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PETA INTERNATIONAL SCIENCE CONSORTIUM LTD.

Perspectives on the Development, Evaluation, and Application of *in Silico* Approaches for Predicting Toxicity

9 January 2018

This webinar will cover

- Part 1
  - (Q)SARs
  - Grouping approaches, chemical categories, read-across

- Part 2
  - Integrated Approaches to Testing and Assessment (IATA)
  - General framework and where non-testing approaches fit
  - Adverse Outcome Pathways (AOPs) and AOP-informed IATA

Webinars in this series

Current and Future Perspectives on the Development, Evaluation, and Application of in Silico Approaches for Predicting Toxicity	Dr. Grace Patlewicz, US EPA Prof. Mark Cronin, Liverpool John Moores University
Skin Irritation and Corrosion 25 January 2018, 4–5 pm GMT	Dr. Gertrude-Emilia Costin, Institute for In Vitro Sciences Dr. Costanza Rovida, TEAM Mastery and CAAT-Europe
Skin Sensitisation 1 February 2018, 4–5 pm GMT	Dr. Susanne Kolle, BASF SE Dr. Silvia Casati, EURL ECVAM
Eye Irritation and Corrosion 15 February 2018, 4–5 pm GMT	Dr. Kim Norman, Burt's Bees Dr. Els Adriaens, Ghent University

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

Today’s speakers

- Dr. Christopher Faßbender, PETA International Science Consortium Ltd
- Dr. Grace Patlewicz, US EPA
- Prof. Mark Cronin, Liverpool John Moores University

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Perspectives on the Development, Evaluation, and Application of *in Silico* Approaches for Predicting Toxicity

Grace Patlewicz, NCCT, U.S. EPA, RTP, NC, USA
Mark Cronin, Liverpool John Moores University, England

9 January 2018

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA or Liverpool John Moores University

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 non-testing approaches 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 (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 prioritization is also an important aspect of regulatory frameworks in Canada (the Domestics Substance List), Australia and the EU.
- Non-testing approaches offer a means of facilitating the regulatory challenges in chemical safety assessment

Aims of this webinar

- To review current practices in the development and assessment of non-testing approaches; focussing on (Q)SAR and read-across
- To provide an overview of integrated approaches to testing and assessment (IATA) and where non-testing approaches fit within such a framework
- To highlight advances in the Tox21 field that are shaping how Adverse Outcome Pathways (AOPs) are informing IATA development and application with particular emphasis on read-across

Outline – Part 1

- Non-testing approaches
- Definitions
- (Q)SARs
- Grouping approaches, chemical categories, read-across
- Frameworks for development and assessment of read-across
- Read-across tools
- Challenges in read-across and research directions

Outline – Part 2

- Integrated Approaches to Testing and Assessment (IATA)
- General framework and where non-testing approaches fit
- Adverse Outcome Pathways (AOPs) and AOP-informed IATA
- Defined approaches (DA) for skin sensitisation in the context of AOP-informed IATA

Part 1

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 formatio
- Structure-Activity
- Quantitative Struc (QSAR)
- Expert Systems

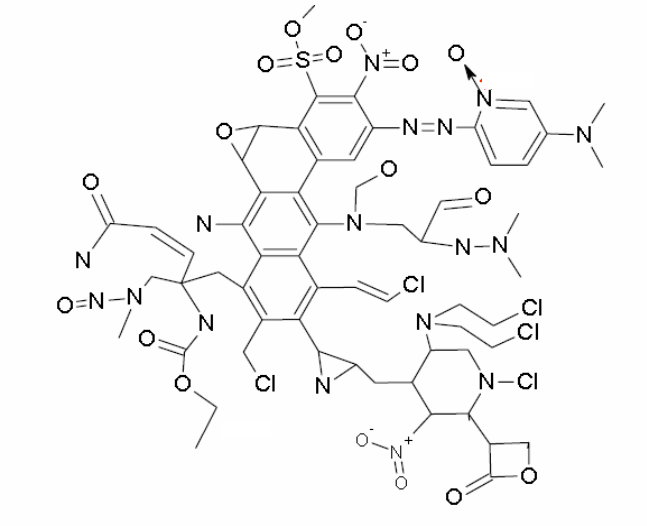
Non-Testing Approaches

- 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

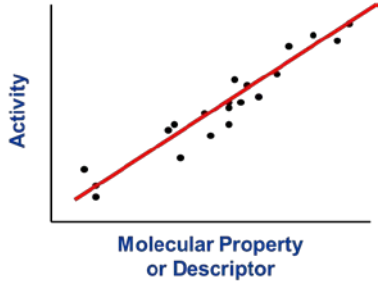
E.g. Carcinogenicity alerts reflected in the **"Supramolecule"**
Ashby and Tennant (1988) Mut. Res. 204:17-115



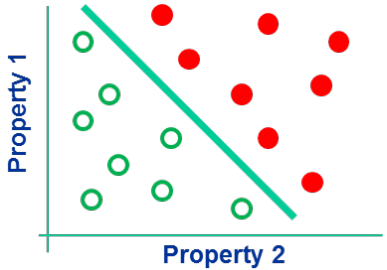
Quantitative Structure-Activity Relationships (QSARs)

- 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, Leadscope
  - knowledge bases such as SARs e.g. Derek Nexus, Toxtree
  - or a hybrid of the two e.g. TIMES, ChemTunes

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 rationalise spurious results in experimental data – since the (Q)SAR is based on a larger body of data, provides a more compelling Weight of Evidence (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
- To add another line of evidence as part of a WoE within the context of an IATA

Current Experiences of (Q)SAR Approaches

- As replacements - (Q)SARs are most promising for physicochemical, ecotoxicity and environmental fate properties e.g. Log Kow, acute fish toxicity, ready biodegradability.
- (Q)SARs can also be used as “supporting information” in category/analogue approaches or as additional information as part of a Weight of Evidence assessment (WoE) – most progress has been made with (Q)SARs for endpoints such as skin/eye irritation, or 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

Regulatory Use of (Q)SARs

- For regulatory purposes, there is an expectation that an assessment of the QSAR model and associated prediction are undertaken

- Under REACH, it is stated that “Results obtained from valid qualitative or quantitative structure-activity relationship models may be used instead of testing when the following conditions are met to indicate the presence or absence of a certain dangerous property”.

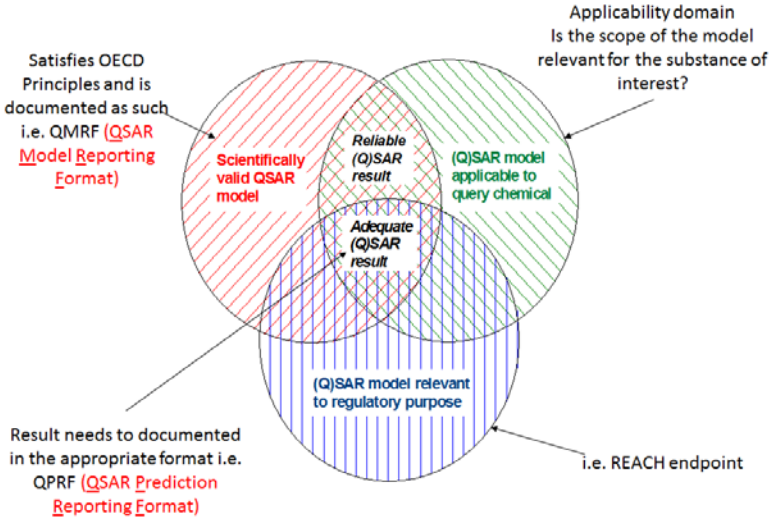


Figure taken from ECHA guidance on QSARs and read-across approaches, 2008

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
- Principles were agreed by OECD in 2004 and associated guidance was published in 2007

Scientific Validity: OECD Principles for (Q)SAR Validation

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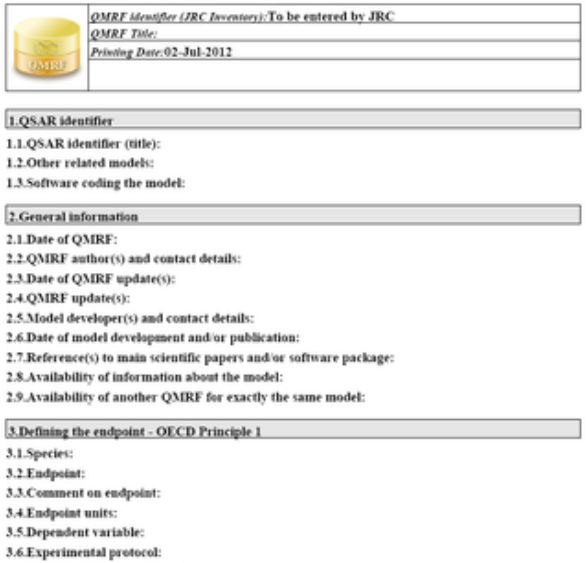
Assessing Applicability Domain to Determine if the Model is Valid for Use for a Specific Substance

- 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:

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QSAR Prediction Reporting Format (QPRF)

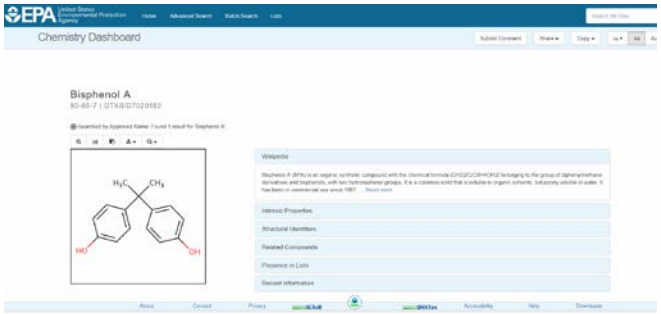
- The QSAR Prediction Reporting Format (QPRF) is a harmonised template for summarising and reporting substance-specific predictions generated by (Q)SAR models
- QPRF requires information on:
  - The substance
  - General information (e.g. date and author)
  - Description of QSAR according to OECD Principles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

