# Emerging Strategies for Evidence Integration

## NAS Workshop on Evidence Integration in Chemical Assessments

Washington, June 3rd, 2019

Presented by:
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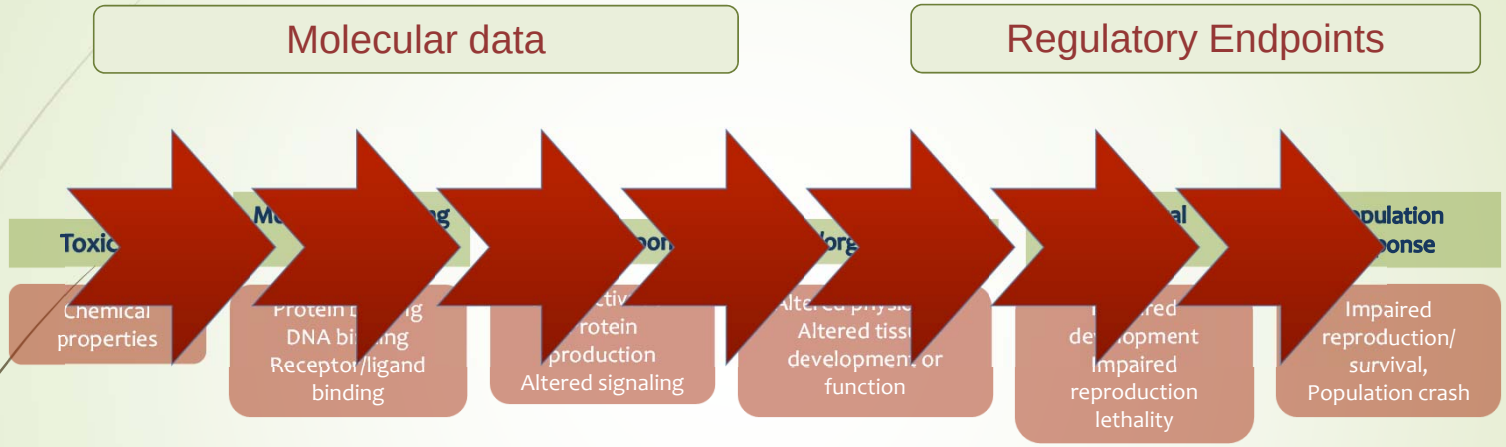
# *Outline*

- 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



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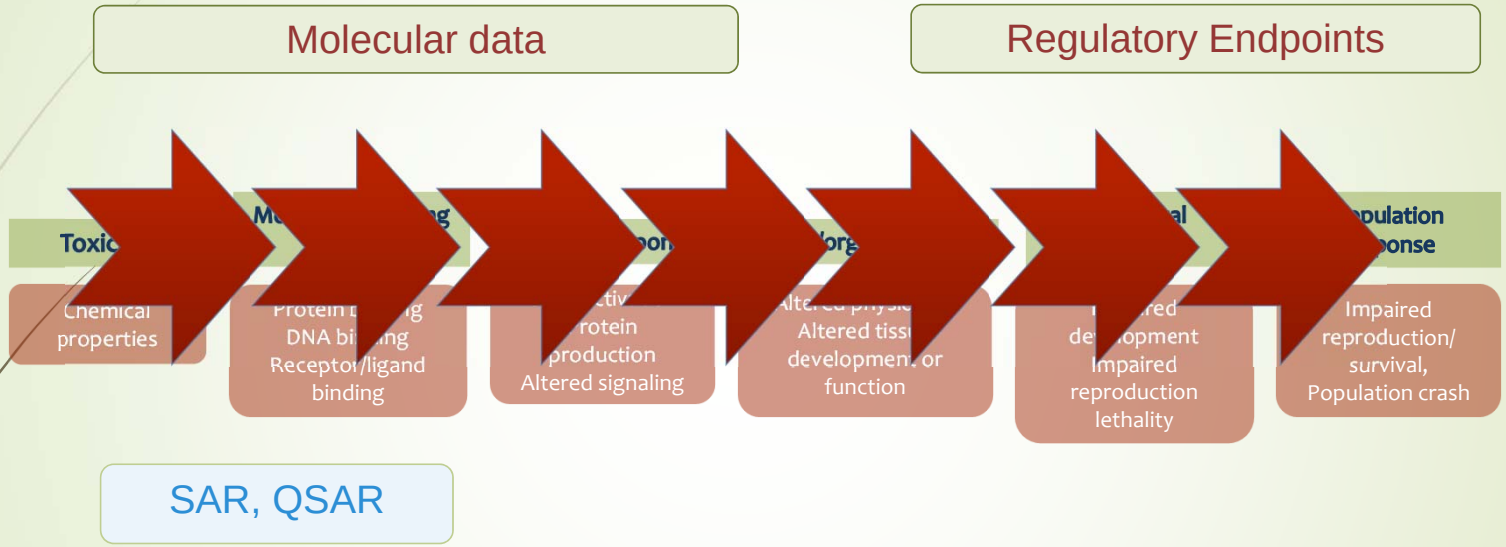

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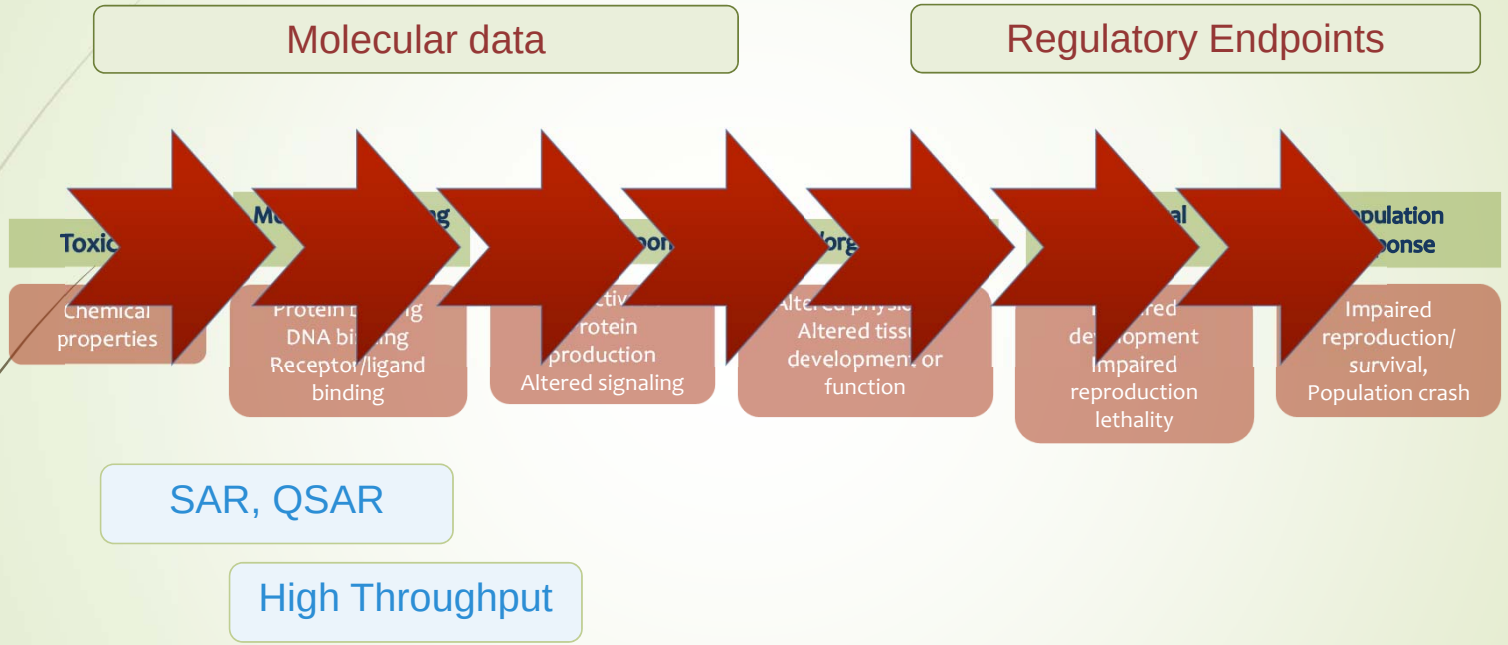

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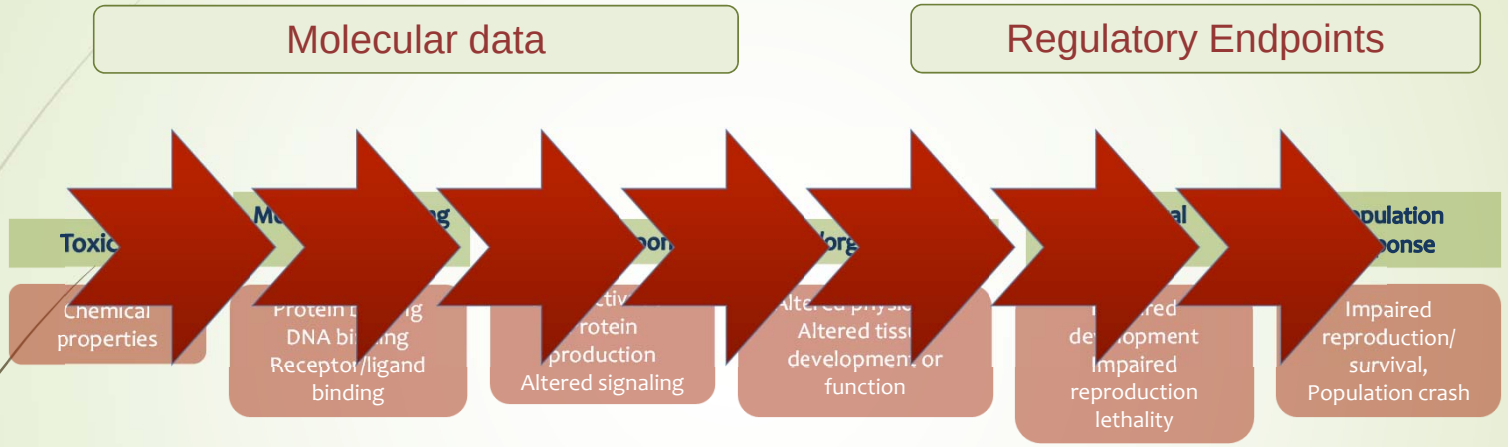


SAR, QSAR

High Throughput

Mechanistic Toxicology Data ('omics, biomarkers)

