Emerging Strategies for Evidence Integration

NAS Workshop on Evidence Integration in Chemical Assessments

Washington, June 3rd, 2019

Presented by:
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Outline

- Integrating Evidence
  - Mode of Action (MOA) and Adverse Outcome Pathways (AOP) Analysis
- Assessing the Weight/Extent of Integrated Evidence
  - WOE/Confidence Considerations in MOA/AOP Analysis
- Evidence Integration in Assessment Planning
  - ANSES (the French Agency for Food, Environmental and Occupational Health and Safety) Weight of Evidence Initiative
- Implications
MOA: AOPs – Integrating Constructs

Molecular data

- Protein binding
- DNA binding
- Receptor/ligand binding

- Gene activation
- Protein production
- Altered signaling

- Altered physiology
- Altered tissue development or function

- Impaired development
- Impaired reproduction lethality

Regulatory Endpoints

- Impaired reproduction/survival, Population crash

Chemical properties

Toxicity
MOA:AOPs – Integrating Constructs

- Molecular data
  - Toxicity
    - Chemical properties
  - Protein binding
  - DNA binding
  - Receptor/ligand binding
  - Gene activation
  - Protein production
  - Altered signaling
  - Altered physiology
  - Altered tissue development or function
  - Impaired development
  - Impaired reproduction
  - Impaired reproduction/lethality
  - Impaired reproduction/survival, Population crash

- Regulatory Endpoints
  - SAR, QSAR

SAR, QSAR
MOA:AOPs - Integrating Constructs

Molecular data

High Throughput

SAR, QSAR

Regulatory Endpoints

Chemical properties

Protein binding

DNA binding

Receptor/ligand binding

Altered signaling

Altered tissue development or function

Impaired reproduction

Impaired reproduction/survival, Population crash
MOA: AOPs – Integrating Constructs

**Molecular data**
- Molecular data
- SAR, QSAR
- High Throughput
- Mechanistic Toxicology Data (‘omics, biomarkers)

**Regulatory Endpoints**
- Impaired reproduction/survival, Population crash
- Impaired reproduction, lethality
- Impaired development
- Altered tissue development or function
- Altered physiology
- Altered tissue development or function
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- Protein production
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- Protein/DNA binding
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**Mechanistic Toxicology Data**
- Gene activation
- Protein production
- Altered signaling
- Receptor/ligand binding
- DNA binding
- Protein/DNA binding
- Chemical properties

**SAR, QSAR**
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MOA: AOPs – Integrating Constructs

Molecular data

Regulatory Endpoints

SAR, QSAR

High Throughput

Guideline Studies

Mechanistic Toxicology Data (‘omics, biomarkers)
MOA:AOPs – Integrating Constructs

Molecular data

- SAR, QSAR
- High Throughput
- Mechanistic Toxicology Data (‘omics, biomarkers)

Regulatory Endpoints

- Guideline Studies
- Clinical, Epidemiology Eco Field Studies

- Impaired reproduction/survival, Population crash
- Impaired reproduction
- Altered tissue development or function
- Altered signaling
- Altered protein production
- Altered transcription
- Altered protein/DNA binding
- Protein binding
- Chemical properties

Mechanistic Toxicology Data

- Impaired reproduction/survival, Population crash
- Impaired reproduction
- Altered tissue development or function
- Altered signaling
- Altered protein production
- Altered transcription
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- Protein binding
- Chemical properties
Systematically Considering Integrated Data

- International Frameworks to consider the extent or weight of evidence for hypothesized modes of action since the late ‘90s
  - World Health Organization International Programme on Chemical Safety (WHO/IPCS)
  - Based on modified Bradford Hill (B/H) considerations
  - Continue to evolve, based on increasing experience in application
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Formalizing AOP Descriptions and Assessment to Support Regulatory Application

• OECD Guidance and Handbook on Developing and Assessing AOPs (2016)
  • Conventions and terminology
  • Information content of an AOP description
  • Weight of evidence (WOE)/confidence evaluation

AOP Wiki home page
AOP development and description case studies
Addressing the Research-Regulatory Interface: The AOP Knowledge Base

Facilitating research collaboration:
- Avoiding duplicative effort
- Accessible, searchable
- Integrating Modular Components
- Building networks

Addressing regulatory needs:
- Systematically organized
- Transparent, well documented
- Extent of evidence assessed
Section 1 – AOP Description

- Biological Plausibility of KERs (S. 6)

Section 2 – KE Descriptions

- Support for Essentiality of KEs (S.7)
- Empirical Support for KERs (S.6)

Section 3 – KER Descriptions

- Key Event Relationships/Associations

Section 4 – Overall Assessment of the AOP

Annex 1

- Section 5b – MIE, KE, and AO descriptions

MIE Page
- Chemical initiator(s)
  - Description
  - Measurement/detection
  - Taxonomic applicability
  - Evidence for chemical initiation

AO Page
- Description
- Measurement/detection
- Evidence for chemical initiation

KER Pages
- Title
- Biological plausibility
- Empirical support
- Quantitative understanding
- Uncertainties and inconsistencies

