

Weight of Evidence Methodology Perspective Based on a Critical Review

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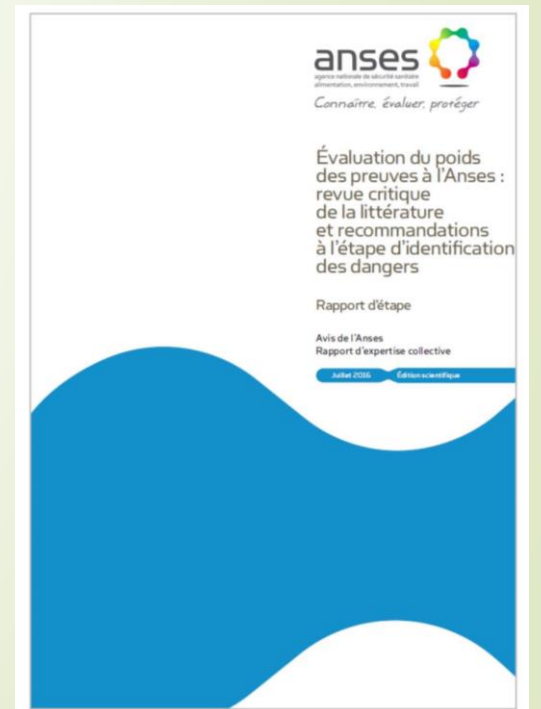
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Outline

- Objectives
- Approach
- Outcome
- Implications
- Related experience



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

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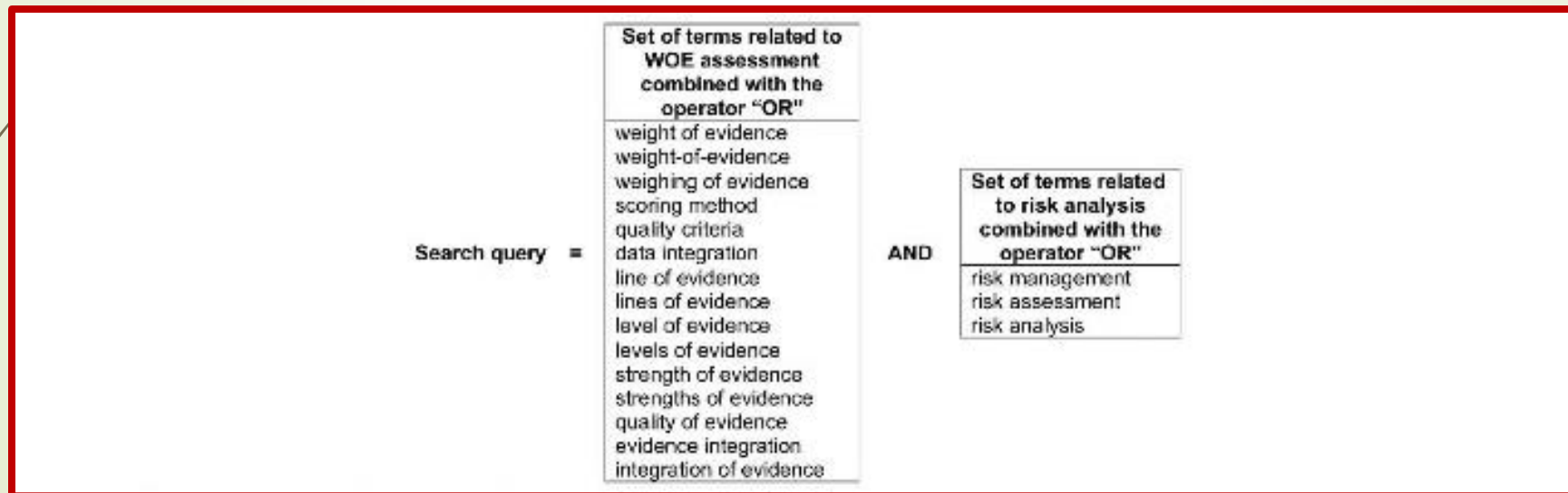
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Objectives

- 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
 - broader than chemical hazards
- Restricted to the structured synthesis of evidence
 - Not addressing aspects related to process, including:
 - the selection of experts and
 - conflicts of interest