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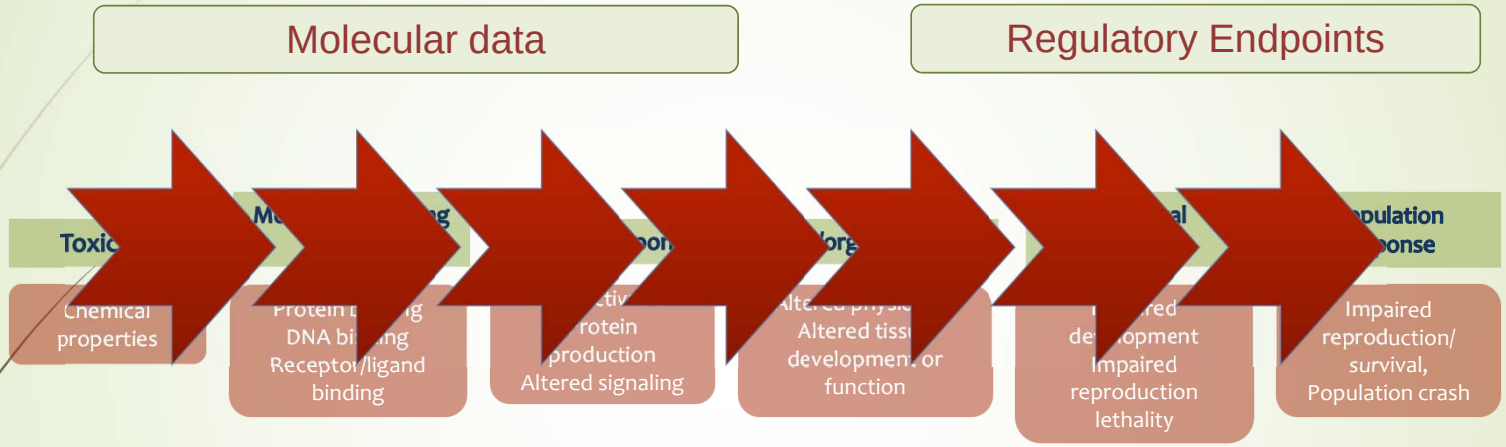


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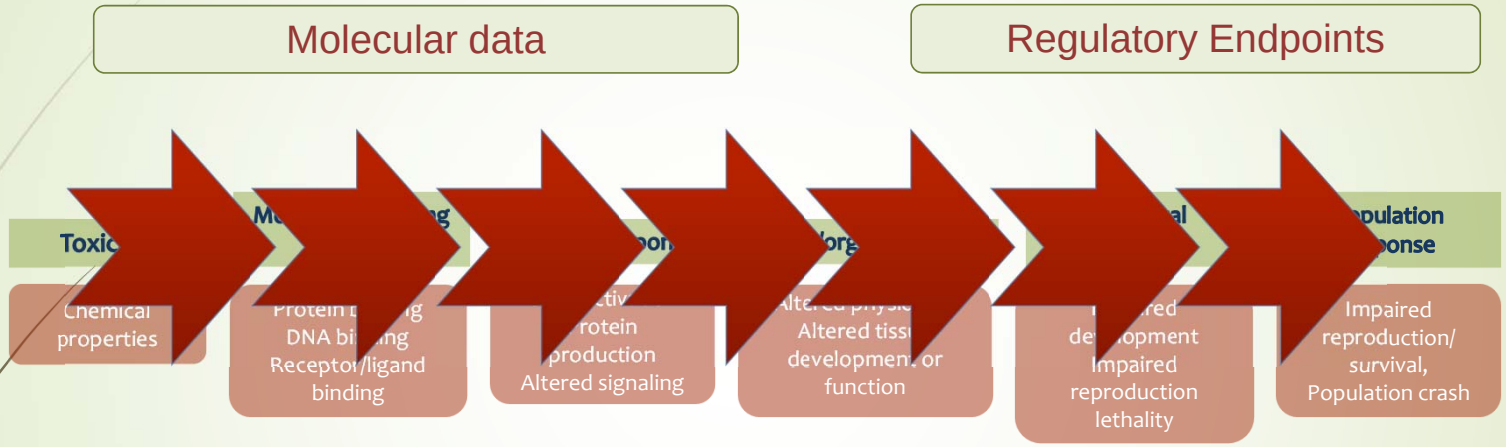


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Clinical, Epidemiology Eco Field Studies

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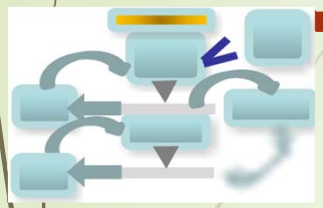

- International Frameworks to consider the extent or weight of evidence for hypothesized modes of action since the late '90's
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- Based on modified Bradford Hill (B/H)considerations
- Continue to evolve, based on increasing experience in application

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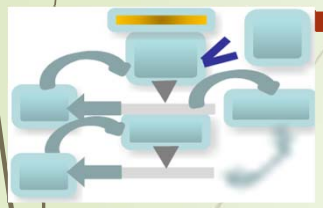

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Review Article

Journal of Applied Toxicology

New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis†

M. E. Meek[a], A. Boobis[b], I. Cote[c], V. Dellarco[d], G. Fotakis[e], S. Munn[f], J. Seed[g] and C. Vickers[h]*

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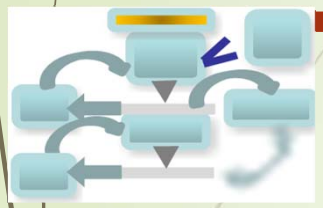

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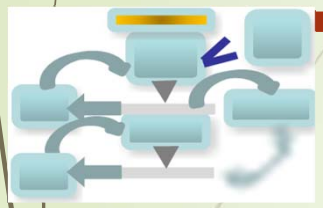

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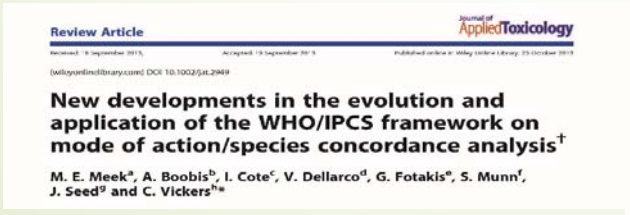

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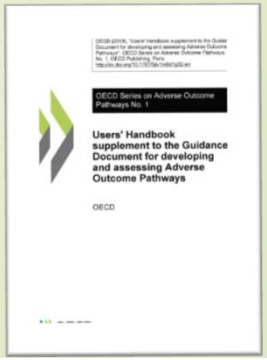


OECD Series on Adverse Outcome Pathways No. 1

Users' Handbook supplement to the Guidance Document for developing and assessing Adverse Outcome Pathways

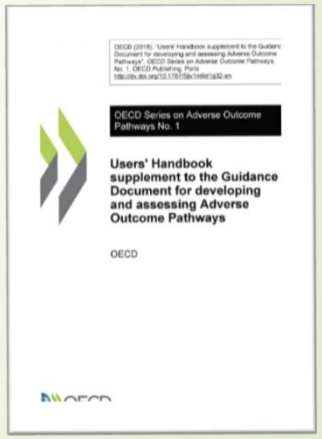
OECD

# *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

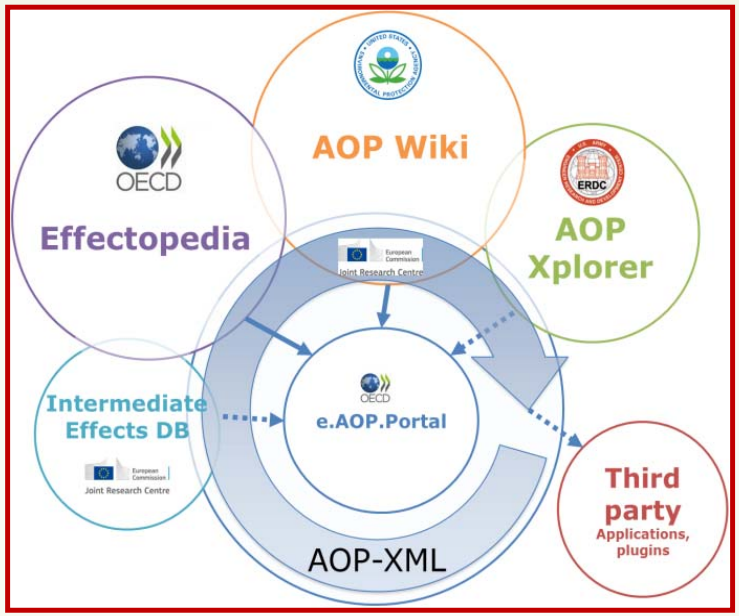

AOPWIKI.org


AOP Development and Description Case Studies
https://www.oecd-ilibrary.org/environment/oecd-series-on-adverse-outcome-pathways_2415170x




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

# *Addressing the Research-Regulatory Interface: The AOP Knowledge Base*




*Facilitating research collaboration:*

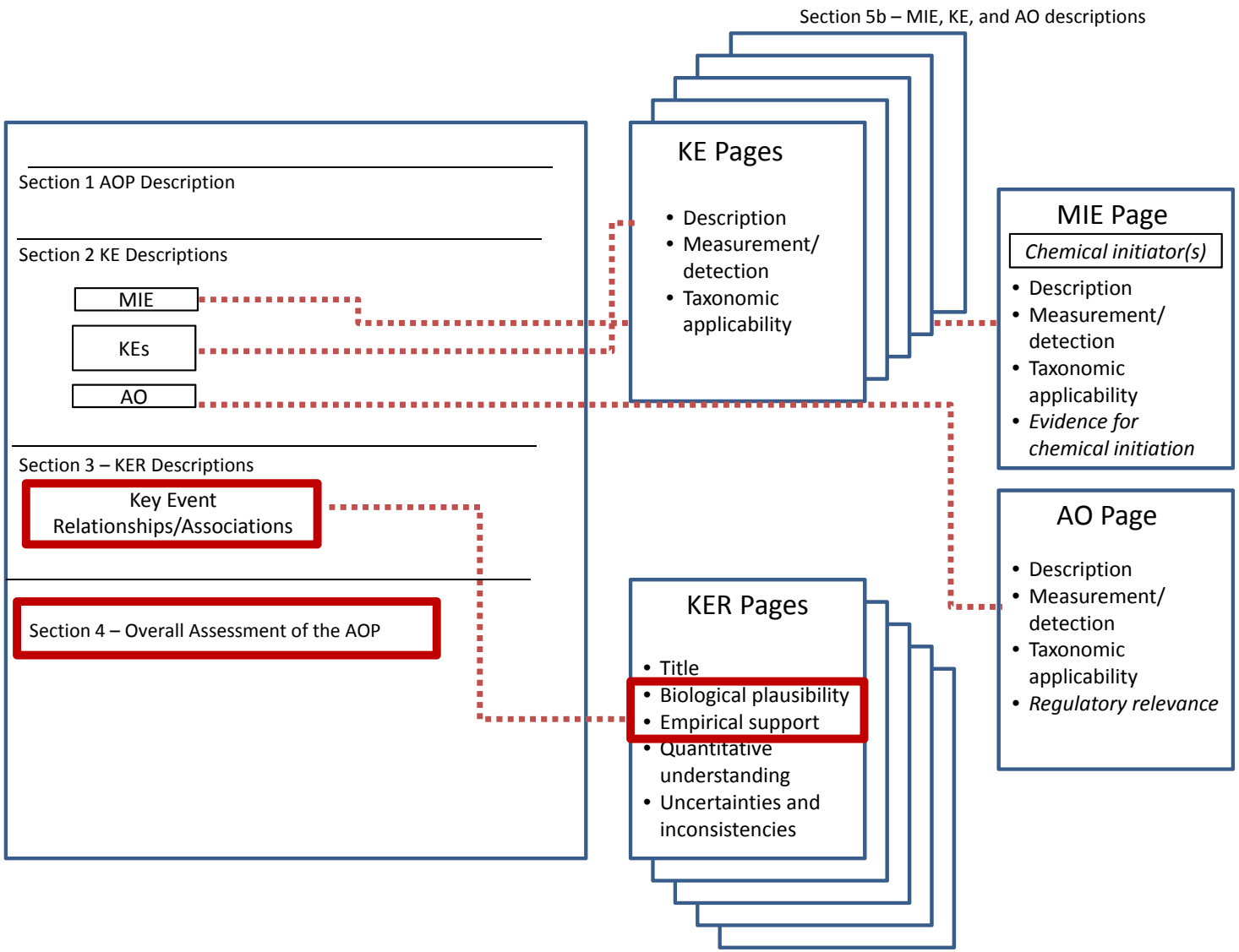
- Avoiding duplicative effort
  - Accessible, searchable
- Integrating Modular Components
- Building networks

