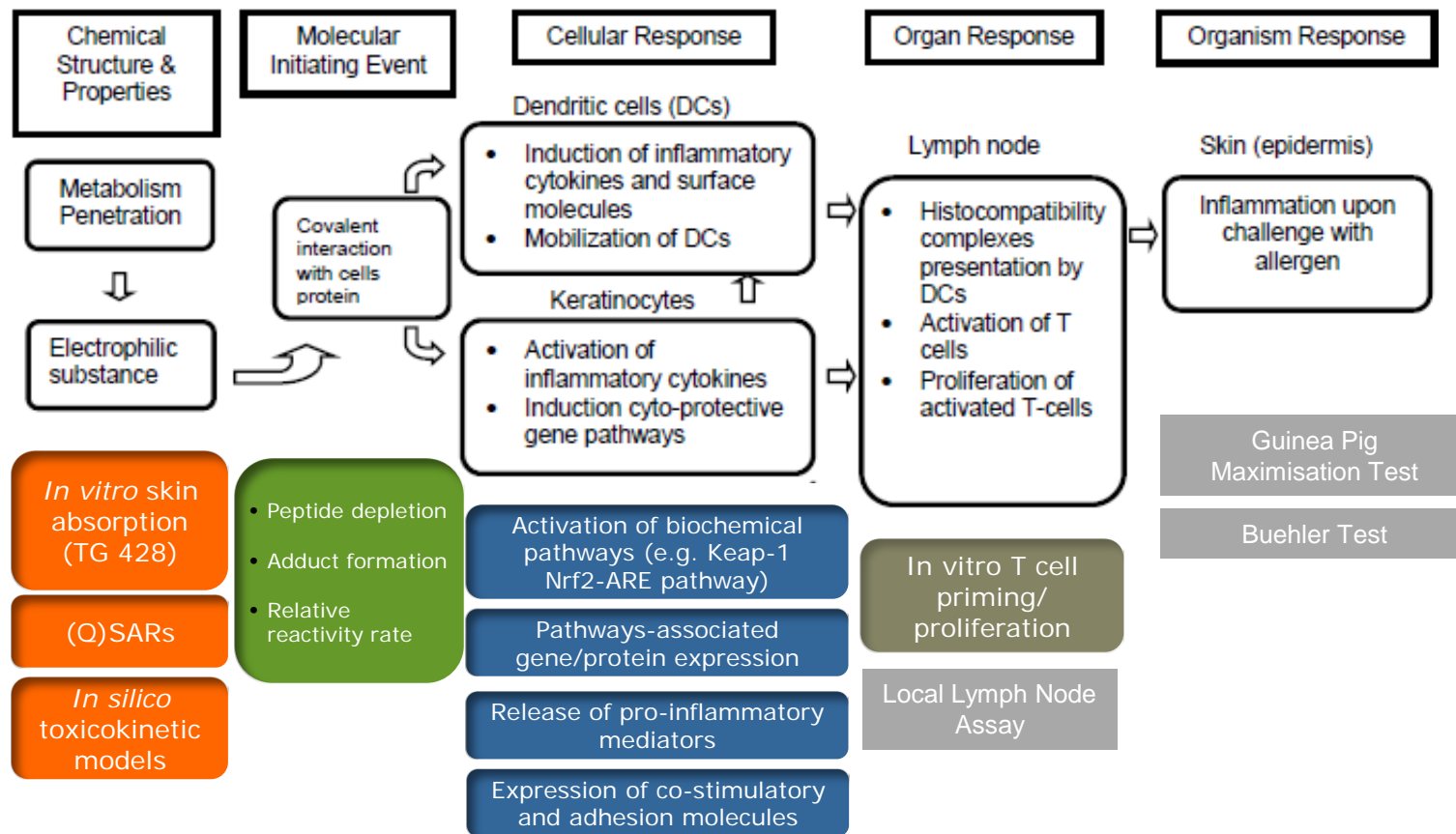
# Defined approaches within IATA

- 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



