Critical aspects in the assessment of adaptations based on read-across:

The role of supporting evidence

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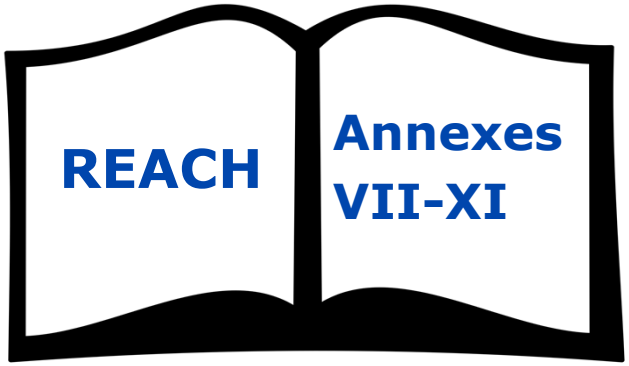
The presentation represents the opinion of the author and is not an official position of the European Chemicals Agency

Outline

- Read-across in the context of REACH
- What is RAAF and how does it work ?
- Role of supporting evidence
- .. and New Approach Methods?

REACH Information Annexes



- REACH Annexes VII to X are tiered according to tonnage bands
- These Annexes describe standard information requirements to characterise properties of the registered substance (“standard testing regime”)
- The EU Test Methods Regulation describes the methods to be used; REACH allows use of other international methods.
- Annex XI sets out general rules for adaptation of the ”standard testing regime”
- Annex XI 1.5 describes the ”grouping and read-across approach”

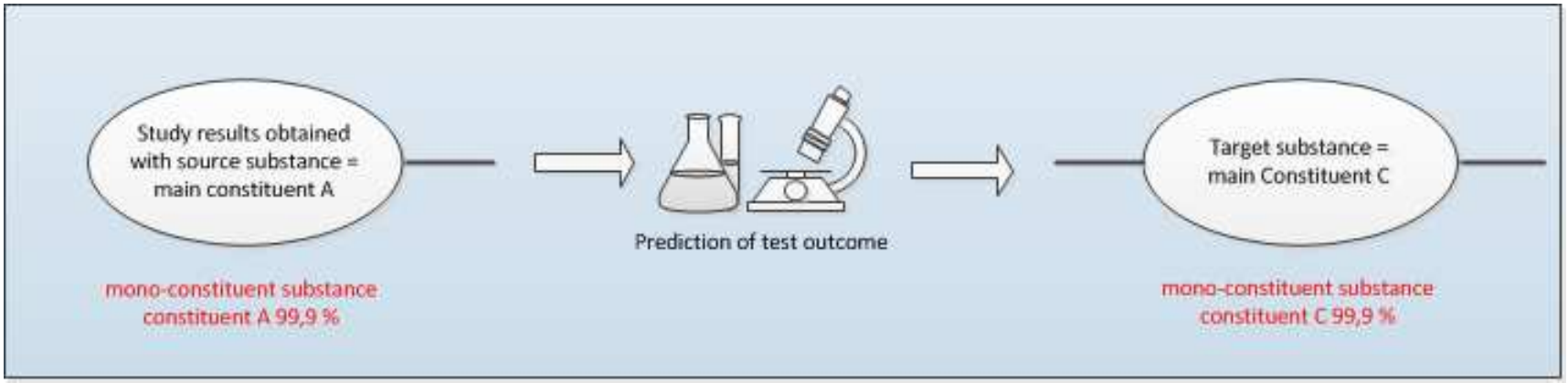
Grouping of substances and read-across approach 1(2)
(Annex XI, 1.5)

'Substances whose physicochemical, toxicological *and ecotoxicological* ***properties are likely to be similar or follow a regular pattern as a result of structural similarity*** *may be considered as a group, or 'category' of substances.*

Application of the group concept requires *that physicochemical properties, human health effects and environmental effects or environmental fate* ***may be predicted from data for reference substance(s) within the group*** *by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint.'*