*Addressing regulatory needs:*

- Systematically organized
- Transparent, well documented
- Extent of evidence assessed

7

# AOP Wiki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Section 2 KE Descriptions
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KEs
AO
Section 3 – KER Descriptions
Key Event Relationships/Associations
Section 4 – Overall Assessment of the AOP
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• Description
• Measurement/ detection
• Taxonomic applicability
MIE Page
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• Description
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• Evidence for chemical initiation
AO Page
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KER Pages
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• Biological plausibility
• Empirical support
• Quantitative understanding
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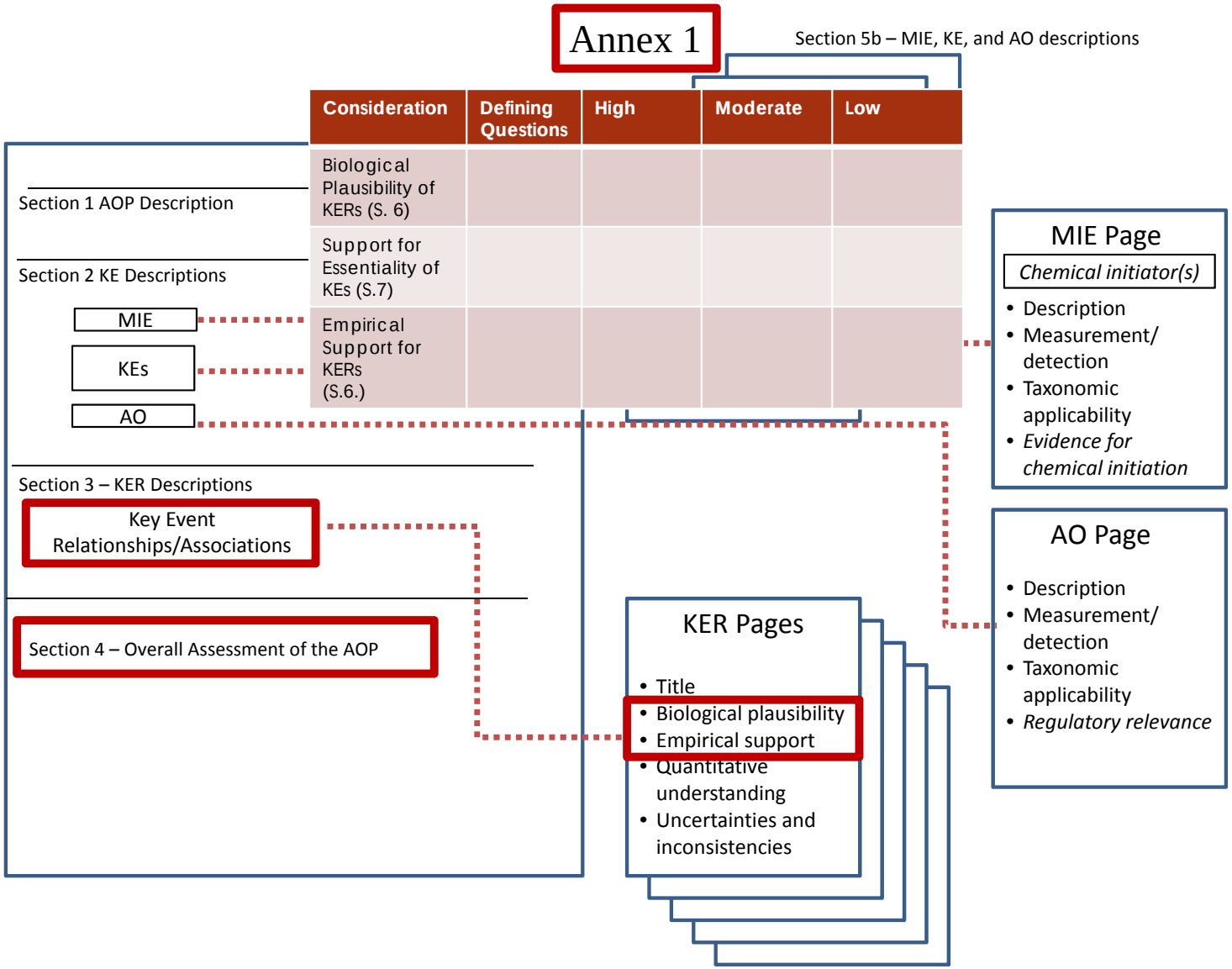
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High
Moderate
Low
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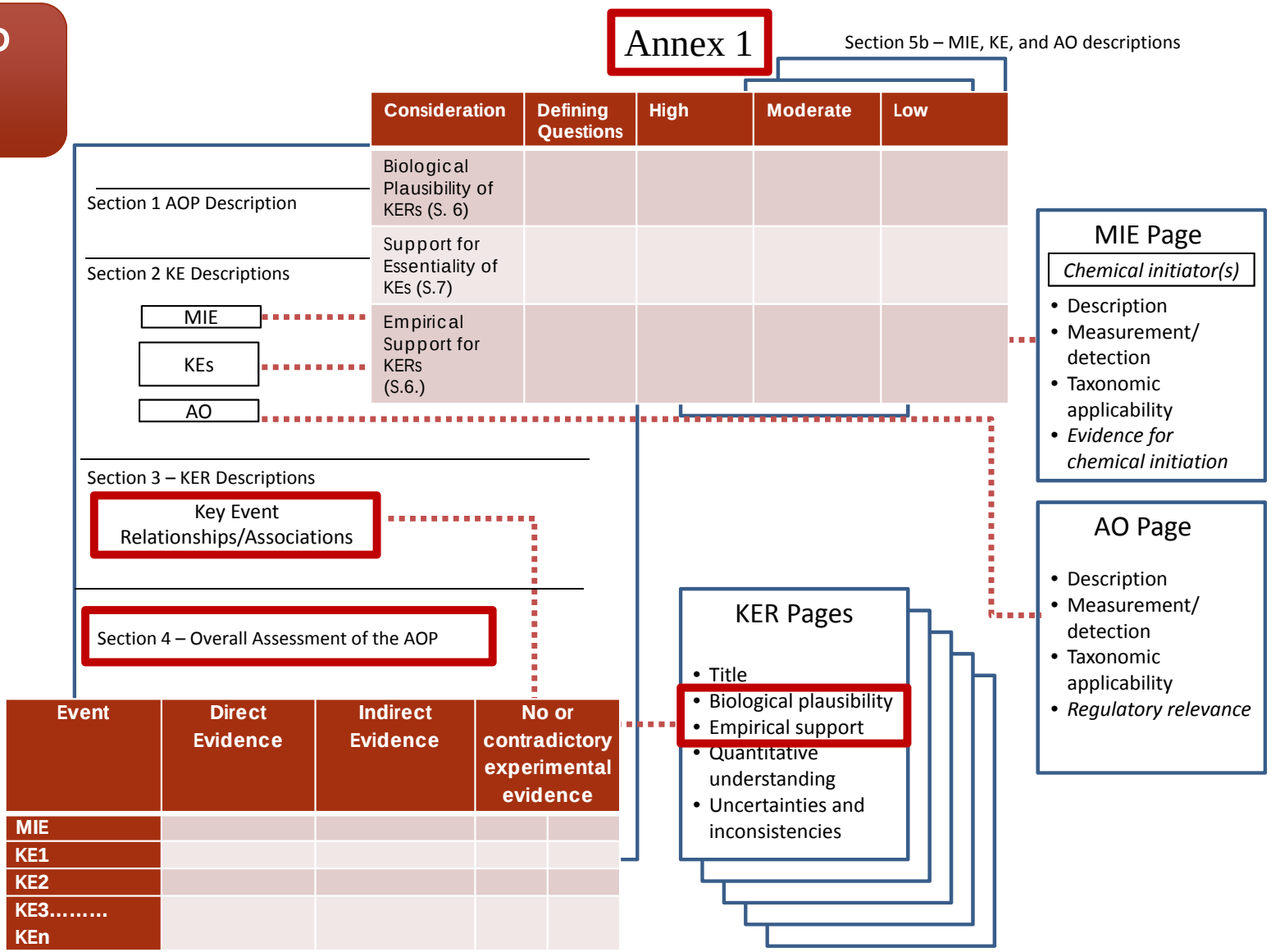
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Event
Direct Evidence
Indirect Evidence
No or contradictory experimental evidence
MIE
KE1
KE2
KE3……
KEn
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# AOP Wiki

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Section 5b – MIE, KE, and AO descriptions

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|---|---|---|---|---|
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Section 1 AOP Description

Section 2 KE Descriptions

MIE

KEs

AO

Section 3 – KER Descriptions

Key Event Relationships/Associations

Section 4 – Overall Assessment of the AOP

| Event | Direct Evidence | Indirect Evidence | No or contradictory experimental evidence | |
|---|---|---|---|---|
| MIE | | | | |
| KE1 | | | | |
| KE2 | | | | |
| KE3…… KEn | | | | |

**MIE Page**

*Chemical initiator(s)*

- Description
- Measurement/ detection
- Taxonomic applicability
- *Evidence for chemical initiation*

**AO Page**

- Description
- Measurement/

**KER Pages**

- Title
- Biological plausibility
- Empirical support
- Quantitative understanding
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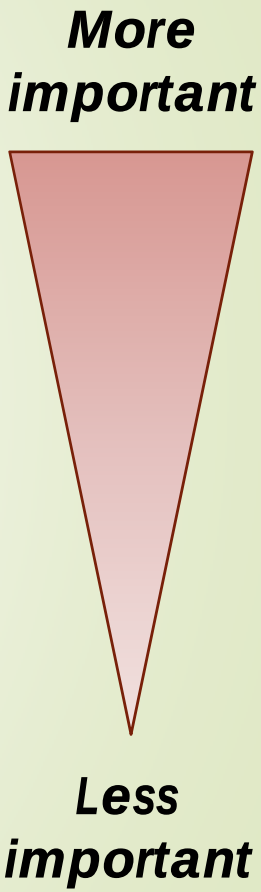
| Species | Chem | Conc. | KE1 | KE2 |
|---|---|---|---|---|
| FHM | A | 1 | | |
| FHM | A | 10 | | |
| FHM | A | 100 | | |
| FHM | B | 0.01 | | |
| FHM | B | 0.1 | | |
| FHM | B | 1 | | |

# 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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# *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

A Section 508–conformant HTML version of this article
is available at https://doi.org/10.1289/EHP3067.