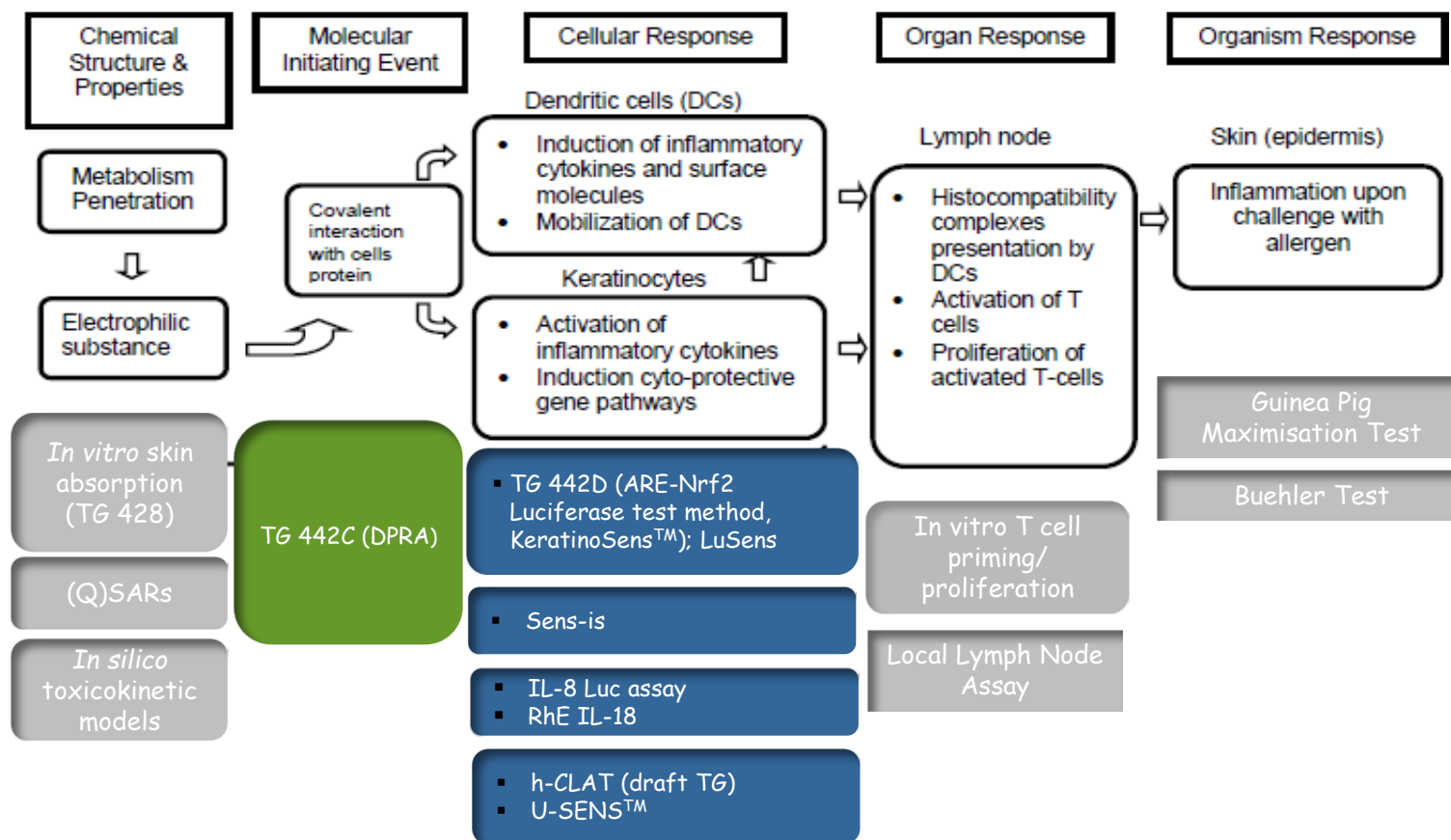
# Defined approaches within IATA: Skin sensitisation

