The European Commission's science and knowledge service

Joint Research Centre

Uncertainty characterisation in Integrated Approaches to Testing and Assessment (IATA) for Chemical Risk Assessment – Mapping of Available Guidance and Identification of Gaps

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International Conference on Uncertainty in Risk Analysis

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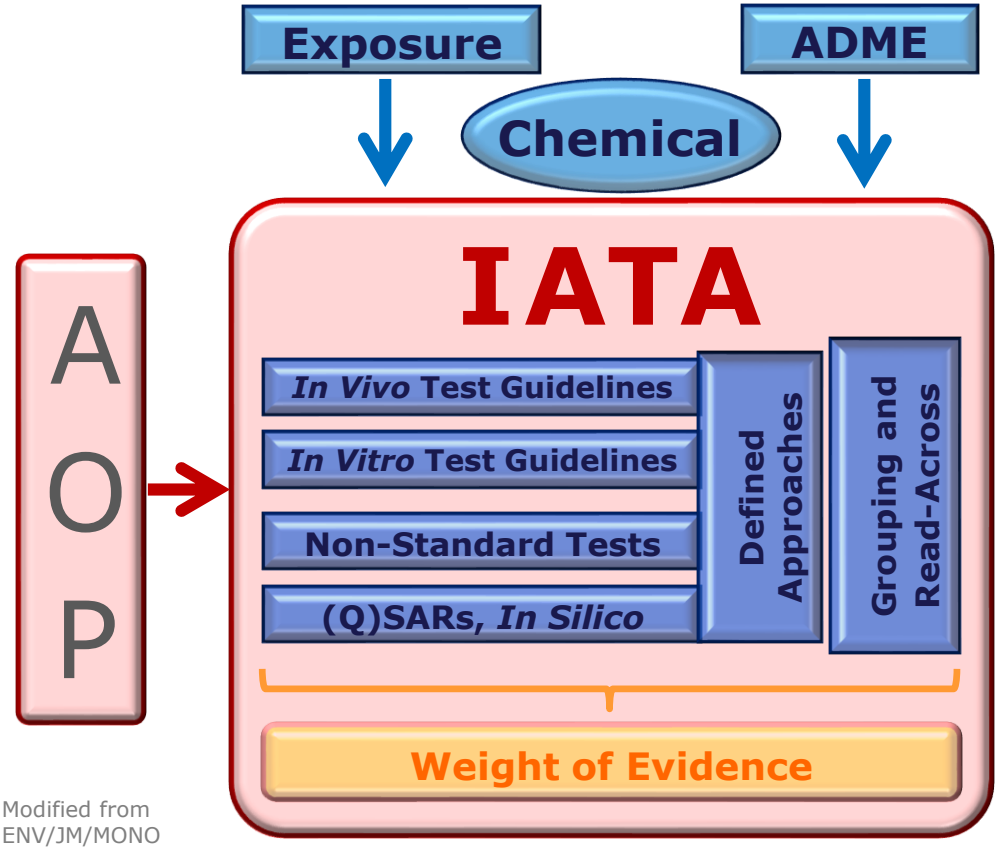
Integrated Approaches to Testing and Assessment