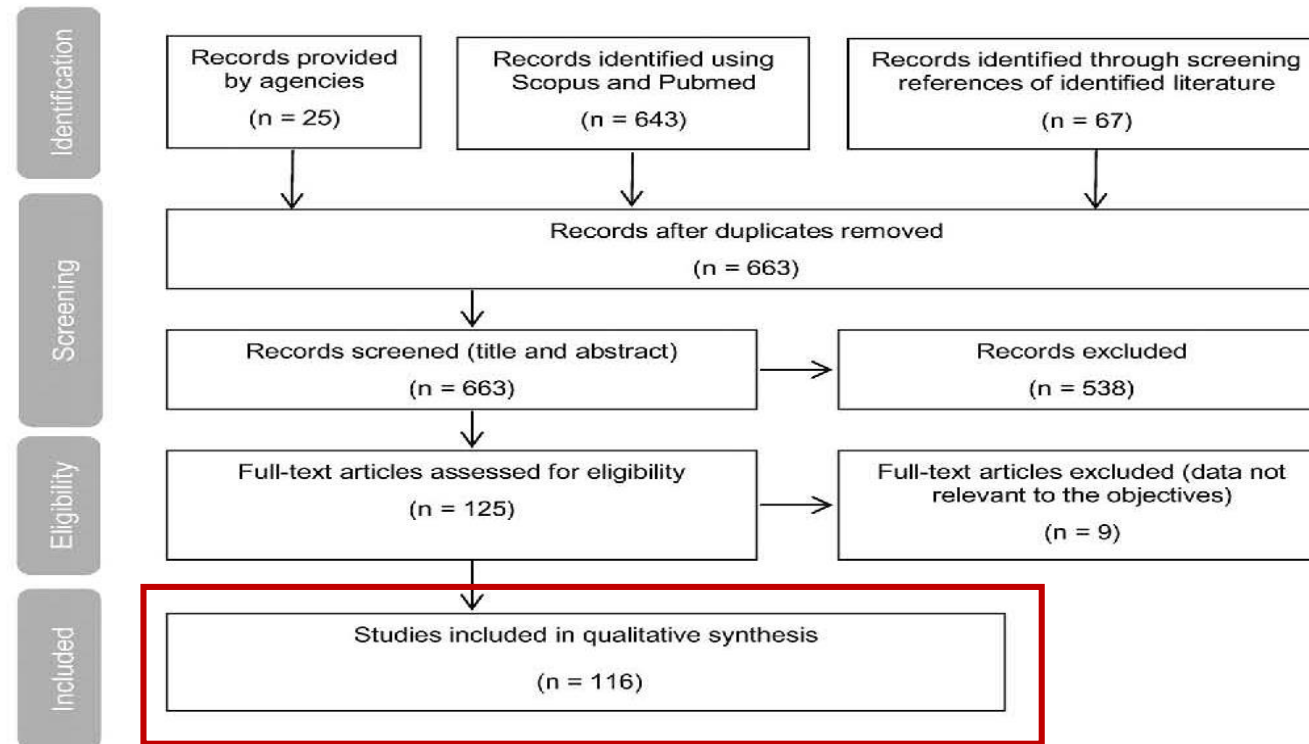
Search Strategy

- ▶ review of the literature
 - ▶ PubMed
 - ▶ Scopus
 - ▶ Screening of identified sources



- ▶ focused consultation of 63 public health and environmental agencies worldwide

