Advancing Systematic Review for Chemical Risk Assessment, Day 2

Systematic Review Relating to Mechanistic Data: What Is Really Needed, and How Can It Be Efficiently Applied?

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Considerations for the systematic review of mechanistic studies

- Focus on utility of mechanistic data in hazard identification and dose-response
  - ➢ Inform decisions regarding:
    - Biological plausibility of a causal interpretation of epidemiology data (e.g., establishing the occurrence of precursor events in humans)
    - Biological plausibility that animal experimental data is relevant to humans
    - Differential susceptibility and variability
- May begin with existing hypothesized mechanistic events or modes of action
  - But process should be comprehensive enough to include potential mechanistic events or MOAs that are less well-developed
  - Iterative process

Systematic review of mechanistic studies

- The objective is to analyze the numerous mechanistic studies efficiently
  - Identify all pertinent studies through well-documented literature searches
  - Organize the studies to facilitate subsequent analyses
  - Evaluate study methods and quality using uniform criteria
    - Maximize efficiency: reserve detailed evaluations for the studies most relevant to informing mechanism
- Considerations of quality
  - Evaluation for in vitro studies challenging
  - Prioritize well-designed studies that directly measure potential key events

Systematic evaluation of mechanistic studies presents unique challenges

- Relevant mechanistic studies may be both numerous and heterogeneous
- Large # of potential assays for similar endpoints exponentially increases the complexity of quality estimation
  - Makes these evaluations extremely time-intensive
- Because mechanistic databases are large and diverse, a "systematic review" or "weight of evidence" evaluation has always been an important part of MOA analyses. However,
  - These evaluations have lacked consistency and transparency
  - Expert judgment required
  - No systematic process exists for evidence integration across a diverse set of mechanistic studies and endpoints

Future mechanistic challenges

- The importance of a systematic, transparent process for the identification, evaluation, and integration of evidence only increases with assessment complexity, and is compounded by future considerations, such as:
  - Identifying human hazards in the absence of human or animal evidence using in vitro data
    - High throughput screening data (Tox21, ToxCast)
    - Epigenetic data (cumulative risk)
  - Estimating human dose-response relationships
  - Assessing cumulative effects of chronic, low-dose exposures to chemical mixtures
  - Identifying chemical interactions with existing disease states or non-chemical stressors

Approaches for the Systematic Review and Quality Assessment of Mechanistic Information

Three proposed phases:

1. Sorting and organization
   - First by hazard domain, then by mechanistic category
   - Title and abstract only
   - Additional targeted lit searches based on more focused terms may be conducted if necessary

2. Prioritizing
   - Proposed out of necessity for managing large databases
   - Focuses on studies most relevant to answering questions on mechanistic events
   - Title and abstract only

3. Evaluating
   - Limit to studies most relevant to mechanistic events
   - Full study review and data extraction

Organization by Key Characteristics of Carcinogens

- Propose using ten key characteristics of carcinogens (Smith *et al*., EHP, 2015) as an organizing principle
- Categories based on abilities of an agent to:
  1. Act as an electrophile (directly or after metabolic activation)
  2. Be genotoxic
  3. Alter DNA repair or cause genomic instability
  4. Induce epigenetic alterations
  5. Induce oxidative stress
  6. Induce chronic inflammation
  7. Be immunosuppressive
  8. Modulate receptor-mediated effects
  9. Cause immortalization
  10. Alter cell proliferation, cell death, or nutrient supply

Prioritization Step

Prioritization of studies for analysis based on:

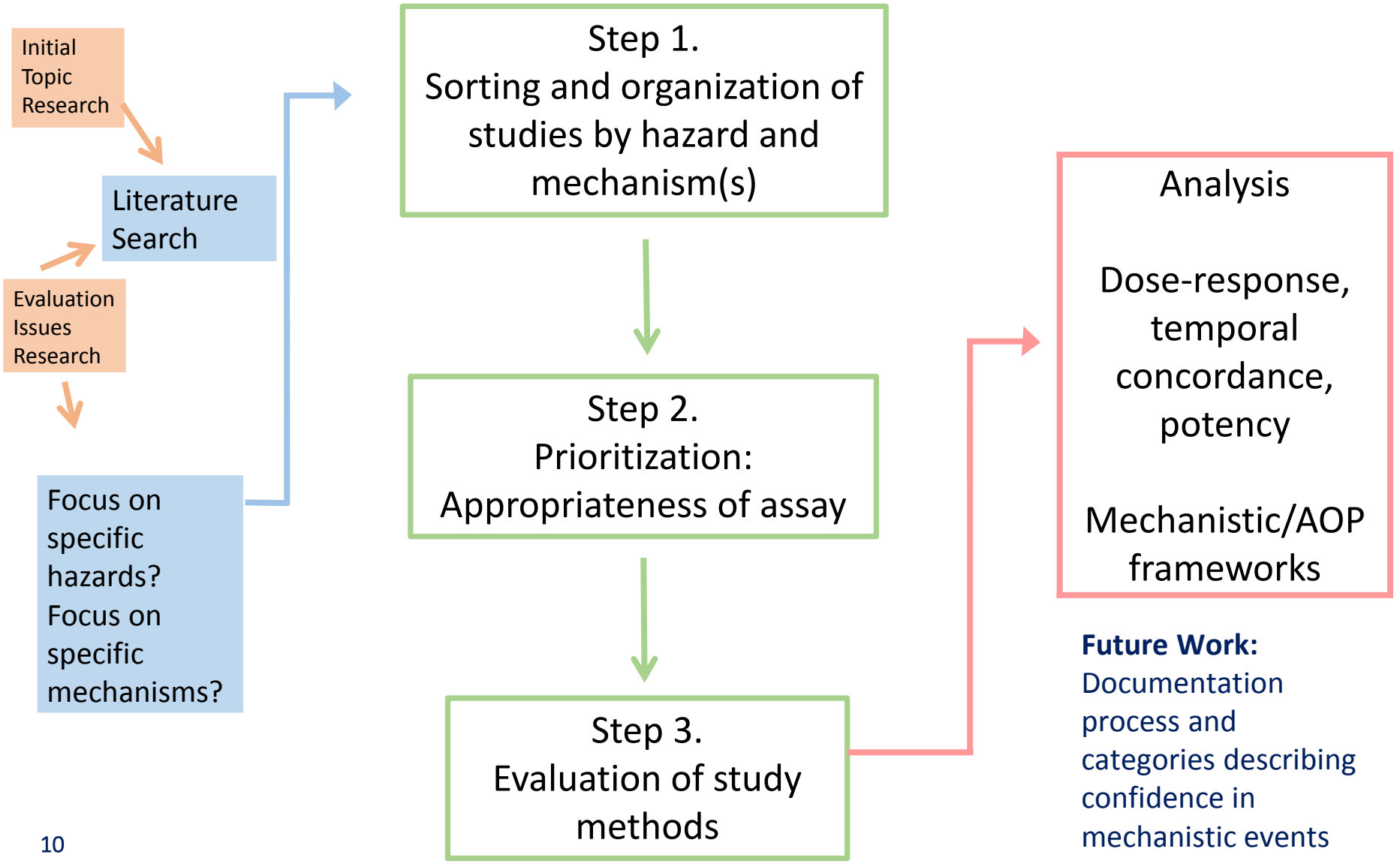
- Relevancy
  - Population: Prioritize phylogenetic relatedness to humans (i.e., human studies > animal bioassays > human ex vivo and in vitro > mammalian in vitro > other species in vitro)
  - Exposure:
    - Optimal dose range (if known)
    - Routes of exposure (in vivo)
    - Point of contact vs. systemic effects and ADME considerations (in vivo)
- Appropriateness of assay to measure selected effect
  - Study-specific considerations (e.g., particular assays that more closely measure and identify key mechanistic events)
    - Direct effects > indirect measures of toxicity
    - Sensitivity vs. specificity
- Reproducibility

Evaluation Step

- Evaluation based on series of focused questions pertaining to methods (design, exposure, outcome, analysis)
  - Optimal number of cells or samples analyzed
  - Appropriate controls used
  - Appropriate tissues and/or cell types analyzed
  - Timing and duration of exposures relative to measurements or observations
  - Considerations of volatility, solubility, and chemical purity
  - Blinding or coding of samples for analysis
  - Randomized selection of cells or tissues during microscopy
  - Appropriate statistical analyses