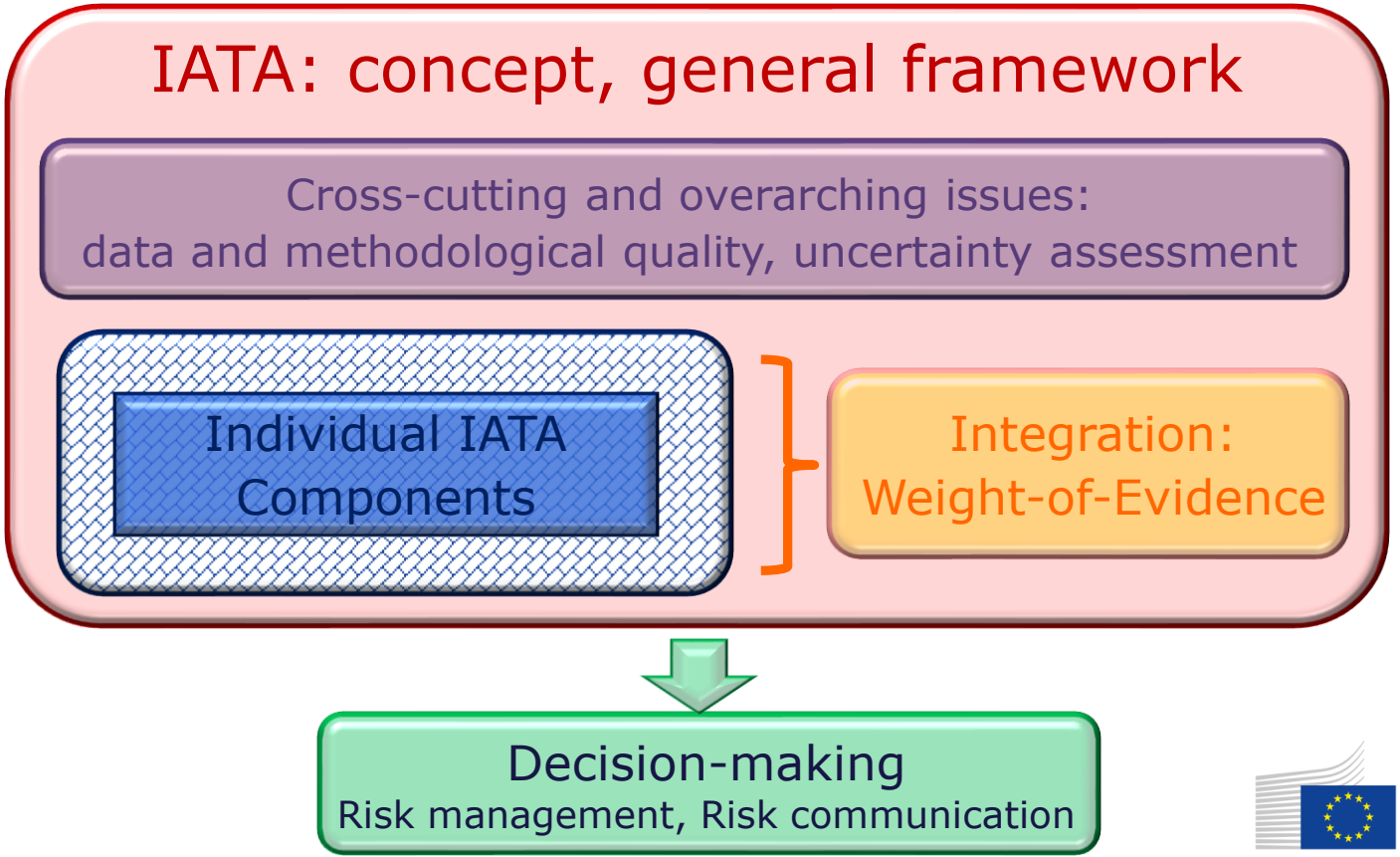


Modified from ENV/JM/MONO (2015)

Framework for hazard identification, hazard characterisation and/or safety assessment of a chemical or group of chemicals

- **based on multiple information sources**
- which **integrates and weights** all relevant existing evidence and guides the targeted generation of new data where required
- to **inform regulatory decision-making** regarding potential hazard and/or risk