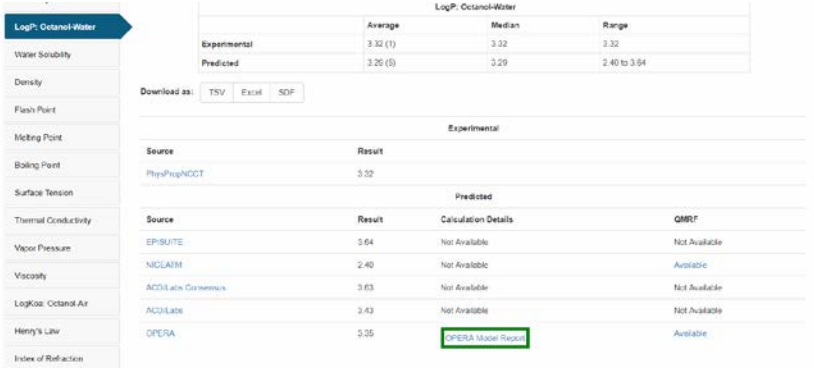
(Q)SAR related Resources

- Since (Q)SARs have become a viable approach to address regulatory purposes, there have been a plethora of tools and resources developed to help facilitate their application.
- The JRC QSAR Model inventory - provides a resource to identify well documented (Q)SARs.
- QSARDB - is a smart repository for (Q)SAR/QSPR models and datasets, ready for discovery, exploring, citing and predicting (https://qsardb.org/).
- Ochem – is a resource for developing new (Q)SARs based on uploaded publicly accessible datasets, or for applying available (Q)SARs (https://ochem.eu/home/show.do)
- US EPA Chemistry Dashboard – is a platform to search for substances within the DSSTox inventory, find associated ToxCast/Tox21 data, toxicity/physical property information, QSAR model predictions, literature resources as well as other related links (https://comptox.epa.gov/dashboard/)

US EPA Chemistry Dashboard

- Available at https://comptox.epa.gov/dashboard/
- For substances within the DSSTox inventory (~750,000 substances), model predictions are available for a range of physchem, ecotox and toxicity endpoints
- For some of these endpoints e.g. OPERA physchem models – QMRFs are available and prediction reports for specific chemicals are available for download





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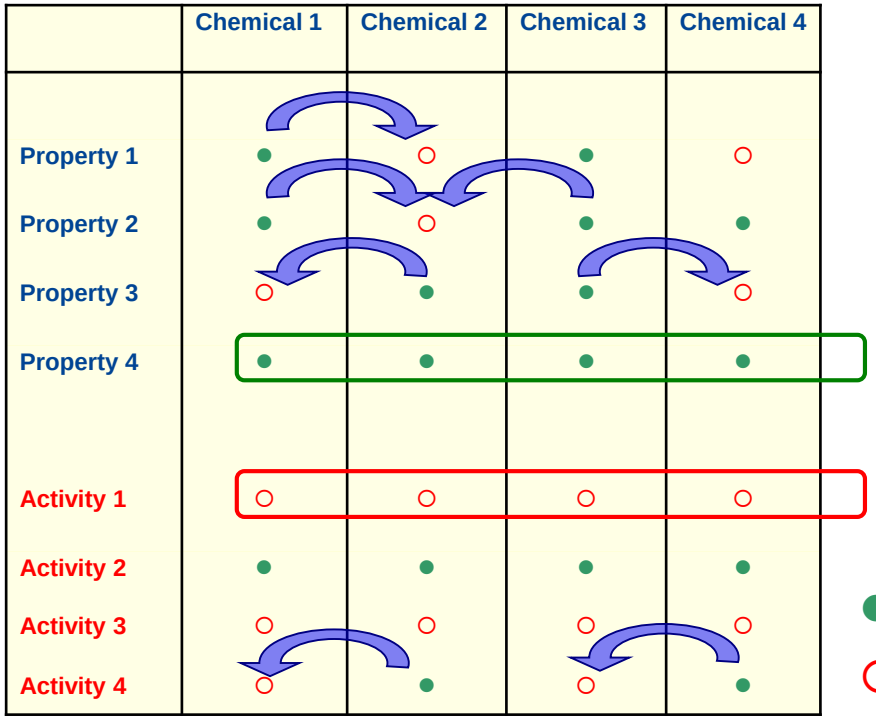
Category Formation (Grouping) for Read-across

- "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"
- OECD definition: "A chemical category is a group of chemicals whose physico-chemical and human heath and/or environmental toxicological and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity (or other similarity characteristics)".

Uses of Read-across



read-across

interpolation

extrapolation

Trend analysis or QSAR

● reliable data point

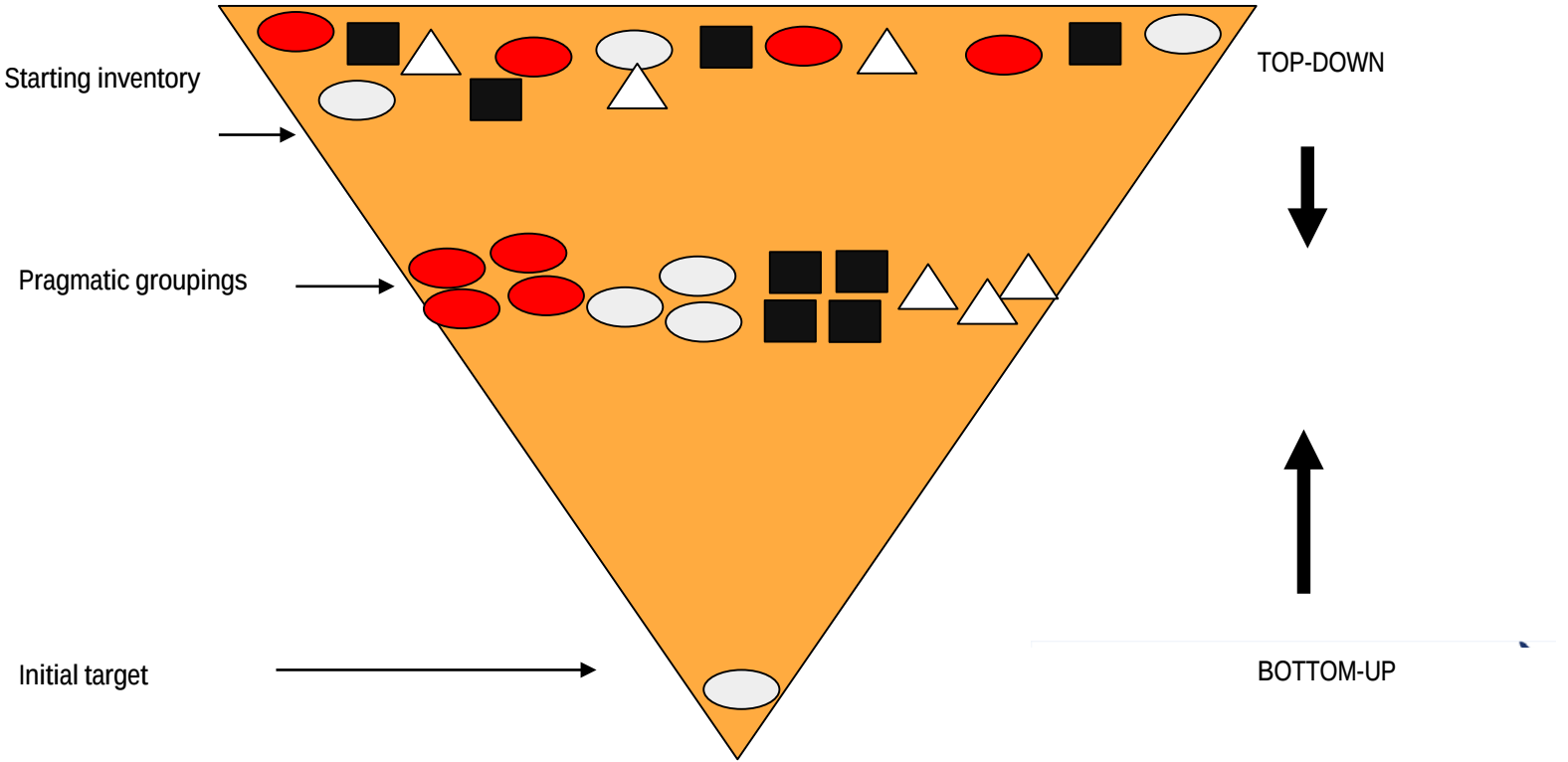
○ missing data point

Uses of Read-across

- Read-across application has been more extensive than (Q)SAR for regulatory purposes – it probably wasn't recognised and categorised as a "read-across" in each case!
- Examples where "read-across" approaches are applied include:
  - US EPA Provisional Peer Reviewed Toxicity Values (PPRTVs) where data is lacking for a specific substance of interest
  - EPA Test Rules – Industry registrants providing information to satisfy a test rule
  - EPA Pre Manufacture Notifications (PMN) – QSARs such as those in Epiwin and ECOSAR are routinely used for e-fate and ecotox predictions but read-across is relied upon for non cancer endpoints
  - ASTDR Emergency response values – an accidental spill that requires an immediate assessment of acute toxicity for first responders
  - REACH registrations – addressing information requirements

Problem formulation/Decision context in read-across

- Decision context is even more important in read-across as the practical approaches can be markedly different

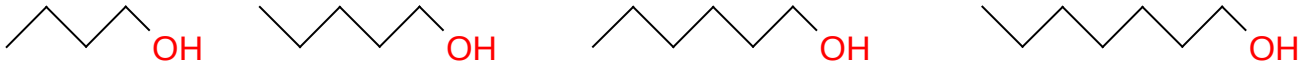


Considerations Before Embarking on a “Read-across”

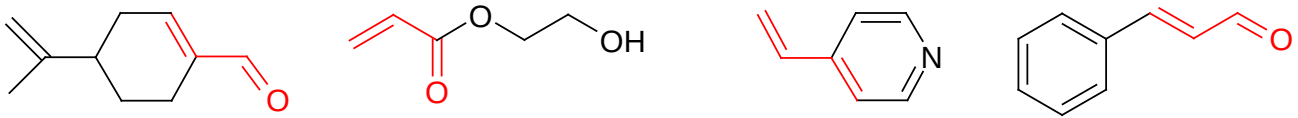
- Decision context –what level of scientific confidence is needed and how does this impact the level of effort and resources that should be applied
- How many data gaps? And for which endpoints?
- Legitimate access to sufficient, reliable data?
- Plausible hypothesis for grouping substances and ease 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