# 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 Makowski[8]*

[1]French Agricultural Research Centre for International Development (CIRAD), Agroecology and sustainable intensification of annual crops (UPR AIDA), Montpellier, France
[2]AIDA, CIRAD, Montpellier University, Montpellier, France
[3]French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Maisons-Alfort, France
[4]McLaughlin Center for Risk Science, University of Ottawa, Ottawa, Canada
[5]WHO 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
[6]Nutritional 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
[7]Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases (B2PHI), INSERM, UVSQ, Pasteur Institute, University of Paris-Saclay, Paris, France
[8]UMR 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

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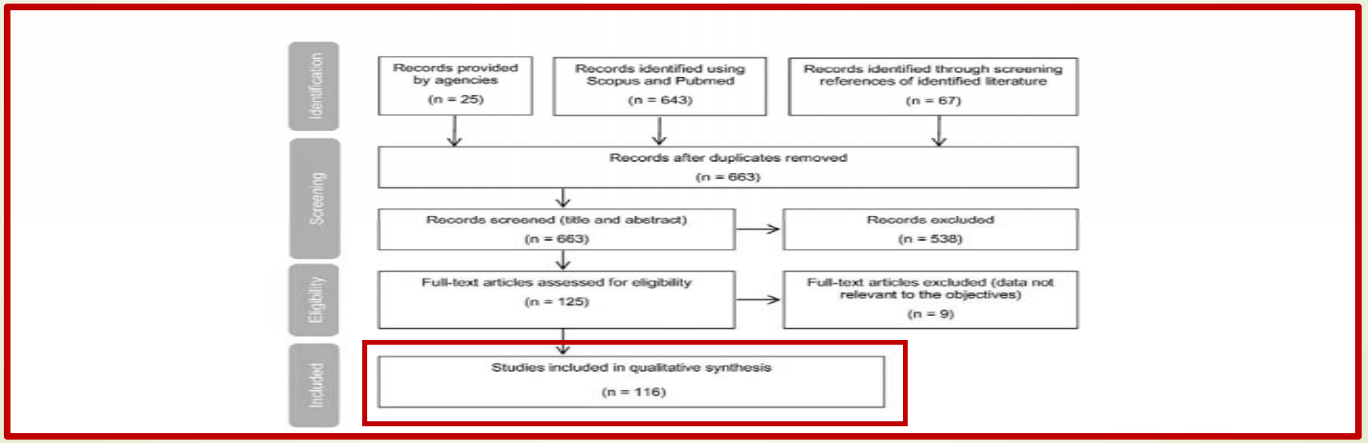
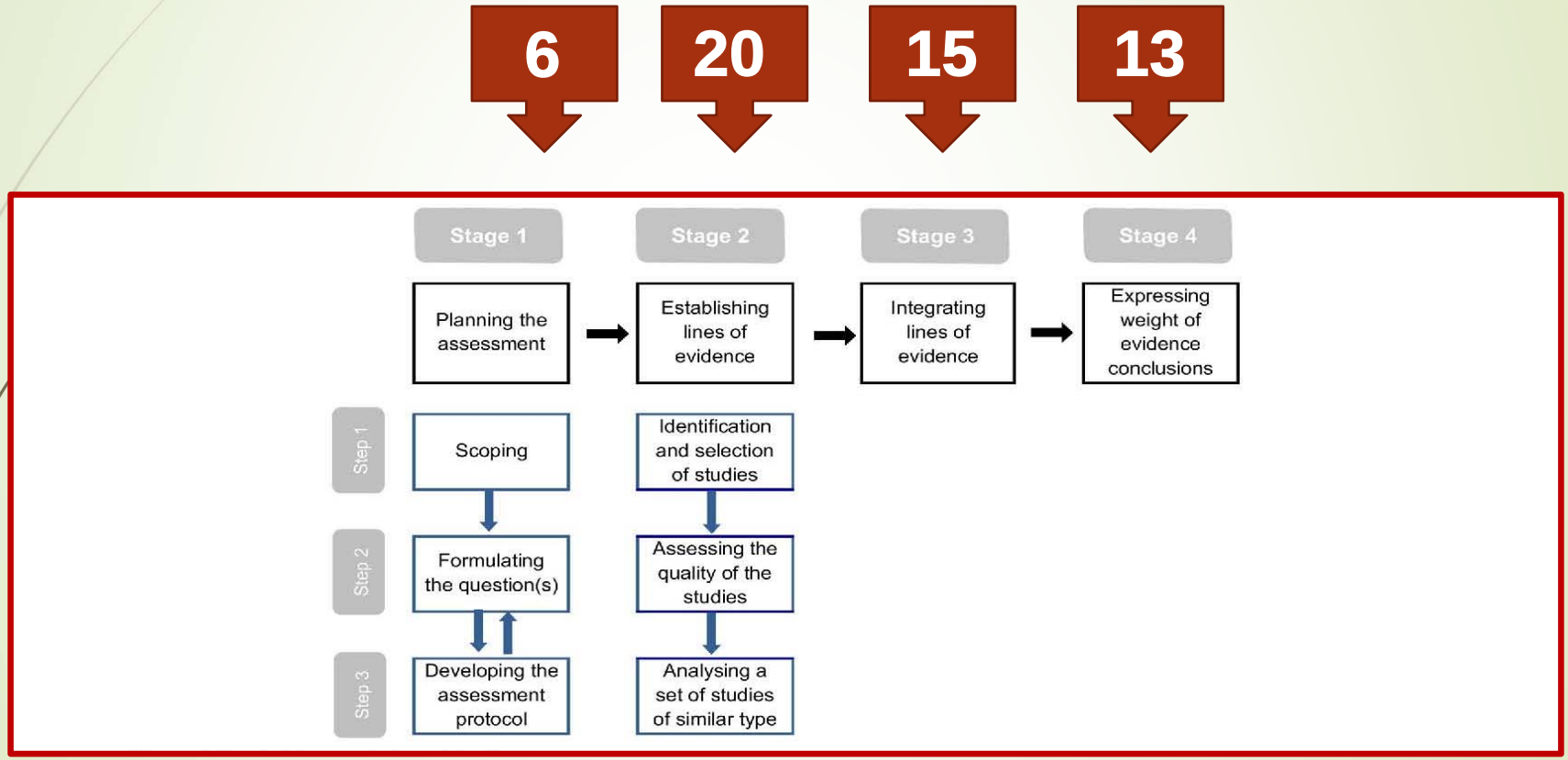
- Review of approaches to weight of evidence (WOE) evaluations of hazard:
  - published literature, and
  - directed requests to 63 international and national agencies




*n=116 relevant studies*

# Results of the Systematic Search



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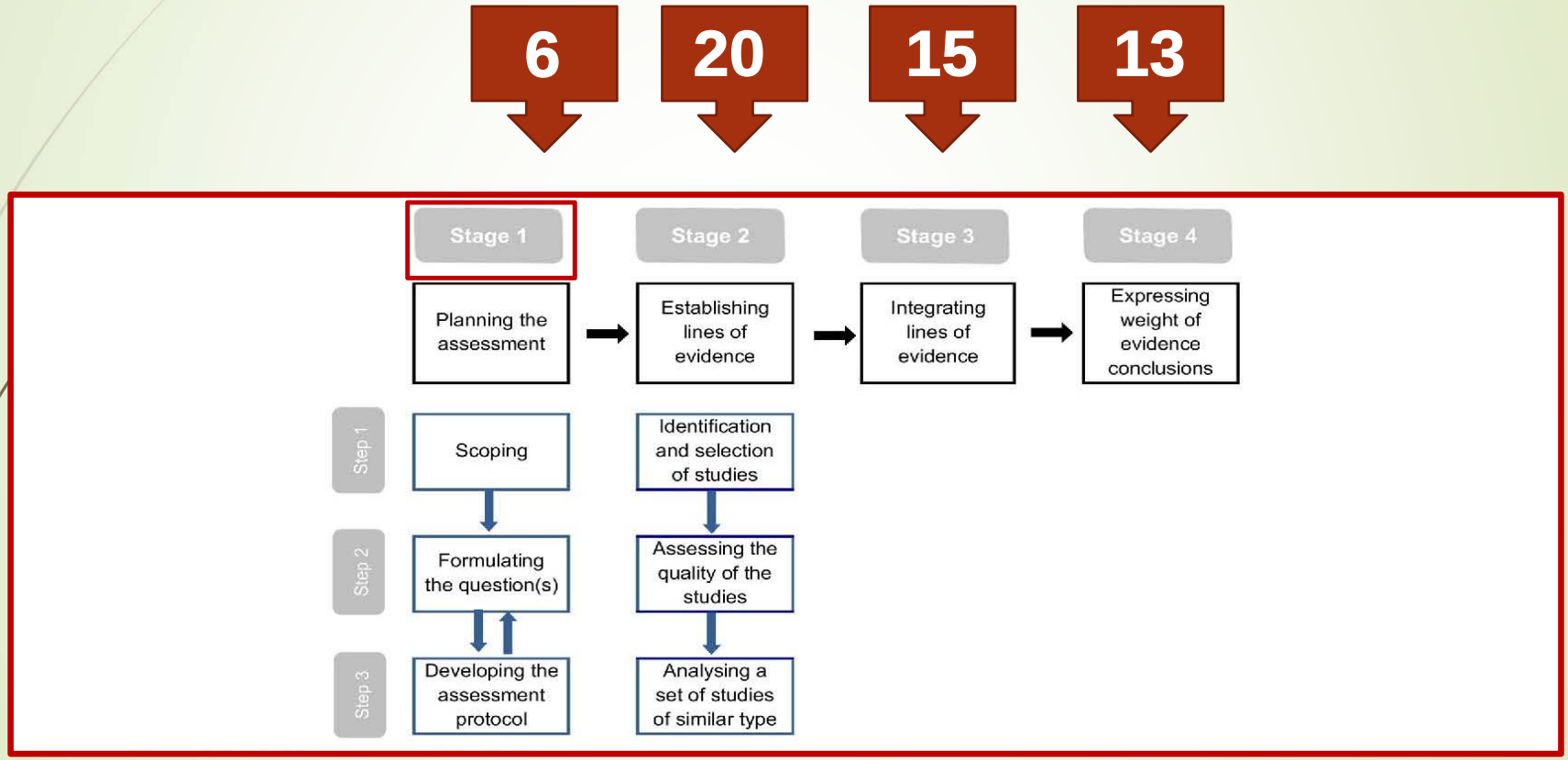