Layers Within a General IATA Framework



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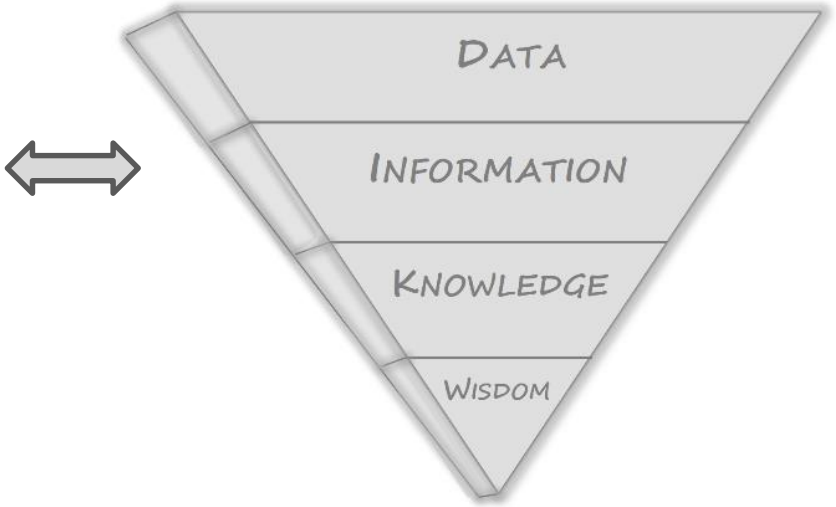
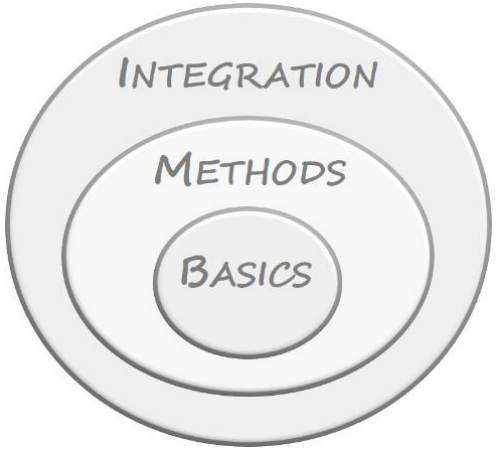
Layers Within a General IATA Framework



Layers of Uncertainty



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Uncertainty Evaluation in Risk Assessment

- IATA → bring different lines of evidence and methods together to reach a conclusion in hazard/risk assessment

- **Uncertainties** in every step, different layers of the IATA

  - **Relating to the input data**
    e.g. data and methodological quality, such as reliability and relevance of the methods and information sources

  - **Relating to the extrapolation**
    e.g. interpretation and integration of the data, assumptions and methodological choices made

Uncertainty Evaluation in Risk Assessment

- Important to
  - **characterise,**
  - **transparently document**
  - **communicate**

  for all different uncertainties of an IATA,
  to allow for informed decision making

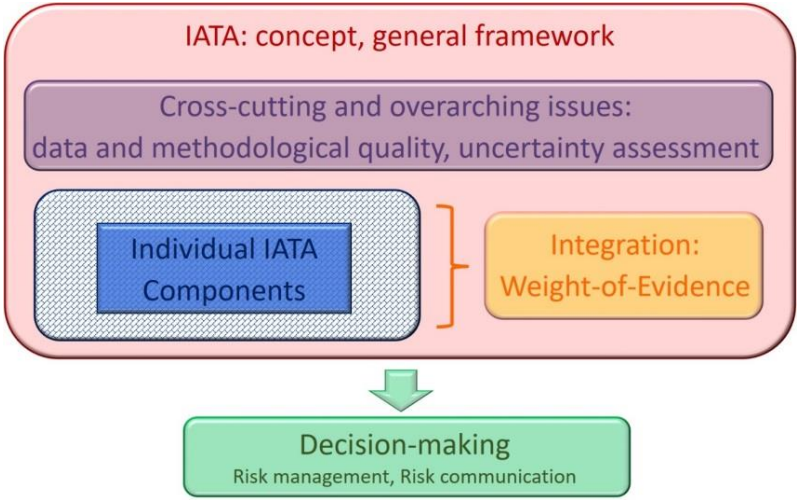
- How to do that?