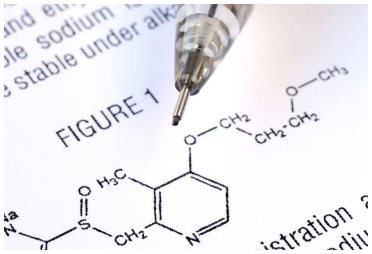
Read-across in the context of REACH (1)

- The results of studies with analogue substance(s) ('source substances') are used to meet the standard information requirement of the registered substance ('target substance') by predicting, instead of measuring the property in a study using the registered substance



- Results from studies obtained with one or more substances (the 'sources') are 'read-across' to another substance (the 'target' or registered substance)

Read-across in the context of REACH (2)



- First step: grouping on the basis of structural similarity and similar properties / regular pattern (a registered substance under REACH does not have a chemical structure, its constituents have chemical structures)
- Second step: predicting properties within the group
- A prediction cannot be supported alone by structural similarity of source and target substances
  - Very similar substances can have very different effects: what about the differences in the structures?
  - Why does a particular structural similarity allow the read-across for the property under consideration?
- Mechanistic explanation: why and how the structural similarity is associated with similar biological properties.

Prerequisites (Annex XI 1.5)

If the group concept is applied, substances shall be classified and labelled on this basis.

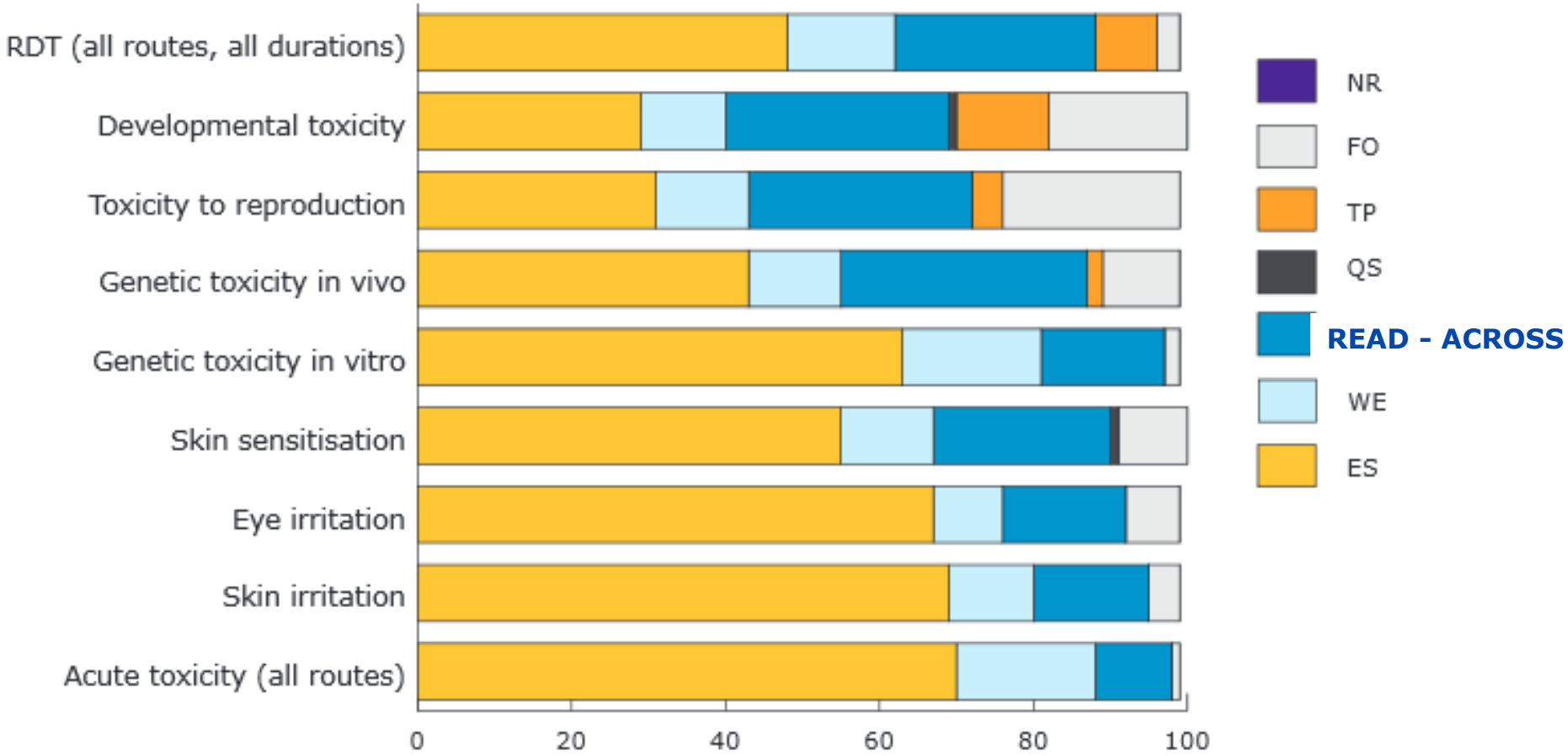
In all cases results should:

- 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.

In short: The result of read-across should be good enough to be used in the same way as the result of the standard test.

Relative proportions of options to meet the information requirements

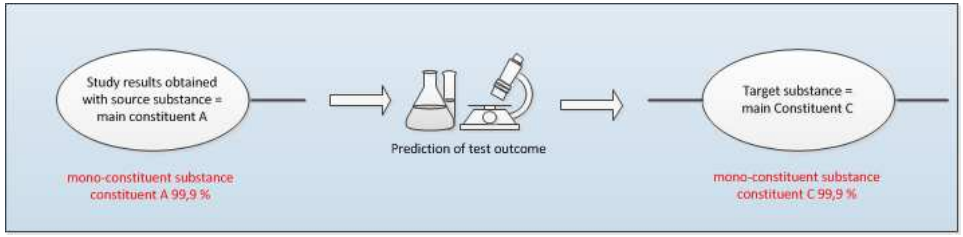
~75% of registrations contain read-across



NR not reported, FO Flags to omit study, TP testing proposal, QS (Q)SAR, WE Weight of evidence, ES experimental study

ECHA: Use of Alternatives to Animal Testing Report, 2014; phase-in 100tpa+; 3662 substances

Assessment of read-across approaches



- ECHA assesses adaptations when evaluating testing proposals and when checking dossiers for compliance
- A wide spectrum of possible scientific arguments and different types of data can be used to justify read-across
- The assessment needs to be organized in such a way that consistency is guaranteed for the relevant aspects of the read-across