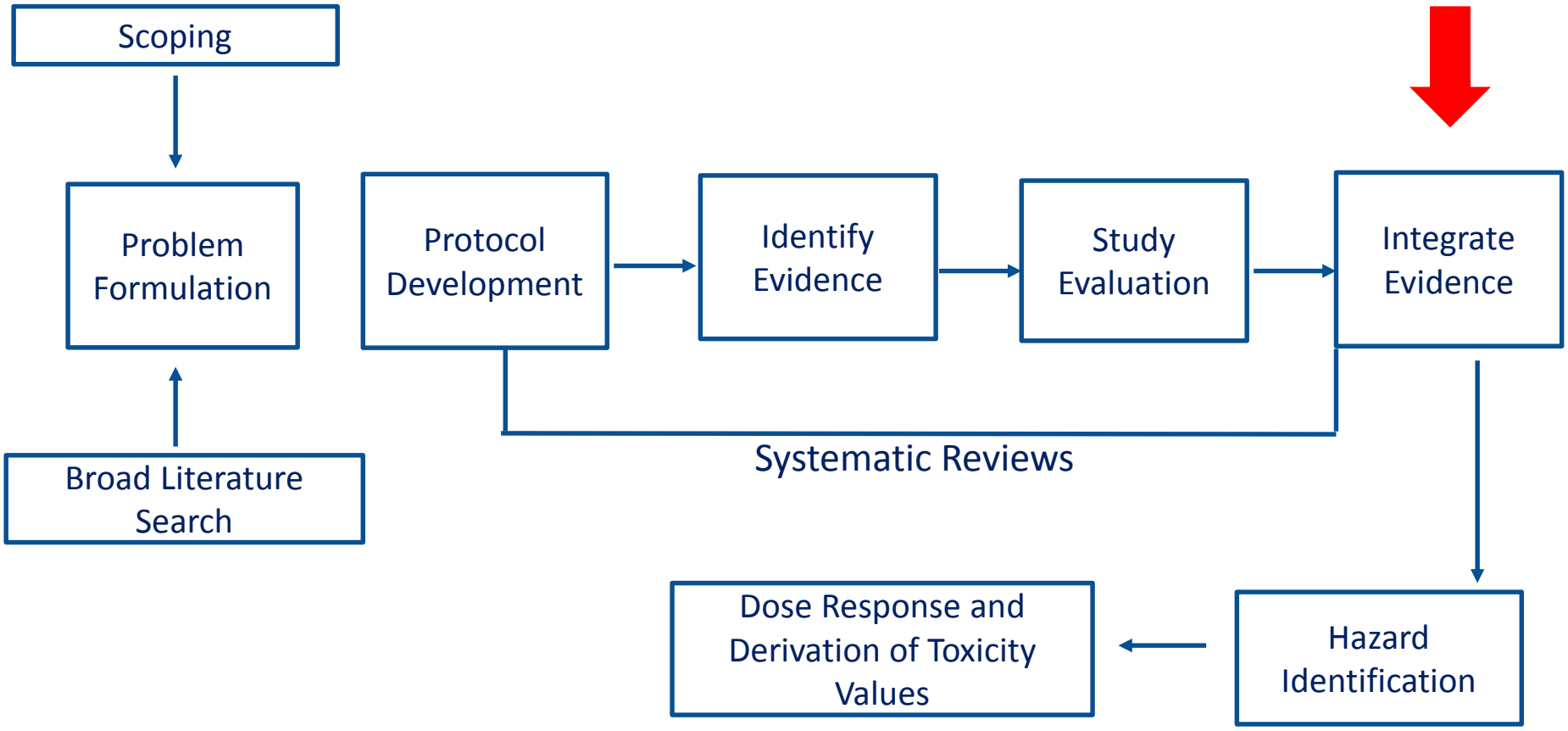
Allows determination of “informativeness” of a study, based on methods

Overview of Mechanistic Data Evaluation and Analysis



Future Work: Documentation process and categories describing confidence in mechanistic events