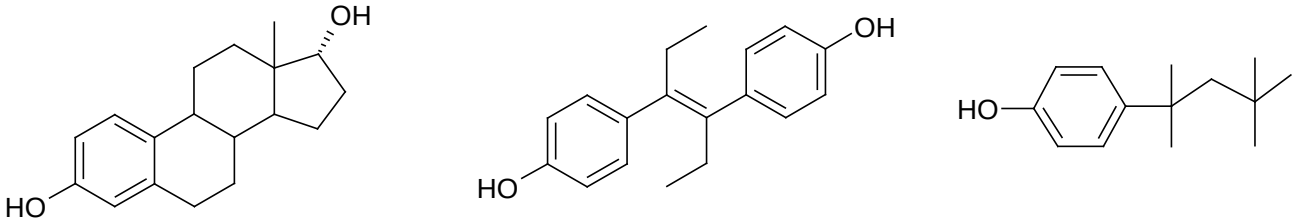
Structural Analogues



Mechanistic Analogues



Mode of Action Analogues



Types of Groupings - 2

- 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

Developing a read-across assessment

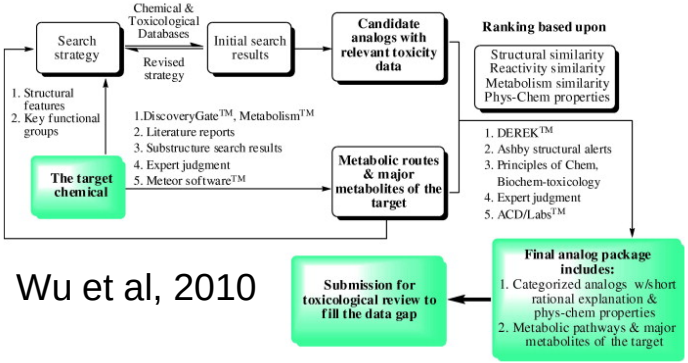
- Existing guidance and resources that can be helpful in developing a read-across assessment:
  - Technical regulatory guidance has been published by OECD and ECHA
  - OECD guidance from 2007 was updated in 2014
  - ECHA Chapter 6 QSARs and Grouping of Chemicals as well as practical guides
- However, many papers have been published that complement and augment the regulatory guidance for development of read-across
  - Wang et al (2012) Application of computational toxicological approaches in human health risk assessment. I A tiered surrogate approach (EPA PPRTVs)

Developing a read-across assessment

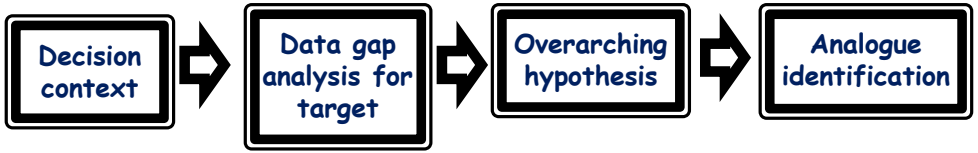
- Selected literature include:
  - ECETOC TR116 category approaches, Read-across, (Q)SAR
  - Wu et al (2010) – Framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate suitability of analogs for SAR based toxicological assessments
  - Patlewicz et al (2013) Use of category approaches, read-across and (Q)SAR general considerations
  - Patlewicz et al (2015) Building scientific confidence in the development and evaluation of read-across
  - Ball et al (2016) Towards Good Read-across Practice

Frameworks for the development of category/analogue approaches

OECD (2014)



Wu et al, 2010



Patlewicz et al, 2015

Frameworks for the development of read-across

Framework	ECHA	OECD	Wu et al	Wang et al	Patlewicz et al
Context	REACH	International regulatory purposes	Product Stewardship	Quantitative risk assessment	Regulatory purposes/Product stewardship
Approach	Analogue/Category – aim is to fill an	Analogue/Category – a generalisation of the ECHA approach	Analogue Systematic stepwise evaluati	Analogue Approach is based on a WOE assessment from DME and	Analogue Stepwise approach considering general (pchem ctivity,) and ecific ons
Terms of refer					ategory
Scope			focused on peated dose toxicity endpoints; quantitative risk assessment	most sim conservative toxicity value	aimed to urce hat can be ress as ints as , even read- diction itself is justified on an endpoint per endpoint basis and some source analogues might be excluded from the prediction itself if they are not appropriate for specific endpoints of interest

Lots of commonality between these frameworks!

Ongoing issues with read-across

- Although there is much guidance for developing read-across assessment, acceptance still remains an issue, especially for regulatory purposes.
- A key issue thwarting acceptance relates to the “uncertainty of the read-across”
- As such there have been many efforts to identify the sources of uncertainty in read-across, characterise them in a consistent manner and identify practical strategies to address and reduce those uncertainties.
- Notable in these efforts have been the development of frameworks for the assessment of read-across. These allow for a structured assessment of the read-across justification.

Sources of uncertainty in read-across

- Analogue or category approach? (no. of analogues)
- Completeness of the data matrix – no. of data gaps
- Data quality for the underlying analogues for the target and source analogues
- Consistency of data across the data matrix – concordance of effects and potency across analogues
- Overarching hypothesis/similarity rationale – how to identify similar analogues and justify their similarity for the endpoint of interest
- Address the dissimilarities and whether these are significant from a toxicological standpoint e.g. ToxDelta
- Presence vs. absence of toxicity
- Toxicokinetics

Frameworks for the assessment of read-across

- Blackburn & Stuard (2014)
- Patlewicz et al (2015)
- Schultz et al (2015)
- ECHA RAAF (2015, 2017)
- These aim to identify, document and address the uncertainties associated with read-across inferences/predictions

Frameworks for the assessment of read-across

READ ACROSS UNCERTAINTY EVALUATION QUESTIONNAIRE FOR:
Target chemical (SOI) = (*list CAS#*)

INSTRUCTIONS
Complete the Questionnaire. Answer the questions for each endpoint where SAR was conducted, and follow instructions listed in each section below. (In general, NO responses indicate potential areas of uncertainty in the proposed read across.)

Questions	Responses by Endpoint	
	Repeat Dose Toxicity	Reproductive Toxicity
Section I. Chemical similarity between source (analogue) and target (SOI)		
1. For each endpoint, list the CAS#s of the source (analogues) contributing the critical study for the read across fo		
	CAS# __	
2. What is the 'suitability rating' of the analogue?		
	____ Suit ____ Suit (skip to se ____ Suit (continue of the inte	
3. Are any differences in functional groups and associ be more reactive than the target)?		
	____ YES ____ NO ____ UNKNOWN ____ No Differences	____ NO ____ UNKNOWN ____ No Differences
	NOTES, if any:	NOTES, if any:

Suitability of Analogs contributing data

Are all features of SOI covered or differences in conservative direction

Blackburn & Stuard (2014)

Table 2
Scientific confidence considerations in Read-across evaluation.

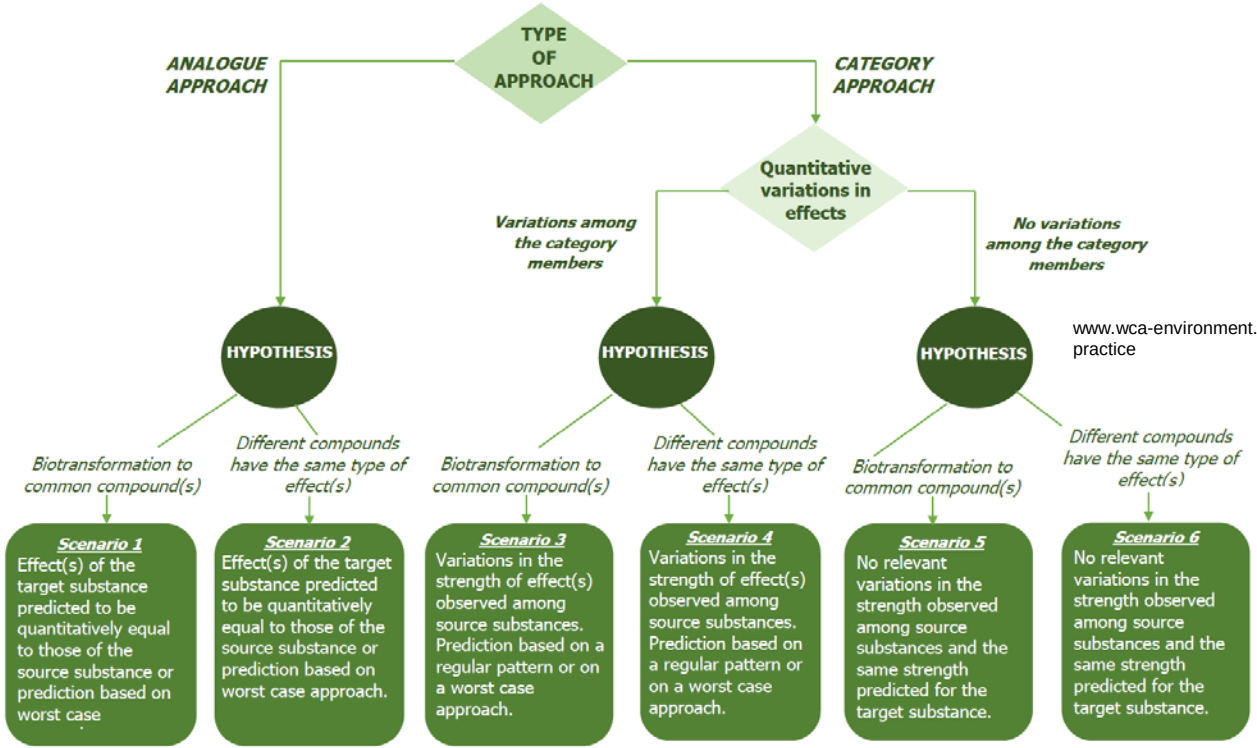
Data issues	Similarity rationale
Analogue/category approach	Similarity rationale/hypothesis that underpins the analogue/category approach – Metabolic transformation – Structural similarity
Completeness of data matrix – No of data gaps e.g. source analogue(s) have many data points to address, target substance has a handful of data gaps.	Analogue validity – Analogue similarity with respect to general and endpoint specific considerations – Rationalization of why structural differences do not impact the toxicity
Quality of data for source analogues – e.g. Klimisch scores of 1 or 2	Concordance of effects and potency (if relevant) per endpoint • Presence or absence of adverse effects • Type of read-across (Qualitative, Quantitative, Trend Analysis)
	Concordance of effects and potency (if relevant) across endpoints

