OECD QSAR Toolbox and read-across Webinar

22 October 2014, 4:00pm BST

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Today's webinar

This webinar will cover:

- Use of integrated approaches to testing and assessment and adverse outcome pathways to organize existing information and plan a non-animal testing strategy;
- How QSARs and read-across can be used to meet REACH requirements;
- Use of the OECD QSAR Toolbox;
- Future research projects.

Speakers

- **Dr. Amy Clippinger**, PETA International Science Consortium Ltd
- **Dr. Grace Patlewicz**, DuPont
- **Dr. Mark Cronin**, Liverpool John Moores University
- Chair: **Emma Chynoweth**, Chemical Watch

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Questions

- Please submit questions during the webinar using your chat box

- Any unanswered questions can be raised on our Forum following the webinar: http://forum.chemicalwatch.com/

Upcoming Webinars

Webinar 2: Skin Irritation and Corrosion

November 11, 2014,

11am ET, 4pm GMT

- **Emilia Costin**, *Institute for In Vitro Sciences*
- **Costanza Rovida**, *CAAT Europe and REACH Mastery*

Webinar 3: Serious Eye Damage and Eye Irritation

December 4, 2014

11am ET, 4pm GMT

- **Kim Norman**, *Institute for In Vitro Sciences*
- **João Barroso**, *EURL ECVAM*

Please contact the PETA International Science Consortium, Ltd., for assistance in avoiding animal testing

pisc@piscltd.org.uk

www.piscltd.org.uk

Non-testing approaches: How can (Q)SARs, read-across and the OECD QSAR Toolbox help in addressing REACH 2018?

Grace Patlewicz, DuPont, Newark, DE, USA

Mark Cronin, Liverpool John Moores University, England

Context – REACH Deadline

- 31st May 2018 marks the deadline for registration of phase-in substances manufactured or imported at 1-100 tonnes per year
- The information requirements for these tonnage bands are described in Annexes VII and VIII of the legal text
- This impacts 10,000s of substances

Context – REACH Legislation

- To address financial and animal welfare concerns, REACH explicitly expresses the need to use non-testing approaches to reduce the extent of experimental testing
- Article 25(1) states: "in order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort."
- Article 13(1) states: "Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, *in vitro* methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across)..."

Aim(s) of this Webinar

- To provide an introduction of how non-testing approaches can be exploited as part of an Integrated Approach to Testing and Assessment (IATA) to address the information requirements within these Annexes
  - Focusing on *in silico* approaches

- To highlight advances in the Tox21 field that could in future impact the type of data that are generated to fulfil these information requirements

Outline

- The IATA construct and related terms
  - Definitions
  - IATA under REACH
- Non-testing approaches
  - Definitions
  - (Q)SARs
- Chemical grouping, category and analogue approaches
  - Definitions
  - Considerations associated with read-across
  - Data gap filling within category/analogue approaches
- Future directions - AOPs
  - Read-across enhancement
  - (Q)SAR and IATA development
- Take home messages
- Useful links

Integrated Approaches to Testing and Assessment (IATA)

"IATA is a means of organising and analysing all the available relevant data on a given substance or group of substances coupled with mechanistic, exposure, and dosimetry information where possible, to focus testing when needed and facilitate an assessment conclusion" – OECD definition

"Integrated Testing Strategies (ITS) are …. approaches that integrate different types of data and information into the decision-making process. In addition to the information from individual assays, test batteries, and/or tiered test schemes, integrated testing strategies may incorporate approaches such as weight-of-evidence and exposure/population data into the final risk assessment for a substance"
http://www.alttox.org/ttrc/emerging-technologies/its/

In practice:
A means of integrating existing data and non-testing data, determining what new information needs to be generated in order to make a decision

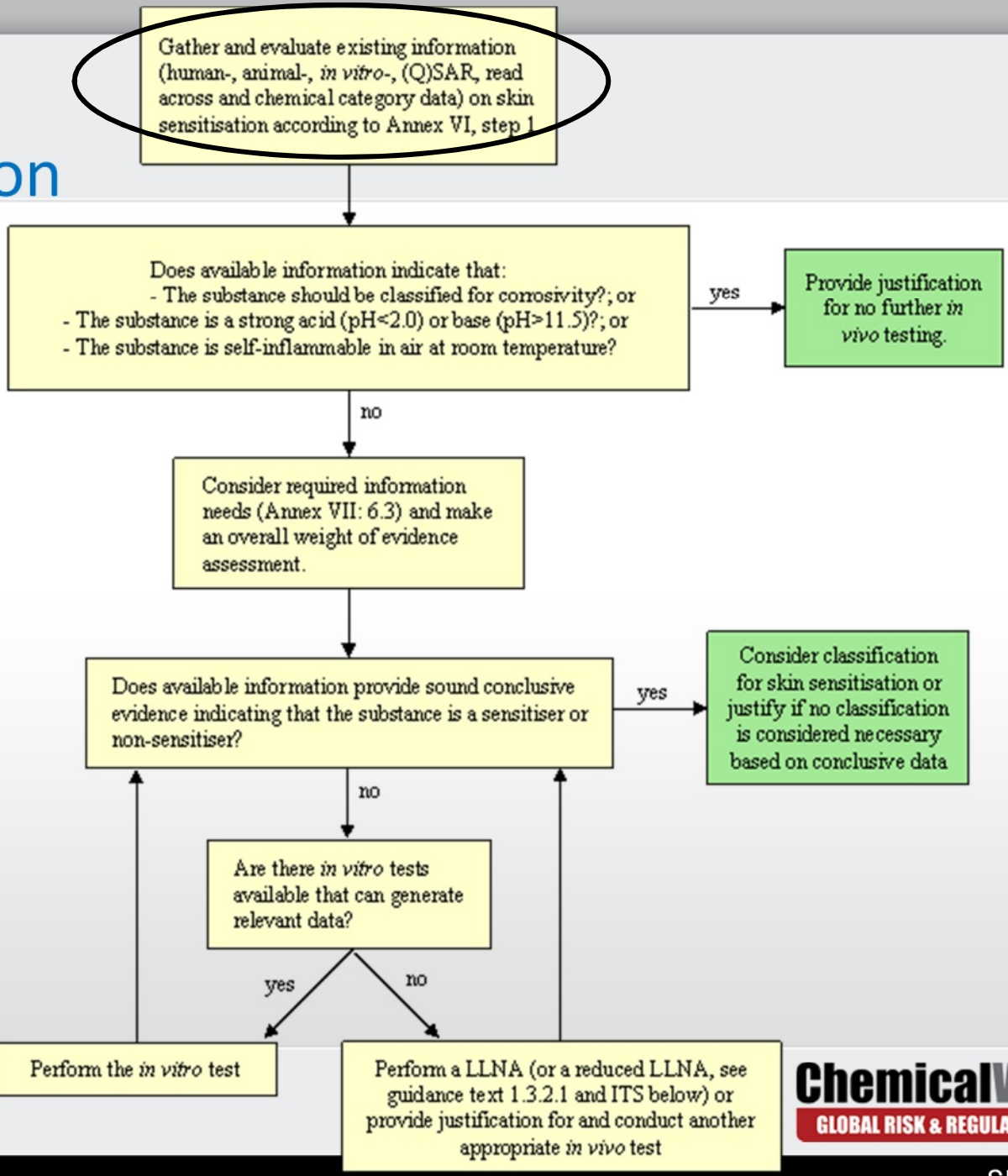
Integrated Testing Strategies (ITS)

- Under REACH, such IATA are termed ITS and one has been described for each of the endpoints of interest
- These ITS can be likened to workflows depicting the different steps of gathering (toxicity) information for a substance in order to evaluate its “fit for purposes” for classification & labelling and/or risk assessment
- Some ITS are more complex than others but the generic building blocks of considering existing data, *in vitro* alternatives, non-testing approaches BEFORE instigating new *in vivo* testing are the same
- Non-testing approaches fit within the context of these ITS schemes and should not be considered in vacuo

Typical Information within an ITS

- 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

REACH ITS for Skin Sensitisation



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Computational (*In Silico*) Toxicology

Databases of existing information

Category formation (grouping) read-across

Structure-Activity Relationships (SAR)

Quantitative Structure-Activity Relationships (QSAR)

Expert Systems

Bioinformatics

Chemoinformatics

Biokinetics (PBPK)

Computational (*In Silico*) Toxicology

Databases of existing information

Category form

Structure-Acti

Quantitative S

Expert Systen

Non-Testing Approaches

Bioinformatics

Chemoinformatics

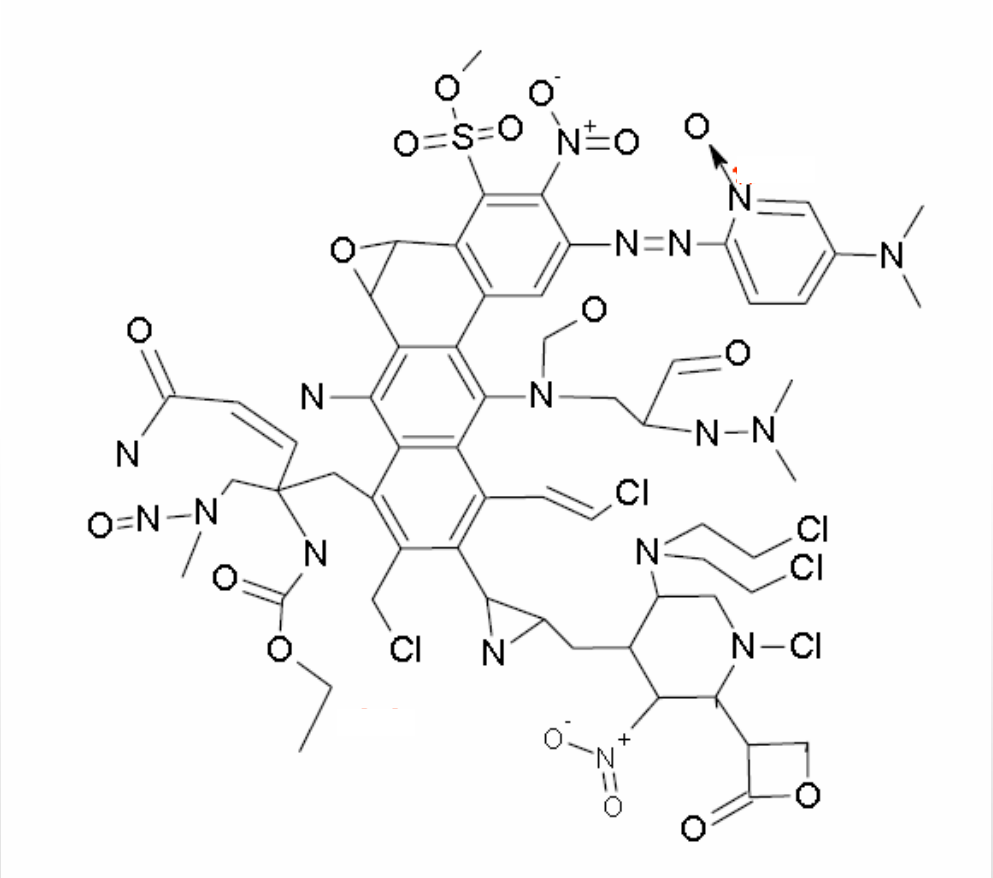
Biokinetics (PBPK)

