Uncertainty Characterisation in IATA for Chemical Safety Assessment: Overview of Available Guidance

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The presenter declares that there exists no real or perceived conflict of interest.
Overview

Guidance for the application of IATA

• Different levels and aspects for which guidance is available/needed
• Uncertainties related to the different levels

• OECD WPHA IATA guidance mapping project
• Examples of available guidance, and inclusion of uncertainty assessment
  ➢ Overarching guidance, specific, and cross-cutting guidance
• Conclusions on gaps, overlaps, divergence, needs
Integrated Approaches to Testing and Assessment

**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

- IATA concept & general framework
- IATA components
- Cross-cutting issues and principles
  - data and methodological quality
  - uncertainties
- Data integration: weight-of-evidence
Uncertainties in IATA

• 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 Layers Within a General IATA Framework

Layers of Uncertainty

IATA: concept, general framework
Cross-cutting and overarching issues: data and methodological quality, uncertainty assessment
Individual IATA Components
Integration: Weight-of-Evidence
Decision-making
Risk management, Risk communication

DATA
INFORMATION
KNOWLEDGE
WISDOM

INTEGRATION
METHODS
BASICS
Uncertainty Evaluation in IATA

- Important to
  - characterise
  - transparently document
  - communicate
  all different uncertainties of an IATA,
  to allow for informed decision making

- How to do that?

- What guidance is available?
  - Scoping exercise EC JRC and OECD WPHA project
International Initiatives on Integrated Safety Assessment of Chemicals and Uncertainty Evaluation

• **OECD** Working Party on Hazard Assessment (**WPHA**): IATA Case Studies Project

• **WHO** International Programme on Chemical Safety (**IPCS**)

• **International Cooperation on Cosmetics Regulation** (**ICCR**): Working Group on Integrated Strategies for Safety Assessments of Cosmetic Ingredients, using new approach methodologies (**NAM**)

• **In Silico Toxicology Protocol** Consortium (supported by NIH grant)

• Grading of Recommendations Assessment, Development and Evaluation (**GRADE**) framework
Project Under OECD Working Party on Hazard Assessment

• Explain 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

• Sources of guidance: in particular international (OECD, WHO), national authorities

➢ Provide easy access to resources:
  — Excel table: Title, region, purpose, link to IATA, templates?, uncertainty assessment?
  — Additional website version planned

➢ Identify gaps, duplications, inconsistencies → needs for further action

Drafting Team: EC JRC, Canada, Germany, The Netherlands
Project Under OECD Working Party on Hazard Assessment

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

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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
Examples: Uncertainty – General Overarching Guidance


• **European Chemicals Agency (ECHA)** Guidance on information requirements and chemical safety assessment: Chapter R.19 Uncertainty analysis (2012)


• **European Food Safety Authority's (EFSA)** Guidance on Uncertainty Analysis in Scientific Assessments (2018)

Examples: Uncertainty – Specific Guidance


  **Principle 6 Consideration of known uncertainties**

  →Templates IATA Case Studies Project


  Structured assessment, assessment scores for confidence


  Emphasises importance of uncertainty assessment including risk of bias
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

Example: *In Silico Models* — QSAR


- **Scientific Literature:**
13 Types of Uncertainty, Variability, Bias, Influence; 47 Assessment Criteria

![Diagram](image.png)

Examples: Omics

- Microarray Gene Expression (MGED) Society: Minimum information about microarray experiments (MIAME) guidelines


- National Research Council, Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment (CATTPTRAeNRC) (2007) Applications of toxicogenomic technologies to predictive toxicology and risk assessment

- Kauffmann et al (2017) Framework for the quality assurance of ’omics technologies considering Good Laboratory Practice (GLP) requirements

- OECD development of a Transcriptomics Reporting Framework (TRF) and Metabolomics Reporting Framework (MRF)

- ECETOC MEtabolomics standaRds Initiative in Toxicology (MERIT)
Examples: Data and Method Quality