Results of the Search



n=116 relevant studies

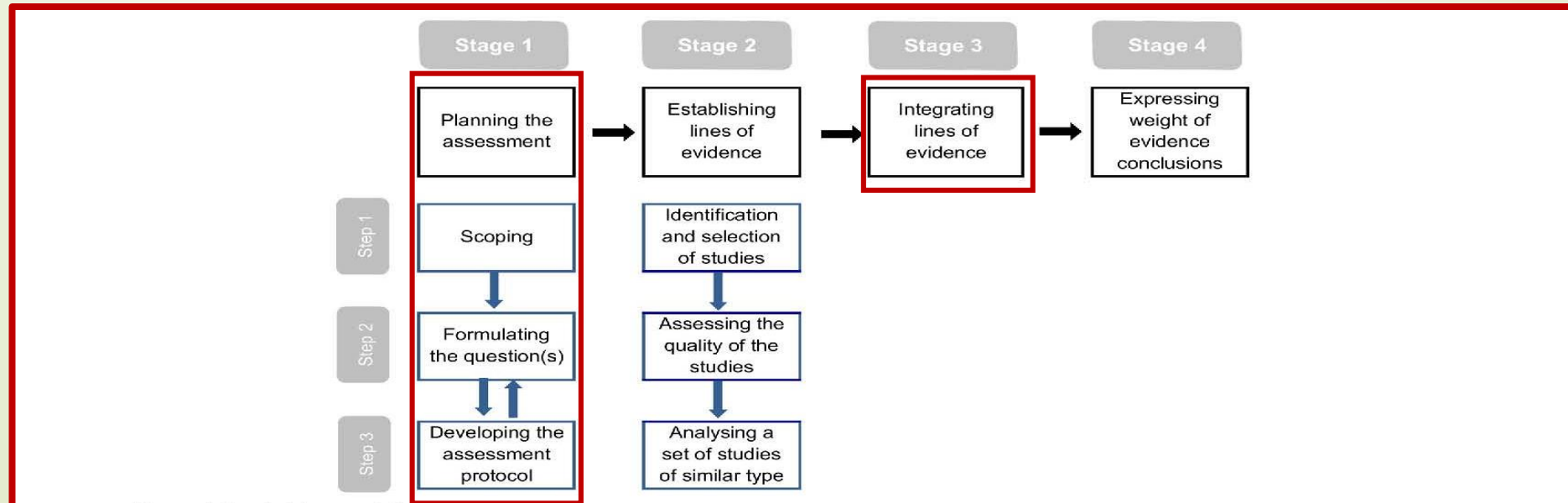
Evaluation Strategy

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- ▶ Titles and abstracts screened by at least two people
- ▶ Descriptions of the approaches by individual authors within their area of expertise
 - ▶ Domain and scope of application
 - ▶ Definition of terms
 - ▶ Methodology for WOE assessment
 - ▶ Nature and number of considerations
 - ▶ Structured in 4 stages

- 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



Evaluation Strategy (cont'd)

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Utility (in ANSES context) rated, based on:

- prescriptive nature,
 - degree of prescription to facilitate implementation
- relevance,
 - extent to which the approaches could be broadly applied, and
- feasibility
 - ease of implementation (time and material/human resources required)

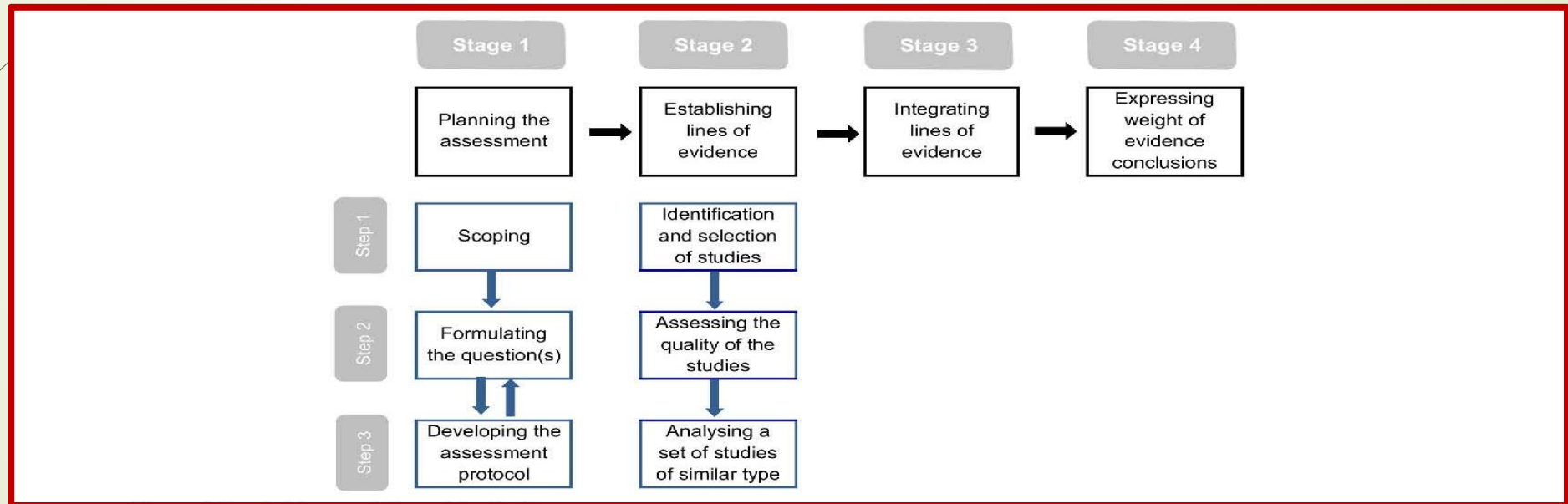
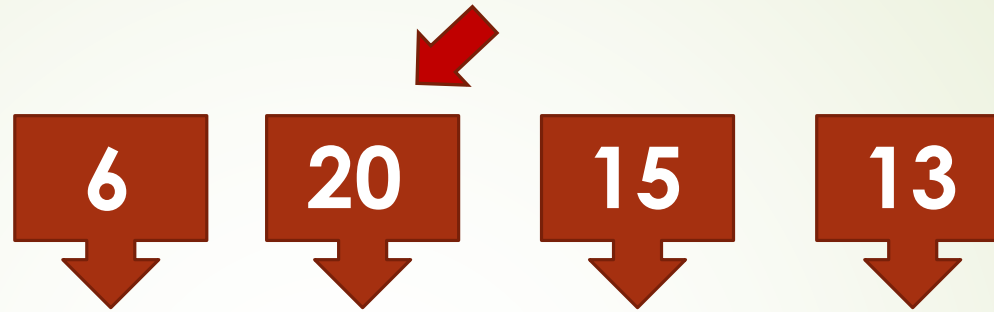
Evaluation Strategy (cont'd)