Structure Activity Relationships and Structural Alerts

- A SAR is a (qualitative) association between a chemical substructure and the potential of a chemical containing the substructure to exhibit a certain biological effect

E.g. Carcinogenicity alerts reflected in the **“Supramolecule”**

Ashby and Tennant (1988) Mut. Res. 204:17-115



(Quantitative) Structure-Activity Relationships ([Q]SARs)

- A (Q)SAR attempts to relate (statistically or otherwise) the activity of one or more molecules to their physico-chemical properties or structural descriptors

- QSAR can be used to predict:
  - Quantitative endpoints e.g. potency
  - Qualitative endpoints e.g. active / inactive

Collections of (Q)SARs

- An Expert System is a formalised system, usually computerised that enables an end-user to make rational predictions of toxicity based on structure alone
- Expert systems are typically categorised by whether they are underpinned by:
  - empirically based algorithms such as QSARs e.g. TOPKAT
  - knowledge bases such as SARs e.g. Derek Nexus
  - or a hybrid of the two e.g. TIMES

Regulatory Applications of (Q)SARs

"Packaged mature knowledge for systematic reuse"

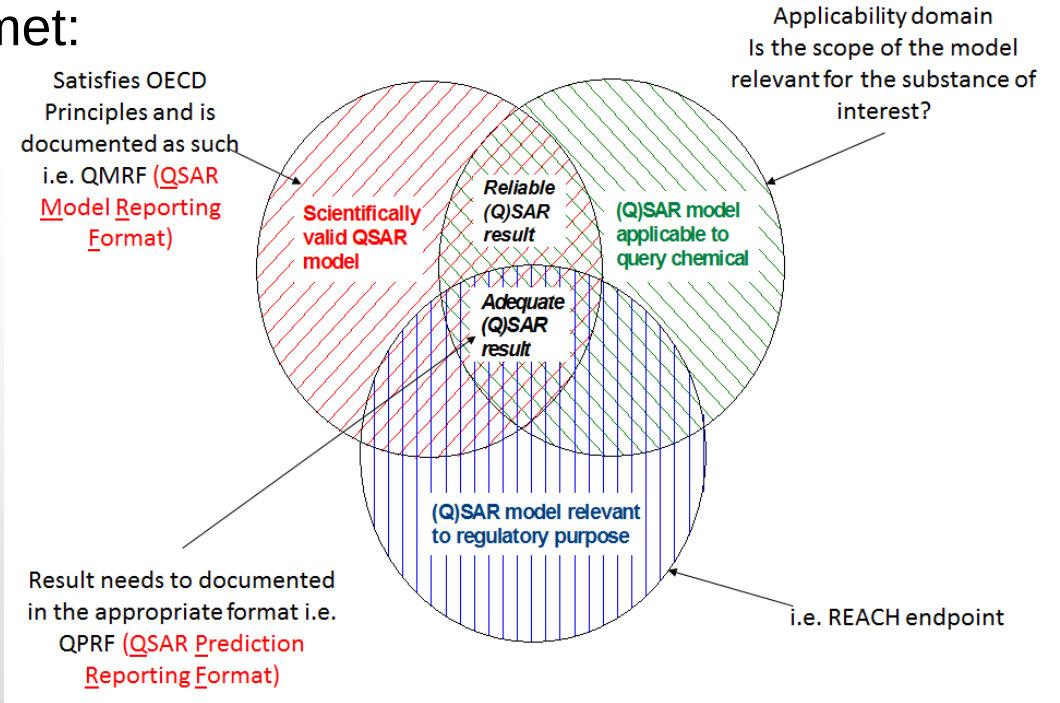
- For data gap filling – to provide an estimate for a given (eco)toxicity/e-fate/phys chem endpoint in lieu of testing (replacement or supporting information)
- To substantiate waivers or as part of ITS by providing another line of reasoning
- To rationalise spurious results in experimental data – since the (Q)SAR is based on a larger body of data, provides a more compelling WoE to rationalise the validity of a potential outlier
- Essential for category development and associated read-across justification - to provide a context of endpoint mechanistic similarity

Using (Q)SARs to Fill Data Gaps

- Under REACH, some of the information requirements within Annexes VII and VIII readily lend themselves to QSAR use
- Examples could include: providing LC_{50} or EC_{50} estimates for fish, daphnid, algae toxicity especially for difficult to test compounds such as gases, providing Log Koc and Log Kow estimates, supporting data for mutagenicity endpoints, skin/eye irritation, skin sensitisation…
- However under REACH certain conditions have to be met and specific documentation has to be provided

Annex XI – Use of (Q)SARs

- Results obtained from valid qualitative or quantitative structure-activity relationship models ((Q)SARs) may indicate the presence or absence of a certain dangerous property.
- Results of (Q)SARs may be used instead of testing when the following conditions are met:



Assessing Scientific Validity: OECD Principles for (Q)SAR Validation

A (Q)SAR should be associated with the following information:

- a defined endpoint
- an unambiguous algorithm
- a defined applicability domain
- appropriate measures of goodness-of-fit, robustness and predictivity
- a mechanistic interpretation, if possible

- Published as OECD guidance

Other Practical Considerations for (Q)SAR Use

- Is it possible to re-create the (Q)SAR model? – what is the availability of the underlying training set, what descriptors were used in the (Q)SAR development?
- To what extent & how can the domain be extracted? What threshold should be set for a substance to be considered within domain? Does that depend on how the prediction is intended to be used?
- What other information exists that might be relevant for the endpoint under consideration (i.e. the ITS) to help determine whether the QSAR estimate should or can be used as a ‘true’ replacement value or as part of a WoE?

Assessing Applicability Domain to Determine if the Model is Valid for Use for a Specific Molecule

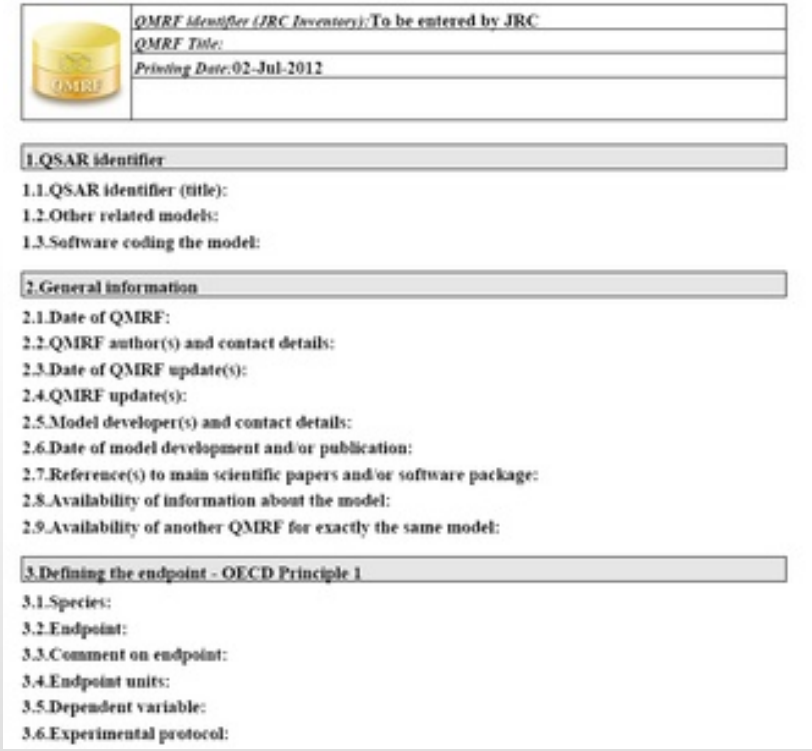
- Applicability domain may be characterised using:
  - Descriptors
  - Structural features e.g. fragments, fingerprints
  - Metabolic transformations
  - Mechanistic information

- Tools exist to assess applicability domains
  - e.g. LMC Domain Manager, AMBIT Discovery etc.

Documenting the Model: QSAR Model Reporting Format (QMRF)

QSAR Model Reporting Format (QMRF) is a harmonised template for summarising and reporting key information on (Q)SAR models, including the results of any validation studies

- The information is structured according to the OECD (Q)SAR validation principles.
- A freely available editor is available
- http://ihcp.jrc.ec.europa.eu/our_labs/predictive_toxicology/qsar_tools/QRF
- http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf



QMRF identifier (JRC Inventory): To be entered by JRC
QMRF Title:
Printing Date: 02-Jul-2012

1.QSAR identifier
1.1.QSAR identifier (title):
1.2.Other related models:
1.3.Software coding the model:

2.General information
2.1.Date of QMRF:
2.2.QMRF author(s) and contact details:
2.3.Date of QMRF update(s):
2.4.QMRF update(s):
2.5.Model developer(s) and contact details:
2.6.Date of model development and/or publication:
2.7.Reference(s) to main scientific papers and/or software package:
2.8.Availability of information about the model:
2.9.Availability of another QMRF for exactly the same model:

3.Defining the endpoint - OECD Principle 1
3.1.Species:
3.2.Endpoint:
3.3.Comment on endpoint:
3.4.Endpoint units:
3.5.Dependent variable:
3.6.Experimental protocol:

QSAR Prediction Reporting Format (QPRF)

- The QSAR Prediction Reporting Format (QPRF) is a harmonised template for summarising and reporting substance-specific predictions generated by (Q)SAR models
- QPRF requires information on:
  - The substance
  - General information (e.g. date and author)
  - Description of QSAR according to OECD Principles and how it relates to target substance
  - Adequacy (optional)