- **What guidance is available?**

➢ Scoping exercise

Levels of Guidance in a General IATA Framework

- IATA concept/**general framework**
- Guidance related to the IATA **input and method building blocks**
- **Cross-cutting issues** related to data and methodological quality, identification and characterisation of uncertainties
- **Integration of data** in a weight of evidence



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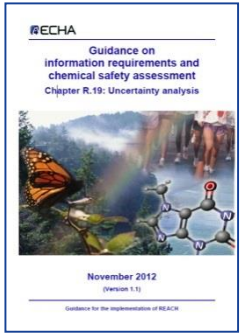
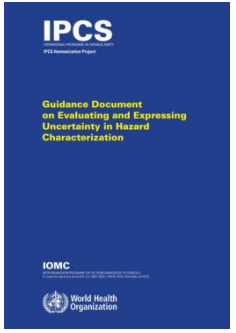
Examples: Uncertainty – Overarching Guidance

- **National Academies of Sciences:** Science and Decisions: Advancing Risk Assessment, Chapter 4: Uncertainty and Variability, The Recurring and Recalcitrant Elements of Risk Assessment (2009)
- **US EPA:** Guidance on the Development, Evaluation, and Application of Environmental Models (2009)
- **European Chemicals Agency's** (ECHA) Guidance on information requirements and chemical safety assessment: Chapter R.19 Uncertainty analysis (2012)
- **WHO International Programme on Chemical Safety** (IPCS): Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization (2017)
- **European Food Safety Authority's** (EFSA) Guidance on Uncertainty Analysis in Scientific Assessments (2018)
- German **Federal Institute for Risk Assessment (BfR)** Guidance document on uncertainty analysis in exposure assessment (2015)

APROBA tool





Examples: Uncertainty – Specific Guidance

- OECD Guidance Document on the **Reporting of Defined Approaches** to Be Used within IATA. STA No. 255, ENV/JM/MONO(2016)28

Principle 6 Consideration of known uncertainties

Principle 6: *Consideration of known uncertainties*

Facilitates consistency in the interpretation of the DIP result, which is typically a prediction. Where feasible and relevant, uncertainty in predictions should be evaluated in the light of the following considerations:

a) the relevance of the "model structure" of the DIP, e.g. the extent of coverage and weighting of AOP key events and other mechanistic considerations;

b) the level of confidence (reliability of prediction) associated with the application of the DIP to different chemicals;

c) the variability of the input data used (generated by the information sources);

d) the variability of the output data associated with the gold standard (e.g. animal or human) data used as benchmark data, especially when these are used as the basis for regulatory decision making (Worth and Cronin, 2001; Hoffmann et al., 2005; Hoffmann 2015; Adriaens et al., 2014) and;

e) any other known source of uncertainty (e.g. uncertainty in estimated exposure levels that are used in a safety assessment).

In each case, the magnitude and impact of the sources of uncertainty should be considered.

- ECHA **Read-Across** Assessment Framework (2015, 2017)

Structured assessment, assessment scores for confidence

AE C.1	Substance characterisation
AE C.2	Structural similarity and differences within the category
AE C.3	Link of structural similarities and structural differences with the proposed regul
AE C.4	Consistency of effects in the data matrix
AE C.5	Reliability and adequacy of the source study(ies)
AE C.6	Bias that influences the prediction

SCENARIO 4	SCENARIO 6	ASSESSMENT ELEMENT TITLE
AE 4.1	AE 6.1	Compounds the test organism is expose
AE 4.2	AE 6.2	Common underlying mechanism, qualita
AE 4.3	AE 6.3	Common underlying mechanism, quantitative aspects
AE 4.4	AE 6.4	Exposure to other compounds than those linked to the prediction
AE 4.5	AE 6.5	Occurrence of other effects than covered by the hypothesis and justi-fication

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Examples: Grouping and Read-Across

Scientific Literature:

- Schultz TW et al (2015) A strategy for structuring and reporting a read-across prediction of toxicity
- Ball N et al (2016) Toward Good Read-Across Practice (GRAP) Guidance
- Patlewicz (2015) Building scientific confidence in the development and evaluation of read-across
- Blackburn et al (2010) A framework to facilitate consistent characterization of read across uncertainty
- Wu et al (2010) A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments
- Schultz et al (2019) Assessing uncertainty in read-across: Questions to evaluate toxicity predictions based on knowledge gained from case studies

Templates in MS Word

Comparison of substituents, functional groups, and extended structural fragments.