Patlewicz et al (2015)

Frameworks for the assessment of read-across

- Schultz et al (2015)
- Outlined a strategy for structuring and reporting a read-across
- Defined different read-across scenarios
- Two main aspects tackled:
  - an assessment of the similarity of the source analogues
  - an assessment of the mechanistic relevance and completeness of the read-across (number of analogues, absence/presence of toxicity, quality of underlying data, temporal and dose response relationship between mechanistically relevant endpoints
- Three scale grading of the overall read-across confidence Low, Medium, High

Frameworks for the assessment of read-across: RAAF



www.wca-environment.com/blog/putting-read-across-assessment-framework-practice

Frameworks for the assessment of read-across: RAAF

- Six scenarios identified
- For each scenario there will be a number of scientific considerations
- Each is associated with an “assessment element” (AE)
- Each AE is scored from 1-5 where 5 is “acceptable with high confidence” to 1 is not acceptable
- These scores are termed Assessment Options (AO)
- A minimum score of 3 is needed for a read-across to be taken up and used to inform decision making
- There are common assessment elements e.g. reliability of the underlying data and there are scenario specific elements e.g. common underlying mechanism for scenario 2

Frameworks for the assessment of read-across

Framework	ECHA RAAF (2017)	Blackburn and Stuard (2014)	Patlewicz et al (2015)	Schultz et al (2015)
Context	REACH	Product Stewardship	Regulatory purposes &	Regulatory purposes & Product stewardship
Scope				
Framework	number of assessment elements (AE) (both common and scenario specific).	the data across the analogues and relative to the target		teria. eness

Lots of commonality between these frameworks!

Ongoing issues with read-across

- These frameworks allow for a structured assessment of the read-across justification.
- The next step is how those uncertainties can be addressed
- One approach per Blackburn and Stuard (2014) is to use assessment factors
- Alternatively the RAAF and the work by Schultz et al (2015) advocate the use of New Approach Methods (NAM) (e.g. High Throughput Screening (HTS) data) to enhance the scientific confidence of a read-across
- Examples have been published by Schultz (2017) and colleagues
- These examples rely on the qualitative use of NAM data and preferably in the context of an organising framework such as an AOP to ensure the appropriate biological context for interpretation (see Part 2)
- Others such as Shah et al (2016) have explored quantifying the uncertainties of read-across and using NAM data in conjunction with chemical structure information in a 'QSAR-like' read-across (Generalised Read-Across (GenRA)
- Some of these efforts have been implemented into read-across tools

Selected read-across tools

Tool	AIM	ToxMatch	AMBIT	OECD Toolbox	CBRA	ToxRead	GenRA
Analogue identification	X	X	X	X	X	X	X
Analogue Evaluation	NA	X	X by other tools available	X	X	X For Ames & BCF	NA
Data gap analysis	NA	X	X Data matrix can be exported	X Data matrix viewable	NA	NA	X Data matrix can be exported
Data gap filling	NA	X	User driven	X	X	X	X
Uncertainty assessment	NA	NA	NA	X	NA	NA	X
Availability	Free	Free	Free	Free	Free	Free	Beta for Internal testing

Selected read-across tools

Computational Toxicology 3 (2017) 1–18

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox

Navigating through the minefield of read-across tools: A review of in silico tools for grouping

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ARTICLE INFO

Article history:
Received 29 March 2017
Received in revised form 22 May 2017
Accepted 25 May 2017
Available online 29 May 2017

Keywords:
Category approach
Analogue approach
Data gap filling
Read-across
(Q)SAR
Trend analysis
Nearest neighb

ABSTRACT

Read-across is a popular data gap filling technique used within analogue and category approaches for regulatory purposes. In recent years there have been many efforts focused on the challenges involved in read-across development, its scientific justification and documentation. Tools have also been developed to facilitate read-across development and application. Here, we describe a number of publicly available read-across tools in the context of the category/analogue workflow and review their respective capabilities, strengths and weaknesses. No single tool addresses all aspects of the workflow. We highlight how the different tools complement each other and some of the opportunities for their further development to address the continued evolution of read-across.

Published by Elsevier B.V.

OECD QSAR 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

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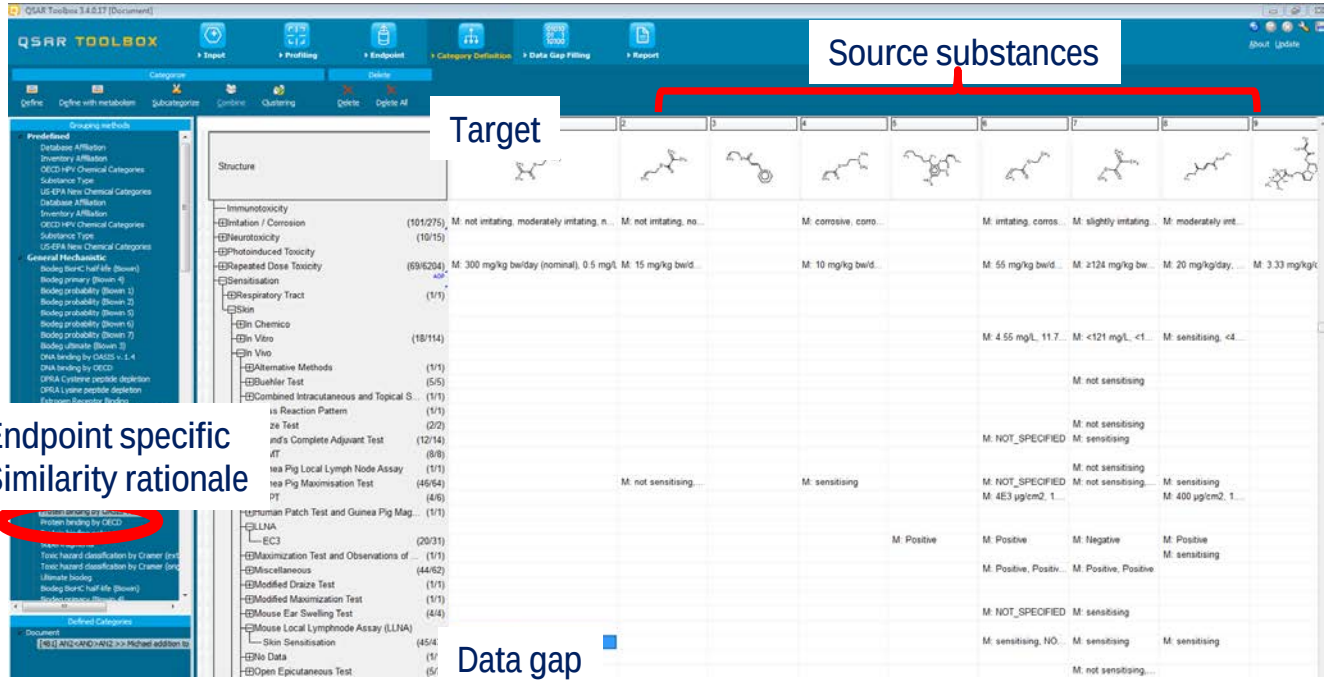
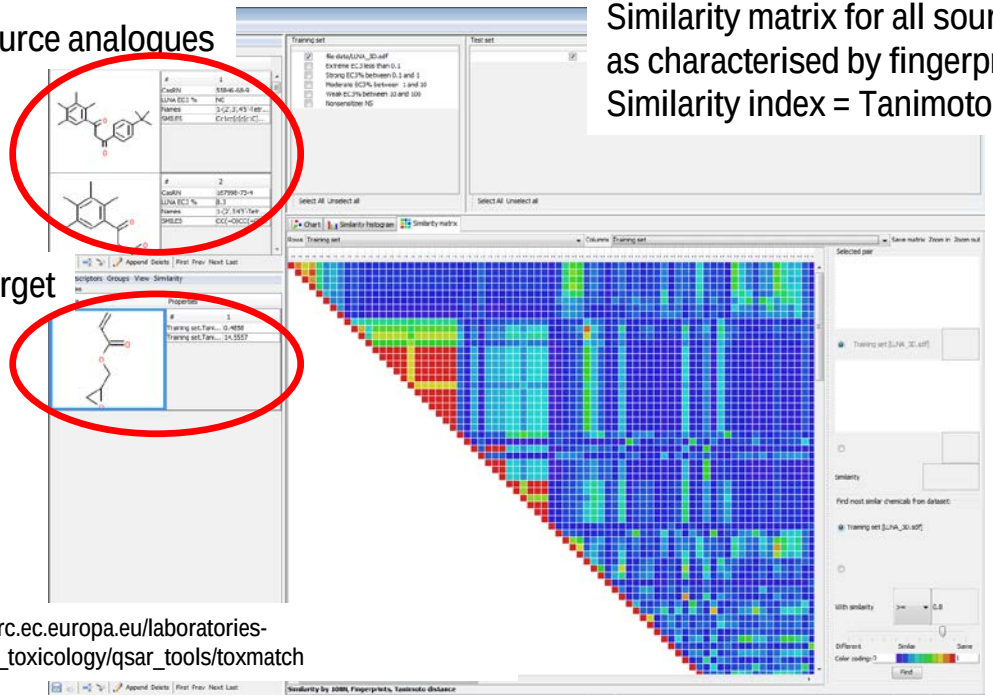
Selected read-across tools: OECD QSAR Toolbox