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Relative ranking of each of the methodologies (1-4):

- prescriptive nature,
 - no explicit rules provided ➡ defined in significant detail
- relevance,
 - specificity of use to a narrow application ➡ broadly applicable to ANSES applications
- Feasibility
 - resource and expertise intensive ➡ limited requirement for specialized expertise, material resources and/or time

Results - Overall



Results - Stage 1

Assessment Planning

Approach	Prescriptive nature	Relevance	Feasibility
GRADE	4	3	3
Hope and Clarkson	2	2	3
NRC	4	3	3
OHAT	4	3	3
SR-Cochrane	4	3	3
SR-EFSA	4	3	3

GRADE, Grading of Recommendations Assessment, Development and Evaluation; EFSA, European Food Safety Authority; NRC, U.S. National Research Council; OHAT, Office of Health Assessment and Translation; SR, Systematic Review

Note: the rankings were assigned to the methods by the authors collectively and reflect relative consideration of each of the three aspects defined and outlined in the Methods and Table 1. Note: the rankings were assigned to the methods by the authors collectively and reflect relative consideration of each of the three aspects defined and outlined in the Methods and Table 1. the extent of prescriptive nature contributing to transparency and reproducibility, relevance to be broadly applied within Anses, and ease of implementation in terms of time and material/human resources (feasibility). Each aspect is ranked from 1 (i.e., the least) to 4 (i.e., the most).

Results - Stage 2 - Establishing Lines of Evidence

Approach	Identifying and selecting studies			Assessing the quality of the studies			Analyzing a set of studies of similar type		
	PN	REL	FEA	PN	REL	FEA	PN	REL	FEA
AMSTAR				4	3	4			
Bradford Hill							2	4	4
Epid-Tox				2	4	4	2	4	3
FDA				3	4	4	2	3	3
GRADE				4	3	3	2	3	4
Hope and Clarkson				2	3	3	2	3	3
IARC				2	4	4	2	3	4
ILSI				2	3	3	3	2	3
INCa	3	2	4	3	2	4			
Klimisch				2	3	4			
Meta-analysis							4	4	1
Modified Bradford Hill							3	3	3
Multi-criteria analysis				2	4	3	2	4	3
Navigation Guide	1	3	2	1	3	4	1	3	3
OHAT	3	3	2	3	3	4	2	3	3
SR-Cochrane	3	3	2	2	4	4			
SR-EFSA	3	3	2						
SCENIHR				2	3	4	1	3	4
WCRF/AICR				2	4	4	4	4	2
Weighted Bradford Hill							3	3	3

AMSTAR, Assessing the Methodological Quality of Systematic Reviews; EFSA, European Food Safety Authority; FDA, U.S. Food and Drug Administration; FEA, Feasibility; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IARC, International Agency for Research on Cancer; ILSI, International Life Sciences Institute; INCa, Institut National du Cancer/French National Cancer Institute; NA, Not applicable; NRC, U.S. National Research Council; OHAT, Office of Health Assessment and Translation; PF, Practical Framework; PN, Prescriptive nature; REL, Relevance; SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks; SR, Systematic Review; WCRF/AICR, World Cancer Research Fund and American Institute for Cancer Research. Note: the rankings were assigned to the methods by the authors collectively and reflect relative consideration of each of the three aspects defined and outlined in the Methods and Table 1. the extent of prescriptive nature contributing to transparency and reproducibility, relevance to be broadly applied within Anses, and ease of implementation in terms of time and material/human resources (feasibility). Each aspect is ranked from 1 (i.e., the least) to 4 (i.e., the most).