The RAAF structures expert judgement …

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

Confidence

Assessment Elements

Scenarios

Scientific Explanation Types

Assessment Options

… and provides means for registrants to improve

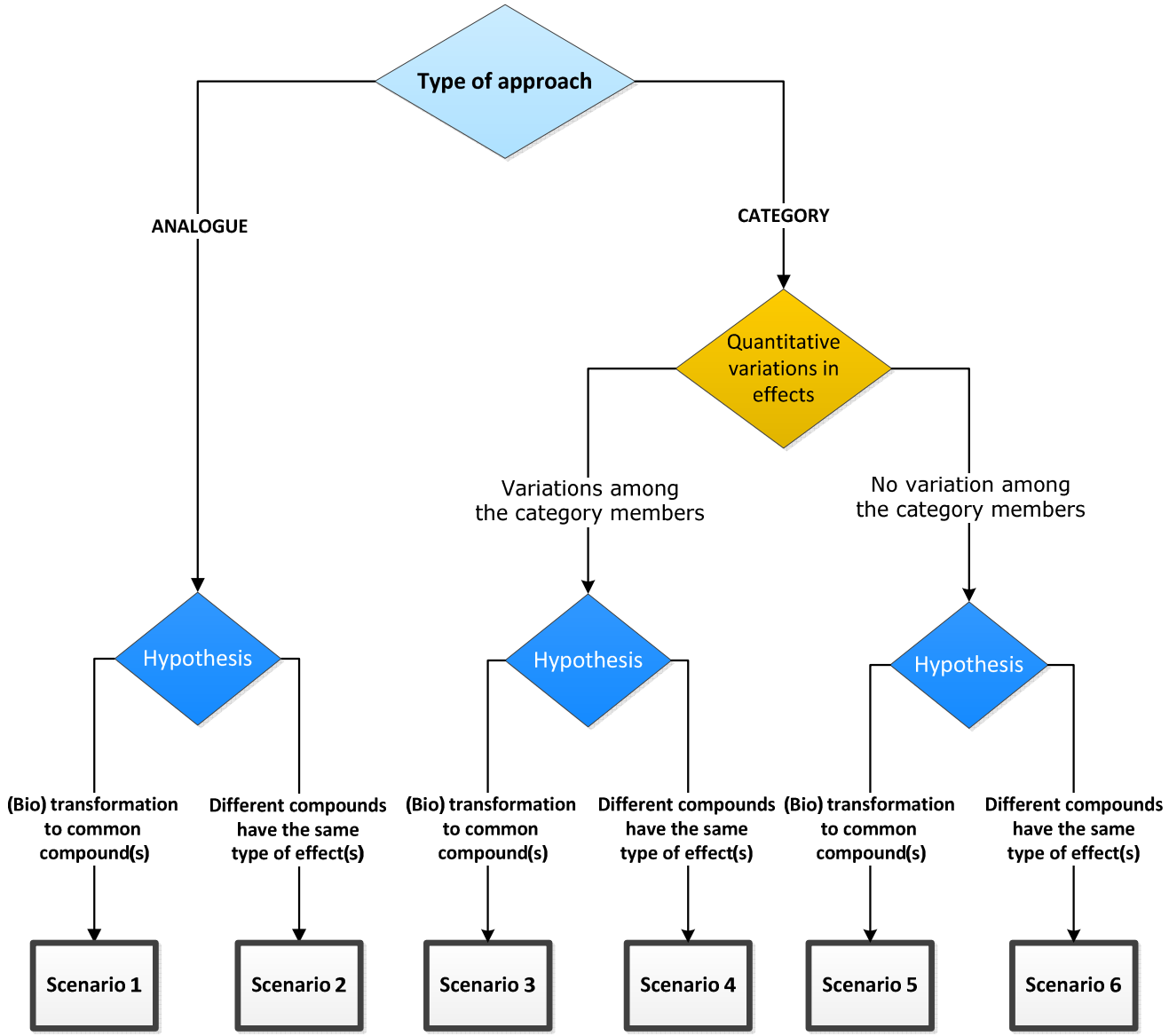
The RAAF – how does it work?

- The RAAF defines different **scenarios** for different read-across approaches, the respective scenarios are selected and applied to the proposed cases
- Each scenario is associated with particular aspects **(assessment elements, AEs**) that are deemed crucial
- Each AE poses questions which lead an assessing expert to select pre-defined conclusions **(assessment options, AOs)**
- The selected assessment options reflect the strengths and weaknesses of the read-across, and so, its acceptability
- It is a **scientific framework;** it needs to be handled flexibly
- The outcome is: What **degree of confidence** is associated with the proposed read-across?
- If the confidence is low, the prediction based on read-across will not be acceptable

Scenario selection (1)

Table 1 - Overview for scenario selection			
Scenario	**Approach**	**Read-across hypothesis based on**	**Quantitative variations**
1	Analogue	(Bio)transformation to common compound(s)	Effect(s) of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach.
2	Analogue	Different compounds have the same type of effect(s)	Effect(s) of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach.
3	Category	(Bio)transformation to common compound(s)	Variations in the strength of effect(s) observed among source substances. Prediction based on a regular pattern or on a worst-case approach.
4	Category	Different compounds have the same type of effect(s)	Variations in the strength of effect(s) observed among source substances. Prediction based on a regular pattern or on a worst-case approach.
5	Category	(Bio)transformation to common compound(s)	No relevant variations in strength of effects observed among source substances and the same strength predicted for the target substance.
6	Category	Different compounds have the same type of effect(s)	No relevant variations in strength of effects observed among source substances and the same strength predicted for the target substance

Scenario selection (2)