## AOP and available toolbox of non-animal methods

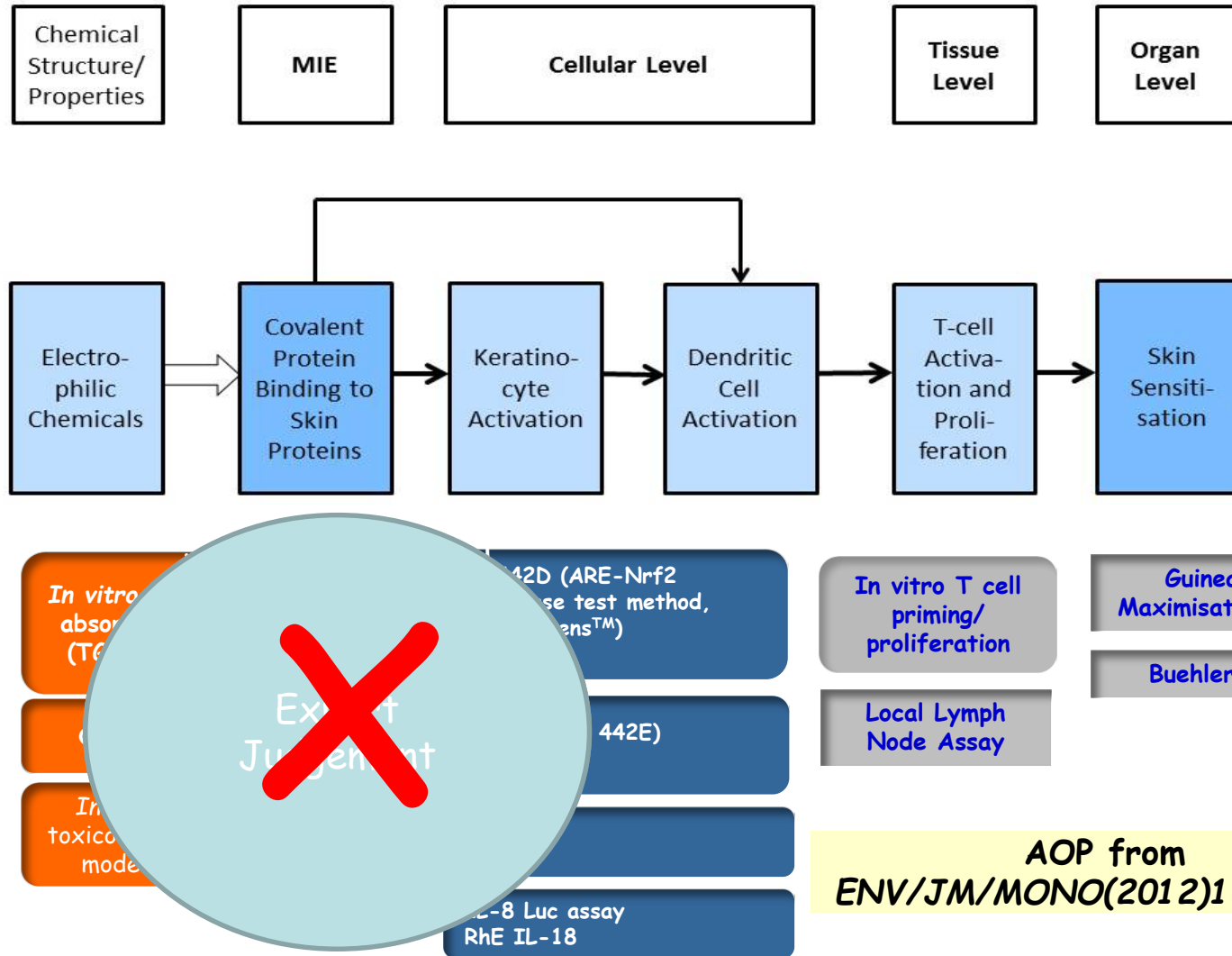


Presented by S Casati, JRC

# Defined approaches within IATA: Skin sensitisation (SS)

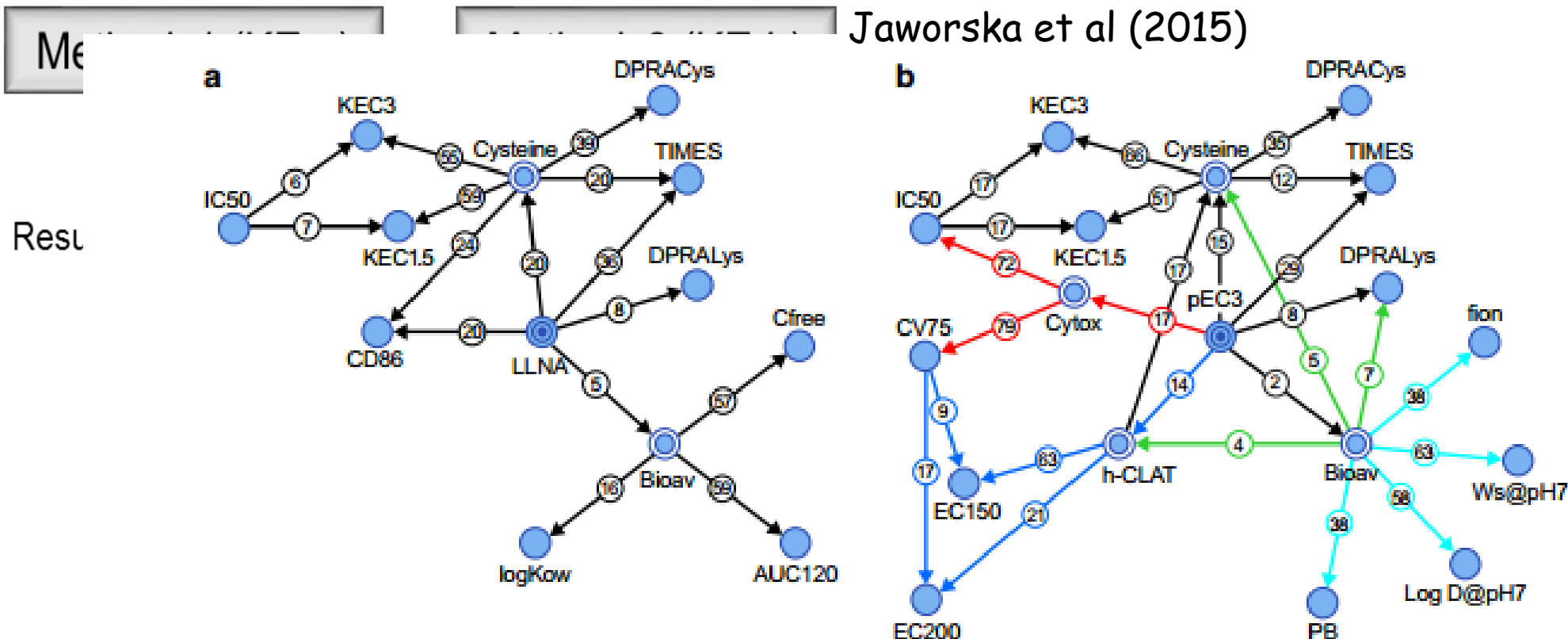