http://ihcp.jrc.ec.europa.eu/our_labs/predictive_toxicology/qsar_tools/QRF

http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

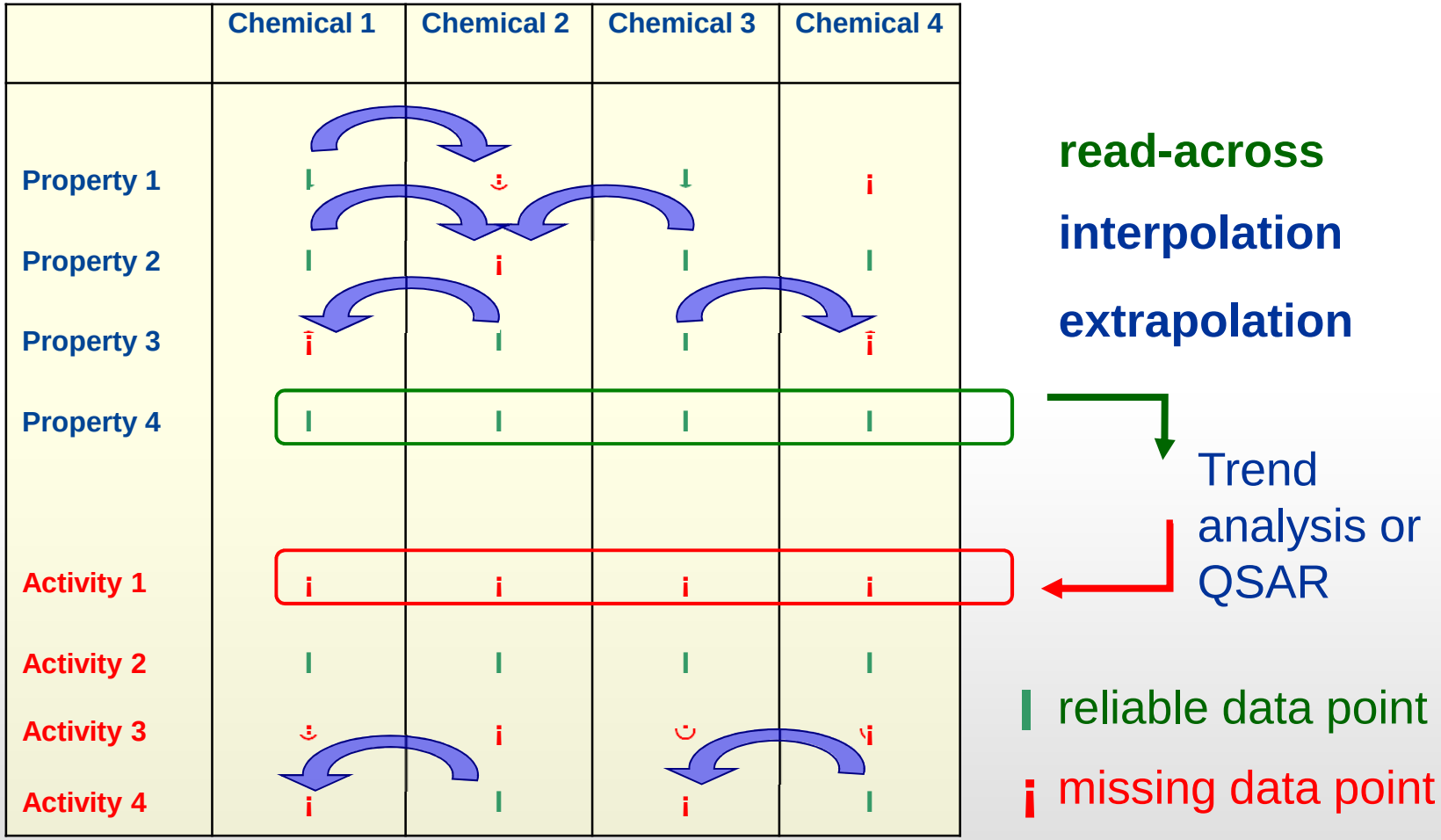
Current Experiences of (Q)SAR Approaches

- As replacements - most promising for physicochemical, ecotoxicity and environmental fate properties e.g. Log Kow, acute fish toxicity, ready biodegradability. Much progress has also been made in the area of genetox specifically - Ames mutagenicity and to a large extent on skin sensitisation
- As supporting information in category approaches or as additional information as part of an WoE – most progress has been made with (Q)SARs for endpoints such as skin/eye irritation, or other genotoxicity endpoints
- (Q)SARs for repeated dose toxicity endpoints are not sufficiently evolved to be used as replacements but can play an useful role in supporting read-across within category/analogue approaches

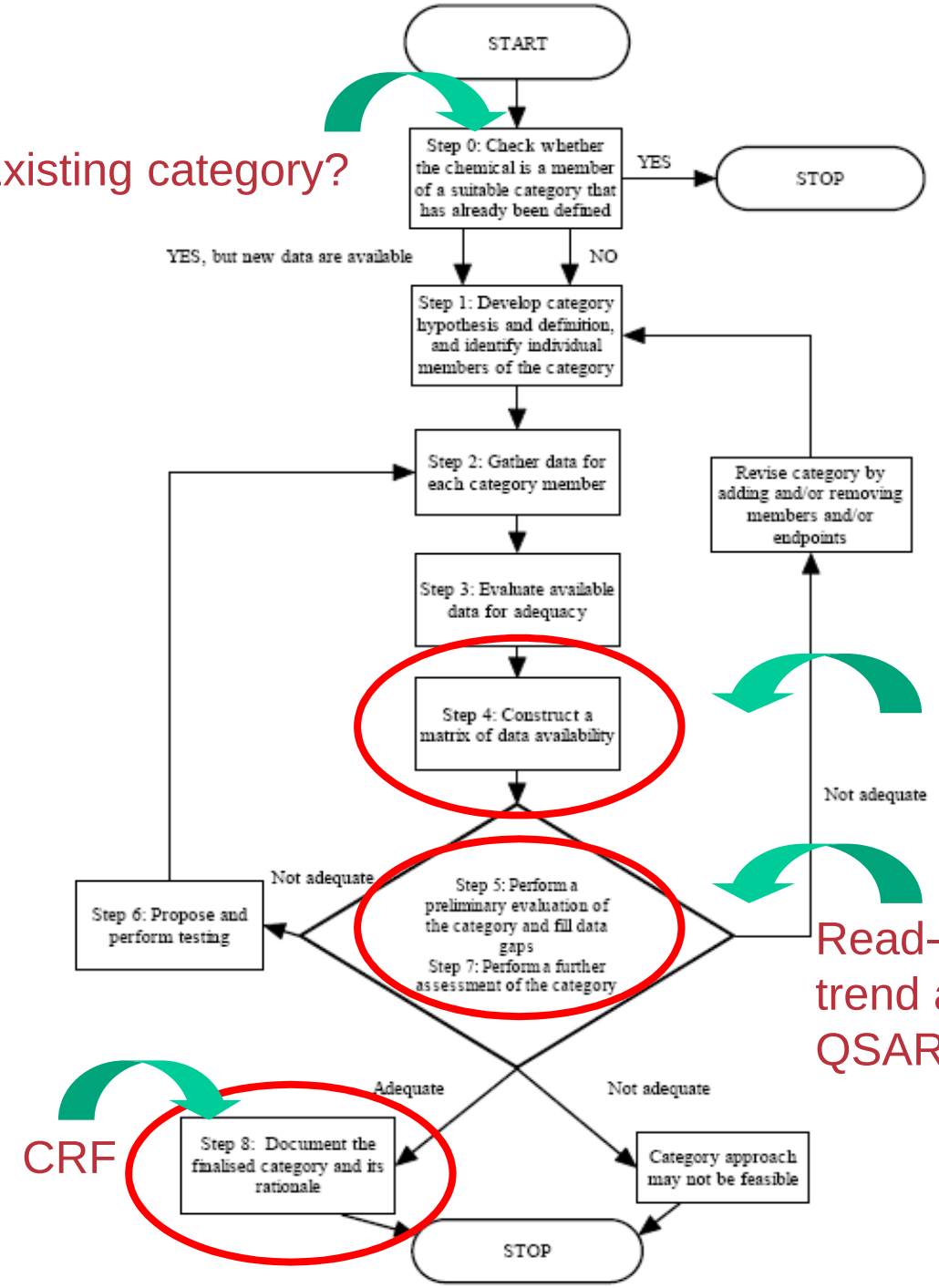
Category Formation (Grouping) for Read-across

- “Analogue approach” refers to grouping based on a very limited number of chemicals (e.g. target substance) + source substance)
- “Category approach” is used when grouping is based on a more extensive range of analogues (e.g. 3 or more members) and there may be an apparent trend in property
- Read-across describes one of the methods for filling data gaps in either the analogue or category approaches i.e. not to be confused with the “analogue approach”

Read-across


Chemical 1
Chemical 2
Chemical 3
Chemical 4
Property 1
Property 2
Property 3
Property 4
Activity 1
Activity 2
Activity 3
Activity 4
read-across
interpolation
extrapolation
Trend analysis or QSAR
reliable data point
missing data point

REACH Workflow for Categories



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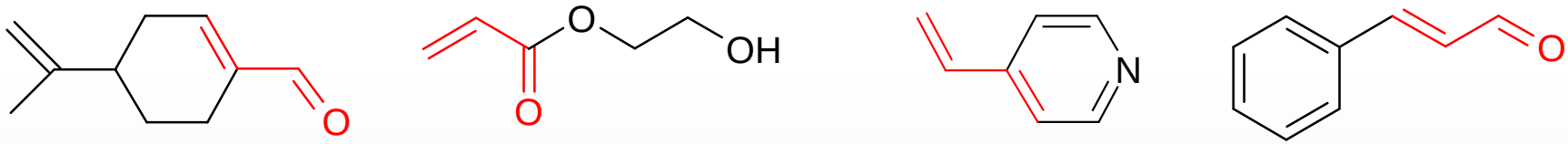
Considerations Before Embarking on a “Read-across”

- How many data gaps? And for which endpoints?
- Legitimate access to sufficient, reliable data?
- Plausible hypothesis for grouping substances and ease and cost of substantiating that hypothesis?
- Accurate and credible assessment of the hazards for the substance in question? Is the scientific confidence sufficient for the purpose required?
- Consequence and cost of the read-across approach not being accepted?

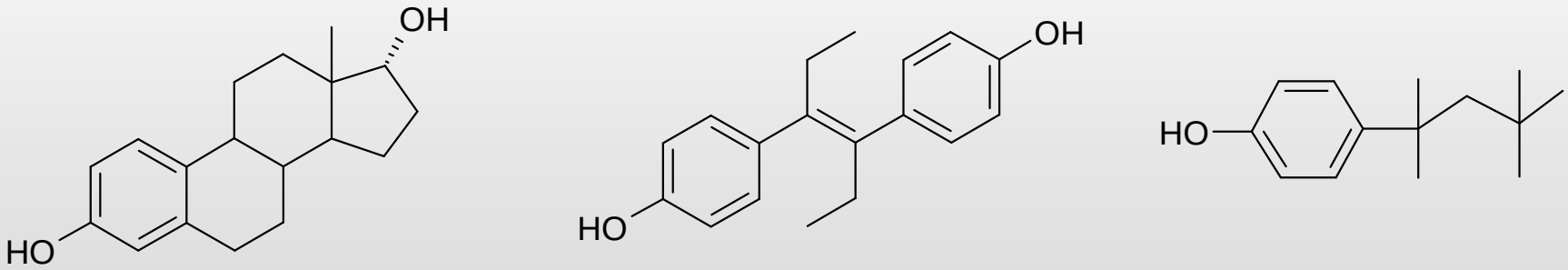
Types of Groupings – See Annex XI

Structural Analogues

Mechanistic Analogues



Mode of Action Analogues



Types of Groupings

Substances that are **metabolised** to a common molecule

Substances that are **degraded** rapidly to common products

- The rationale underpinning the category/analogue approach might be based on 1 or more of these rationales

Identifying Source Analogues…With Data

Based on own internal company inventory

Using computational tools to help identify potential analogues and in some cases to help evaluate those analogues for their suitability

- OECD QSAR Toolbox
- ToxMatch
- Toxtree
- ChemProp
- Leadscope
- Analogue Identification Method
- AMBIT
- VITIC
- ECHA dissemination database ....has the substance been registered already?

