Using new Approach Methodologies in Regulatory Science: Tools and Methods for Integration of Evidence

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Overview

NAM generated data as part of evidence in regulatory science

NAM generated data within a Weight of Evidence approach

Weight of Evidence approach steps/principles

Tools/Methods for NAM generated data assessment and integration

Conclusions

Evidence

Evidence is any type of information that contributes to hazard assessment:

- Experimental data from one or more (similar) chemicals):
  - *In vitro* assays
  - *In vivo* assays
- Non Experimental data:
  - Similar chemicals based (QSAR models, read-across)
- General biology/chemistry knowledge

Evidence

Evidence can be generated with:

- Standard Guidelines (e.g. EC/OECD Test Guidelines)
- Non Standard Guidelines (e.g. NAM generated Data)

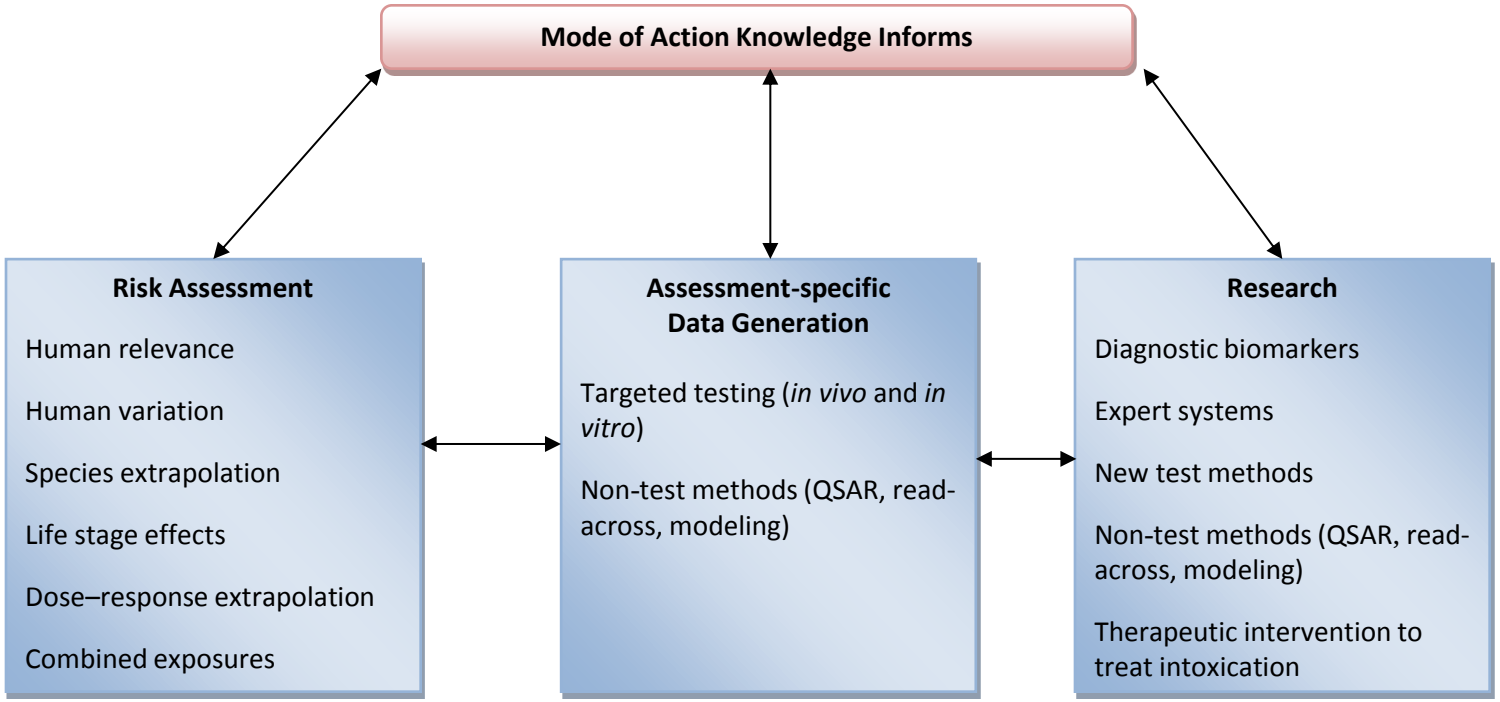
Evidence can be reported for regulatory purposes in:

- OECD Harmonised Templates (OHTs)/IUCLID for endpoint specific information
- **New OHT 201** for NAM generated data that cannot be reported with standard endpoint specific OHT

