Advances in Systematic Review

Presentation for the TMBs Augmented Chemical Assessment Advisory Committee of the Science Advisory Board

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In 2011, the NRC Recommended Expanded Descriptions and Standardization of Methods

- Evidence Identification:
  - Develop standard protocols for systematic literature search and screening
  - Describe search strategies, exclusion and inclusion criteria
  - Develop a template for description of search/screen approach
  - Use a database (i.e., HERO) to document search results

- Evidence Evaluation:
  - Use standardized approaches to evaluate strengths and weaknesses of studies
  - Establish protocols for review of major types of studies
- Evidence Presentation:
  - Standardize presentation of studies in tabular or graphic form
  - Create standardized evidence tables

In response, IRIS adopted principles of systematic review to help ensure standardized approaches across assessments and to ensure major science decisions are rigorously vetted.

Initial Approach to Evidence Identification

- New section in the Toxicological Reviews
- Strategy for literature search/screening processes
- Overview of database search strategy in a table (databases, keywords)
- Visually represented the inclusion and exclusion of studies in a flow diagram
- Integrated citations within HERO

Initial Approach to Evidence Evaluation

- Initiated development of approaches to transparently and uniformly identify and understand strengths and limitations that would affect interpretation of results

- Better documentation and transparent discussion of strengths and weaknesses of studies based on EPA guidance documents (U.S. EPA 2005, 2002, 1998, 1996, 1994, 1991)

Initial Approach to Evidence Presentation

- New document structure with distinct sections for
  - Literature Search/Screening Strategy and Study Selection
  - Hazard Identification
  - Dose-Response sections
- Subsections based on organ/system-specific hazards
- Standardized summary and evidence tables
- Exposure-response arrays

Programmatic Efforts Related to Systematic Review

- Preamble transparently communicates the systematic assessment development processes
- Draft Handbook for IRIS Assessment Development
- A Federal Summit on Evaluating and Synthesizing Evidence: Applying Systematic Review to Questions of the Health Effects of Chemical Exposures (February 2013)
- A public workshop, for Applying Systematic Review to Assessments of Health Effects of Chemical Exposures (August 2013)
- Reorganization of IRIS staff into discipline-specific workgroups

Advances in Implementing Systematic Review in IRIS

- Substantial progress in the application of evidence identification
  - Developed approaches to identifying evidence
  - Created detailed descriptions of search/screening strategies
  - Established documentation in tables and figures
  - Increased integration with HERO for documentation of search/screening process, housing citations, and information
- Application of evidence evaluation and presentation is on-going
  - Involved the public and other federal agencies to better understand and apply systematic review principles
  - Considering similar, on-going efforts (e.g., Navigation Guide; NTP-OHAT) and relevant literature (IOM, 2011; Higgins and Green, 2008, etc)
  - Investigating various approaches to evaluating study quality and establishing protocols for review
  - Development of methods to transparently communicate results continues

Advances in Implementing Systematic Review in IRIS

- Progress in the application of evidence presentation
  - Refined approaches to considering and presenting evidence to:
    - Synthesize within data sets for each target organ/system
    - Integrate across all data sets for each target organ/system and across different target organs/systems
    - Developed tables and figures for standardized presentation of literature search/screening and reviewed studies

Current Approach to Evidence Identification

- Improved strategies for identifying and screening large numbers of references in a transparent and objective manner
- Detailed description of Literature Search/Screening Strategy
  - Emphasizes how studies were selected to be included
  - If applicable, explains the rationale for excluding potentially relevant studies
- Summary of detailed search strategies in a table (databases, dates of search, search terms and fields, and context of search)
- Updated descriptive summary of literature search/screening depicted by PRISMA diagram

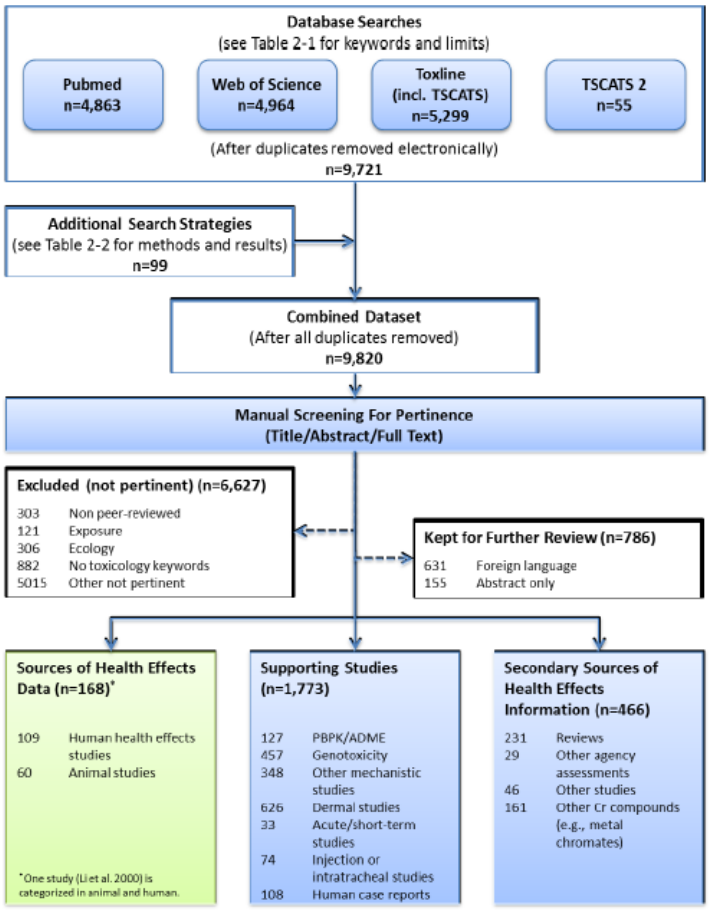


Figure 2-1. Literature search approach for hexavalent chromium.