# Defined approaches within IATA-SS



# Defined approaches for skin sensitisation

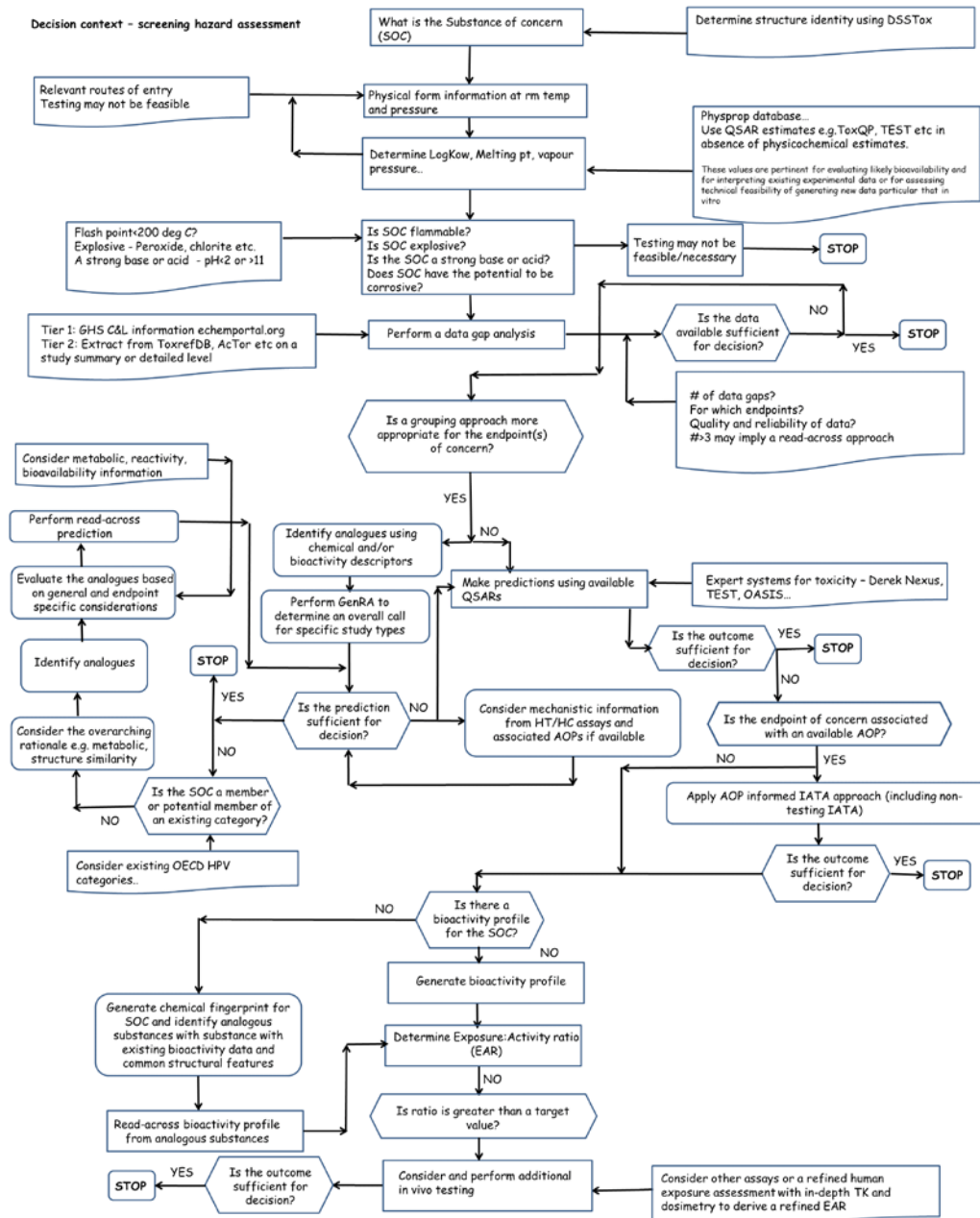
Bayesian Networks for  
Skin sensitization  
Jaworska et al (2015)