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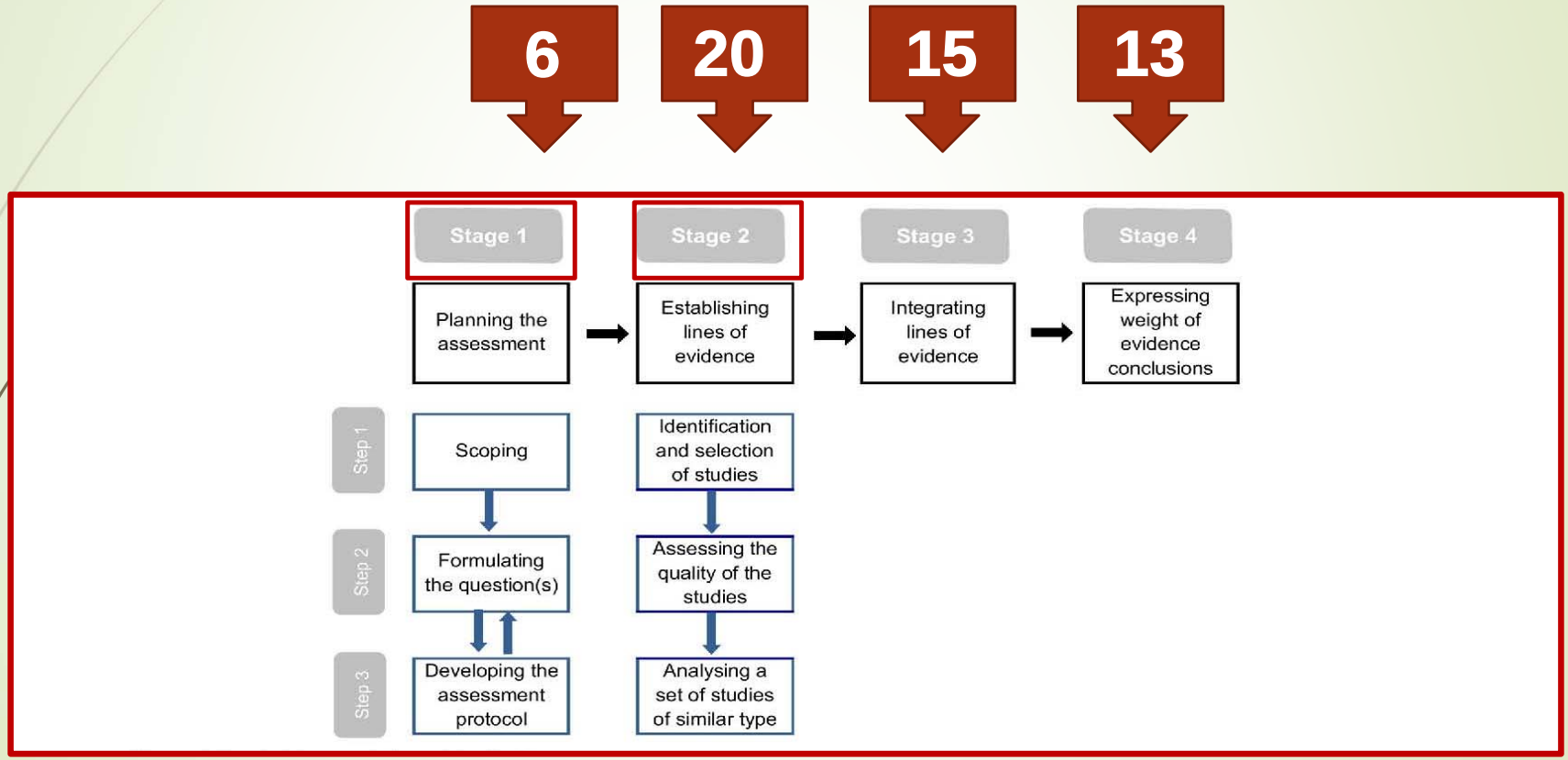

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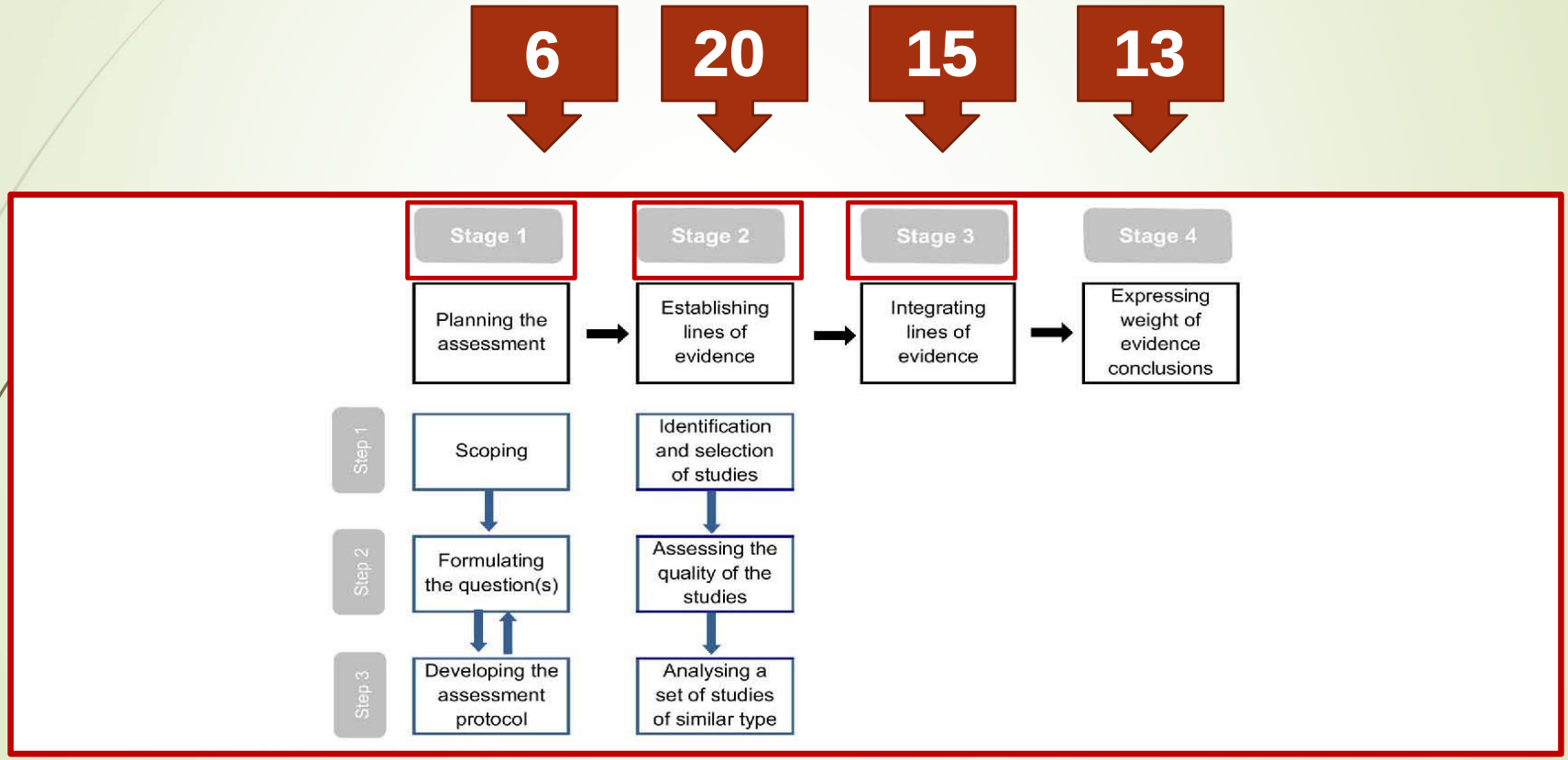

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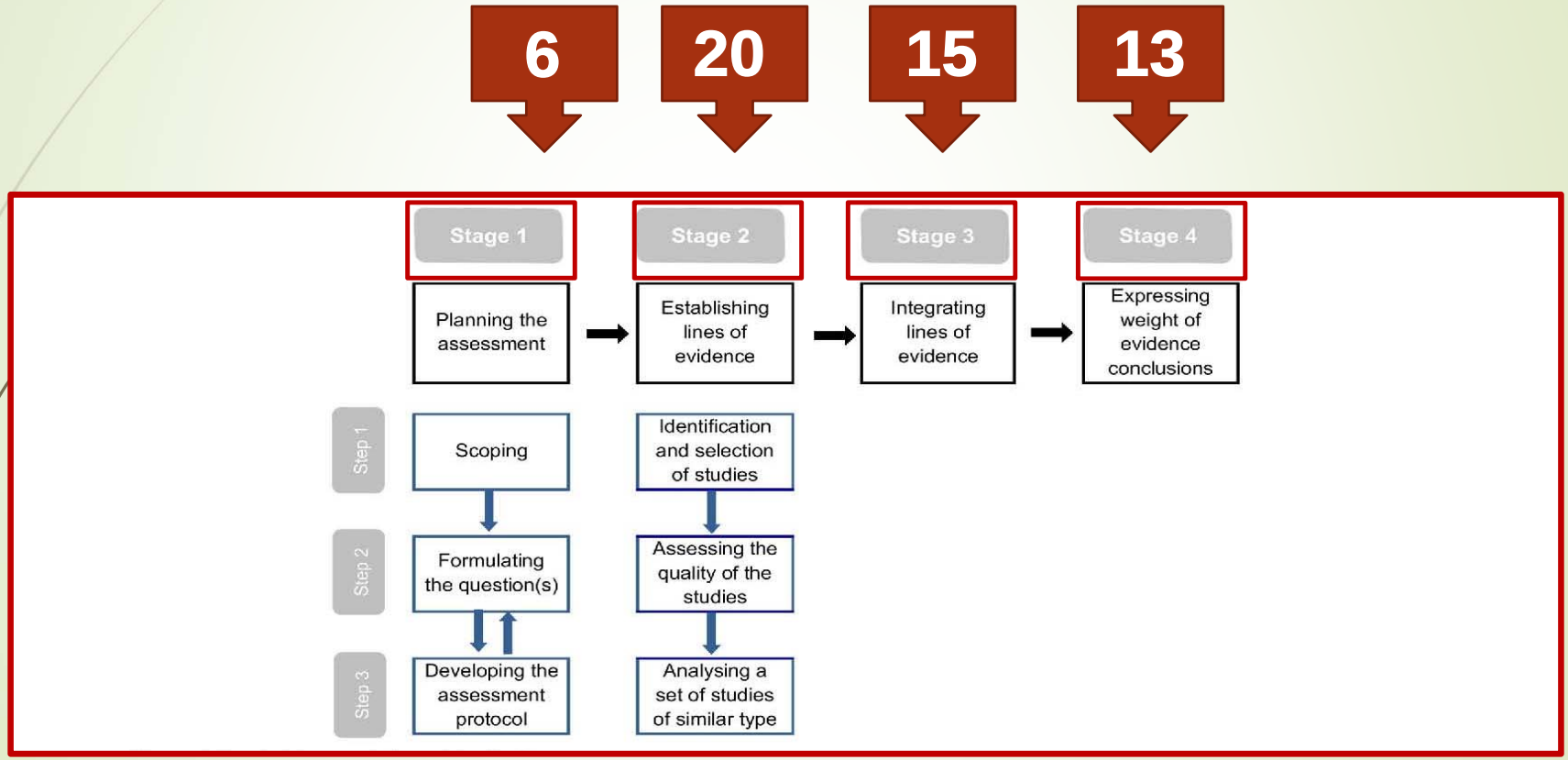