OECD (Q)SAR Toolbox

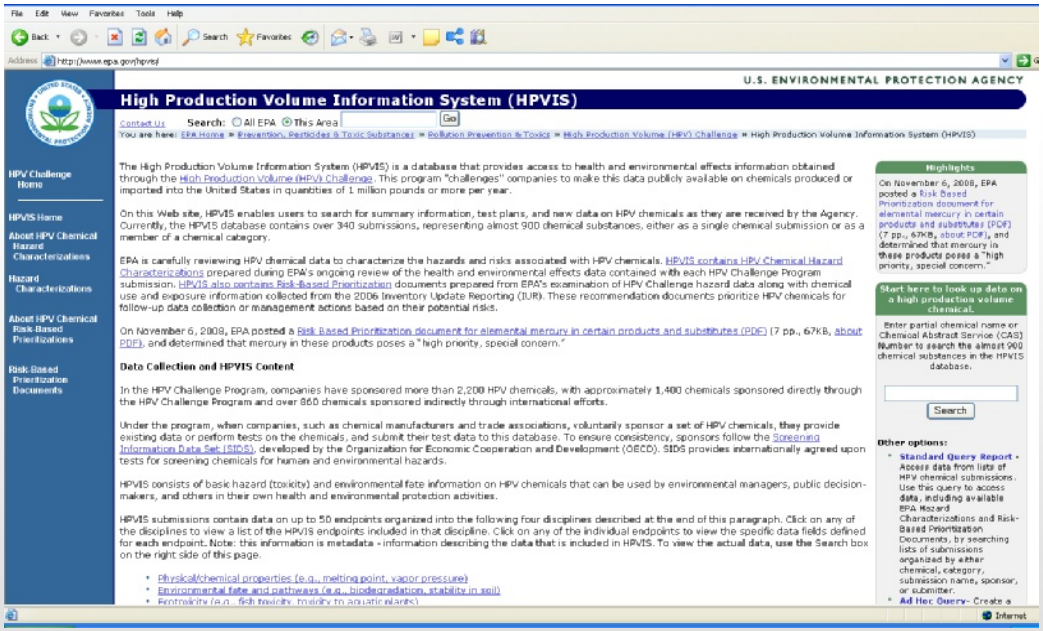
- A software tool which facilitates the development, evaluation, justification and documentation of chemical categories for read-across
- Software workflow mimics that described in the OECD and REACH guidance on categories
- Contains regulatory inventories and data plus “profilers” which encode SAR type information which represent molecular initiating events (MIEs) within Adverse Outcome Pathways (AOPs)
- Profilers include those for “DNA Binding”, “Protein Binding”, “Aquatic toxicity MOAs” etc – hence works best for skin sensitisation, mutagenicity and aquatic toxicity endpoints
- Ongoing development is focusing on how to implement new MIEs and AOPs into the Toolbox to facilitate read-across for repeated dose toxicity endpoints
- First AOP implemented into the OECD Toolbox - skin sensitisation

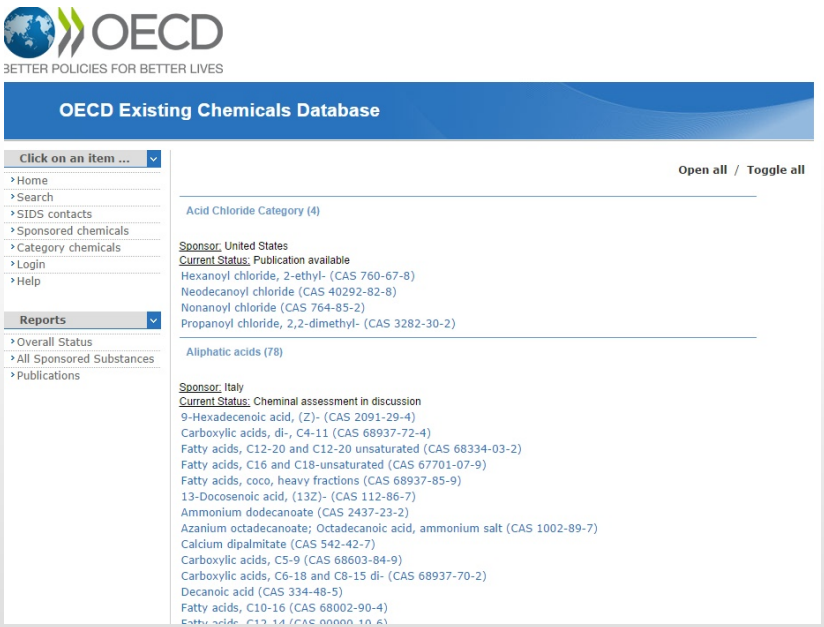
Is Substance Already a Member of an Existing Category?

- Is there an existing HPV category already available e.g. HPVIS, OECD, OECD Toolbox

http://webnet.oecd.org/hpv/ui/Default.aspx

http://www.epa.gov/hpvis/





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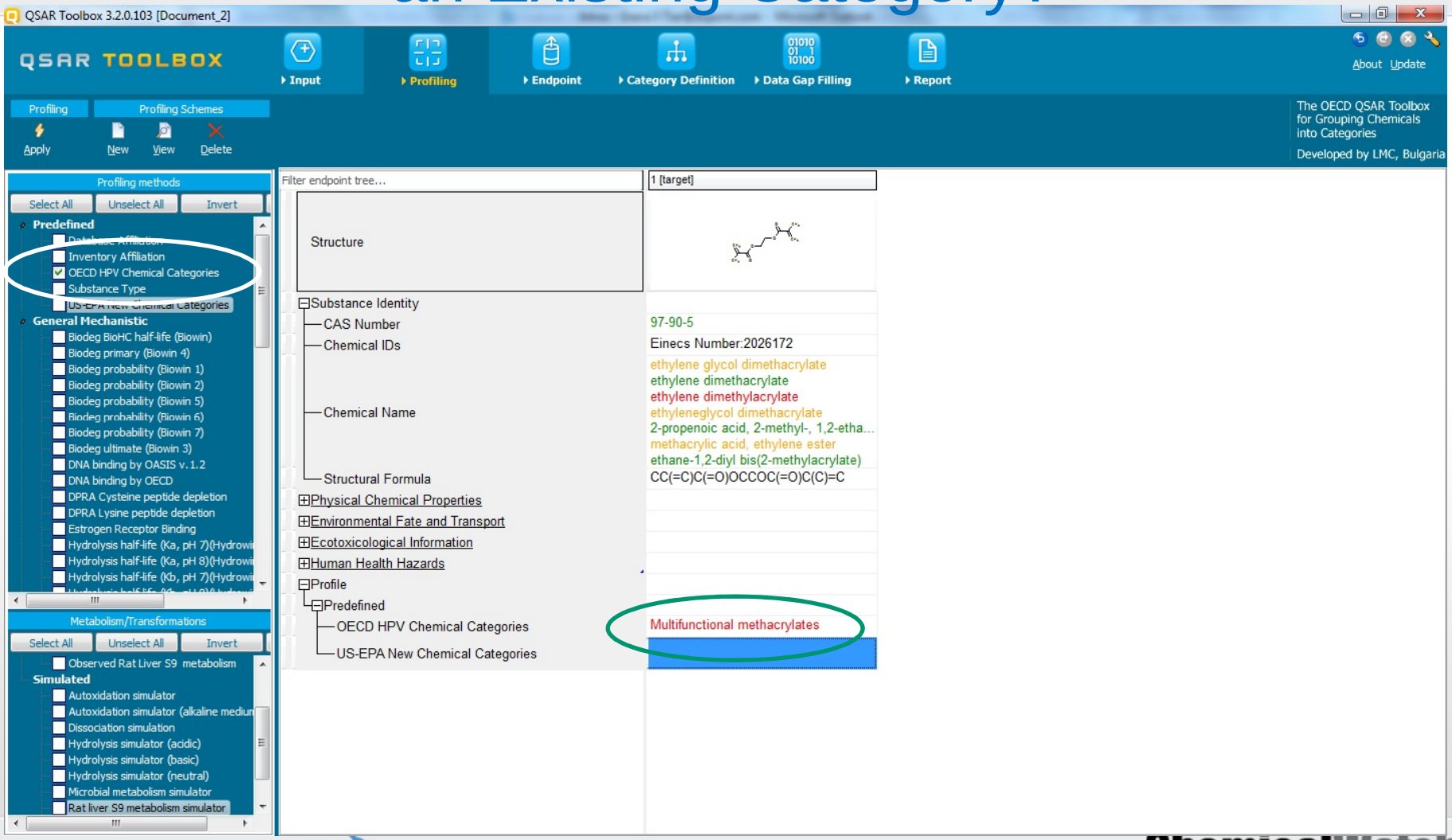
Is Substance Already a Member of an Existing Category?



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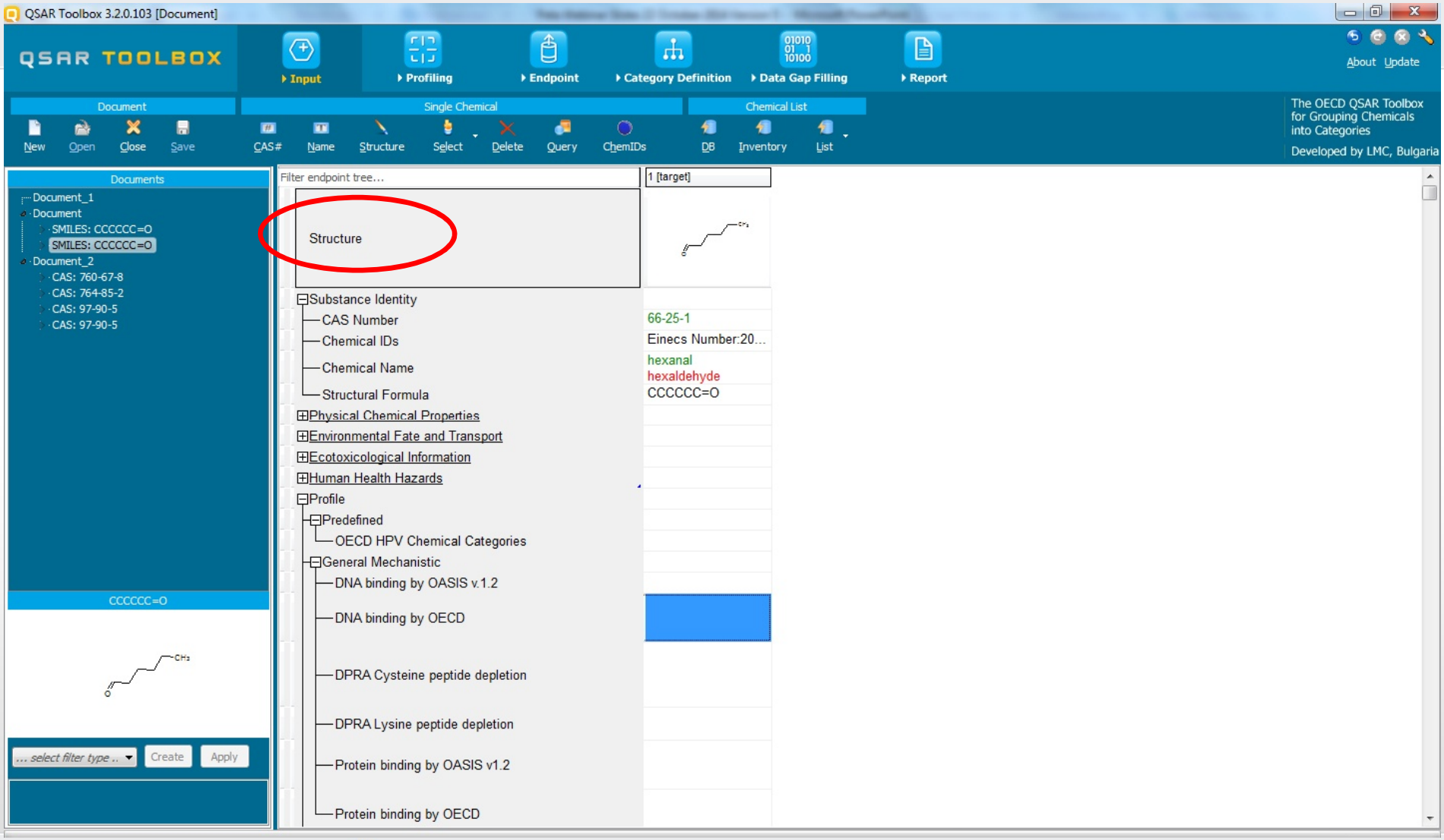
Compound Entry and Data Retrieval