# 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

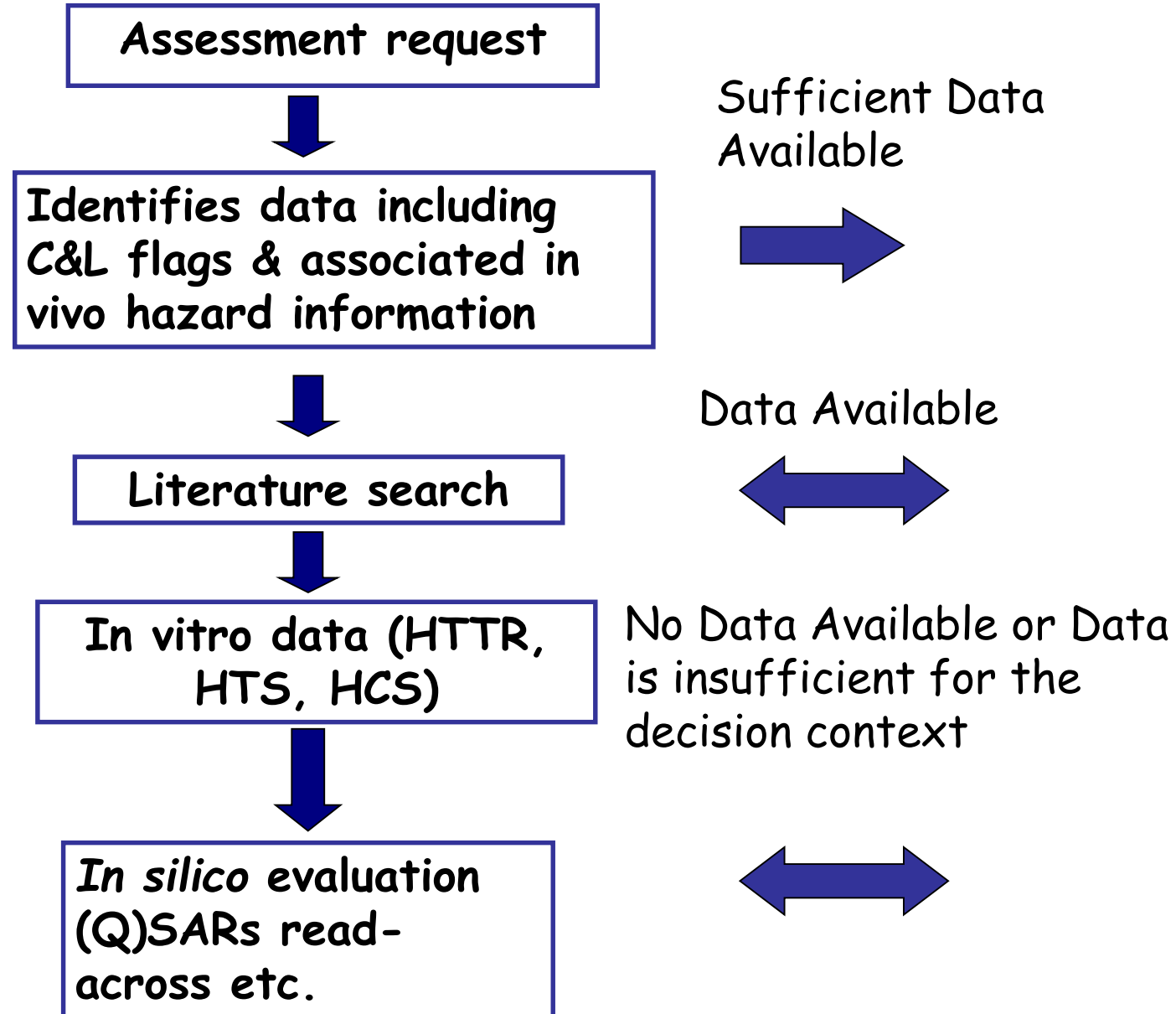


# Decision contexts

- **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

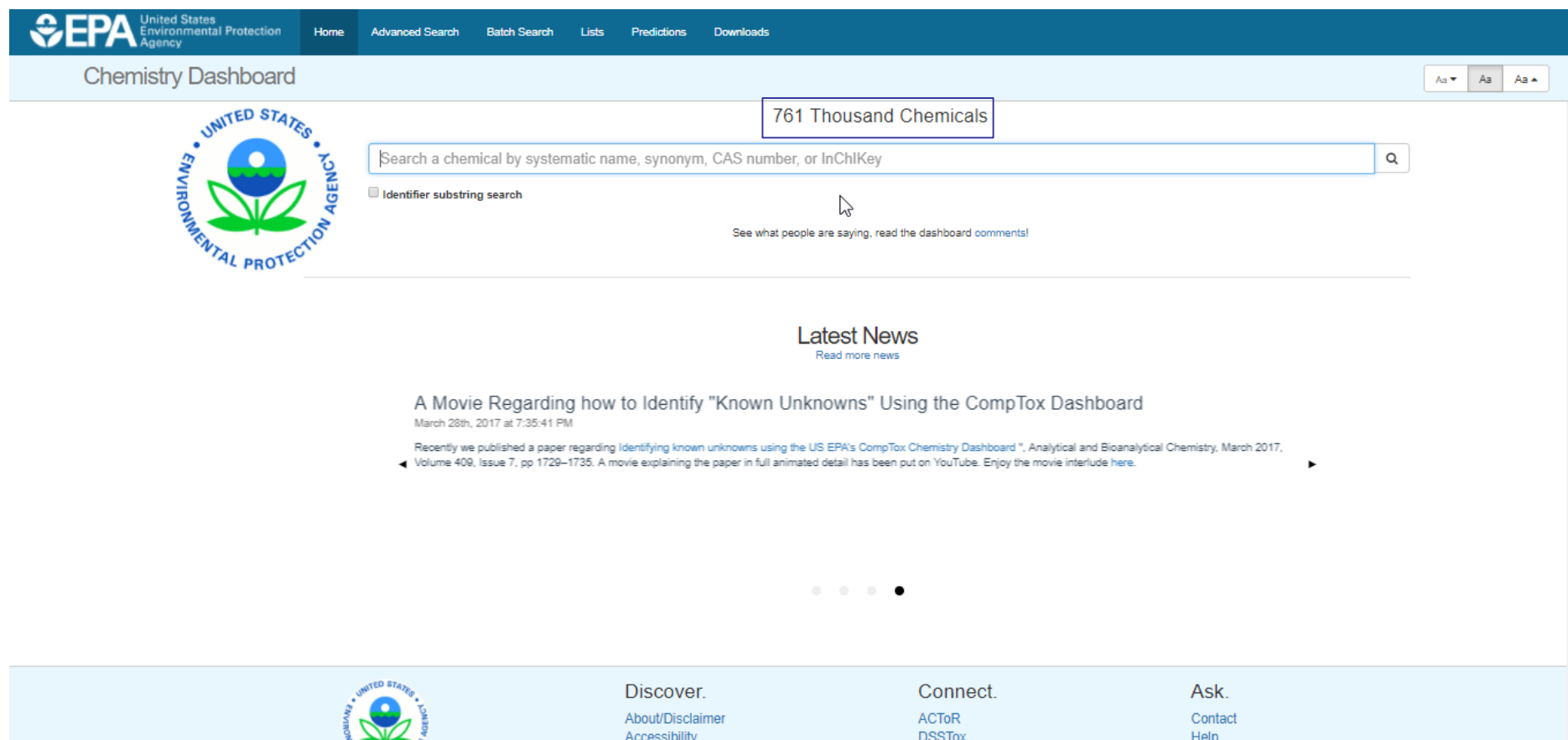


# The CompTox Chemistry Dashboard

- 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>



The screenshot shows the CompTox Chemistry Dashboard interface. At the top is a dark blue navigation bar with the EPA logo and links for Home, Advanced Search, Batch Search, Lists, Predictions, and Downloads. Below this is a light blue header with the text "Chemistry Dashboard" and a font size selector (Aa). The main content area features a large search bar with the text "761 Thousand Chemicals" and a search button. To the left of the search bar is the EPA logo. Below the search bar is a checkbox for "Identifier substring search" and a link to "See what people are saying, read the dashboard comments!". The "Latest News" section is titled "A Movie Regarding how to Identify 'Known Unknowns' Using the CompTox Dashboard" and includes a date, a brief description, and a link to the movie. The footer is a light blue bar with the EPA logo and three columns of links: "Discover." (About/Disclaimer, Accessibility), "Connect." (ACToR, DStox), and "Ask." (Contact, Help).

EPA 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](#).

Discover.  