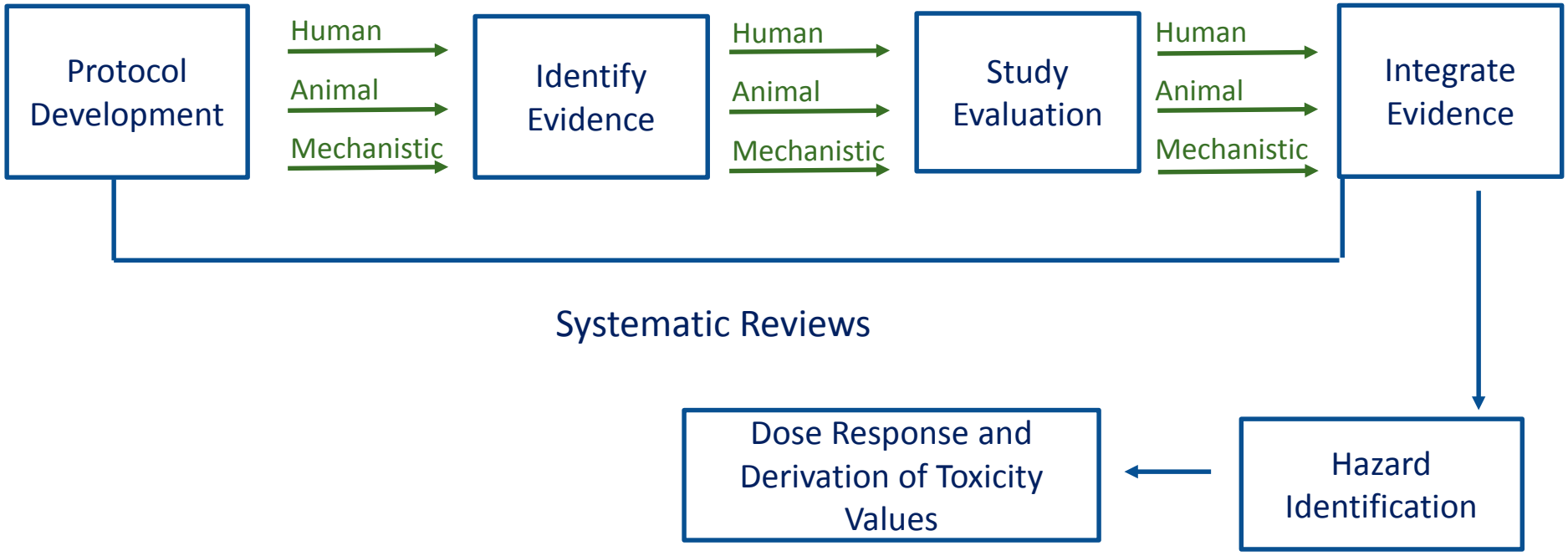
The Next Steps



NRC 2014, Review of EPA's IRIS Process

How Separate Are the Separate Streams?

United States Environmental Protection Agency



NRC 2014, Review of EPA's IRIS Process

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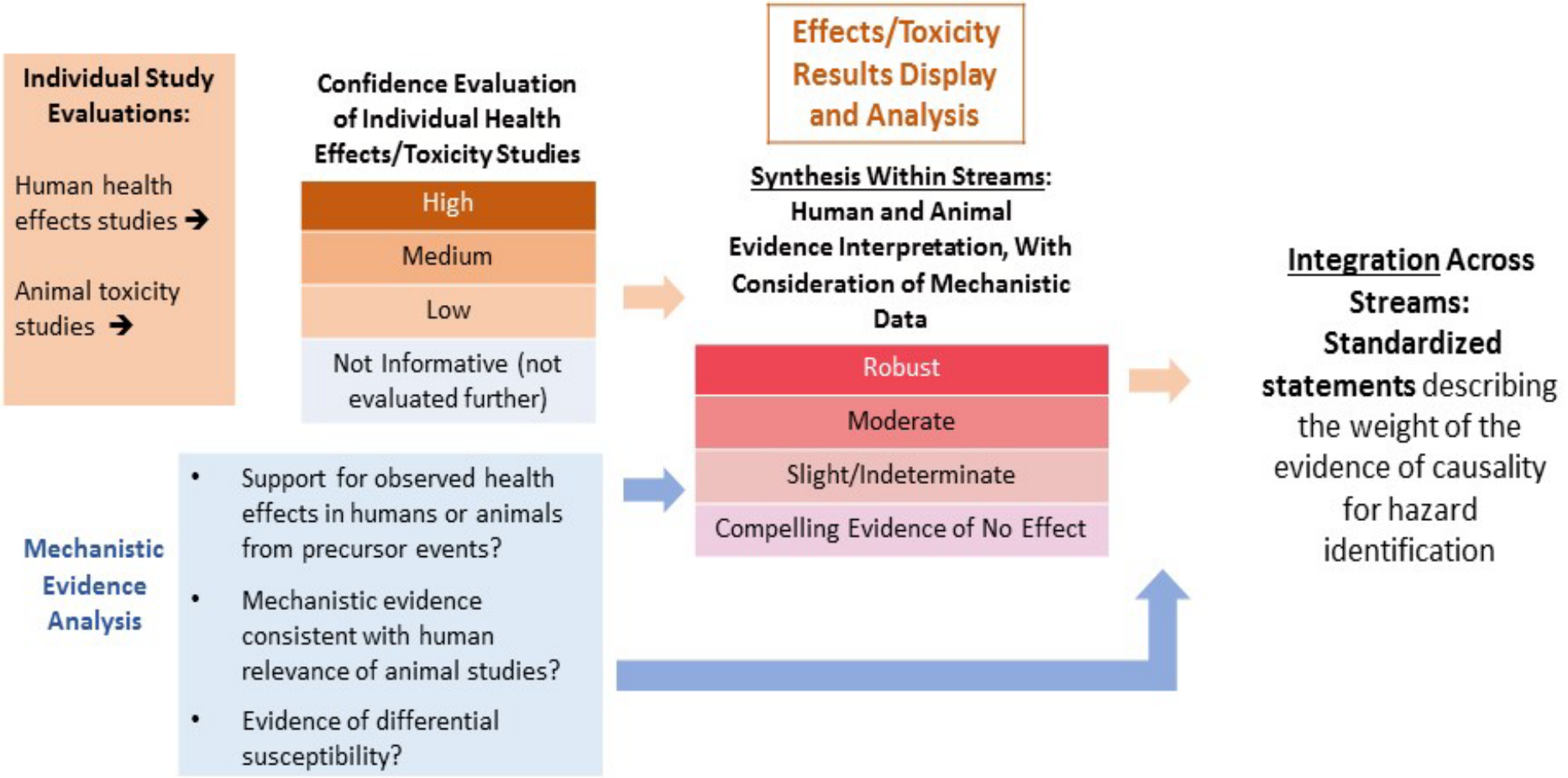
Synthesis Within Streams (Epidemiology and Animal Toxicology, and Including Mechanism Data)