	Target Substance	Analogue 1	Analogue 2
Name			
Key Substituent(s)			
Functional Group(s)			
Extended Fragment(s)			

Comparison of mechanistic plausibility and AOP-related event data.

	Target Substance	Analogue 1	Analogue 2	
Name				
Mechanistic Plausibility				
Adverse Outcome Pathway or Mode of Toxic Action:				
Molecular Initiating Event:				
Key Event 1 etc.:				
Key Event Relationship 1 etc.:				
Other Mechanistically-Relevan Events				

Scores

Template for assessing uncertainty associated with mechanistic relevance and completeness of the read-across.

Factor	Uncertainty (low, medium, high)	Comment
The problem and premise of the read-across		**Example:** The endpoint to be read across, developmental toxicity, for the category of branched carboxylic acids is well-studied and well-understood, The scenario of the read-across hinges on the inhibition of beta-oxidation of the acid and the subsequent build up of acid in the embryo leading to histone deacetylase inhibitors, increased cell adhesion and concomitant reduced cell motility, prevention of convergent extension during ontogenetic development.
In vivo data read across		
Number of analogues in the source set		**Example:** There are 3 suitable category members with *in vivo* apical endpoint data usable for read-across.
Quality of the *in vivo* apical endpoint data read across		**Example:** High quality empirical data from standard test guidelines for the stated regulatory endpoint exists for 1 category member. Similar non-standard test data of lower quality exists for 2 other category members. All these data are consistent in regards to qualitative description of effects and, where available, similar in quantification.
Severity of the apical *in vivo* hazard		**Example:** Potency data for the *in vivo* apical endpoint (25 mg/kg/day) is limited to a single source substance.
Evidence to biological argument for RA		
Robustness of analogue data set		**Example:** The available data from *in silico*, *in chemico* and *in vitro* studies for the category members were judged to be reliable and conducted under the appropriate conditions.

Decision tree

Assessment criteria

Examples: Weight of Evidence

- **WHO/IPCS** MoA Human relevance Framework, WoE for establishing Mode of Action

MoA Analysis Template in MS Word

- **ECHA** (2011) Guidance on Information Requirements and Chemical Safety Assessment; Chapter R.4: Evaluation of Available Information

Plus Template for weight of evidence/uncertainty in hazard assessment

- **ECHA** (2010) Practical guide 2: How to report weight of evidence
- **EFSA** (2017) Guidance on the use of the weight of evidence approach in scientific assessments

Includes uncertainty and influence analysis

- **ANSES** (2016) Assessment of the weight of evidence at ANSES
- **SCHEER** (Scientific Committee on Health, Environmental and Emerging Risks) (2018) Memorandum on weight of evidence and uncertainties
- Current **OECD** Project: **Guiding Principles for Establishing Weight of Evidence for Chemical Assessment**

Considering data quality, relevance, dealing with uncertainty

Examples: Data and Method Quality

Study reporting

- OECD Harmonised Templates, e.g. OHT 201 Intermediate effects
- ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guideline

Method description and quality

- OECD Guidance Document for Describing Non-Guideline *In Vitro* Test Methods
- OECD Guidance Document on Good *In Vitro* Method Practices (GIVIMP)

Data reliability, method acceptance

- SciRAP (Molander et al 2014); ToxR Tool (Schneider et al 2009)
- OECD Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment

Conclusions from Scoping Exercise

- **Guidance is available** related to uncertainty assessment: in different forms and detail, **for different types/layers of uncertainty**

- More guidance available on **basic aspects related to the input data and methods** than for the integration and weight of information