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[Accessibility](#)


Connect.  
[ACToR](#)  
[DStox](#)

Ask.  
[Contact](#)  
[Help](#)

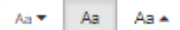
# Detailed Chemical Pages

 United States  
Environmental Protection  
Agency






Home Advanced Search Batch Search Lists Predictions Downloads

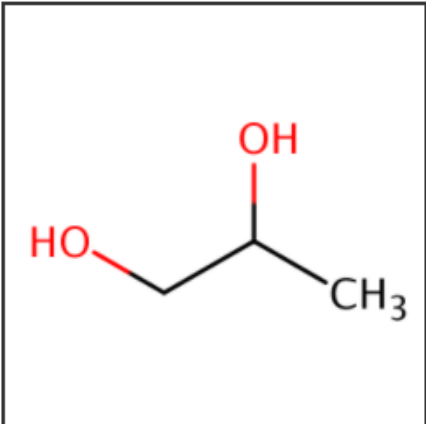
Search All Data 

Chemistry Dashboard | EPAHFR

Submit Comment Copy 

1,2-Propylene glycol  
57-55-6 | DTXSID0021206



Wikipedia

Propylene glycol (IUPAC name: propane-1,2-diol) is a synthetic organic compound with the chemical formula C<sub>3</sub>H<sub>8</sub>O<sub>2</sub>. 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


United States  
Environmental Protection  
Agency

[Home](#)
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[Batch Search](#)
[Lists](#)
[Predictions](#)
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Chemistry Dashboard | EPAHFR

[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:

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

# In Vitro Bioassay Screening

## ToxCast and Tox21





# 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)

<a href="#">Categorization type</a>	<a href="#">Number of Unique Products</a>
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

very then 2) click on Retrieve. <sup>i</sup>

Retrieve Articles <sup>i</sup>

13 of 13 articles loaded...