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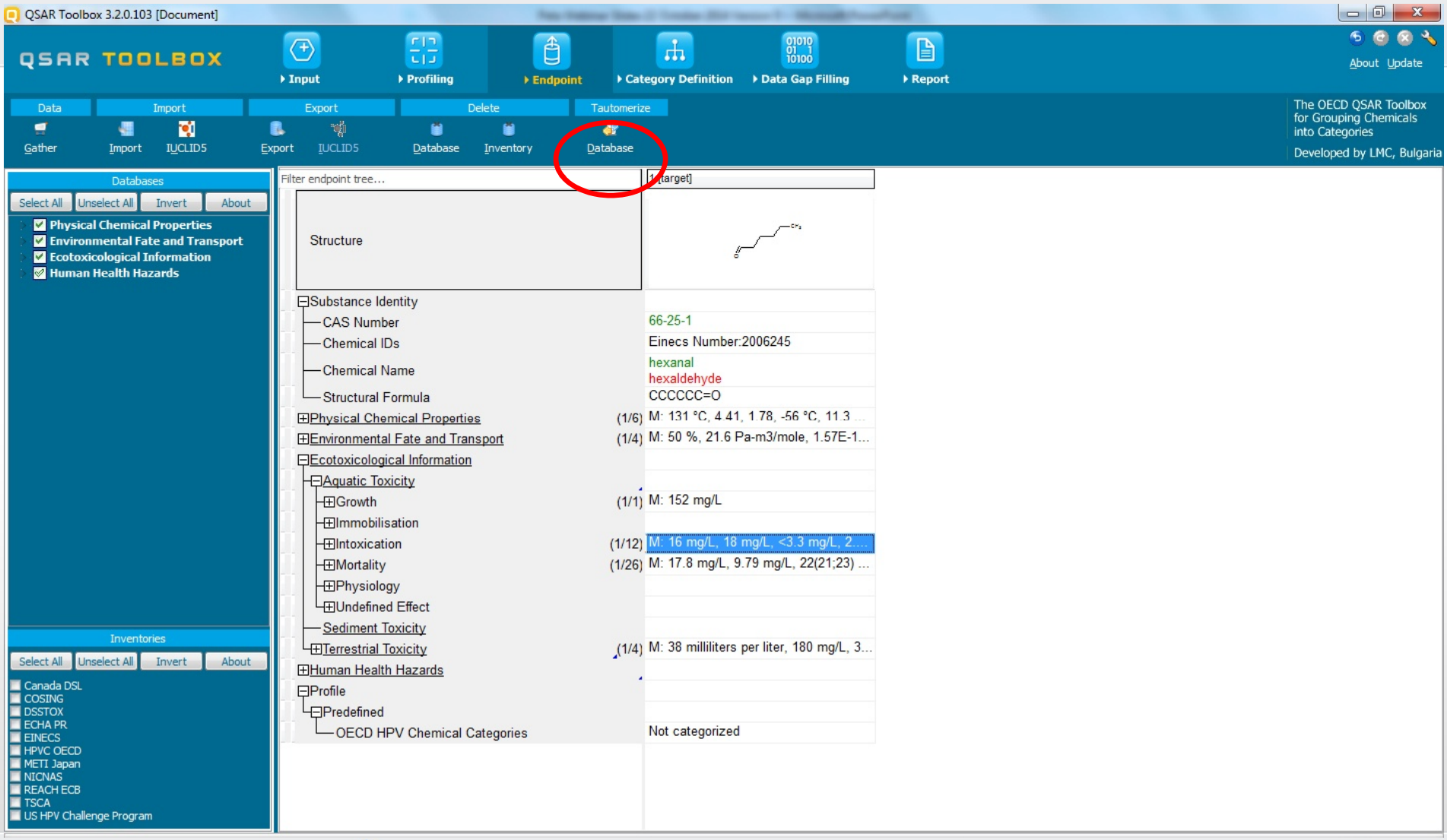
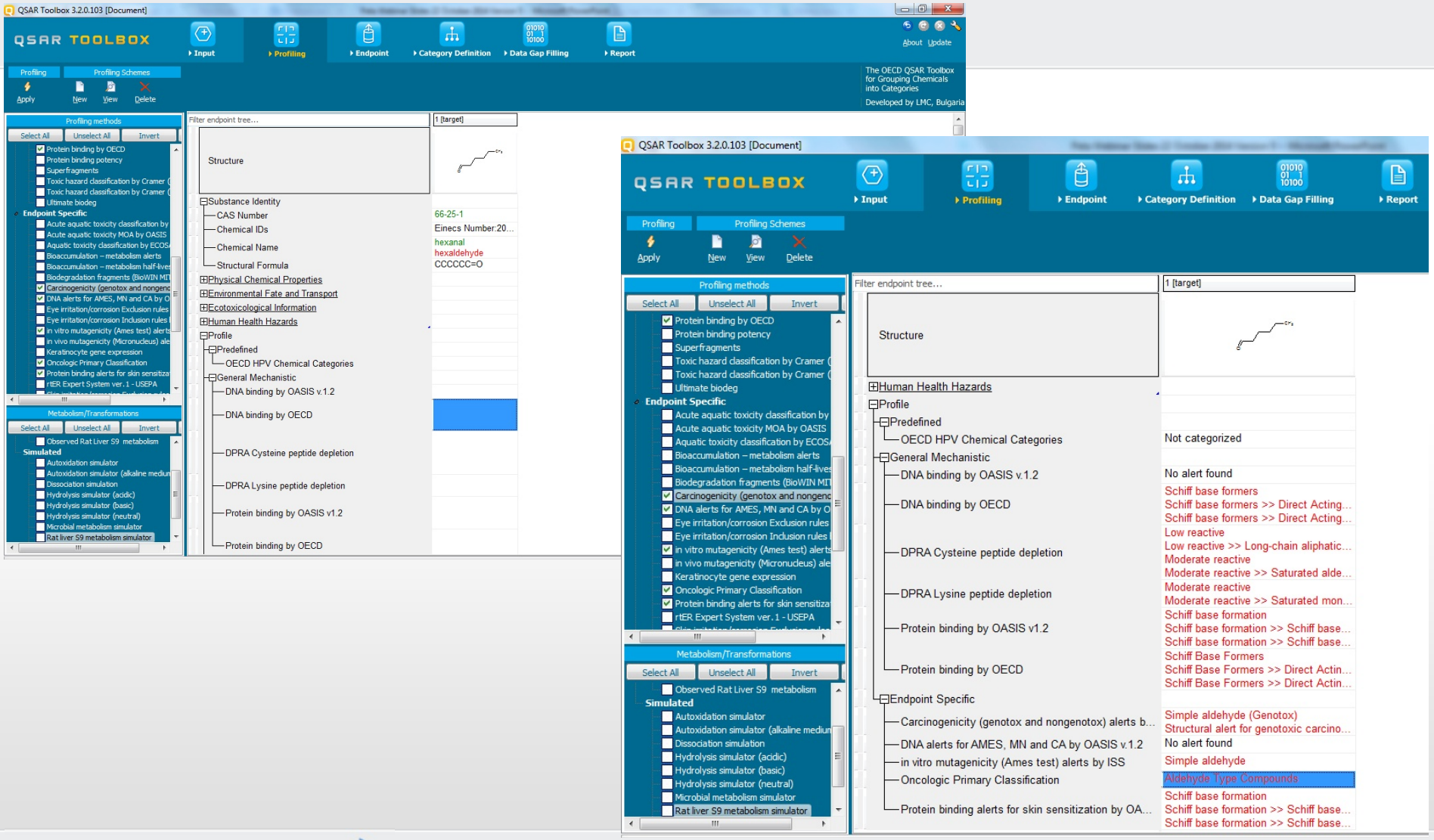


Profiling Outcomes



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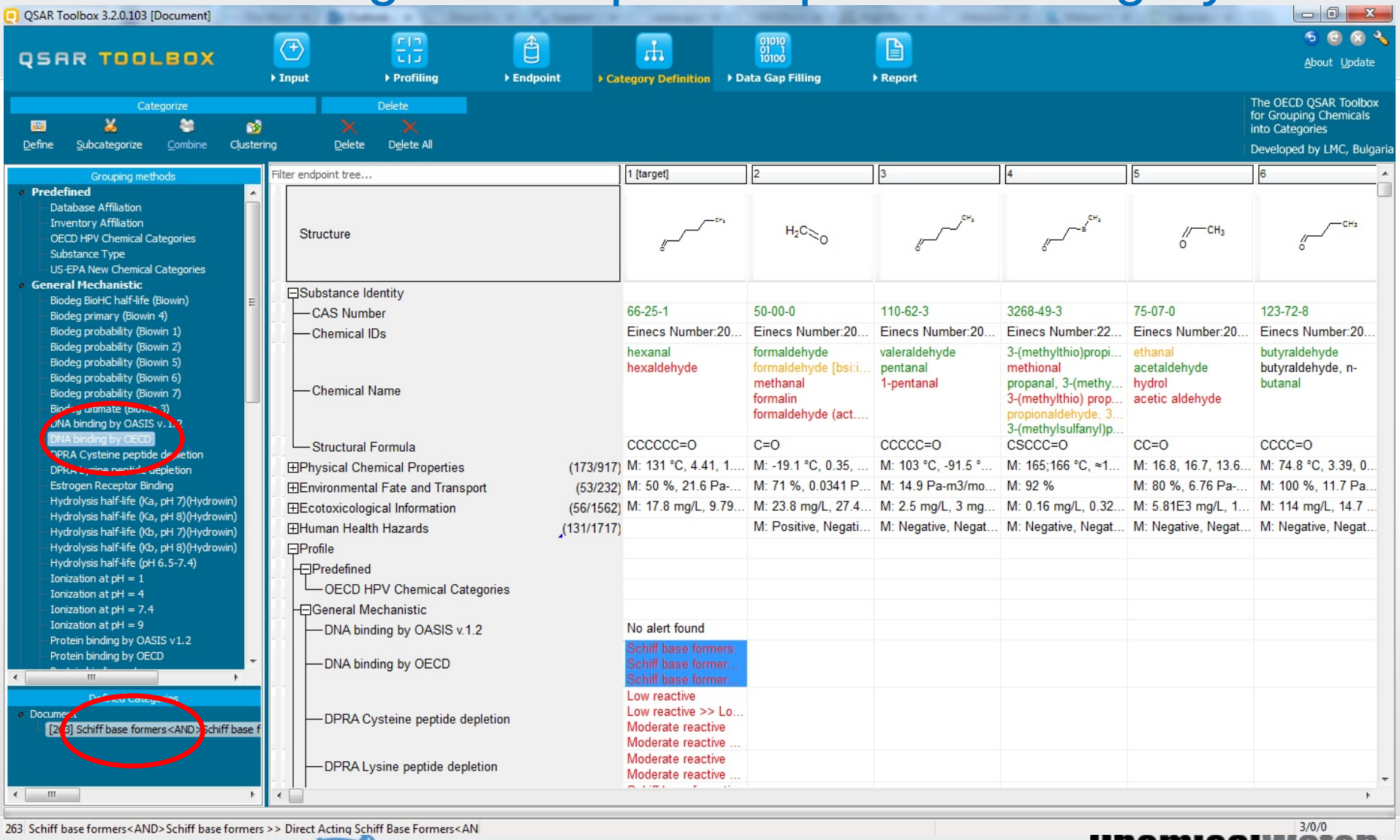
Creating an Endpoint Specific Category