Systematic Review Relating to Mechanistic Data

Part 1: Current Applications

10:15 – 10:35	**John Bucher, NTP** Approaches for considering mechanistic information in systematic reviews
10:35 – 10:55	**Andy Rooney, NTP** (via webinar) Analysis of *in vitro* studies
10:55 – 11:15	**Ed Perkins, U.S. Army Corps of Engineers** Improving systematic review and usability of NexGen/high throughput data in studies of chemical toxicity using AOPs
11:15 – 11:45	Questions and Discussion

Systematic Review Relating to Mechanistic Data

Part 2: Systematic Review Focused on Carcinogenic Mechanisms

12:45 – 1:05	**Martyn Smith, UC Berkeley** Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis
1:05 – 1:25	**Kate Guyton, IARC** (via webinar) Systematic identification of the mechanistic evidence for cancer hazard assessment: Experience of the IARC Monographs programme
1:25 – 1:45	**Ivan Rusyn, Texas A&M University** Epigenetic alterations induced by genotoxic occupational and environmental known human carcinogenic chemicals: A systematic literature review
1:45 – 2:15	Questions and Discussion

Systematic Review Relating to Mechanistic Data

Part 3: Application of systematic review principles for linking noncancer mechanistic data to hazard characterization decisions

2:30 – 2:55	**Katherine von Stackelberg, Harvard Center for Risk Analysis** The adverse outcome pathway as an integrating framework for systematic reviews
2:55 – 3:10	**Xabier Arzuaga, U.S. EPA, NCEA, IRIS Program** Examination of human relevance of anti-androgenic effects observed following exposure to dibutyl phthalate
3:10 – 3:35	**Andrew Kraft, U.S. EPA, NCEA** Noncancer MOA decision points: Examples from the draft formaldehyde inhalation assessment of respiratory tract effects
3:35 – 4:10	**Katya Tsaioun, Johns Hopkins University** Evidence-based methodologies in toxicology: Application to test methods

Systematic Review Relating to Mechanistic Data: Discussion

4:10 – 4:55 Questions and Discussion—to include all speakers from session plus invited discussants:

- **Lyle Burgoon**, U.S. Army Corps of Engineers
- **Deborah Cory-Slechta**, University of Rochester Medical School Center
- **Elaine Faustman**, University of Washington (via webinar)
- **Natalia Garcia-Reyero**, Mississippi State University (via webinar)
- **Daniele Wikoff**, ToxStrategies

4:55 – 5:15 Conclusion

Issues focusing on specific needs of IRIS

- Implementation of systematic review of mechanistic studies should:
  - Be adaptable to databases of varying size and complexity
  - Be iterative: adapt to long time-frame for development/review
  - Identify all relevant mechanisms of toxicity, including those less well studied
  - Facilitate integration with human and animal evidence relating to apical indications of toxicity
- Flexibility: How to be as consistent as possible—e.g., by using frameworks—but still allowing for the expert judgment that is needed and the chemical-specific considerations that are important
- Level of documentation needed: how to show clear and transparent justification for conclusions without generating overly cumbersome assessments
  - Most importantly, how to increase efficiency and scientific accuracy without unnecessarily delaying assessments