Results - Stage 3 – Integrating Lines of Evidence

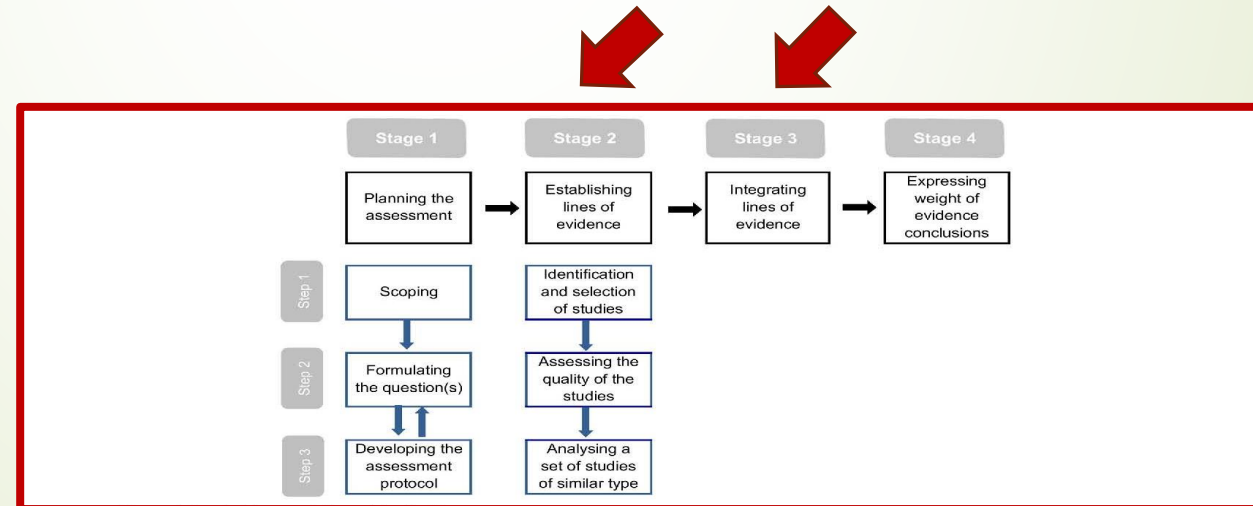
Approach	Prescriptive nature	Relevance	Feasibility
Bayesian inference	3	4	2
Bradford Hill	2	4	4
Decision tree	1	3	3
Epid-Tox	2	4	3
Hope and Clarkson	3	3	3
Hypothesis based	2	3	3
IARC	3	3	4
INCa	3	3	4
Multi-criteria analysis	2	4	3
Modified Bradford Hill	3	3	3
Navigation Guide	1	3	3
OHAT	3	3	4
SCENIHR	2	3	4
WCRF/AICR	3	3	4
Weighted Bradford Hill	3	4	4

IARC, International Agency for Research on Cancer; INCa, Institut National du Cancer/French National Cancer Institute; OHAT, Office of Health Assessment and Translation; SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks; WCRF/AICR, World Cancer Research Fund and American Institute for Cancer Research Note: the rankings were assigned to the methods by the authors collectively and reflect relative consideration of each of the three aspects defined and outlined in the Methods and Table 1. Note: the rankings were assigned to the methods by the authors collectively and reflect relative consideration of each of the three aspects defined and outlined in the Methods and Table 1. the extent of prescriptive nature contributing to transparency and reproducibility, relevance to be broadly applied within Anses, and ease of implementation in terms of time and material/human resources (feasibility). Each aspect is ranked from 1 (i.e., the least) to 4 (i.e., the most).

Objectives of the Relative Ranking

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- ▶ 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
 - ▶ Extent of potential public and environmental health impacts
 - ▶ Societal issues
 - ▶ data availability
- ▶ Consider the appropriate focus for different stages (WOE)



Observations -Complexity of Approach (Feasibility)

- Methods applied most broadly in the environmental health/human food and nutrition area
- Preferred (often more quantitative) approaches 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
- Semi-quantitative, more prescriptive methods a valuable intermediate option that:
 - conserves resources and
 - increases the transparency and consistency of assessments
 - (OHAT (NTP) and modified Bradford Hill for mechanistic data)

Observations - Integration and Expression of Results

- Principles of the range of methods available for **integration** are similar
 - Expert-informed weighting of components
 - 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- Expert Informed “Codification” for Weighting for Integration

- ▶ value of acquired experience in contributing to expert-informed prescription of the relevant factors to be considered in reporting templates
- ▶ requires that contributing experts be much more explicit about the factors being taken into consideration/weighted
 - ▶ E.g., prescriptive approach to assessment planning, review and evaluation of OHAT (Office of Health Assessment, U.S. NTP)
 - ▶ Facilitates adoption
 - ▶ Increases common understanding of relevant elements for consideration
 - ▶ versus
 - ▶ More variable approaches
 - ▶ E.g., IARC, multi-criteria decision analysis