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])

s to sift abstracts. <sup>i</sup>

Download / Send to... <sup>i</sup> Download Sifter for Excel <sup>i</sup>

	Authors	Journal	Rev
garettes: a systematic review of available studies on hea...	Zulkifli; 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 Efinaconazole 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	
ilogically-based pharmacokinetic modeling to address n...	Kimman; Sweeney; Corley; Gargas	Risk analysis : an official publication of the Society f...	
of 2-methoxypropionic acid formed from beta-propylene...	Carney; Pottenger; Johnson; Liberacki; Tomesi; 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
<b>General</b>	<b>Toxicology</b>	<b>Publications</b>	<b>Analytical</b>	<b>Prediction</b>						
EPA Substance Registry ...	ACToR	Toxline	RSC Analytical Abstracts	2D NMR HSQC/HMBC Pr...						
Household Products Data...	DrugPortal	Environmental Health Per...	Tox21 Analytical Data	Carbon-13 NMR Prediction						
PubChem	CCRIS	NIEHS	MONA: MassBank North ...	Proton NMR Prediction						
CPCat	ChemView	National Toxicology Progr...	NIST NIST IR Spectrum	ChemRTP Predictor						
DrugBank	CTD	Google Books	NIST NIST MS Spectrum	LSERD						
Wikipedia	eChemPortal	Google Scholar								
MSDS Lookup	Gene-Tox	Google Patents								
ChEMBL	HSDB	PPRTVWEB								
Chemical Vendors	ToxCast Dashboard 2	PubMed								
NIOSH Chemical Safety ...	LactiMed	IRIS Assessments								
ToxPlanet	International Toxicity Esti...	EPA HERO								
ACS Reagent Chemicals	ATSDR Toxic Substances...	RSC Publications								
Wikidata	ACToR PDF Report	BioCaddie DataMed								
ChemHat: Hazards and A...	CREST	Springer Materials								
Wolfram Alpha		Federal Register								

# Integrated Linkouts

A Substance Registry ... ACToR Toxline

usel  
oCh  
Cat  
igBa

ikipedia  
DS Lookup

eChemPortal  
Gene-Tox

Google Scholar  
Google Patents

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.

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

ToxPlanet International Toxicity E

Substance Registry ... ACToR Toxline

el  
Ch  
at

Bank  
edia

CTD  
eChemPortal

Google Books  
Google Scholar

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

# Integrated Linkouts

## Comparative Toxicogenomics DB



Illuminating how chemicals affect human health.

YOUR QUERIES | CONTACT US

Comparative Toxicogenomics Database

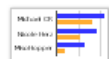
Home Search Analyze Download Help

### 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

ALL

Association type

ALL

Filter

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

M▼

Mass

Da

±

Error

Da

ppm

Search Q

### Molecular Formula Search?

Molecular Formula

☒ MS Ready Formula?

☐ Exact Formula?

Search Q

### Generate Molecular Formula(e)?

±

Min/Max

Mass

Da

±

Error

Da

ppm

Search Q

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

±

 ☒ ppm

# Advanced Searches

United States  
Environmental Protection  
Agency

Home
Advanced Search
Batch Search
Lists
Predictions
Downloads

Search All Data

Chemistry Dashboard

Download / Send

Sort by: Mass Difference

298 of 298 chemicals visible

Search Results

Searched by Mass: '191.31 +/- 5 ppm'

Hide:

Multicomponent Chemicals

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

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

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

Display All Chemicals Download Chemical Data

# 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)

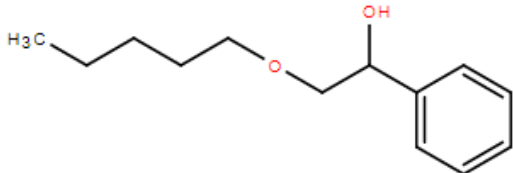
C6H12O3  
C7H7N3  
C8H11NO  
C7H5NOS  
C9H15NO  
C11H12O  
C9H8O3  
C6H12O5  
C9H15NO2

- ☐ 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)

# Excel Output

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

# Real-Time Predictions


OCC(O)Cc1ccccc1

H  
C  
N  
O  
S  
P  
F  
Cl  
Br  
I  
PT

Chiral

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 <sup>-4</sup>	-3.078 Log10 8.356*10 <sup>-4</sup>	-3.720 Log10 1.907*10 <sup>-4</sup>		-2.427 Log10 0.004
Estrogen Receptor Binding		true	true	true	false	true

# Real-Time Predictions

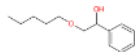
Predicted Water solubility at 25°C for OC(C=1C=CC=CC1)COCCCCC from Consensus method