Example for assessment elements in a scenario

Table A1 – Assessment elements (AEs) for Scenario 1

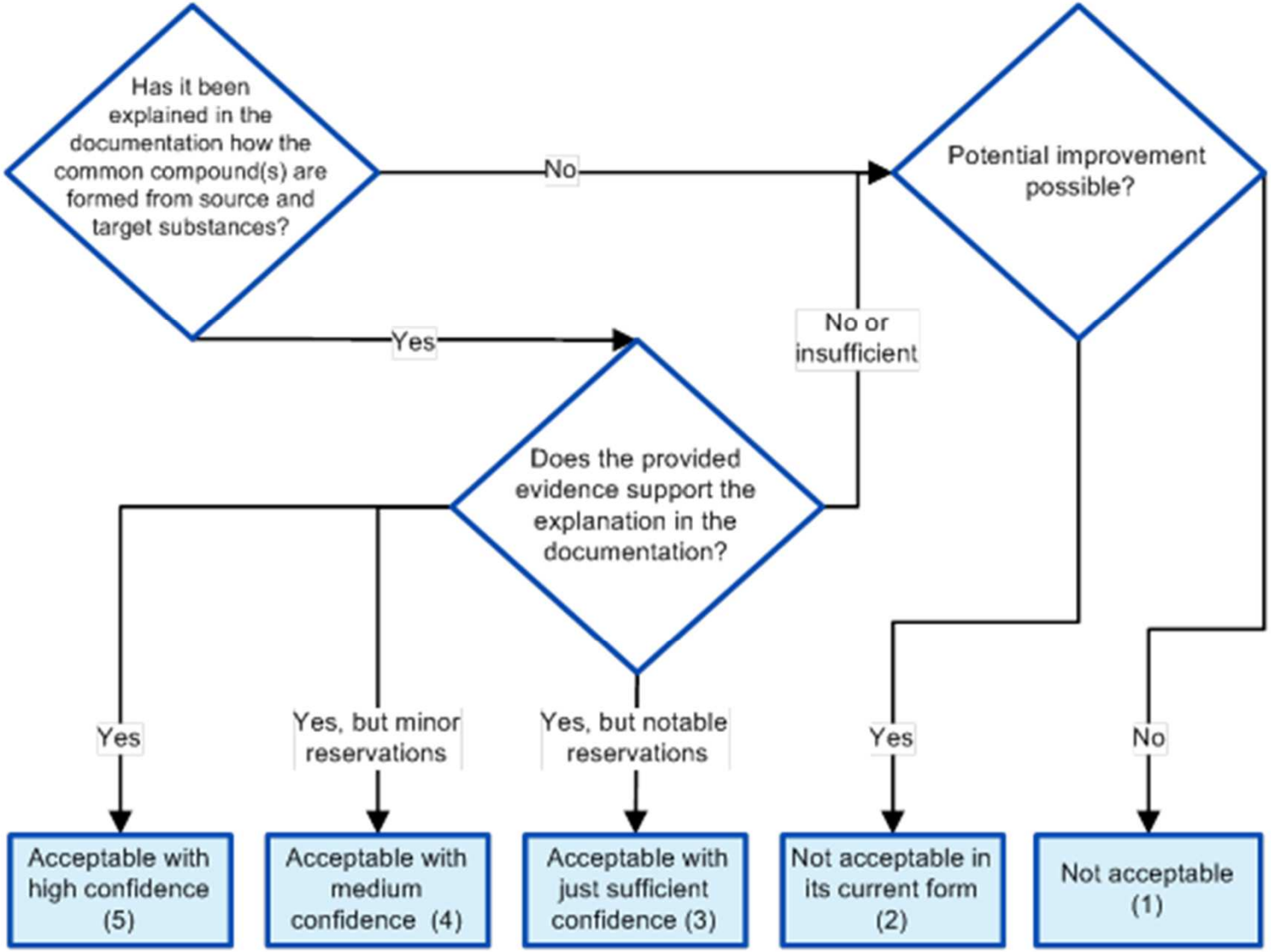
ASSESSMENT ELEMENTS (AEs) FOR SCENARIO 1		
AE #	**AE type**	**AE title**
AE A.1	Common	Characterisation of source substance
AE A.2	Common	Link of structural similarity and differences with the proposed prediction
AE A.3	Common	Reliability and adequacy of the source study
AE 1.1	Scenario-specific	Formation of common (identical) compound(s)
AE 1.2	Scenario-specific	The biological targets for the common compound(s)
AE 1.3	Scenario-specific	Exposure of the biological target(s) to the common compound(s)
AE 1.4	Scenario-specific	The impact of parent compounds
AE 1.5	Scenario-specific	Formation and impact of non-common compounds
AE A.4	Common	Bias that influences the prediction