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Consideration

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Species | Chem | Conc. | KE1 | KE2 |
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Extent of the Evidence - AOPs

- Biological Plausibility - KERs
  - Biology of the pathway
  - Knowledge of the structural-functional relationships

- Essentiality - KEs within AOP
  - Necessity of Key Events
  - Experimental support normally from specialized studies to block or modify key events, stop/recovery studies

- Empirical Support - KERs
  - Pattern of Quantitative Associations among Key Events often considered through application of stressors
Context: Extent/Weight of Evidence in Integrating Constructs (MOA/AOP)

- Comprehensive, integrated judgment of supporting evidence:
  - Causal Question Definition and Data Selection*
  - Individual Study Review
  - Systematic review of pertinent studies using pre-defined criteria and applying them uniformly
  - Data Synthesis and Evaluation
  - Application to Decision-Making

*Rhomberg et al., 2013; Crit. Rev. Toxicol.
DOI: 10.3109/10408444.2013.832727
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  **Data Synthesis and Evaluation**

- Application to Decision-Making

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Weight of Evidence/Confidence Analysis for Integration
What We’ve Learned from MOA/AOP Analysis

- The value of integrating constructs
  - Encourages a broader perspective/overview of different evidence streams from the outset of assessment
- The need to facilitate engagement/application in addition to increasing transparency/consistency in evidence integration
  - Balancing the extent of prescription of considerations for assessment of integrated evidence with simplicity
- An integrating construct sufficient to assimilate adequate (but not too much) detail
  - e.g., key events at different levels of biological organization for AOPs/MOA sufficient for regulatory purposes
- A limited number of expert informed most influential “determinants” for assessing the extent of supporting data
- A user-friendly interface and platform for assimilation and dissemination
Review

Weight of Evidence for Hazard Identification: A Critical Review of the Literature

Pierre Martin, Claire Bladier, Bette Meek, Olivier Bruyere, Eve Feinblatt, Mathilde Touvier, Laurence Watier, and David Mukowski

1French Agricultural Research Centre for International Development (CIRAD), Agroecology and sustainable intensification of annual crops (UPR AIDA), Montpellier, France
2AIDA, CIRAD, Montpellier University, Montpellier, France
3French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Maisons-Alfort, France
4McLaughlin Center for Risk Science, University of Ottawa, Ottawa, Canada
5WHO Collaborating Center for Public Health Aspects of Musculo-Skeletal Health and Aging, Department of Public Health, Epidemiology, and Health Economics, University of Liège, Liège, Belgium
6Nutritional Epidemiology Research Team (EREN), Center of Research in Epidemiology and Statistics, Sorbonne Paris Cité (CRESS), Institute for Health and Medical Research (INSERM, U1153), French National Institute of Research for Agriculture (INRA, U1125), National Conservatory of Arts and Crafts (CNAM), Paris University, Bobigny, France
7Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases (B2PHI), INSERM, UVSQ, Pasteur Institute, University of Paris-Saclay, Paris, France
8UMR Agronomy, INRA, AgroParisTech, University of Paris-Saclay, Thiverval-Grignon, France

https://ehp.niehs.nih.gov/ehp3067 (July, 2018)
Objectives

- to consider methodology in the assessment and communication of weight of evidence (WOE), as a basis to make recommendations, to;
- the French Agency for Food, Environmental and Occupational Health and Safety (ANSES)
  - to harmonize to the extent possible approaches in environmental, occupational and food safety, plant and animal health
- Restricted to the structured synthesis of evidence
  - Not addressing aspects related to process, including:
    - the selection of experts and
    - conflicts of interest
Review

Weight of Evidence for Hazard Identification: A Critical Review of the Literature

Pierre Martin,1,2 Claire Bladier,3 Bette Meek,4 Olivier Bruyere,5 Eve Feinblatt,3 Mathilde Touvier,6 Laurence Watier,7 and David Makowski5

- Review of approaches to weight of evidence (WOE) evaluations of hazard:
  - published literature, and
  - directed requests to 63 international and national agencies

n=116 relevant studies
Results of the Systematic Search

6 20 15 13

Stage 1
Planning the assessment

Stage 2
Establishing lines of evidence
Identification and selection of studies
Assessing the quality of the studies
Analysing a set of studies of similar type

Stage 3
Integrating lines of evidence

Stage 4
Expressing weight of evidence conclusions
Results of the Systematic Search

- Planning the assessment: 6
- Establishing lines of evidence: 20
- Integrating lines of evidence: 15
- Expressing weight of evidence conclusions: 13

**Stage 1**
- Scoping
- Formulating the question(s)
- Developing the assessment protocol

**Stage 2**
- Identification and selection of studies
- Assessing the quality of the studies
- Analysing a set of studies of similar type

**Stage 3**
- None

**Stage 4**
- None
Results of the Systematic Search

Stage 1: Planning the assessment
- Scoping
- Formulating the question(s)
- Developing the assessment protocol

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Stage 4: Expressing weight of evidence conclusions

6 20 15 13
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Stage 4: Expressing weight of evidence conclusions

Numbers:
- 6
- 20
- 15
- 13
Results of the Systematic Search

**Stage 1**: Planning the assessment
- Scoping

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6 20 15 13
Results of the Systematic Search