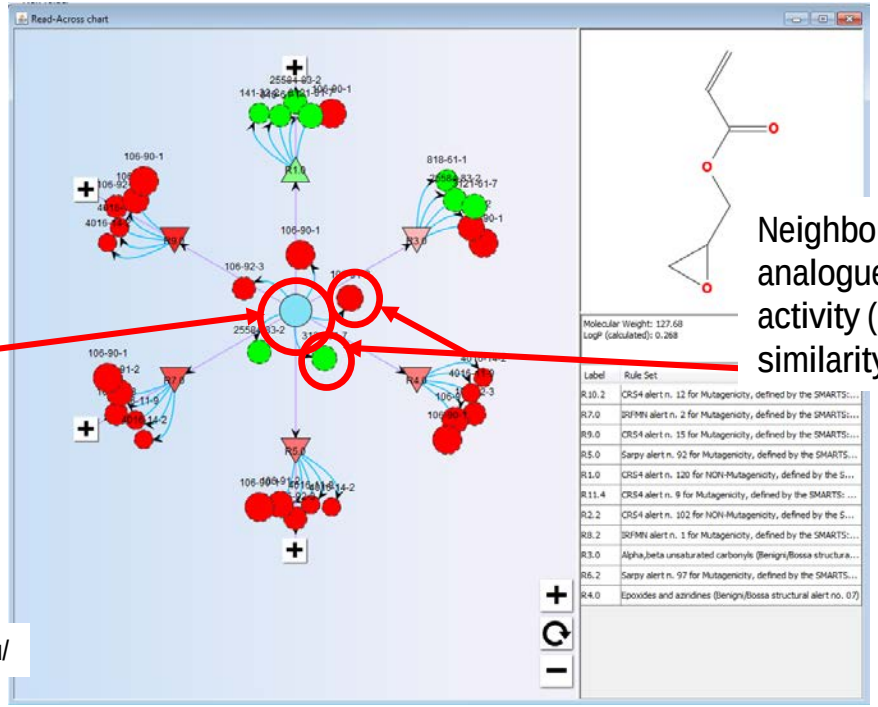
Selected read-across tools: Toxmatch



Similarity matrix for all source analogues as characterised by fingerprints
Similarity index = Tanimoto distance

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

Selected read-across tools: ToxRead

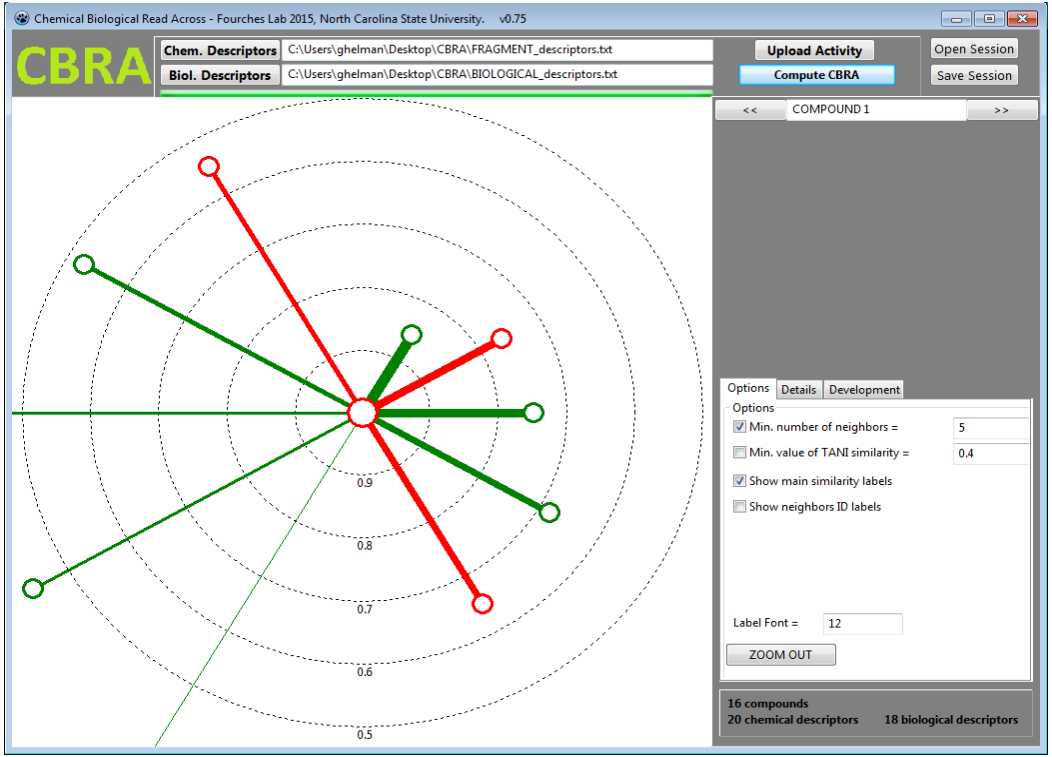


Target

Neighbouring source analogues, colour coded by activity (positive = red) and by similarity index

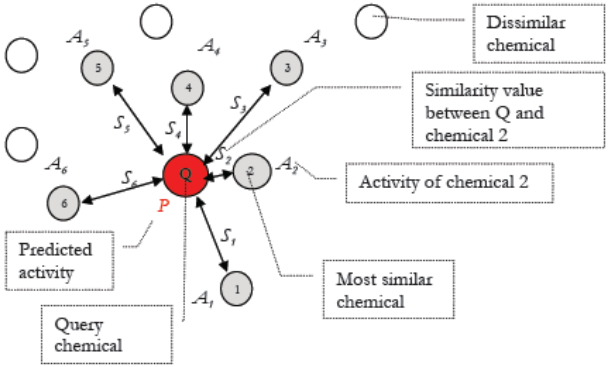
http://www.toxgate.eu/

Selected read-across tools: CBRA



Generalised Read-Across (GenRA)

- GenRA (Generalised Read-Across) is a “local validity” approach
- Predicts toxicity (toxicity binary outcomes observed from different study types) as a similarity-weighted activity of nearest neighbors based on chemistry and/or bioactivity (HTS) descriptors
- Generalised version of Chemical-Biological Read-Across (CBRA) developed by Low et al (2013)
- Systematically evaluates read-across performance and uncertainty using available data



Generalised Read-Across (GenRA)

I. Data

1,778 Chemicals
3,239 Structure descriptors (chm)
820 Bioactivity assays (bio)
ToxCast
574 Apical outcomes (tox)
ToxRefDB

II. Define Local neighborhoods

Use K-means analysis to group chemicals by similarity
Use cluster stability analysis
~ 100 local neighborhoods

III. GenRA

Use GenRA to predict apical outcomes in local neighbor hoods
Evaluate impact descriptors (chm, bio, bc) on prediction
Quantify uncertainty

Use GenRA to predict the similarity weighted toxicity scores for each:
Toxicity type (β)
Descriptor ={chm,bio,bc} (α)
No. of nearest neighbors (k)
Similarity score threshold (s_{ij}^{α})
Calculate performance by comparing predicted y^{tox} and true x^{tox} for all chemicals using area under ROC curve (AUC)

$$y_i^{\beta,\alpha} = \frac{\sum_j^k s_{ij}^{\alpha} x_j^{\beta}}{\sum_j^k s_{ij}^{\alpha}}$$

Jaccard similarity:

$$s_{ij} = \frac{\sum_l (x_{il} \wedge x_{jl})}{\sum_l (x_{il} \vee x_{jl})}$$

$\alpha \in \{chm, bio, bc\}$

$\beta \in \{bio, tox\}$

y_i = predicted activity of chemical (c_i)

x_j^{β} = activity of c_j in β

s_{ij}^{α} = Jacccard similarity between $x_i^{\alpha}, x_j^{\alpha}$

k = up to k nearest neighbours

Selected read-across tools: GenRA

Part 2

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/

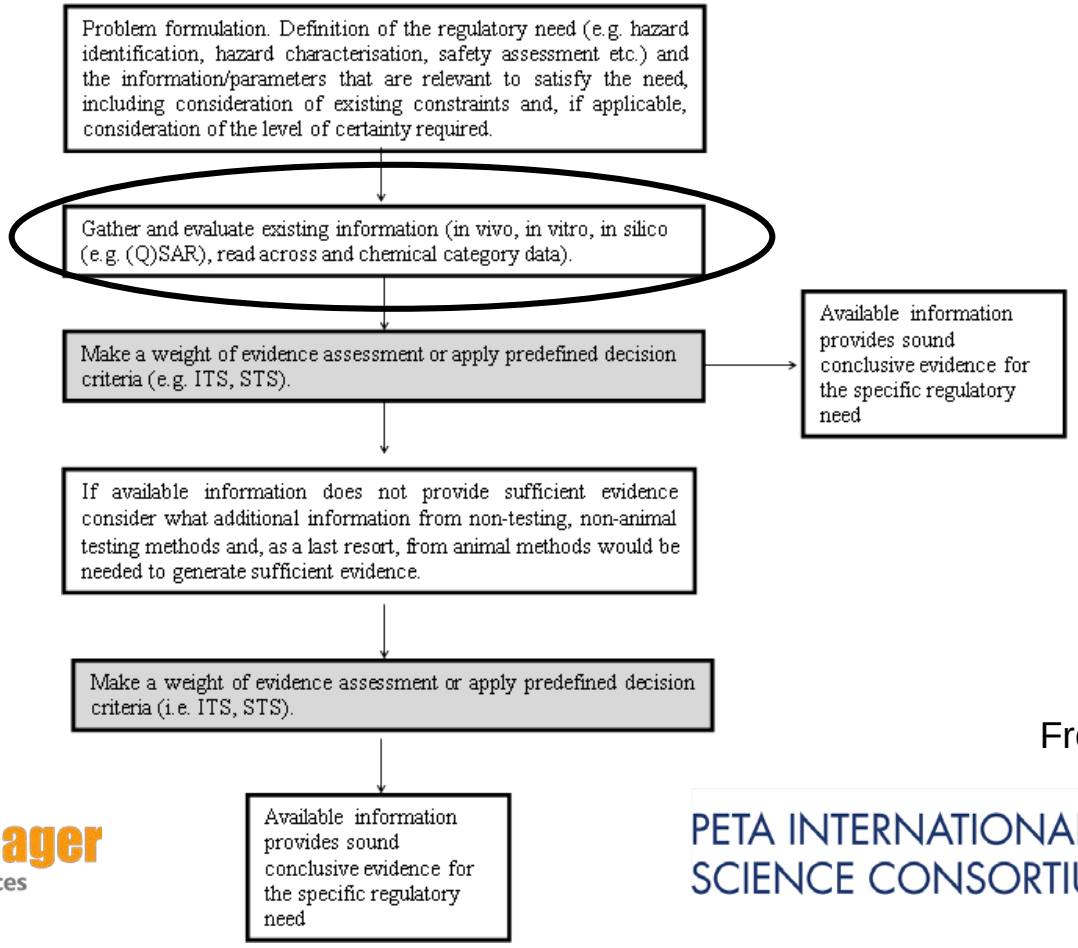
Integrated Approaches to Testing and Assessment (IATA)