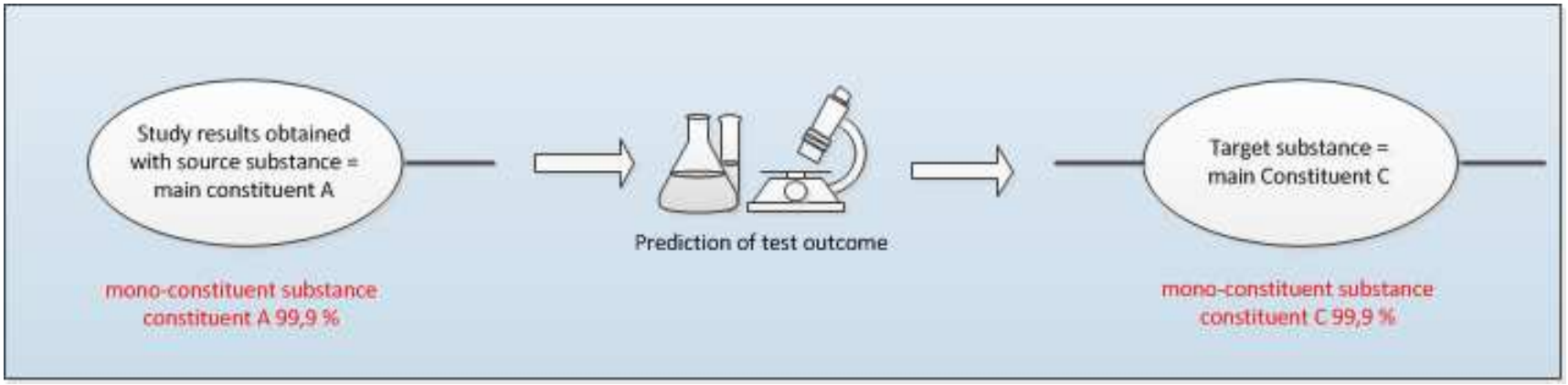
Table 3 - Overview of the analogue common AEs (scenarios 1 and 2)	
AE A.1	Identity and characterization of the source substance
AE A.2	Link of structural similarities and differences with the proposed prediction
AE A.3	Reliability and adequacy of the source study
AE A.4	Bias that influences the prediction

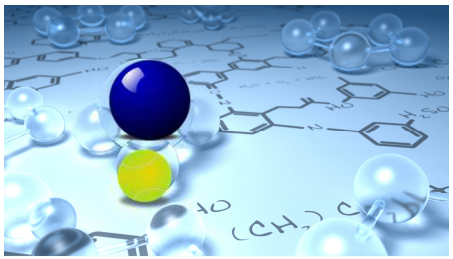
Table 4 - Overview of the scenario 1 specific AEs	
AE 1.1	Formation of common (identical) compound(s)
AE 1.2	The biological targets for the common compound(s)
AE 1.3	Exposure of the biological target(s) to the common compound(s)
AE 1.4	The impact of parent compounds
AE 1.5	Formation and impact of non-common compounds

Table 5 - Overview of the Scenario 2 specific AEs	
AE 2.1	Compounds the test organism is exposed to
AE 2.2	Common underlying mechanism, qualitative aspects
AE 2.3	Common underlying mechanism, quantitative aspects
AE 2.4	Exposure to other compounds than to those linked to the prediction
AE 2.5	Occurrence of other effects than covered by the hypothesis and justification

Example for assessment options in an assessment element



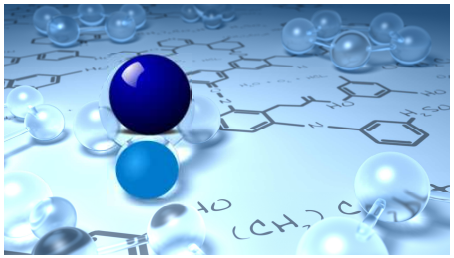




Chemical Structure Source Substance (constituent A)