OHTs/IUCLID provide the information/fields that are needed for the assessment of the evidence in line with ECHA and OECD Guidance document on assessment of information (quality of data)

NAM Generated data within the Weight of Evidence Approach

NAM generated data usually provide insight for mode of action and can assist in test design. In line with the WHO/IPCS MoA Roadmap (Meek et al, 2013):



NAM Generated data within the Weight of Evidence Approach

Regulatory application of NAM generated data in hazard assessment has same requirements as for all types of evidence:

- Recording of evidence collection
- Assessment of individual evidence in terms of quality
- Integration of all evidence
- Derivation of confidence levels
- Conclusions

- ➢ Different level of detail depending on purpose of assessment
- ➢ Varies from priority setting to complete hazard assessment

Weight of Evidence uses/terminology

Table I. Uses of "Weight of Evidence" (WOE) in Current Practice (1994–2004)

- Metaphorical (no method described)
  - WOE collection of studies
  - Single study contributing to a WOE
  - WOE approach
- Methodological
  - WOE method versus a "strength of evidence" approach
  - WOE method using "all" rather than a selected subset (e.g., standard test assay) of the evidence
  - WOE method pointing to other "established" or familiar interpretative methodologies
    - Systematic narrative review
    - Quality criteria for toxicologic studies
    - Epidemiology's causal criteria
    - Meta-analysis
    - Mixed epidemiology-toxicology methods
  - WOE method employing a quantitative weighting scheme
- Theoretical
  - WOE theory of pattern recognition in cognitive science
  - WOE and the court's evidentiary gate-keeping role

WOE = weight of evidence.
Note: Categorization arose from 92 published scientific papers in which "weight of evidence" appeared in the abstract ($n = 71$) in 2003 and 2004 or appeared in the title ($n = 21$) from 1994 through 2002.

Douglas L. Weed, Weight of evidence: A review of concepts and methods; Risk Analysis, Vol 25, No 6, 2005

Weight of Evidence Approach

A number of available descriptions of WoE approach from ECHA, WHO/IPCS, SCENHIR, OECD, EFSA, US OSHA

Weight of Evidence can be generally described as a stepwise process/approach of collecting evidence and weighing them to reach a conclusion on a particular problem formulation with (pre)defined degree of confidence

Similar principles as in WHO/IPCS MoA/HRF, OECD AOP and IATAs

Weight of Evidence Approach

Weight of Evidence Approach

1. **Problem formulation**

2. **Collection of lines of evidence**

Documentation of search strategy

Documentation/reporting of evidence

3. **Assessment of quality of individual evidence**

4a **WoE analysis (comprehensive analysis of evidence collected)**

4b **WoE documentation**

5. **Confidence levels**

6. **Conclusions /Remaining uncertainty**

Increasing WoE:

Increasing confidence
Reducing uncertainty

Weight of Evidence Approach

Structured and transparent way of performing and presenting hazard assessment (hazard identification, hazard characterisation).

Following the steps of the WoE approach drives the assessor to identify the needs and gaps in the hazard assessment and facilitates regulatory dialogue and decision making.

The WoE approach/process is iterative: all steps are interconnected and changes might be needed if for example it is recognised in a later stage that some evidence initially given less weight or even disregarded should be taken into account or vice versa.

Weighing of Evidence in regulatory science

- Partial weighing of evidence occurs firstly at the step of assessment of quality of individual evidence (reliability, adequacy & relevance are used in weighing the evidence for the purpose of the assessment)
- The weighing of evidence occurs at the step of WoE analysis: combination of assessment of quality with consistency and plausibility

3. Assessment of quality of individual evidence

4a WoE analysis (comprehensive analysis of evidence collected)

Weight of Evidence Approach

3. Assessment of quality of individual evidence

- Adequacy
- Reliability
- Relevance

The Klimisch criteria for the assessment of reliability of experimental data

NAM generated data might not fulfil standard Klimisch criteria for reliability, but within the integration step consistency and plausibility will determine the confidence

For other type of evidence (e.g. QSAR, use of read-across, non-standard in vitro assays) ECHA Guidance provides criteria for their assessment

Weight of Evidence Approach

3. Assessment of quality of individual evidence

NAM generated data:

- OECD Guidance on non standard assays
- OHT 201 for reporting

For other type of experimental and non experimental evidence OECD and ECHA Guidance available

Weight of Evidence Approach
Integration of Evidence

4a WoE analysis (comprehensive analysis of evidence collected)