Discussion: Limitations of the Current Analysis

- ▶ Didn't address aspects of process which influence outcome
 - ▶ E.g., expert selection
 - ▶ A priori criteria?
 - ▶ Especially critical for relatively non-prescriptive approaches, which are almost completely dependent upon expert review
 - ▶ Selection by an independent third party based on specified areas of expertise?
 - ▶ A priori consideration of proportion of experts addressing what (critical) aspects, balance, etc.?
 - ▶ Scores developed for the prescriptive nature, relevance and feasibility meaningful in a relative context only and limited to generalized considerations for assessment
 - ▶ Metrics not completely independent
- ▶ restricted to hazard identification
 - ▶ Broader purview of assessment planning
 - ▶ Uncertainty analysis, exposure

Implications: The Need for Formal Assessment Planning/Templates

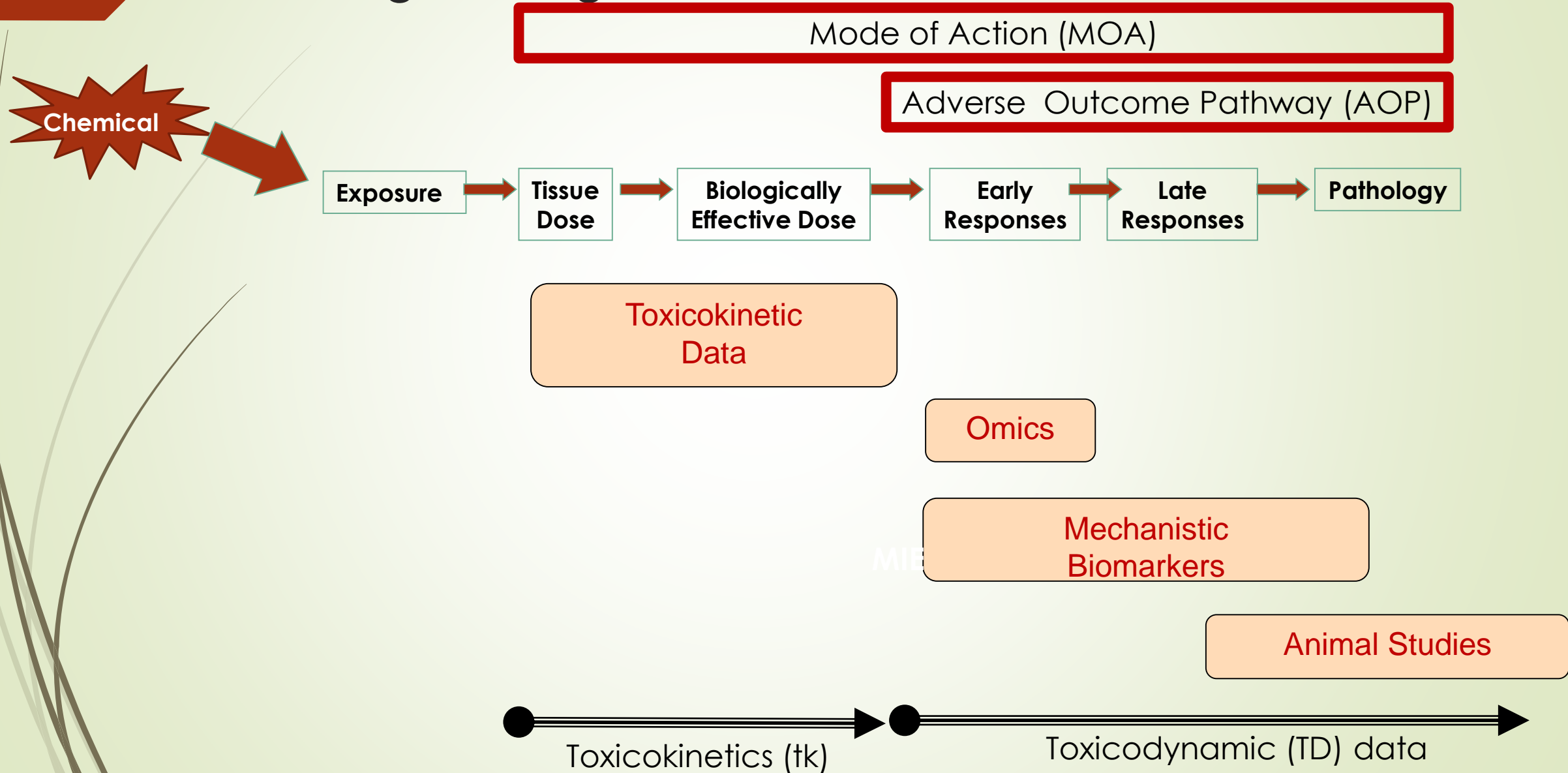
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- ▶ Considering approach taking into account, **the context**:
 - ▶ assessment objectives
 - ▶ Including urgency
 - ▶ resources and
 - ▶ a preliminary overview of available data
- ▶ Considering method selection in a broader (normally risk-related) context, to focus resources early on:
 - ▶ Critical issues, and
 - ▶ Critical data
- ▶ Providing rationales a priori for method selection (including WOE)
 - ▶ Critical for early communication to stakeholders
- ▶ Provides accountability for efficiency – maximizing resource impact e.g., considering steps in context of likely impact for early focus
 - ▶ Underscores the value of application of integrating constructs from the outset