Explanation

Supporting evidence



Chemical Structure Target Substance (constituent C)

Ball et al. 2016*

Reasons for rejections of read-across in ECHA decisions

- Lack of supporting information, e.g.
  - Source data not available
  - Hypothesis not substantiated
  - Systemic exposure profile not known
- Scientific plausibility, e.g.
  - Metabolism data conflicting to the hypothesis
  - Toxicity profiles contradictory to claimed similarity
  - Extrapolation vs interpolation
- Substance identity
  - Composition of source and target substance

*Toward Good Read-Across Practice (GRAP) Guidance, ALTEX Online, Feb 11, 2016

Types of supporting evidence

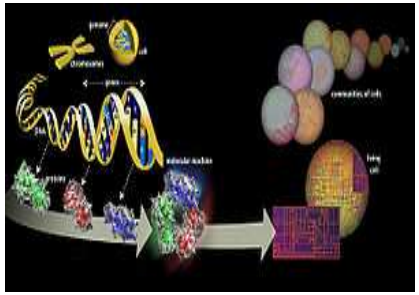
- Depends on property under consideration (complex multi-parameter vs single parameter)
- Prerequisites
  - Substance characterisation of the source substance(s)
  - Source data are reliable and adequate to meet the requirements for the property under consideration
- A mechanistic explanation is needed to justify why structural similarity is associated with similar biological properties. Supported by:
  - Data matrix: consistency? studies with target substance?
  - Category (more data) vs. analogue (one to one)
  - Toxicokinetics: qualitative, quantitative
  - Toxicodynamics: mechanistic basis, support by information on AOPs, in vivo, in vitro, structural alerts

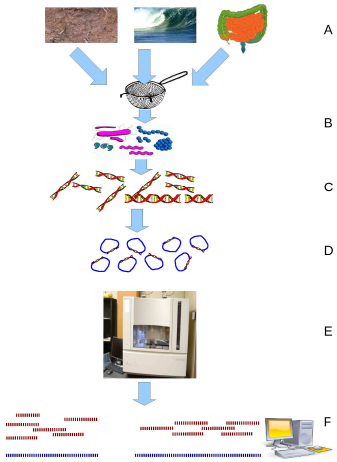
Supporting evidence for read-across found in registration dossiers

- Grouping supported by similarity (e.g. Toolbox, Ambit)
- Grouping supported by alerts/no alerts (e.g Toolbox, Derek)
- Metabolite pattern predictions
- Predictions on uptake
- In vitro information on uptake/metabolism
- In vivo information on ADME
- In vivo studies on target substance
- Information on AOP
- Categories with/without supporting study results

Not yet found in registration dossiers

- Results from batteries of high throughput assays (e.g. ToxCast)
- Supporting Evidence based on “Omics”-techniques
- So called “Big Data” approaches – combining public data bases on structures, in silico predictions, *in vitro* and *in vivo* data





What will be discussed today?

- Case studies on read-across:
  - Perfluorinated alkyl acids: direct acting toxicant category supported by ToxCast data
  - β-Unsaturated alcohols: indirect acting toxicant category supported by SEURAT-1 evidence
  - Read-across with metabolomics for phenoxy herbicides
- The RAAF was used to structure the cases
- How do the new-approach methods in these case studies support the read-across justifications?
  - Specifically? In general?
  - Limitations? Confidence?
  - For which properties? Absence of effects?
  - Further research and development?

Scope of the discussion?

- The cases have been selected and prepared to discuss the contributions of NAM data to support read-across justifications for the properties as defined in the case studies
- It will be tempting to put the cases in the context of past, ongoing or proposed regulatory measures
- It will be tempting to discuss other properties then those covered in the case studies
- It will be tempting to enter into a extensive discussion on uncertainty and associated uncertainty factors
- The case studies are not meant to be REACH registration dossiers. Therefore the workshop discussions and results are not pre-empting any possible regulatory conclusions on the substances discussed

Thank You

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