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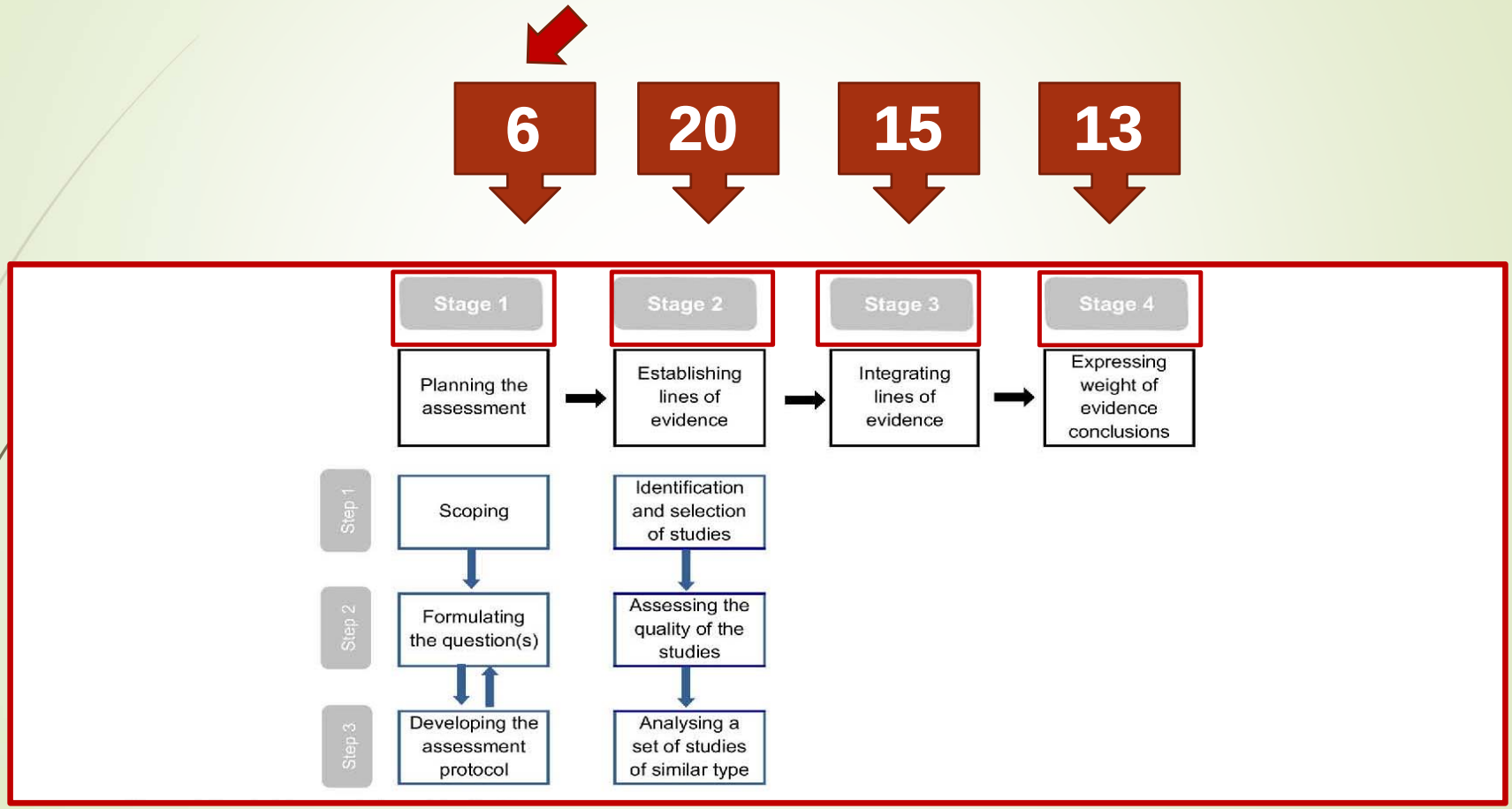

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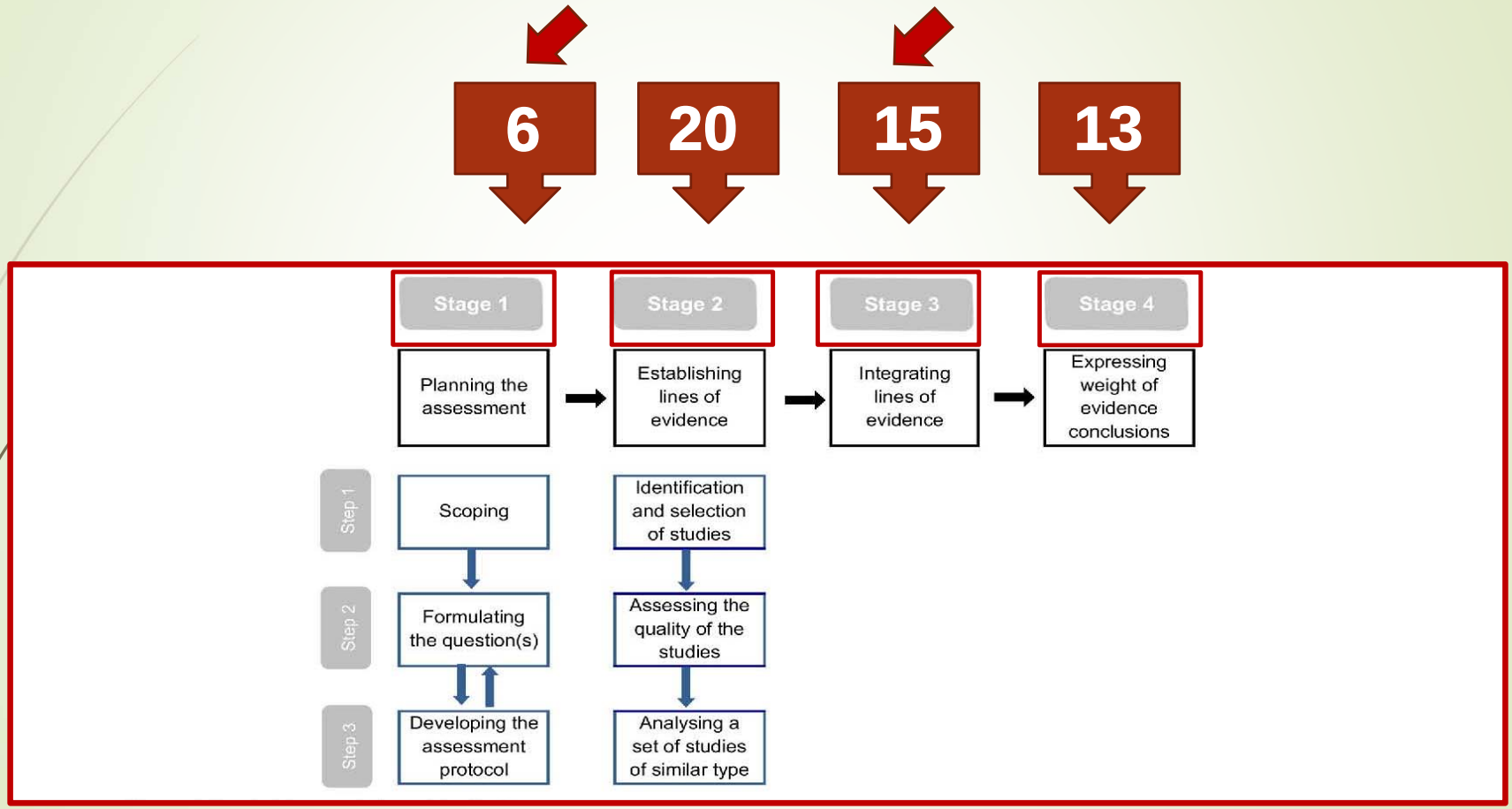


# *Evaluation Strategy for Identified Approaches*

*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*

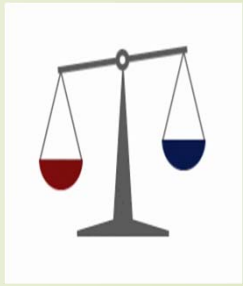
- To facilitate formal assessment planning, including selection of appropriate approaches (WOE) in ANSES assessments, depending on:
  - resourcing
  - Objectives/Problem Formulation/Level of acceptable uncertainty
  - priority
    - potential public and environmental health impacts
    - societal issues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