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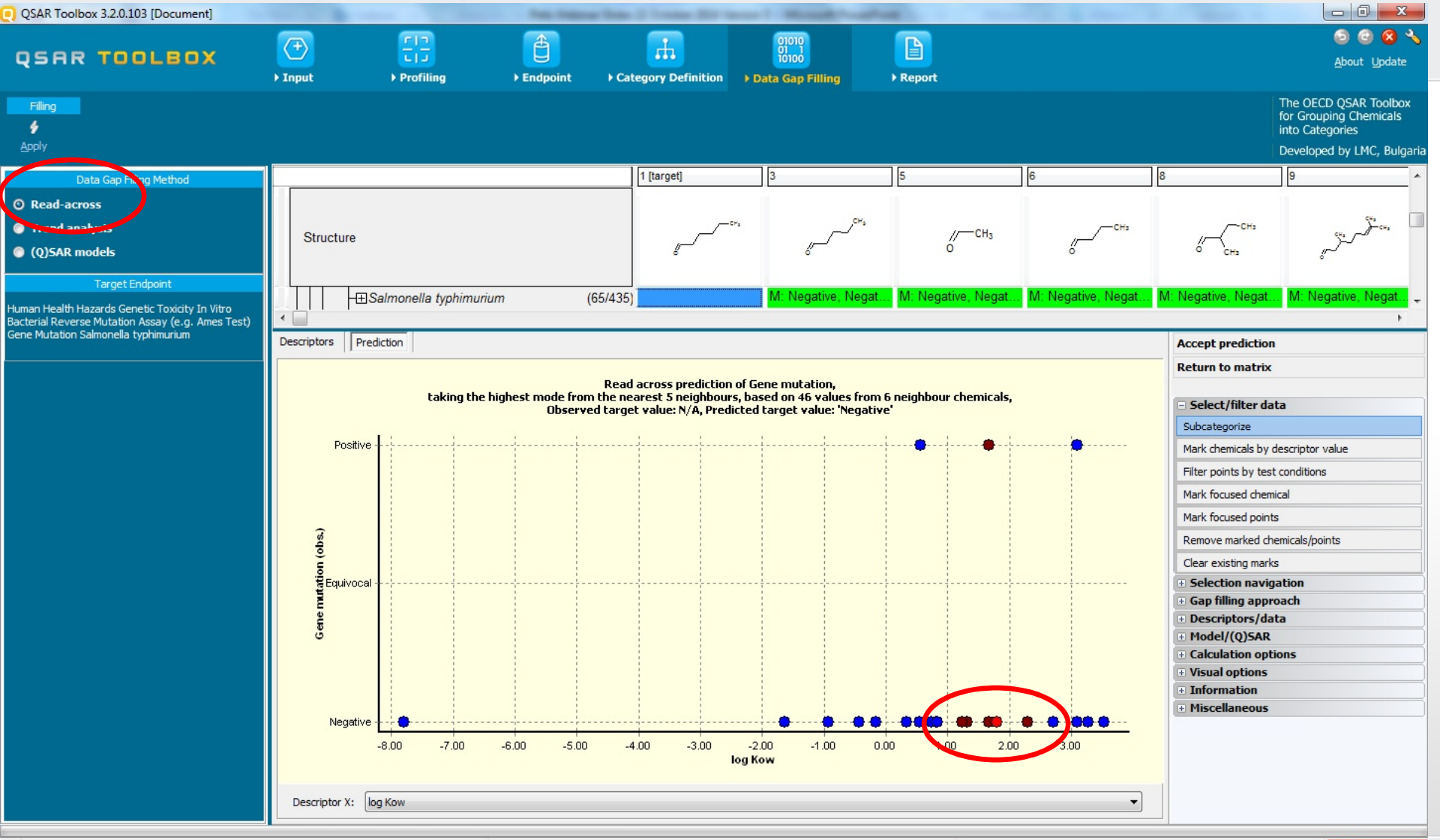
Data Gap Filling Using Read-across



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Annex XI of REACH: Grouping and Read-across

- If the group concept is applied, substances shall be classified and labelled on this basis.
- In all cases results should:
  - be adequate for the purpose of classification and labelling and/or risk assessment
  - have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3)
  - cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and
  - adequate and reliable documentation of the applied method shall be provided

Category Reporting Format (CRF) Should Provide a Detailed Account of the Rationale for Performing a Category or Analogue Approach

A) information about the category members

B) what the rationale/hypothesis for formulating the grouping

C) whether the purities/impurities will affect toxicity

D) the scope (domain) of the grouping

E) the endpoints covered and the extent to which the group formulated aims to address all endpoints or a subset of these

F) Rationale for the validity of the grouping

G) Data matrix providing a summary of experimental data for the grouping members

H) Classification & Labelling information

This document is not trivial to prepare

R.6.2.6.2 Reporting Format for a chemical category

1.	**Category definition and its members**
1.1.	Category Definition
1.1.a.	Category Hypothesis Describe the molecular structure a chemical must have to be included in the category. Provide a brief hypothesis for why the category was formed: the hypothetical relational features of the category i.e. the chemical similarities (analogues), purported mechanisms and trends in properties and/or activities that are thought to collectively generate an association between the members. All functional groups of the category members need to be identified. If there is a mechanistic reasoning to the category, describe the foreseen mode of action for each category member and if relevant describe the influence of the mode of administration (oral, dermal, inhalation).
1.1.b.	Applicability domain (AD) of the category Describe the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members. Clearly indicate the borders of the category and for which chemicals the category does not hold. For example, the range of log K_{ow} values or carbon chain lengths over which the category is applicable. The justification for the inclusion and/or exclusion rules should be reported under Section 2) *Category justification* below.
1.2.	Category Members Describe all category members as comprehensively as possible. Provide CAS numbers, names and chemical structures of all category members.
1.3.	Purity / Impurities Provide purity/impurity profiles for each member of the category, including their likely impact on the category endpoints. It should be discussed which influence these impurities are thought to have on physico-chemical parameters, fate and (eco)toxicology, and hence on the read-across.

Endpoint Justification

- Overarching rationale (type of groupings) provides a basis to grouping the chemicals together but is essentially a starting hypothesis
- Next step is to justify the grouping on the basis of considerations such as bioavailability, reactivity, metabolism
- And factor how these impact individual endpoints in turn – this is where QSARs and other information from the Toolbox can help

(Q)SAR Endpoint Justifications

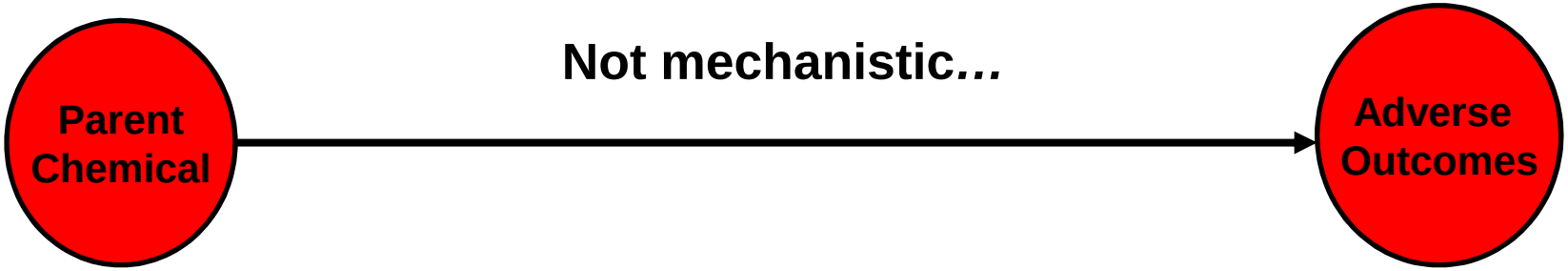
- Acute oral – considerations include bioavailability, chemical reactivity and metabolism, similarity in structure, Cramer structural classifications.
- Acute dermal – concordance with oral results? skin penetration?
- Acute inhalation – volatile substances – neutral organics appear to be well correlated with Vapour pressure.
- Skin/Eye irritation – some overlap with the alerting groups for electrophilicity, pKa?
- Sensitisation – alerting groups encoding electrophilic features, Log Kow may be a consideration for some reaction types.

(Q)SAR Endpoint Justifications

- Mutagenicity – lots of focus on Ames but little on other endpoints let alone *in vivo* endpoints
- Carcinogenicity – empirical binary QSAR models exist i.e. yes/no prediction but are of limited utility in terms of providing mechanistic justification
- Reproductive/Development – handful of empirical models, some (Q)SARs on estrogen binding
- Repeated dose toxicity – handful of empirical models which aim to predict LOAEL but not sophisticated to estimate likely target organs.

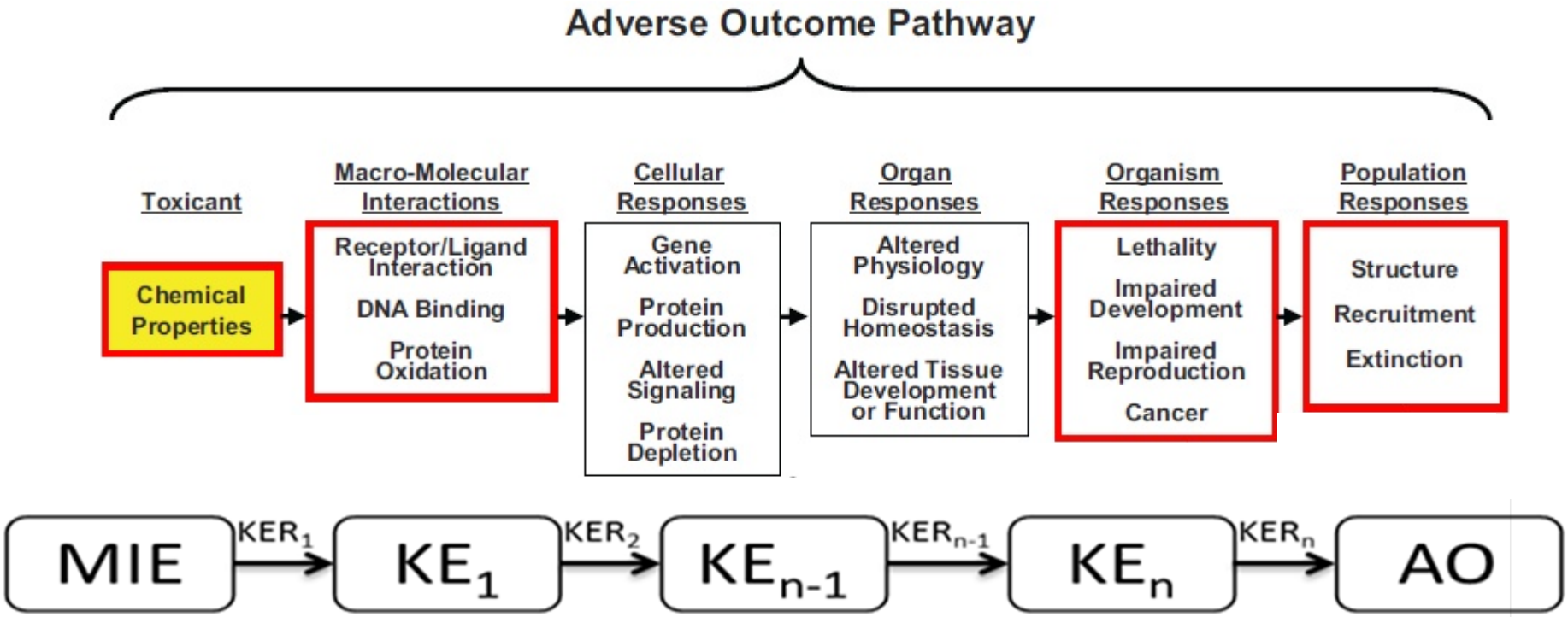
Read-across prone to uncertainty – how can one relate structure to such a downstream endpoint with any reliability?