Implications: The Importance of Integrating Constructs and “Codified” Expert Input

- ▶ Formal assessment planning and documentation should be helpful in shifting the focus to the more influential steps in WOE consideration
- ▶ underscores the need for:
 - ▶ scoping the assessment in an integrative context, from the outset
 - ▶ Rather than a series of sequential steps
 - ▶ Need for more **integrative** constructs for data consideration at outset and throughout the assessment
 - ▶ Importance of “codified” expert judgment in the consideration of weighting for integration
 - ▶ Transparency

Assimilating Information at Different Levels of Biological Organization – Mechanistic Data

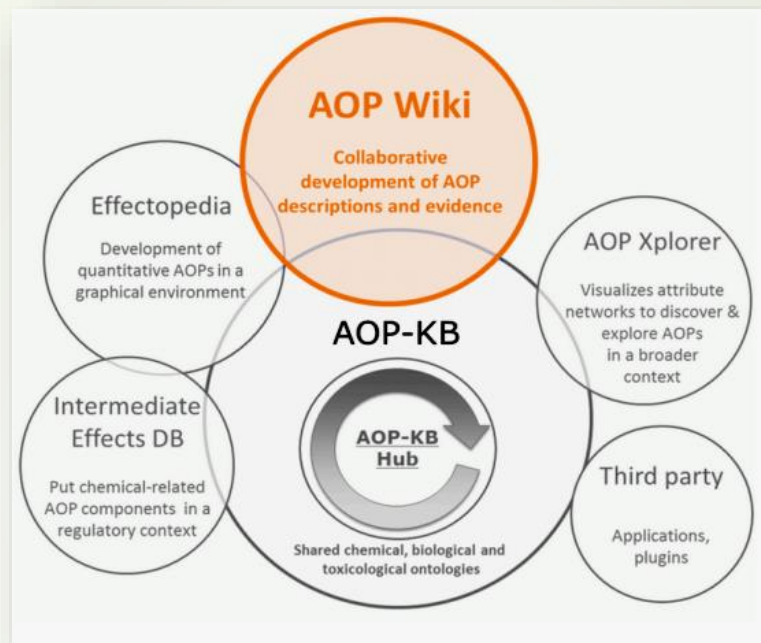


Addressing the Research-Regulatory Interface: The AOP Knowledge Base

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OECD

AOP devt and
assessment (2012)
Test Guidelines
Hazard Evaluation



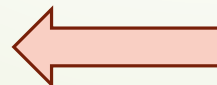
AOPKB.org
AOPWIKI.org

Facilitating research collaboration:

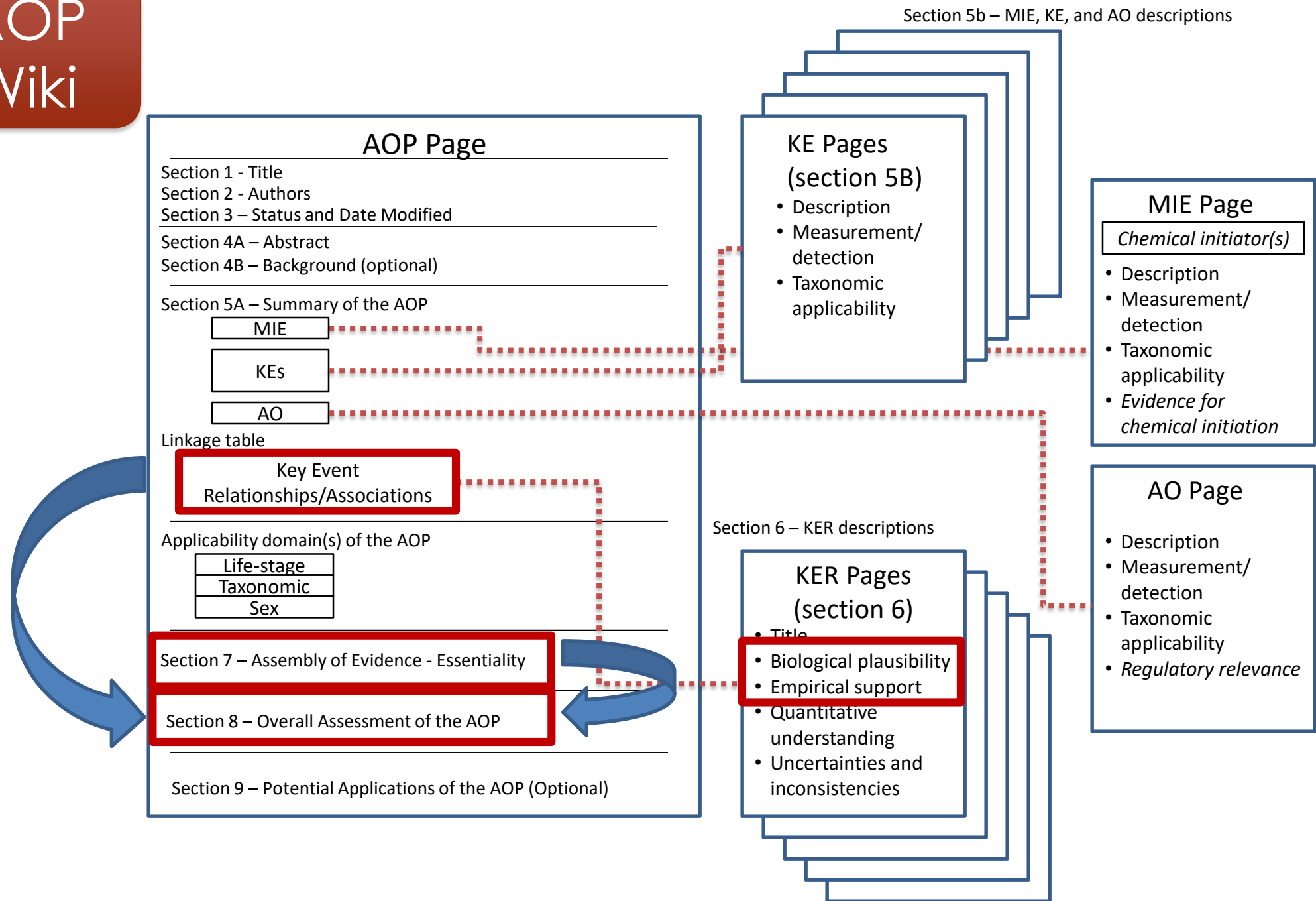
- Avoiding duplicative effort
- Integration and analysis
- Building networks
- Accessible and searchable

Addressing regulatory needs:

- Systematically organized
- Transparent, well documented
- Scientifically-defensible, credible



Identifying data gaps relevant to application



(OECD, 2014) Users' Handbook Supplement To The Guidance Document For Developing And Assessing AOP

Annex 1 – Assessing Confidence Definition, Basis for Calls, Examples

Consideration	Defining Questions	High (Strong)	Moderate	Low (Weak)
Biological Plausibility of KERs (S. 6)				
Support for Essentiality of KEs (AOP) (S.7)				
Empirical Support for KERs (S.6.)				

https://aopkb.org/common/AOP_Handbook.pdf

So What's Important

- Early (public) delineation of the protocol for assimilating, selecting, weighting and integrating evidence (template?)
 - rationale for selection of approaches/tools, taking into account:
 - 1.objectives, **2.resourcing**, 3.level of acceptable uncertainty, and
 - 4.stages/steps that have **greatest impact**
- Recognizing that:
 - preferred tools often most resource intensive but may **not** be **required**
- What's most important?
 - **transparency reproducibility/consistency**
- What contributes most?
 - level of prescription of an approach based on assimilated experience, balanced against feasibility
 - clearly delineated objectives in the **context** of intended application



So, What's Worked?

Critical Elements in Managing (Assimilating, Integrating and Weighting) Evidence in Hazard Assessment

- ▶ An integrating construct sufficient to assimilate an adequate level of detail
 - ▶ e.g., key events at different levels of biological organization for AOPs/MOA
 - ▶ relevant to application in regulatory context
 - ▶ Requires regulatory/research interface
- ▶ A limited number of expert informed most influential “determinants” for:
 - ▶ considering the extent of the supporting data (i.e., weight of evidence)
- ▶ A user friendly interface and platform for dissemination
 - ▶ Associated Development and Application Guide

What's been Challenging?



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Balancing the scientific - regulatory interface

- ▶ the need for:
 - ▶ consistent terminology and documentation/description of construct and supporting evidence
 - ▶ Not the forte of the research community; essential for the regulatory community
- ▶ appropriate (not extensive) level of complexity
 - ▶ only as complex as it needs to be to address needs for regulatory application



- ▶ i.e., focussed on critical (not all) aspects to facilitate communication and application within regulatory agencies (sensitivity – important or not?)
- ▶ sufficient experience and motivation/capacity to “codify” the important components of description and integration/weighting of evidence to enable incorporation in electronic tools