- **Stage 1**: Planning the assessment
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- **Stage 3**: Integrating lines of evidence
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- **Stage 4**: Expressing weight of evidence conclusions

Numbers: 6, 20, 15, 13
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Stage 3
- Integrating lines of evidence

Stage 4
- Expressing weight of evidence conclusions

Numbers:
- 6
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Evaluation Strategy for Identified Approaches

Utility (in ANSES context) rated, based on (relative ranking of 1 – 4):
- prescriptive nature,
  - degree of prescription/detail for considerations
  - no explicit rules provided → defined in significant detail
- relevance,
  - extent to which the approaches could be broadly applied within ANSES
  - specificity of use to a narrow application → broadly applicable to ANSES applications
- feasibility
  - ease of implementation (time and material/human resources required)
  - resource and expertise intensive → limited requirement for specialized expertise, material resources and/or time
Objectives of the Relative Ranking

- To facilitate formal assessment planning, including selection of appropriate approaches (WOE) in ANSES assessments, depending on:
  - resourcing
  - Objectives/Problem Formulation/Level of acceptable uncertainty
  - priority
    - potential public and environmental health impacts
    - societal issues
  - data availability
Observations (1) - Integration and Communication

- Principles of the range of methods available for integration (studies of similar types and lines of evidence) are similar
  - Expert-informed weighting of components
  - B/H considerations figure prominently
  - Range from semi-quantitative to quantitative, but with significant differences in their degree of prescription/process
    - “Codified” experience derived from a formal analysis of previous examples
    - Expert judgment of an individual or group
- The need for contextual communication
  - Specifying the context (application)
  - Preponderance of evidence vs. degree of hazard
Observations (2) - Complexity of Approach (Feasibility)

- Preferred (often more quantitative) approaches are generally the least feasible, limiting application
  - the most complex requiring significant resources
    - Time and/or specialized expertise

- Feasibility of implementation of purely qualitative methods is high, but:
  - transparency (degree of prescription)/consistency of outcome often limited

- Methods which offer an intermediate degree of prescription easiest to implement (e.g., semi-quantitative):
  - conserve resources, while
  - increasing transparency and consistency
  - Simpler to communicate
Observations (3)- Expert Informed “Codification” for Weighting for Integration

- Drawing on accumulated experience to delineate content of reporting templates for integration
- Requires analysis of previous experience to delineate specifically the factors being taken into consideration/weighted in integration
  - Contributing experts
- Promotes greater consistency by increasing common understanding of relevant elements for consideration, taking into account prior experience
- Preferred to variable ad hoc approaches based on convening of expert groups?
  - Transparency on selection criteria and approach is often less
Observations (4): The Need for Formal Assessment Planning/Templates

- Providing rationales for a priori selection of methodology for all steps in the assessment at outset, to focus resources on:
  - Objectives
  - Critical stages
    - E.g., data integration, dose-response analysis
  - Critical issues, and
  - Critical data
- Provides for early communication to stakeholders
- Provides accountability for efficiency – maximizing resource impact
  - e.g., considering impact of various stages in the process to focus preferred tools?
Ensuring that the approach for the early stages of evidence assimilation/consideration facilitates data integration
Formal Assessment Planning/Templates (Cont’d)

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Formal Assessment Planning/Templates (Cont’d)

- Ensuring that the approach for the early stages of evidence assimilation/consideration facilitates data integration
Implications: Best Practice in Evidence Integration

- Selection in assessment planning of methods for data identification and assimilation that facilitate integration from the outset:
  - to identify early relevant patterns across studies and lines of evidence, based on:
    - a priori considerations that draw upon accumulated experience
      - E.g., Integrating hazard and mechanistic data from the outset, considering “patterns” of relevant determinants such as empirical support
    - Early consideration of concordance of dose and temporal response across studies and lines of evidence
Early Integration

- Problem Formulation
- Assessment Planning
- Communication

Hazard Characterization

Dose Response Assessment & Characterization

Risk Assessment & Characterization

Exposure Assessment & Characterization
Early Integration

Problem Formulation
Assessment Planning
Communication

Hazard Characterization

Dose Response Assessment & Characterization

Exposure Assessment & Characterization

Risk Assessment & Characterization
Early Integration

Hazard Characterization

- Dose Response Assessment & Characterization
- Exposure Assessment & Characterization
- Risk Assessment & Characterization

Including consideration of patterns across different levels of biological organization, e.g., empirical support

Problem Formulation
Assessment Planning
Communication
Acknowledgements

- Members of the OECD Extended Advisory Group on Molecular Screening and Toxicogenomics (EAG MST) Handbook and Training Teams

- Members of the Anses GTMER (Comité D'expert Méthodologie De L'évaluation Des Risques) on Weight of Evidence
  - [https://ehp.niehs.nih.gov/doi/10.1289/EHP3067](https://ehp.niehs.nih.gov/doi/10.1289/EHP3067) (manuscript in English)
  - [https://www.anses.fr/fr/content/avis-gt-mer](https://www.anses.fr/fr/content/avis-gt-mer) (full report in French)