Current Approach for Non-testing Development and Application



Can relating structure to such downstream adverse outcomes be performed with sufficient scientific confidence?

AOP: Offers a Framework for Developing Non-testing Approaches Differently

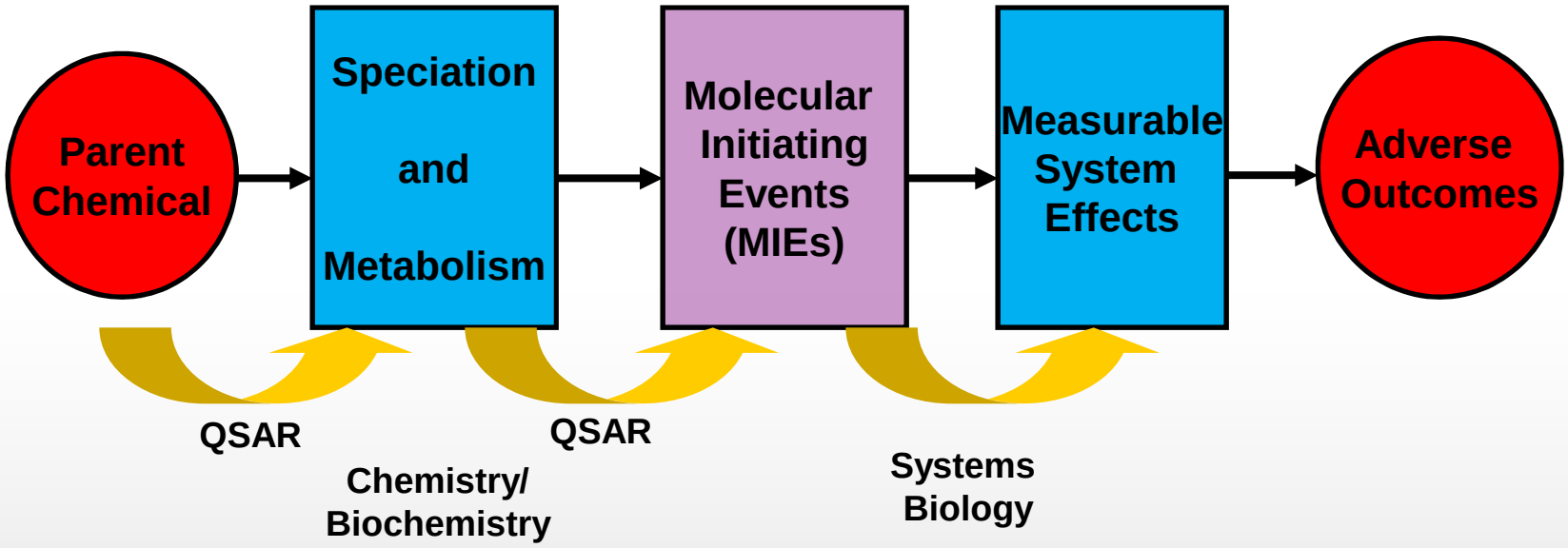


An AOP represents existing knowledge concerning the sequence of events and causal linkages between initial molecular events, ensuing key events and an adverse outcome at the individual or population level.

Why are AOPs Important?

- A framework to organise information
- AOPs provide the linkage from chemistry, through the MIE to Adverse Effect
- Data from key events provides support to, and will enhance, read-across especially for regulatory acceptance
- Data from key events will support definition of domains for MIEs
- Will inform ITS or IATA for risk assessment and provide a roadmap for future QSAR development

Refining how non-testing approaches are developed in the context of an AOP

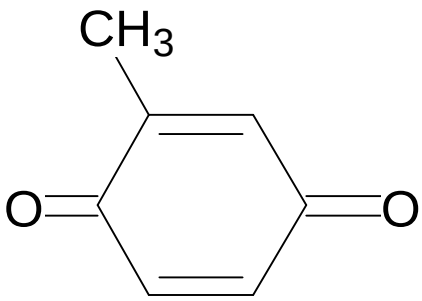


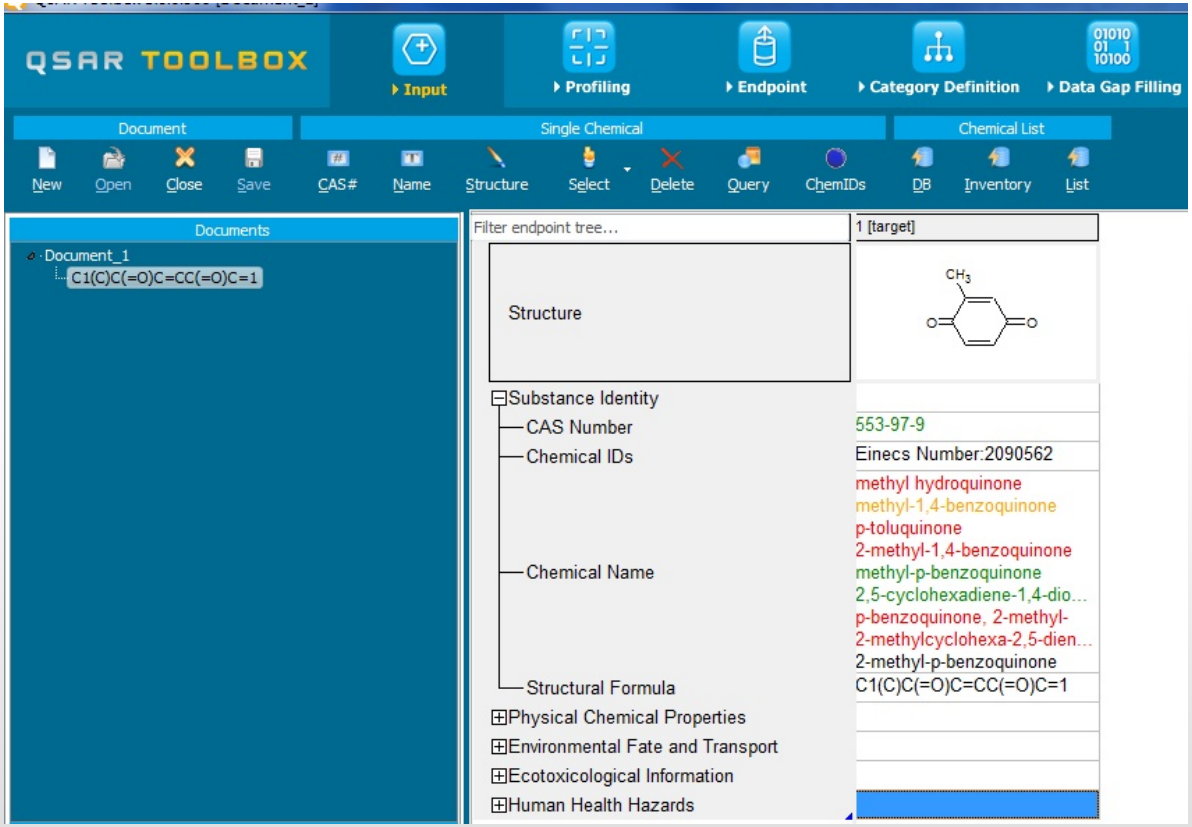
1. Identify Plausible MIEs
2. Explore Linkages in Pathways to Downstream Effects
3. Develop QSARs to predict MIEs from Structure or characterise other KEs as SARs