- 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”
- Some IATA are more complex than others but the generic building blocks of considering existing data, *in vitro* methods, non-testing approaches BEFORE instigating new *in vivo* testing are the same
- Non-testing approaches fit within the context of these IATA schemes and should not be considered *in vacuo*

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

General framework of an IATA

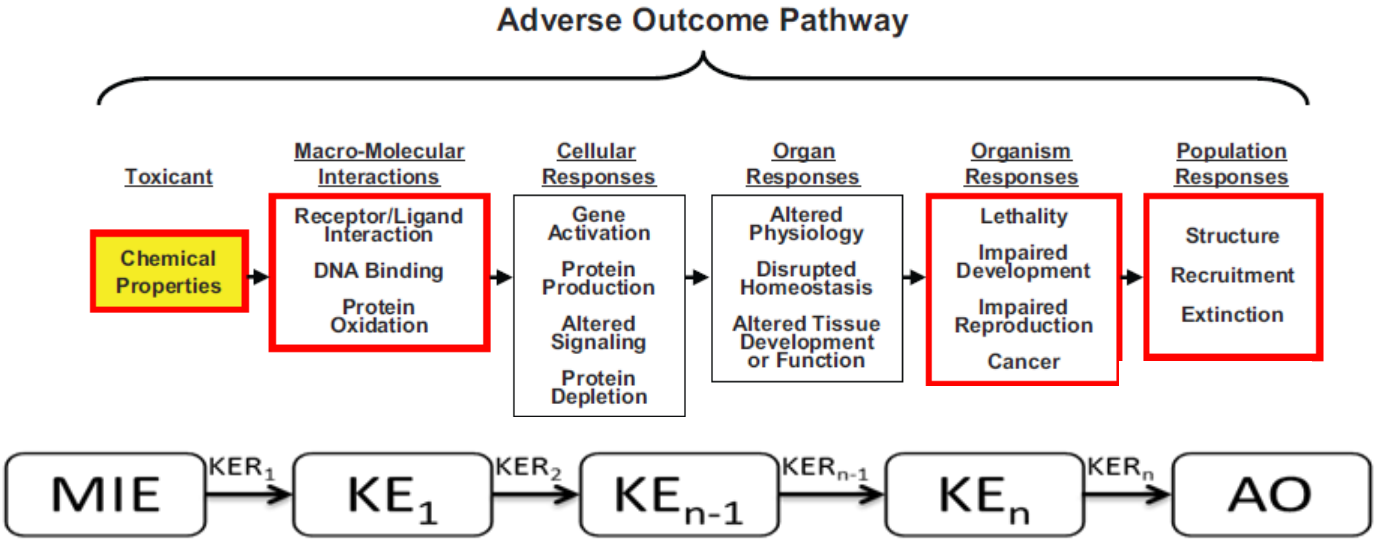


From OECD

Mechanistic based and AOP-informed IATA

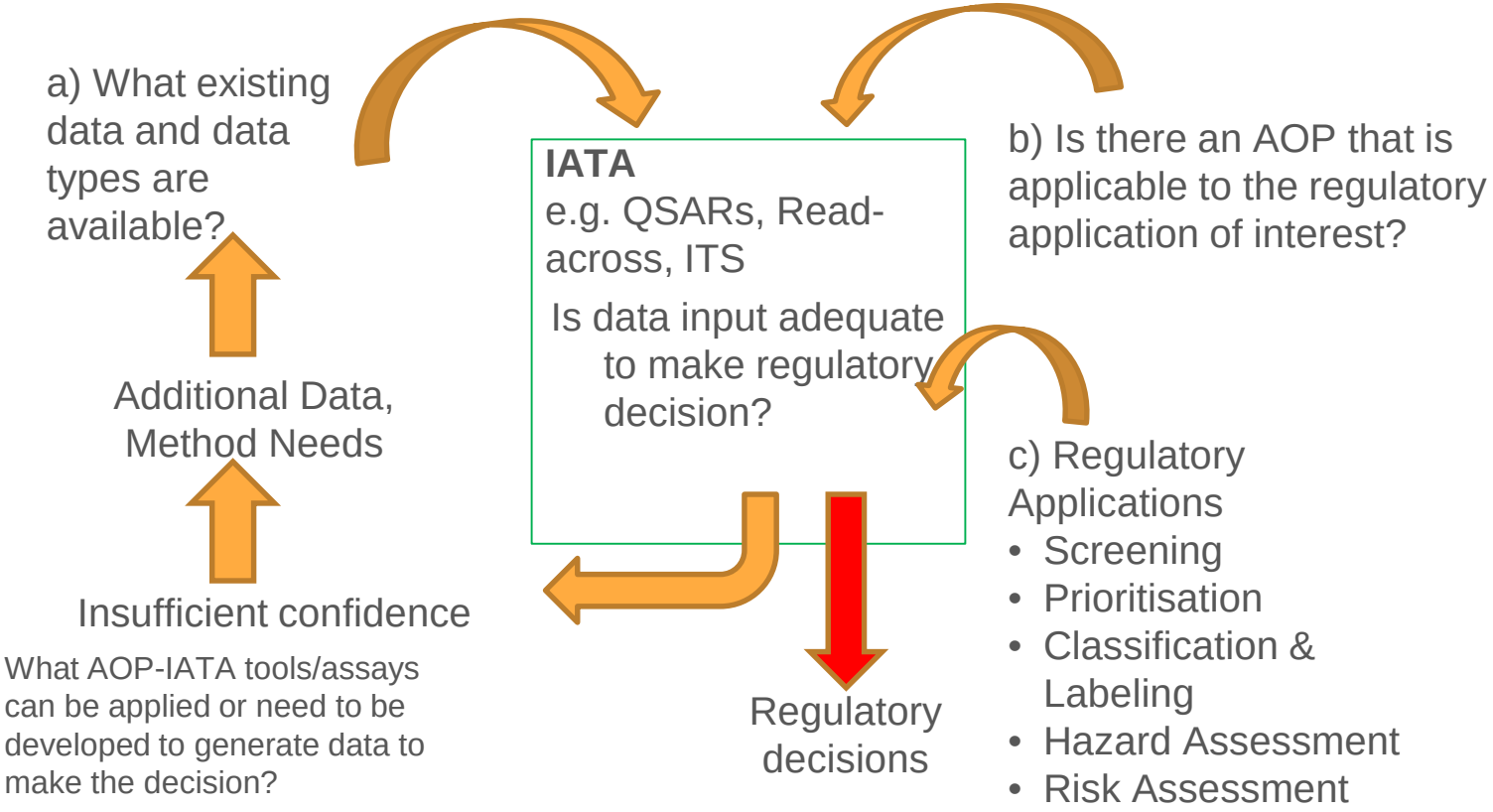
- As noted earlier, there is a shift towards non animal alternatives as a response to regulatory drivers
- Integration of different non-animal approaches requires an organising framework to ensure that the different information sources are being interpreted in their appropriate context. This is particularly 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
- Data from key events provides support to, and will enhance, read-across especially for regulatory acceptance as well as supports definition of domains for MIEs

AOPs



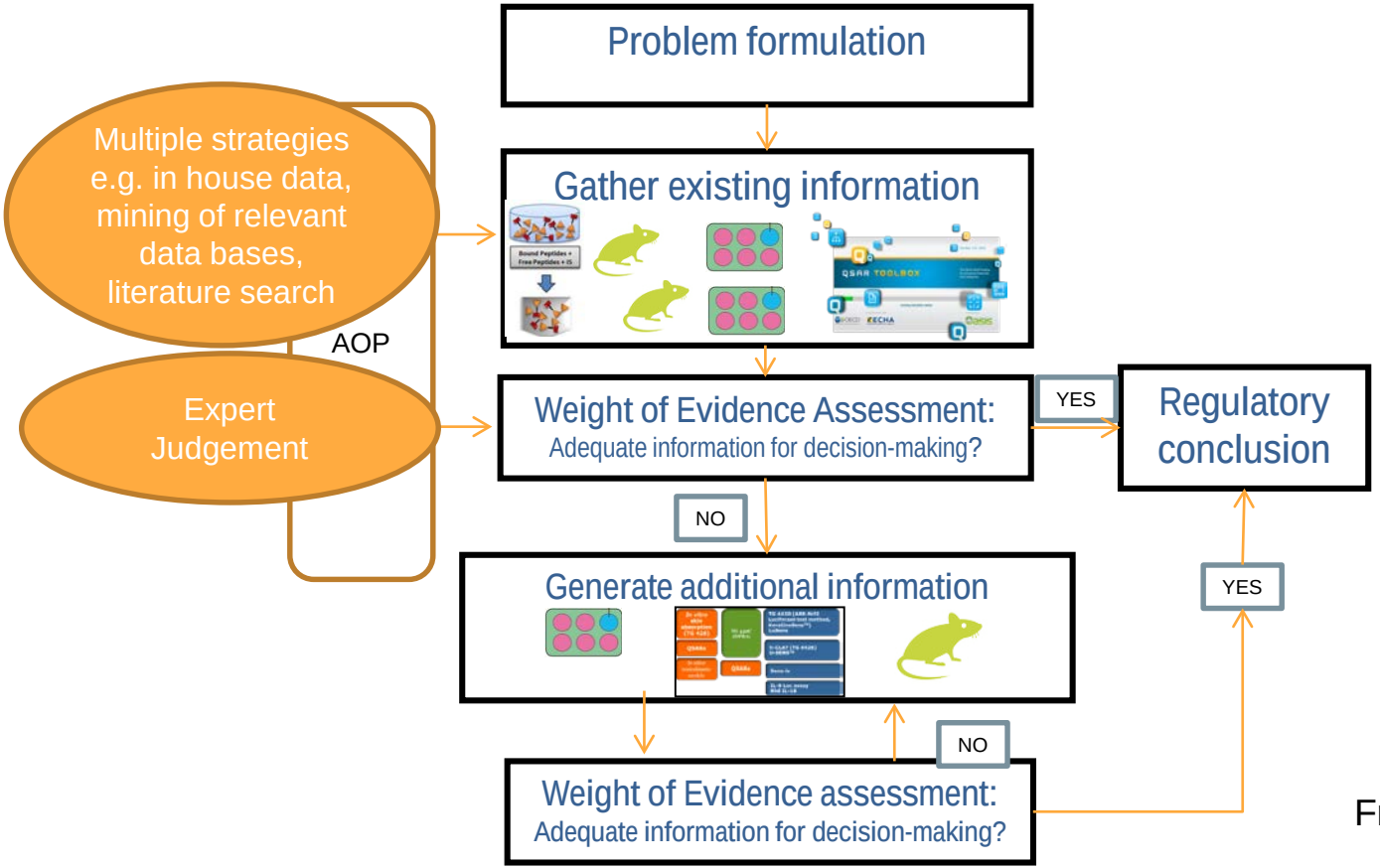
An AOP represents existing knowledge concerning the sequence of events and causal linkages between initial molecular events, ensuing key events and an adverse outcome at the individual or population level.