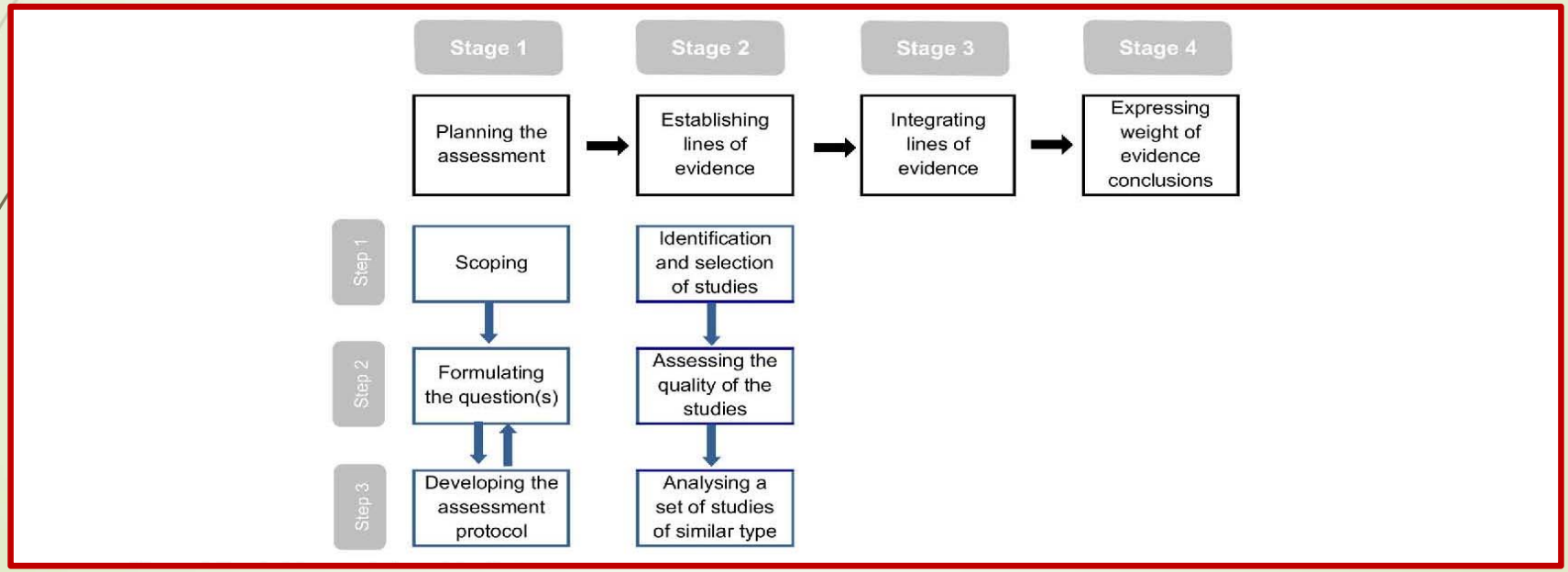
- Drawing on accumulated experience to delineate content of reporting templates for integration
- requires analysis of previous experience to delineate specifically the factors being taken into consideration/weighted in integration
  - Contributing experts
- Promotes greater consistency by increasing 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?

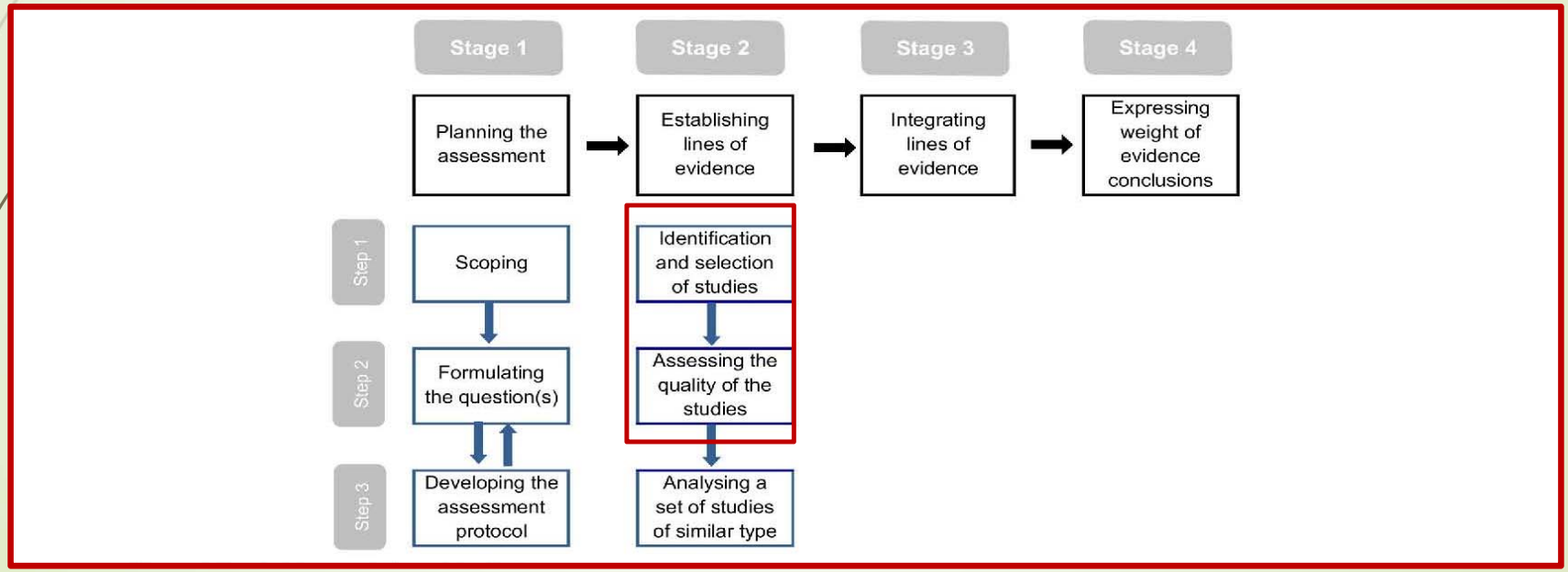
# *Formal Assessment Planning/Templates (Cont'd)*

- Ensuring that the approach for the early stages of evidence assimilation/consideration facilitates data integration



# *Formal Assessment Planning/Templates (Cont'd)*

- Ensuring that the approach for the early stages of evidence assimilation/consideration facilitates data integration



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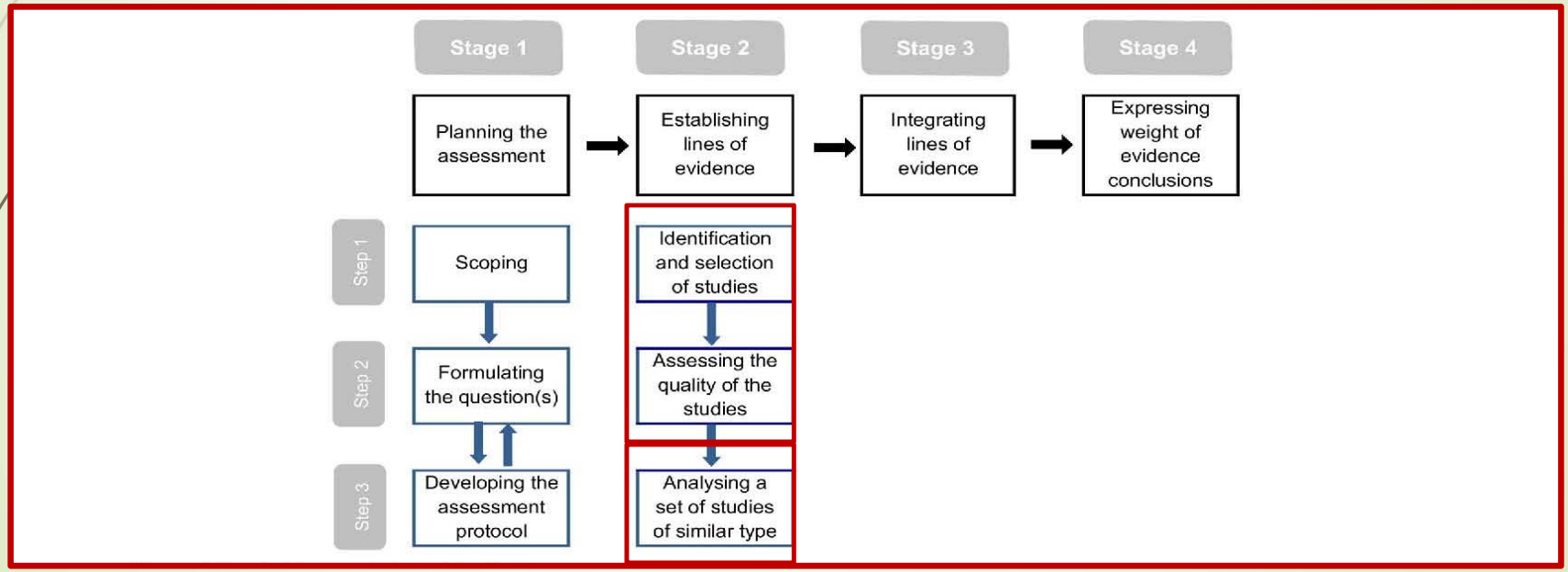
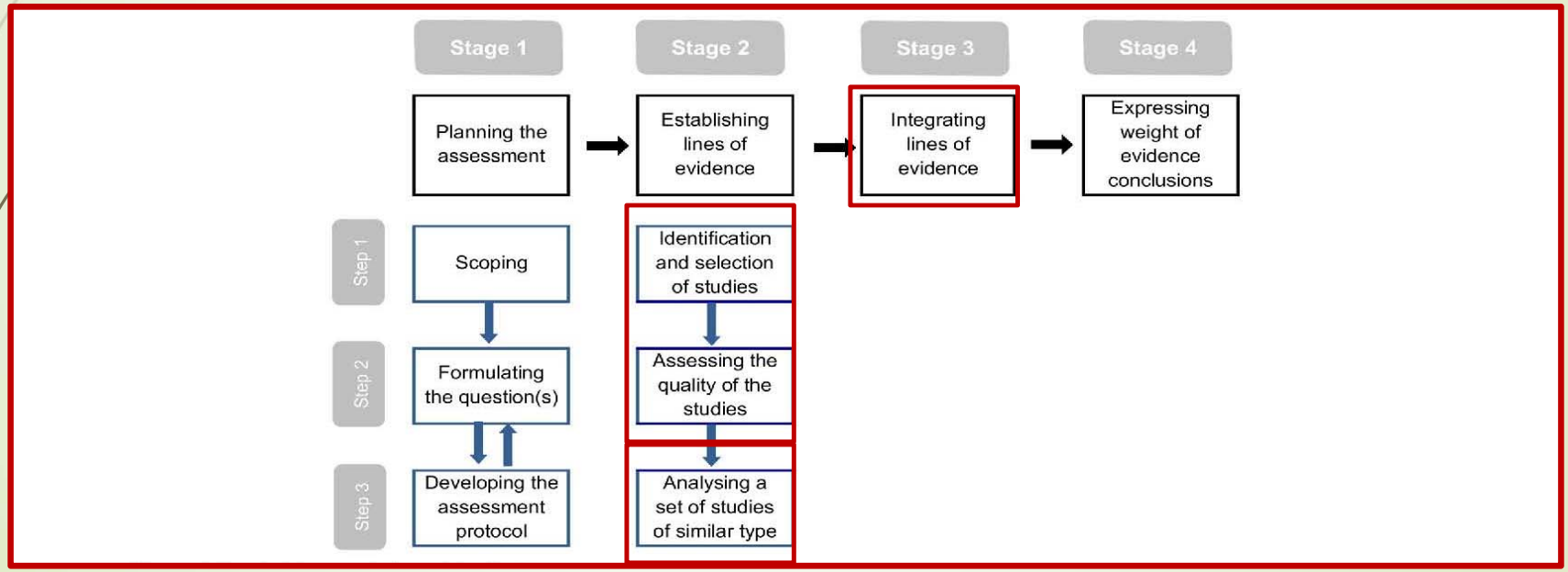
- Ensuring that the approach for the early stages of evidence assimilation/consideration facilitates data integration