- Guidance is **fragmented and sometimes overlapping**

Project Under OECD Working Party on Hazard Assessment (WPHA)

- **IATA key concepts and terminology**
- **Overview of existing guidance on IATA (components) and relevant cross-cutting topics**,
  with a specific focus on inclusion of uncertainty
- **Conclusions and recommendations**
  - Inconsistencies and gaps (needs for further guidance)
  - Overarching principles?
- Additional **website version**

Drafting Team:

JRC, Canada, Germany, The Netherlands

European Commission

Project Under OECD Working Party on Hazard Assessment (WPHA)

- IATA key concepts

CAVEAT:

- **No recommendation or endorsement** of any particular guidance
- But: comprehensive overview of the guidance landscape
- Helping to identify gaps or duplications

guidance)

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Guidance Mapping

Information extracted from Guidance documents

Guidance source (organisation, sector, region) and purpose
Nature of guidance, link to IATA framework
Does it include template, checklist, tool, flowchart?
Uncertainty characterisation and reporting included? **What type(s) of uncertainty (data variability *vs* knowledge)?** **Qualitative or quantitative? Scoring system?** **Uncertainties related to the input data or extrapolations?**

- uncertainties related to the input data
- uncertainties related to the extrapolations

Guidance Mapping

Guidance listed in Excel tables

→ can be searched, filtered

- Overarching guidance related to IATA Framework
- Guidance related to individual IATA components
- Guidance for overarching issues of data/methodological quality
- **Guidance on uncertainty assessment**
- Guidance related to Weight of evidence (WoE), data integration

Sources of Guidance

- Sources of guidance included in first instance:
  - International, e.g. OECD, WHO/IPCS
  - National authorities

  - Exclude endpoint-specific guidance
  - Exclude highly (method-)specific guidance, but focus on general and overarching principles

- In the case of gaps in available guidance: extend search to scientific peer-reviewed literature
  - if no official guidance exists, it is “guidance-like” and taken up in regulatory risk assessment context

Issues Identified

Gaps?

- Guidance for in silico methods, reporting, uncertainty assessment, good modelling practice?
- Guidance read-across, i.e. concrete template for reporting including uncertainty assessment