AOP-informed IATA



Tollefsen et al, 2014

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



From OECD

Defined approaches within IATA

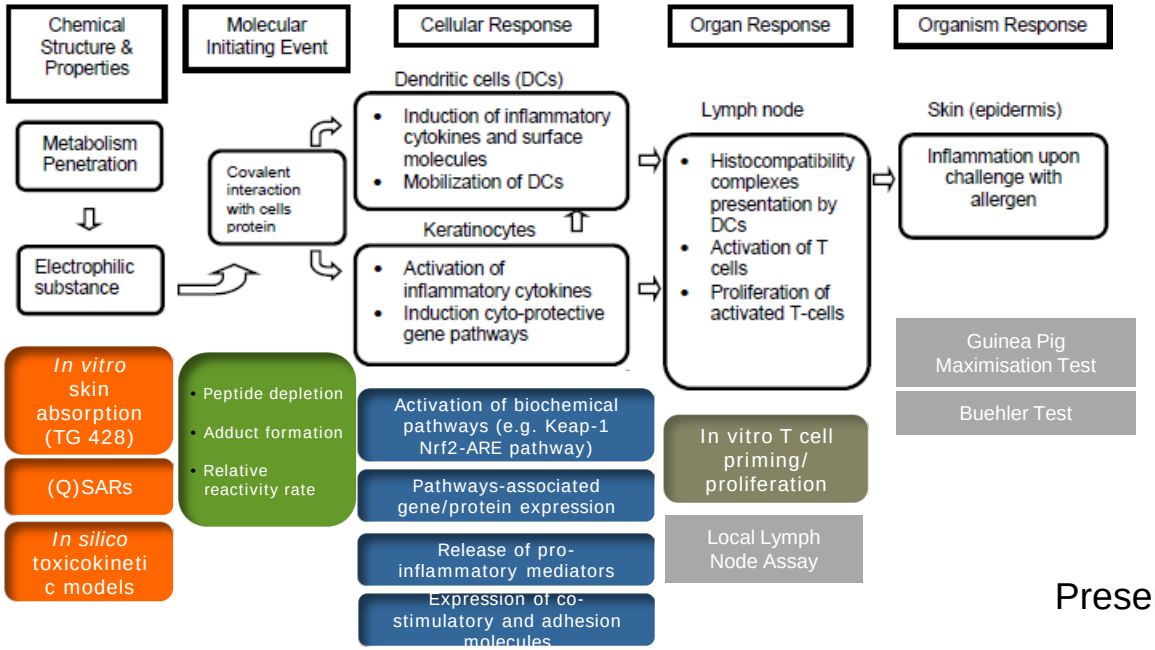
- A defined approach to testing and assessment consists of a fixed data interpretation procedure (DIP) used to interpret data generated with a defined set of information sources, that can either be used alone or together with other information sources, to satisfy a specific regulatory need.
  - Guidance 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

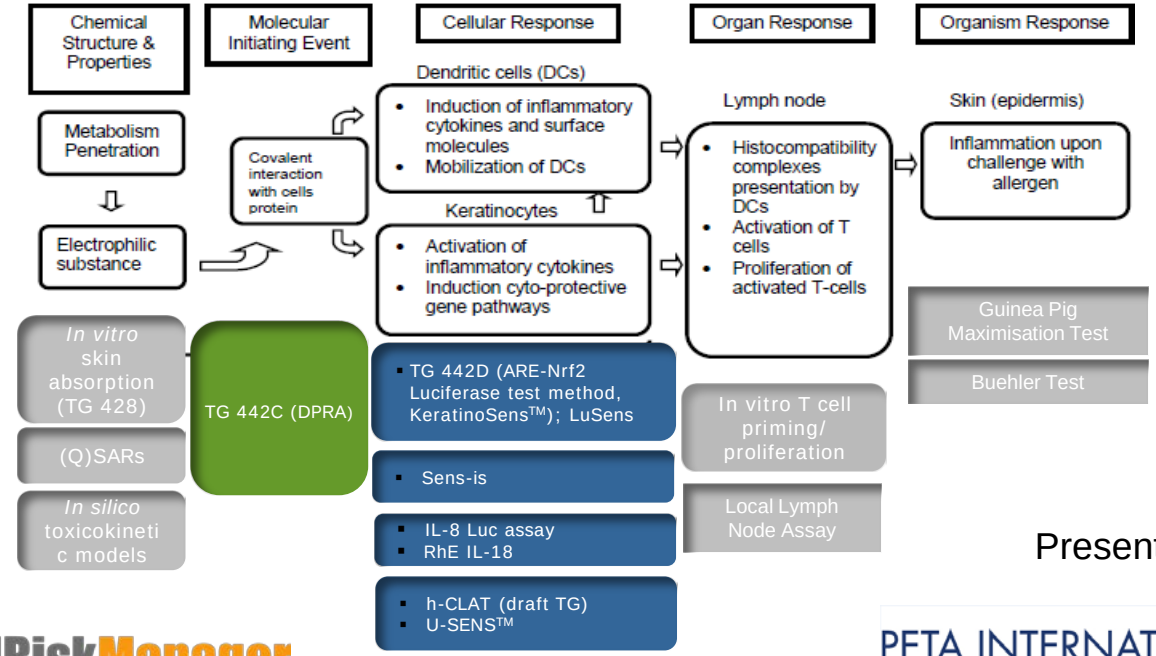
AOP and available toolbox of non-animal methods



Presented by S Casati, JRC

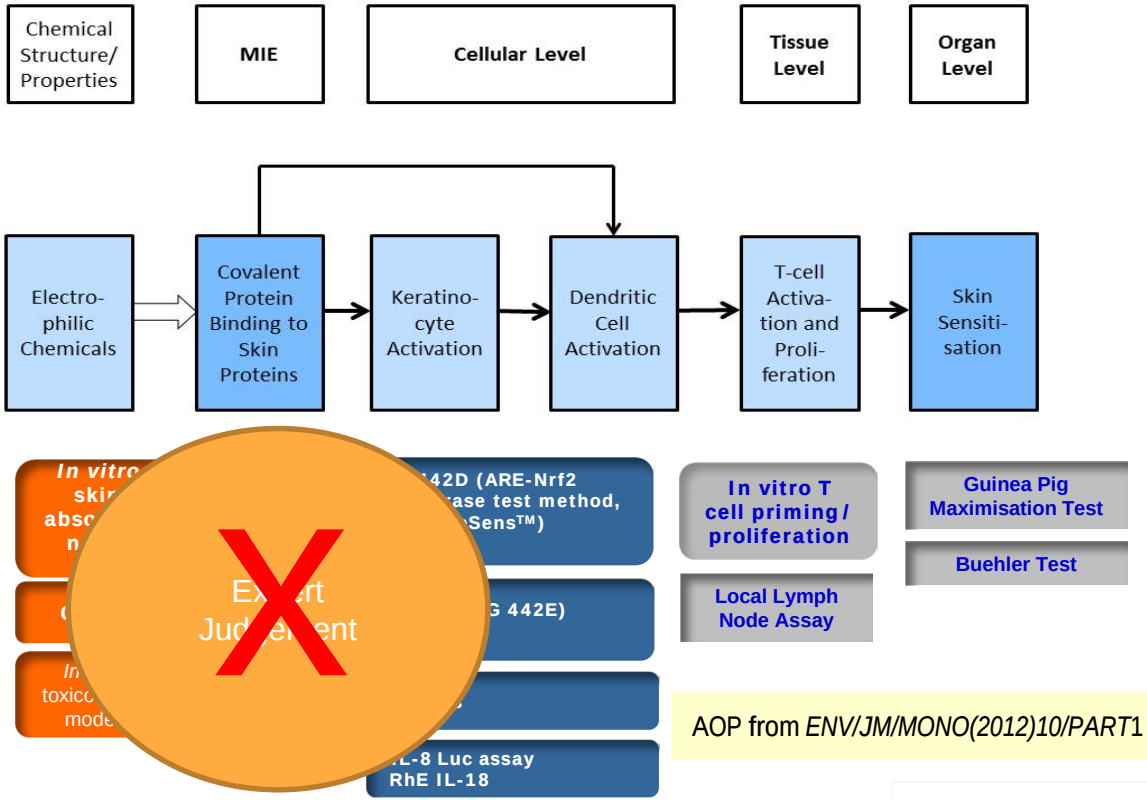
Defined approaches within IATA: Skin sensitisation

AOP and *some* of the more advanced non-animal methods (i.e. OECD adopted, evaluated or under evaluation in ring trials)