# *Formal Assessment Planning/Templates (Cont'd)*

- Ensuring that the approach for the early stages of evidence assimilation/consideration facilitates data integration

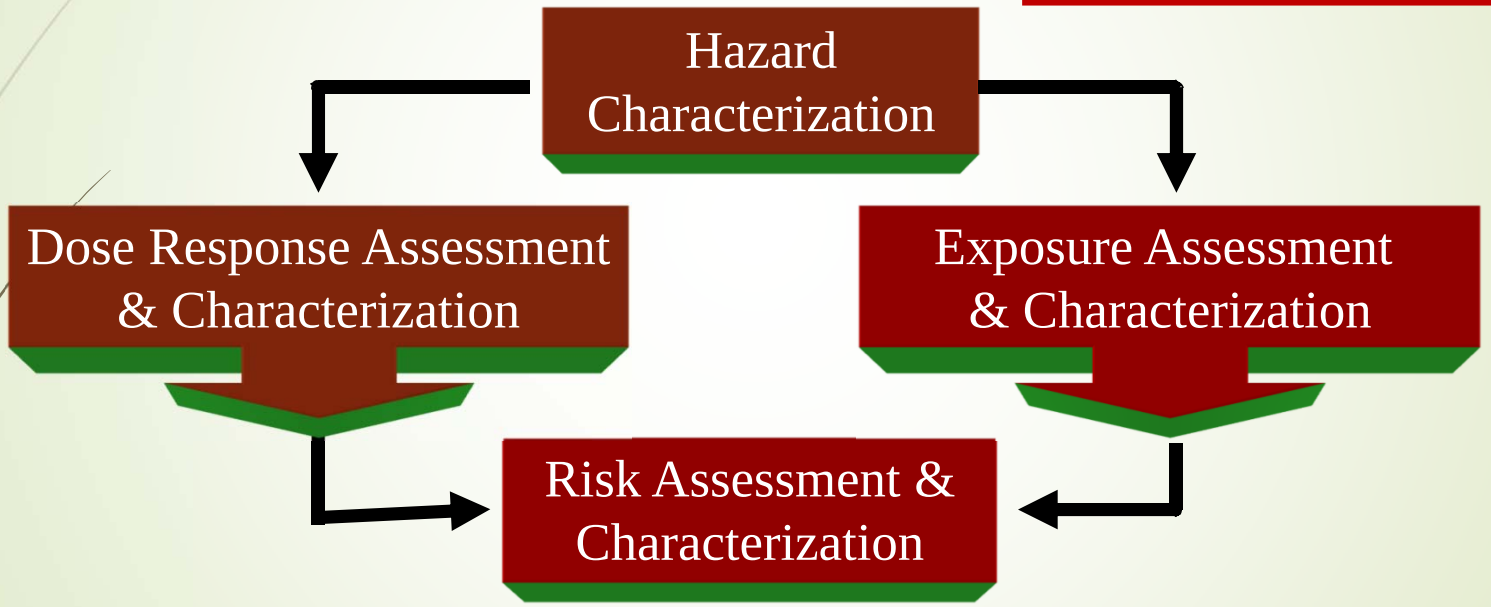


# *Implications: Best Practice in Evidence Integration*

- 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

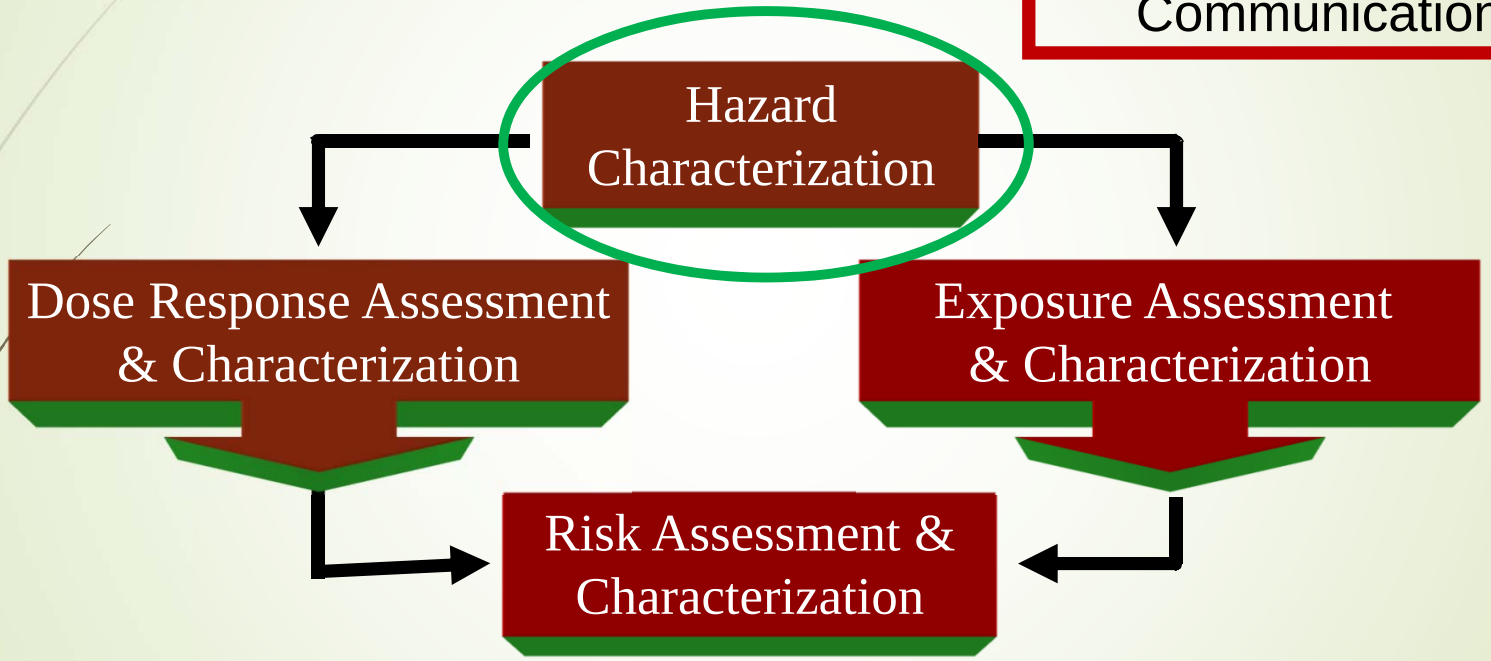
# Early Integration

Problem Formulation
Assessment Planning
Communication



# Early Integration

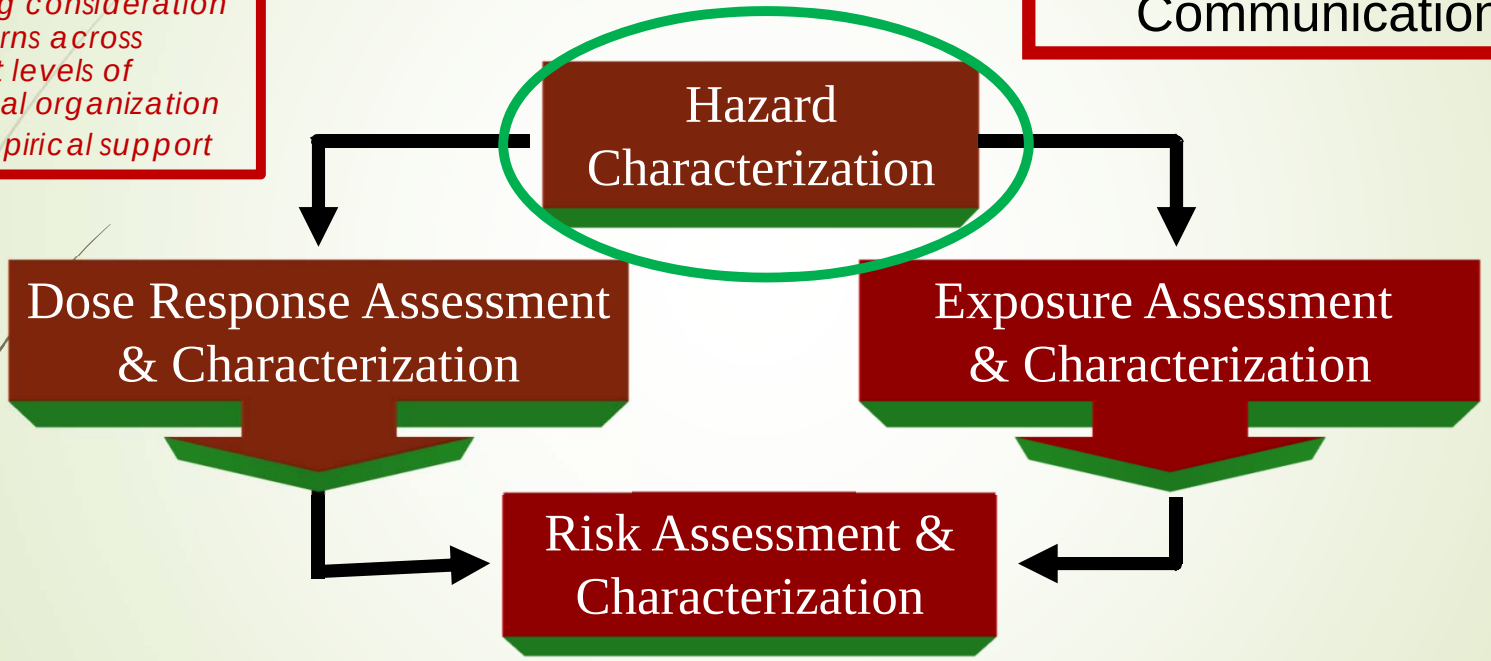
Problem Formulation
Assessment Planning
Communication



# Early Integration

Problem Formulation
Assessment Planning
Communication

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



# Acknowledgements


- Members of the OECD Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST) Handbook and Training Teams
  - https://aopwiki.org/training/wiki/story_content/external_files/OECD%20Users%20Handbook%20-2016.pdf

- 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 (manuscript in English)
  - https://www.anses.fr/fr/content/avis-gt-mer (full report in French)