Implementation of AOP for Skin Sensitisation in the OECD QSAR Toolbox

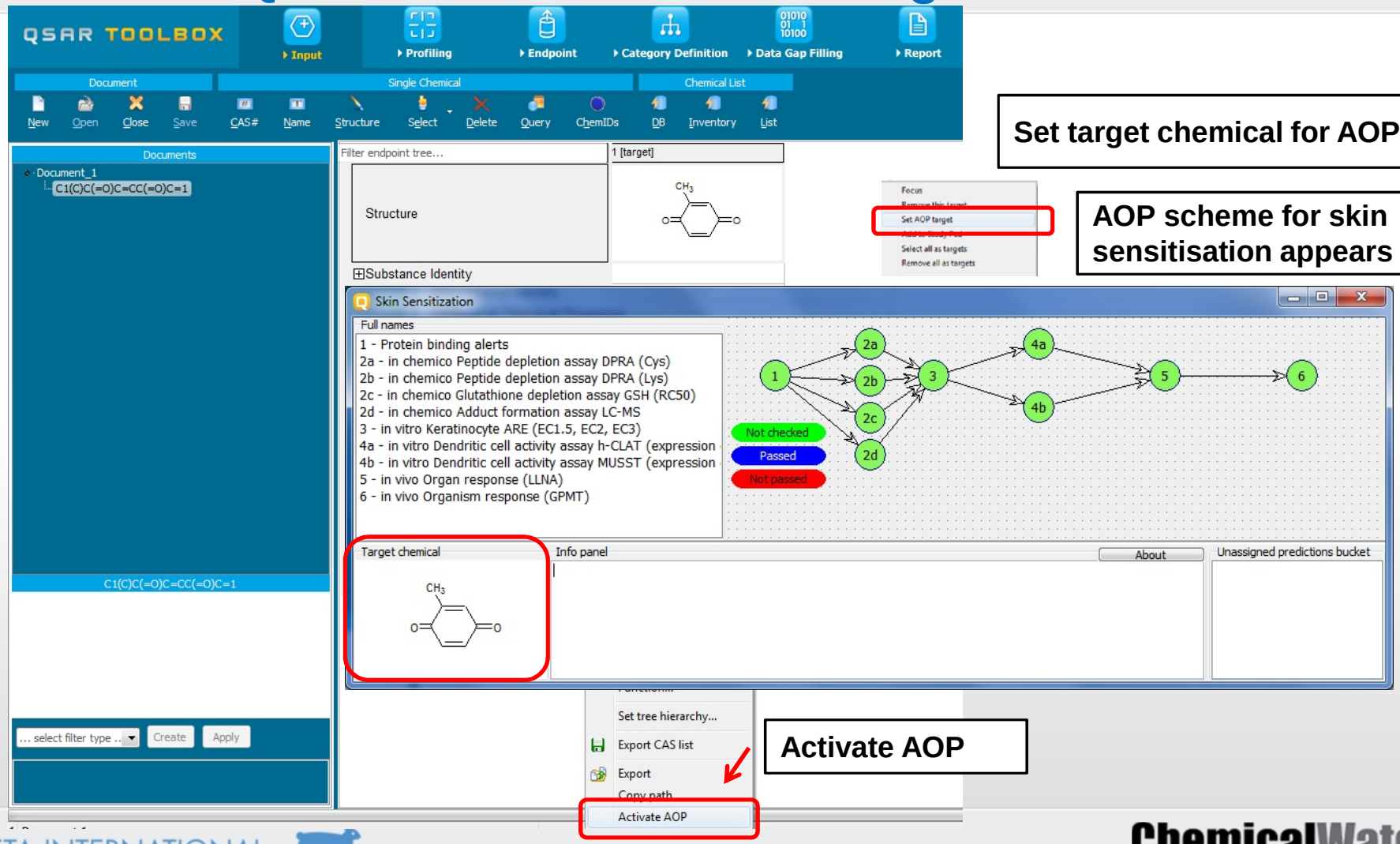
Input target chemical by CAS number

autoxidised to methyl quinone





Overview of the AOP implementation in the OECD QSAR Toolbox: Activating the AOP



Set target chemical for AOP

AOP scheme for skin sensitisation appears

Activate AOP

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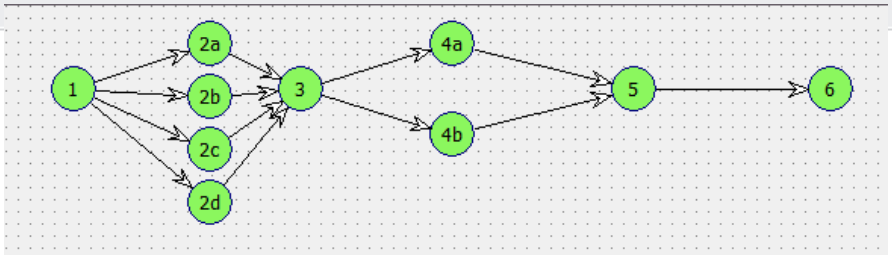
Overview of implemented AOP scheme



Key node

1 Protein binding alerts → Protein binding – in silico/theoretical

2a *in chemico* Peptide depletion assay DPRA (Cys)

2b *in chemico* Peptide depletion assay DPRA (Lys)

2c *in chemico* Glutathione depletion assay GSH (RC50)

2d *in chemico* Adduct formation assay LC-MS

→ Protein binding potency in chemico

3 *in vitro* Keratinocyte ARE (EC1.5, EC2, EC3)

4a *in vitro* Dendritic cell activity assay h-CLAT (expression of CD54 and CD86)

4b *in vitro* Dendritic cell activity assay MUSST (expression of CD86)

→ Cellular response

5 *in vivo* Organ response (LLNA) → Organ response

6 *in vivo* Organism response (GPMT) → Organism response

Key event

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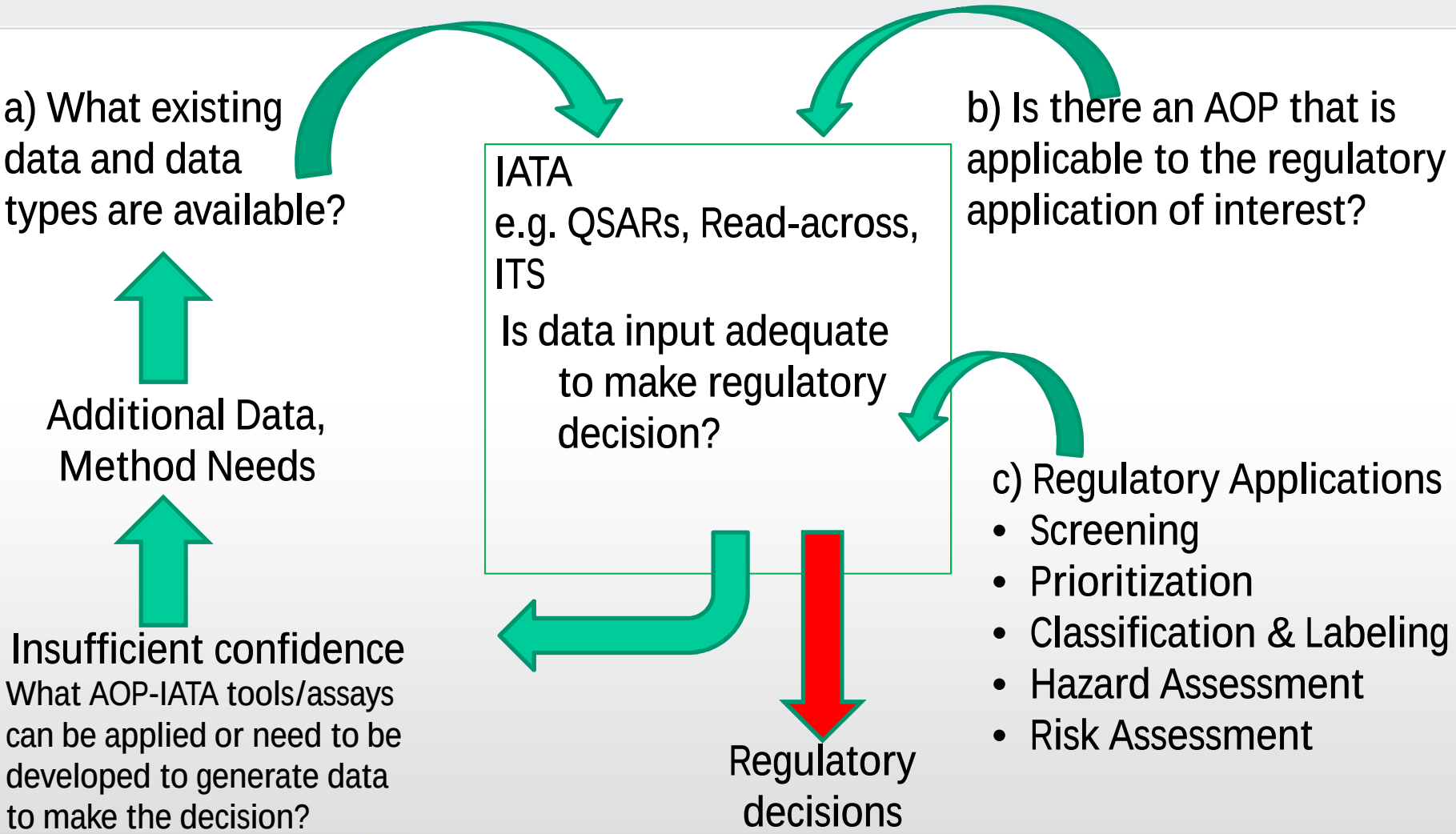
Enhancing Read-across

- AOP for skin sensitisation is the first AOP that has been implemented into the Toolbox
- Enables a read-across to be enhanced with information from other downstream key events thereby increasing the confidence in the prediction made and thus its regulatory applicability

AOP-informed IATA



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Take Home Messages - 1

- REACH 2018 represents a significant task of compiling the information requirements for Annexes VII and VIII for a large number of substances
- Annex IX provides opportunities for using adaptations prior to any experimental testing
- Considerations include:
- Has the substance already been registered by another party?
- Are there promising analogues to explore read-across within an analogue/category approach?
- How many datagaps and for which endpoints? This will drive the practical strategy of whether QSARs or grouping approaches are more feasible

Take Home Messages - 2

- QSARs are most effectively used for ecotox, efate and physchem endpoints as replacement values and as supporting information for “simpler” mammalian endpoints within an IATA
- The OECD principles need to be evaluated for the QSAR(s) and documented in an QMRF together with an QPRF for the prediction itself
- For “more complex” endpoints such as repeated dose 28 day or developmental toxicity screening tests – an analogue/category approach is likely to be more effective – an overarching hypothesis and evidence to support the read-across is essential – (Q)SARs can be helpful in providing some of this evidence

Take Home Messages - 3

- In future, Tox21 approaches using an AOP construct offer prospects for providing different type of information that is structured in an mechanistic IATA
- This also has implications for how read-across could be justified in future or how QSARs might be developed and applied
- To date an AOP for skin sensitisation has been successfully implemented into the OECD Toolbox to facilitate such a step change in read-across enhancement
- A number of software tools, technical guidance and literature references are available that could be helpful – see useful links pages for a non exhaustive selection

Acknowledgements

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Members of the CAAT read-across initiative

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Useful Links - 1

Domain tools

http://ambit.sourceforge.net/download_ambitdiscovery.html

http://oasis-lmc.org/

Technical regulatory guidance

https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology

http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

http://echa.europa.eu/support/grouping-of-substances-and-read-across

http://echa.europa.eu/practical-guides

OECD Toolbox

http://www.qsartoolbox.org/

Industry guidance and experiences

ECETOC TR116 Category approaches, read-across, (Q)SAR

Blackburn, K., and Stuard, S. B. A framework to facilitate consistent characterization of read across uncertainty. *RegToxicol Pharmacol* **2014**, 68, 353-362.

Useful Links - 2

Ankley, G.T., Bennett, R.S., Erickson, R.J., et al. (2010). Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. *Environ Toxicol Chem 29*, 730-741.

Ball N, Bartels MJ, Budinsky, RA, Klapacz J, Hayes SM, Kirman CR, **Patlewicz GY**. The challenge of using Read-Across within the EU REACH regulatory framework; how much uncertainty is too much? Dipropylene Glycol Methyl Ether Acetate, an exemplary case study. *Reg. Toxicol. Pharmacol*. **2014**, 68: 212-221.

Patlewicz G, Ball N, Booth ED, Hulzebos E, Zvinavashee E, Hennes C. Use of Category approaches, Read-across and (Q)SAR: General considerations. *Reg. Toxicol. Pharmacol*. **2013**, 67(1): 1-12.

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Patlewicz G, Chen MW, Bellin CA. Non-Testing approaches under REACH – help or hindrance? Perspectives from a practitioner within Industry. *SAR QSAR Environ. Res*. **2011**, 22(1-2): 67-88.

Cronin MTD et al (**2013**) *Chemical Toxicity Prediction: Category Formation and Read-Across.* Royal Society of Chemistry.

Cronin MTD and Madden JC (**2010**) *In Silico Toxicology. Principles and Applications.* Royal Society of Chemistry.

Tollefsen, K. E, Scholz, S., **Cronin, M. T.,** et al. (2014). Applying Adverse Outcome Pathways (AOPs) to support Integrated Approaches to Testing and Assessment (IATA). *Reg Toxicol Pharmacol*, in press.

Useful Links - 3

The next training course for the OECD Toolbox is in Barcelona from Nov. 17-to Nov. 21, organized by ReachMonitor (http://www.reachmonitor.com/index.php?lang=2&aptd=0) and delivered by LMC – developers of the OECD Toolbox (http://www.oasis-lmc.org/).

Thank You!

… any questions?

Thank you for attending

What did you think about the webinar? Please take part in our email survey (in your inbox now)

A downloadable recording of this presentation (with slides) will be available shortly.

If you have any questions, please contact Lorna (lorna@chemicalwatch.com)

NEXT

Webinar 2: Skin irritation and corrosion, 11 Nov, 4pm GMT
Click here to register

Webinar 3: Serious Eye Damage and Eye Irritation 4 Dec, 4pm GMT
Click here to register

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