Presented by S Casati, JRC

Defined approaches within IATA: Skin sensitisation



https://aopwiki.org/wiki/index.php/Aop:40

Defined approaches for skin sensitisation examples

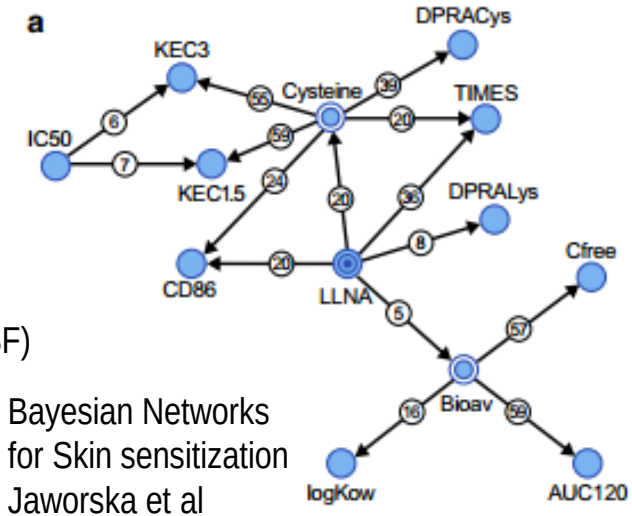
Method 1 (KE a)

Method 2 (KE b)

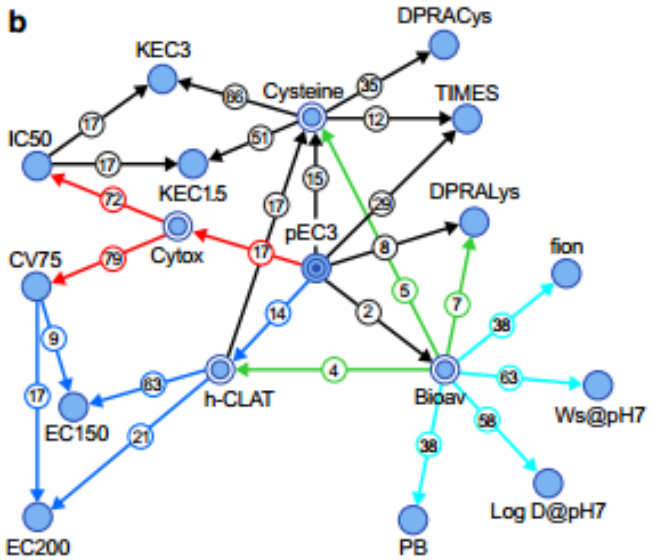
Results concordar

M

Defined Approach (BASF)
'2 out of 3 approach'



Bayesian Networks for Skin sensitization Jaworska et al (2015)



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Take Home Messages - 1

- 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 provide a framework to assess a QSAR model and its prediction and document both
- Many QSAR resources exist to identify QSARs, make/extract predictions, or develop new models
- Read-across tends to be more routinely relied upon 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
- There is much guidance for read-across, and many frameworks exist that guide how to develop a read-across. Many of these frameworks are very complementary to each other.

Take Home Messages - 2

- Despite these development frameworks, acceptance of read-across remains a challenge. The main reason thought to be thwarting acceptance is characterising and addressing the uncertainties of the read-across prediction.

- Many frameworks exist that provide a structure for how to characterise these uncertainties. Research has been undertaken to explore to what extent NAM can be used to enhance the scientific confidence in read-across. Most approaches have been limited to a qualitative application of NAM. Other researchers have attempted to quantify the uncertainties in order to explore the performance of read-across and how and to what extent NAM is impactful in improving that performance.

- There are many tools that can be used in the development and assessment of read-across. A selection have been highlighted from those tools that are publicly available.

Take Home Messages - 3

- (Q)SARs and read-across are categorised as non-testing approaches and ordinarily form components of an IATA
- There are different ways in which IATA can be constructed but there is a lot of commonality in the main steps
- Increasingly IATA are being underpinned by mechanistic information such as captured within AOPs
- For the skin sensitisation endpoint, an AOP is available and efforts have been made to explore to what extent more formalised prediction models can be developed that integrate different KE information. These sorts of prediction models are termed defined approaches (DA).
- OECD is undertaking work to explore to what extent performance based standards can be established for defined approaches to obviate formalised & lengthy validation exercises of specific DA.
- Examples of DA developed for skin sensitisation are highlighted to demonstrate the range of complexity that a DA might encompass

Acknowledgements

- Colleagues at NCCT including Imran Shah, George Helman, Tony Williams, Ann Richard, Chris Grulke, Richard Judson

- Mark Cronin acknowledges the following financial support:

  - The European Community's Seventh Framework Program (FP7/2007-2013) COSMOS Project under grant agreement n° 266835 and from Cosmetics Europe

  - The European Community's 7th Framework Programme Innovative Medicines Initiative Joint Undertaking (IMI-JU) eTox Project (grant agreement n° 115002).

  - European Chemicals Agency (EChA) Service Contract No. ECHA/2008/20 /ECA/203.

Useful Links – (Q)SARs

QSAR resources (Models, Formats etc.)

- http://ihcp.jrc.ec.europa.eu/our_labs/predictive_toxicology/qsar_tools/QRF
- US EPA Chemistry Dashboard comptox.epa.gov/dashboard/
- QSARDB - https://qsardb.org/
- Ochem https://ochem.eu/home/show.do
- Applicability Domain software tools
- http://ambit.sourceforge.net/download_ambitdiscovery.html
- http://oasis-lmc.org/

Useful Links – (Q)SARs and Read-across

Technical regulatory guidance

- 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
- http://www.oecd.org/chemicalsafety/risk-assessment/validationofqsarmodels.htm
- http://www.oecd.org/chemicalsafety/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm
- ECHA. 2015. Read-across Assessment Framework (RAAF). ECHA-15-R-07-EN
- ECHA. 2017. RAAF ECHA-17-R-01-EN
- ECHA. 2017. RAAF - considerations on multi-constituent substances and UVCBs ECHA-17-R-04-EN

Useful Links – Read-across

Read-Across tools

- AMBIT - http://cefic-lri.org/toolbox/ambit/
- OECD QSAR Toolbox - http://www.qsartoolbox.org/
- CBRA - https://www.fourches-laboratory.com/software
- ToxRead - http://www.toxread.eu/download.php
- AIM - https://www.epa.gov/tsca-screening-tools/analog-identification-methodology-aim-tool
- Toxmatch - https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/qsar_tools/toxmatch
- Patlewicz G, et al. 2017. Navigating through the minefield of read-across tools. A review of in silico tools for grouping. Computational Toxicology 3: 1-18.

Useful Links – Read-across

Read-Across literature

- 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.
- Wu S et al. 2010. A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments. Regul. Toxicol. Pharmacol. 56(1): 67-81.
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Useful Links – Read-across

Read-Across literature

- Low Y, et al. 2013. Integrative chemical-biological read-across approach for chemical hazard classification. Chem. Res. Toxicol. 26(8): 1199-1208.
- Blackburn K, Stuard SB. 2014. A framework to facilitate consistent characterization of read across uncertainty. Regul. Toxicol. Pharmacol. 68: 353-362.
- Patlewicz G, et al. 2014a Food for thought..Read-across approaches - misconceptions, promises and challenges ahead. ALTEX 31: 387-396.
- Patlewicz G, et al. 2015. Building scientific confidence in the development and evaluation of read-across. Regul. Toxicol. Pharmacol. 72: 117-133.
- Schultz TW, et al. 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72: 586-601.

Useful Links – Read-across

Read-Across literature

- Ball N et al. 2016. Toward Good Read-Across Practice (GRAP) guidance. ALTEX. 33(2): 149-166.
- Zhu H et al. 2016. Supporting read-across using biological data. ALTEX. 33(2): 167-182.
- Schultz TW, Cronin MTD. 2017. Lessons learned from read-across case studies for repeated-dose toxicity. Regul Toxicol Pharmacol. 88:185-191. doi: 10.1016/j.yrtph.2017.06.011.
- Shah I et al. 2016. Systematically evaluating read-across prediction and performance using a local validity approach characterized by chemical structure and bioactivity information. Regul. Toxicol. Pharmacol. 79: 12-24.
- Pradeep P, et al. 2017. A systematic evaluation of analogs and automated read-across prediction of estrogenicity: A case study using hindered phenols. Computational Toxicology, *in press*

Useful Links – Read-across

AOPs, IATA & DA

- http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm
- http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm
- Ankley GT et al. 2010. Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. Environ Toxicol Chem 29, 730-741
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- Villeneuve DL et al. 2014. Adverse outcome pathway (AOP) development I: strategies and principles. Toxicol Sci. 142(2):312-20. doi: 10.1093/toxsci/kfu199.
- Edwards SW et al. 2016. Adverse Outcome Pathways-Organizing Toxicological Information to Improve Decision Making. J Pharmacol Exp Ther. 356(1): 170-181. doi: 10.1124/jpet.115.228239.

Useful Links – Read-across

AOPs, IATA & DA

- OECD 2016a Guidance Document for the Use of Adverse Outcome Pathways in Developing IATA. STA No. 260, ENV/JM/MONO(2016)67
- OECD 2016b. OECD Guidance Document on the Reporting of Defined Approaches (DAs) to Be Used within IATA. STA No. 255, ENV/JM/MONO(2016)28
- OECD 2017 Guidance Document for the Use of Adverse Outcome Pathways in Developing Integrated Approaches to Testing and Assessment (IATA) Series on Testing and Assessment No. 260
- Wittwehr C et al. 2017. How Adverse Outcome Pathways Can Aid the Development and Use of Computational Prediction Models for Regulatory Toxicology. Toxicol Sci.155(2):326-336. doi: 10.1093/toxsci/kfw207.

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Skin Sensitisation 1 February 2018, 4–5 pm GMT	Dr. Susanne Kolle, BASF SE Dr. Silvia Casati, EURL ECVAM
Eye Irritation and Corrosion 15 February 2018, 4–5 pm GMT	Dr. Kim Norman, Burt's Bees Dr. Els Adriaens, Ghent University

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