- Depending on the problem formulation different methodologies can be used to integrate evidence and perform WoE analysis.
- Methodologies vary in terms of complexity and range from general schemas/frameworks consisting of set of questions to more elaborate methodologies
- Within a specific framework, another framework may be needed depending on process/type of work (e.g. CLP categorisation schemes can be considered as upper level frameworks where other frameworks/approaches can be integrated: MoA analysis, AOPs etc)
- Examples of frameworks that are or contain elements of weighing evidence: REACH ITS schemas for specific endpoints, RAAF, WHO/IPCS MoA, AOPs, IATAs)

Weight of Evidence Approach
Integration of Evidence

4a WoE analysis (comprehensive analysis of evidence collected)

Evidence (including NAM generated data) need to be integrated addressing:

- Consistency/Specificity
- Biological Plausibility
- Temporality (case specific when MoA analysis is performed)
- Derivation of Confidence Levels

Integration of evidence as per WHO/IPCS MoA Templates; available at ECHA website formats

OECD AOPs available at https://aopwiki.org/wiki/index.php/Main_Page

Weight of Evidence Approach

5. Confidence levels

Confidence levels can be usually expressed qualitative as:

- High
- Medium
- Low

Quantitative expression of confidence/uncertainty is part of uncertainty analysis

The confidence levels for each line of evidence should feed to the judgement of the overall confidence level that take into account all the evidence in an integrated and weighed mode.

Weight of Evidence

Example of confidence level derivation
OECD AOP

5. Confidence levels

Evidence	Characteristics
Weak	• Low level of evidence on biological concordance • Limited or no studies reporting related change in both events • Lack of data showing temporal/dose-response concordance • Contradictory evidence in literature with no plausible explanation.
Moderate	• Plausible relationship but not well documented • Multiple studies showing change in both events following exposure • Inconsistent evidence in the literature but somewhat explained • Limited evidence for temporal/dose-response concordance
Strong	• Established mechanistic relationship (dogma) • Many studies showing change in both events following exposure • No inconsistent evidence in the literature • Extensive evidence for temporal/dose-response concordance

Weight of Evidence

Example of confidence level derivation
SCENHIR 2012 Opinion

Strong: Coherent evidence from human and one or more other lines of evidence (in particular mode/mechanistic studies) in the absence of conflicting evidence from one of the other lines of evidence (no important data gaps)

Moderate: good evidence from a primary line of evidence but evidence from other lines of evidence is missing (important data gaps)

Weak: weak evidence from the primary lines of evidence (severe data gaps)

Uncertain: due to conflicting information from different lines of evidence that cannot be explained in scientific terms

Weighing of evidence not possible: No suitable evidence available

3. Assessment of quality of individual evidence

ECHA Guidance IR/CSA R.4

OECD Guidance Non Guideline in vitro methods

OHTs/IUCLID

Type of Evidence / Data Source - Reference	Relevance	Reliability	Adequacy

4a WoE analysis (comprehensive analysis of evidence collected)

ECHA Guidance IR/CSA R.4

WHO/IPCS MoA Templates

OECD AOPs

OECD IATAs

Type of Evidence	Consistency & Specificity	Likelihood/ Biological Plausibility	Confidence / Strength of Evidence	Remaining Uncertainty
Conclusion from overall confidence				

Conclusions

Tools and methods available for the use of NAM generated information in regulatory science

OHTs/IUCLID assist in understanding what is needed for reporting

OECD Guidance for non standard guideline generated information

WHO/IPCS MoA templates & AOPs provide the principles for integration of information

Specific examples in OECD AOP lists where NAM data incorporated in AOPs

NAM generated data must be used in a WoE approach for regulatory purposes to increase acceptability

Conclusions

- Further work on improving use of WoE in regulatory processes
- Next IUCLID version will have section on MoA analysis (use of WHO/IPCS templates) for human health systemic toxicity endpoint
- Improvements in reporting tools for the integration of evidence step; to identify further templates for reporting in line with OHT principles and OECD IATA future work

List of available information

- ECHA Guidance IR/CSA R.4 (Evaluation of available information):
http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

- OECD Guidance for describing non-guideline in vitro methods
http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)35&doclanguage=en

- OECD workshop report 2011: Use of mechanistic data to form chemical categories
http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2011)8&doclanguage=en

- OECD AOP wiki: List of AOPs and Guidance Documents
https://aopwiki.org/wiki/index.php/Main_Page

- OECD Harmonised Templates
http://www.oecd.org/ehs/templates/oecdharmonisedtemplates.htm

- WHO/IPCS Mode of action templates
http://echa.europa.eu/support/guidance-on-reach-and-clp-implementation/formats

- WHO/IPCS Mode of Action Framework
http://www.who.int/ipcs/methods/harmonization/areas/cancer/en/

Thank you!