Study reporting

• OECD Harmonised Templates, e.g. OHT 201 Intermediate effects
• MIAME “Minimum Information about a Microarray Experiment for Toxicogenomics” (NRC 2007)
• ARRIVE (Animal Research: Reporting of In Vivo Experiments) guideline (Kilkenny et al 2010)

Method description and quality


Data reliability, method acceptance

• SciRAP (Molander et al 2014); ToxR Tool (Schneider et al 2009)
• Systematic review approach for the evaluation of toxicity studies, including risk of bias

Guidance related to study and data quality and reliability → improves quality of the IATA components and conclusions by reducing overall uncertainties and increasing confidence

- Standardisation of data and reporting format (e.g. ISA-TAB)
- Consensus on study/method content to be reported
  - Minimum information requirements, metadata
- Harmonisation of terminology
  - Ontologies
- Evaluation of study quality, possible bias
  - Systematic reviews
- Unambiguity
- Comparability
- No gaps of relevant information
  - Reduces uncertainty
  - Improves integration of data/results
Examples: Weight of Evidence

- **WHO/IPCS** MoA Human relevance Framework, WoE for establishing Mode of Action
- **ECHA** (2017) Template for Weight of Evidence / Uncertainty in hazard assessment
- **EFSA** (2017) Guidance on the use of the weight of evidence approach in scientific assessments
- **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
- **US EPA** (2016) Weight of Evidence in Ecological Assessment, EPA/100/R-16/001
- **Health Canada** (2019) WoE: General Principles and Current Applications at Health Canada
- **OECD** (2019) Guiding Principles for Establishing Weight of Evidence for Chemical Assessment Considering data quality, relevance, dealing with uncertainty
Examples: Specific IATA Guidance

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

- OECD Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to Be Used within IATA for Skin Sensitisation. STA No. 256, ENV/JM/MONO(2016)29

- Guidance Document for the Use of Adverse Outcome Pathways in Developing IATA. STA No. 260, ENV/JM/MONO(2016)67

- OECD IATA Case Studies project: General Template for IATA Case Studies - Building Blocks

- Endpoint-specific IATA:
  - IATA for skin corrosion and irritation (OECD 2014)
  - IATA for serious eye damage and eye irritation (OECD 2017)
  - More IATA planned / in progress, e.g., non-genotoxic carcinogenicity and developmental neurotoxicity
Conclusions: General

- Wealth of guidance with different levels of detail
- Complex and fragmented landscape, difficult to navigate
- More on data generation and reporting than data integration and use
- Different evaluation frameworks by different scientific communities (*in vivo* toxicological studies vs. *in vitro* vs. *in silico*)
- Missing overarching guidance strategy putting all guidance into perspective
- Challenge to keep up with
  - newly emerging methods
  - parallel developments in scientific community
Conclusions: Gaps

• Need for additional guidance on NAMs
  ➢ how to evaluate individual NAMs, including uncertainty assessment
  ➢ how to integrate NAMs within IATA, including uncertainty propagation

• Need to level playing field between *in silico* and experimental methods
  ➢ Systematic framework for QSAR assessment

• Guidance on uncertainty characterisation and documentation at IATA level

• More practical tools (e.g., templates) needed
Conclusions: Overlaps and Divergence

Overlaps or duplication

• Some overlaps, e.g., documents on WoE and uncertainty assessment
  ➢ Mostly complementary, based on same principles
• Parallel developments evolving in scientific community

Divergence

• No obvious inconsistencies, although some inevitable overlap in content; adhere to commonly-accepted safety assessment principles
• Differences due to different regulatory requirements and procedures
• Inconsistent understanding and use of some key terms
Future Needs

• Harmonisation of definitions of some commonly used terms

• Overarching “roadmap” of guidance

• Overarching uncertainty assessment framework for IATA
  ➢ drawing on existing guidance on uncertainty characterisation, evaluation, reporting and communication
  ➢ reconciling evaluation frameworks of different communities
  ➢ integrating emerging NAM and their uncertainty assessment

• More user friendly templates
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