Ongoing discussions in international working groups

see Poster 3.4.1

Schultz et al (2019) Computational Toxicology 9: 1-11

Cronin et al, submitted

- Guidance for other new approach methodologies

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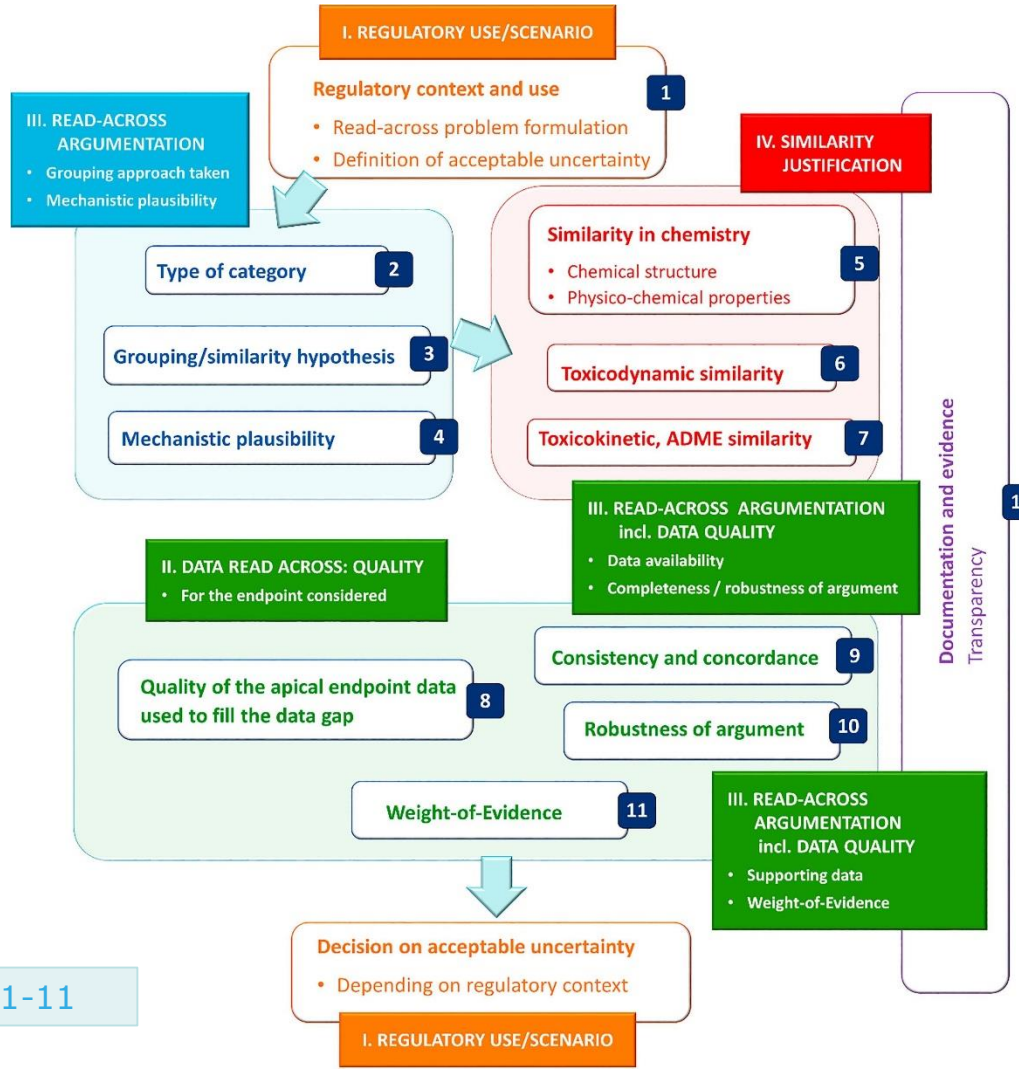
Example: Read-Across Uncertainty Framework

- 4 main sources of uncertainty
  - regulatory use
  - data quality
  - argumentation
  - similarity justification
- 12 types
- 30 assessment criteria



Schultz et al (2019) Computational Toxicology 9: 1-11

Example: QSAR Model Uncertainty Assessment

(13 Types of Uncertainty, Variability, Bias, Influence; 47 Assessment Criteria)

Creation

- Definition of Chemical Structures → 2
- Biological Data → 7
- Physicochemical Properties and Structural Descriptors → 5
- Compilation of the Data Set → 4
- Modelling Approach → 1

Description

- Description of Model → 3
- Statistical Performance → 2
- Applicability Domains → 4
- Mechanistic Relevance → 3
- Absorption, Distribution, Metabolism and Excretion Effects → 2

Application

- Documentation and Reproducibility → 2
- Usability → 8
- Relevance and Adequacy → 4

Courtesy of Mark Cronin, Liverpool. Reg. Toxicol. Pharmacol. submitted

Issues Identified

Overlaps or duplication?

- Yes, e.g. several guidance documents on Weight of Evidence, general uncertainty assessment;

  or several suggestions in parallel (scientific literature)

- Can be complementary
- Conclusions may be different in different regulatory context
- Confusing for the user which guidance to use

Issues Identified

Discrepancies?

- Generally same principles
- Terminology not always harmonised
  e.g. New Approach Methodologies (NAM)
- Different organisations have different focus,
  e.g. on quantitative or qualitative uncertainty assessment
- Different regulatory practice

Future Needs?

- Uncertainty evaluation, reporting and communication for chemical safety assessment currently discussed in many international groups
  - Guidance needs, for specific methodologies

- **Overall harmonisation and integration** of different levels of uncertainty and existing uncertainty assessment practice established in different communities
  - To increase confidence in risk assessment results as well as to support the aim of mutual regulatory acceptance

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