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

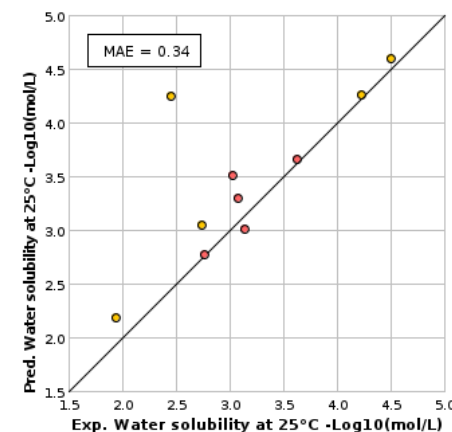
Individual Predictions

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



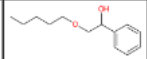

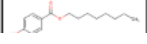
Predictions for the test chemical and for the most similar chemicals

Prediction results (colors defined in table below)



Chemicals	MAE*
Entire set	0.58
Similarity coefficient $\geq 0.5$	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
<a href="#">104-40-5</a>		0.68	4.50	4.60
<a href="#">1219-38-1</a>		0.67	4.22	4.26



## 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

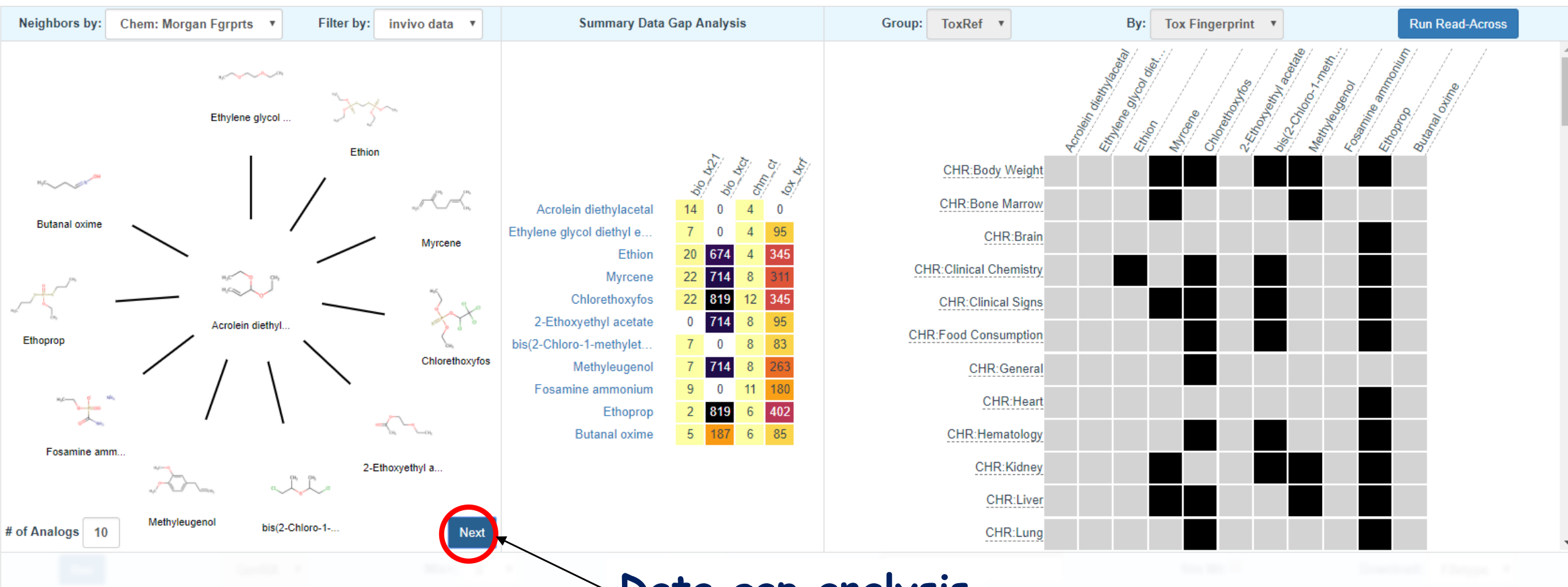
### [DSSTox identifiers mapped to CAS Numbers and Names File](#)

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	casm	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



## Data gap analysis

## Step Three: Run GenRA Prediction

Source analogues

Run GenRA

Target

1

Min+: 0 Min-:

Sim Wt: Download: Filetype

	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											

# 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<sup>1,2,3\*</sup> , Chris M. Grulke<sup>1</sup>, Richard S. Judson<sup>1</sup> and Antony J. Williams<sup>1</sup>

Select properties to predict

T.E.S.T. 18

OPERA

Search

☒ Toxicological  
properties

+ -


☒ Physical properties

+ -

☒ 96 hour fathead minnow LC50

☒ Normal boiling point

# Future Search Possibilities



United States  
Environmental Protection  
Agency

HomeAdvanced SearchBatch SearchListsPredictionsDownloads

Chemistry Dashboard

761 Thousand Chemicals

Chemical

Assay

Gene

Product

☐ 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
- NERL scientists (Jon Sobus, Elin Ulrich) – Mass Spectrometry
- 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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