Current Approach to Evidence Evaluation

The IRIS Program is considering multiple approaches, one involves:

- Start with all pertinent, publicly available studies
- Exclude studies based on problem formulation
- Identify studies with fundamental flaws or limitations in study design, conduct, or reporting that would be less informative
- Documentation may include considerations organized by experimental feature:
  - Epidemiologic: study population, exposure, outcomes, confounding, analysis
  - Experimental animal: test animal, experimental setup, exposure, endpoint assessment, outcomes, and reporting
- Focus on studies with most robust methods
- Summary of evaluation included in the section on methods for identifying and selecting studies
- Information related to evaluation reported in evidence tables and will be documented in synthesis of evidence

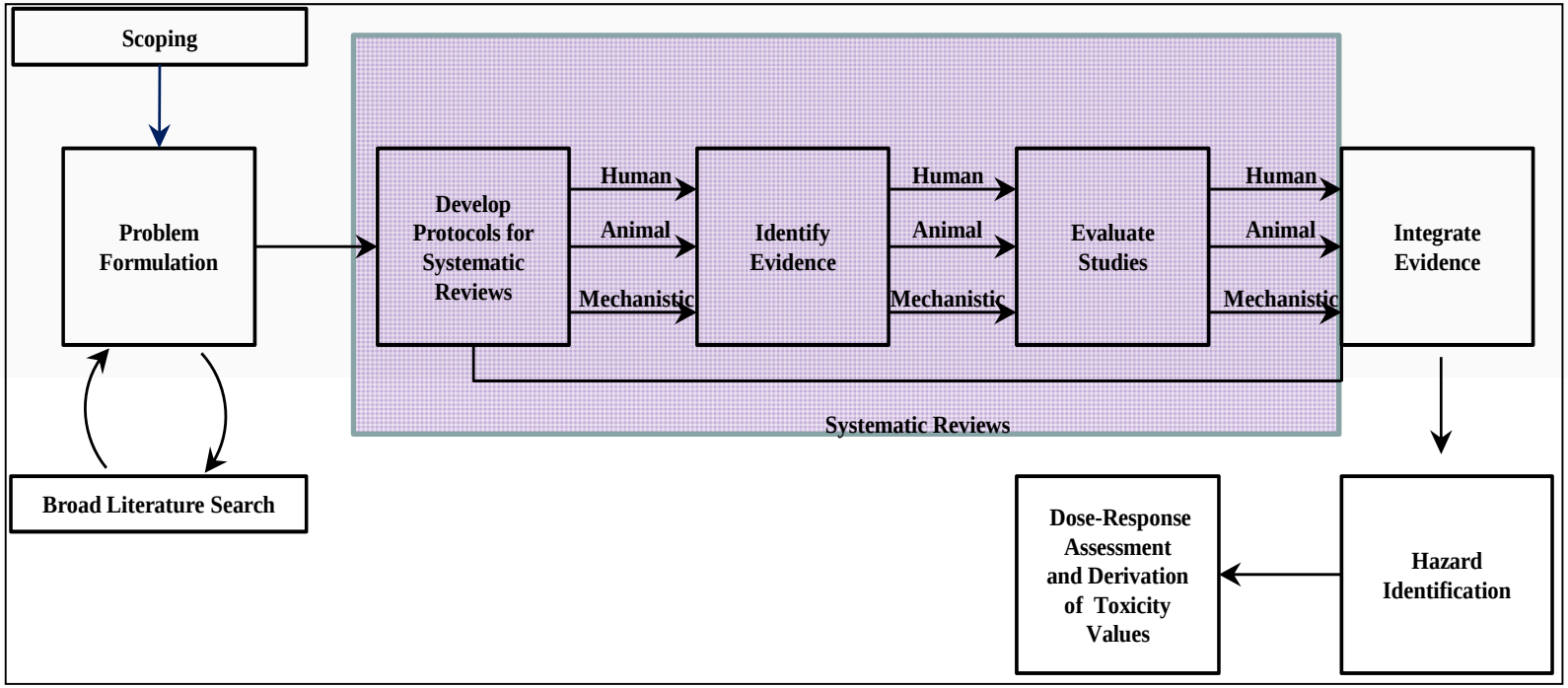
The IRIS Program intends to evaluate how well approaches facilitate subsequent assessment development, promotes constructive public discussion, and makes efficient use of Program resources.

Systematic Review in IRIS: Some Lessons Learned So Far

- Incorporating steps of systematic review are valuable
  - Emphasis on standardization and transparency leads to improvement
- Gaining experience in conducting and documenting systematic searches for varied databases
- Systematic evaluation methods are likely to be time intensive
  - Involve multiple reviewers
  - Applying the approaches to compare and contrast various methods (i.e., efficiency, validity) is essential, and should not be overlooked by a desire to get an approach in place
- Tools for screening, documenting, and extracting are needed to optimize the efficiency
- No single approach will fit all situations; need a flexible and iterative approach
- Continued evaluation of methods as well as communication with experts in systematic review processes will facilitate successful implementation

Future Directions in Evidence Identification, Evaluation, and Presentation

NRC 2014 Systematic Review Recommendations



NRC 2014 Recommendations

Overall, EPA has substantially improved its approach to evidence identification and is well on the way to adopting a more rigorous approach. The Preamble successfully addresses many of the concerns raised by the NRC formaldehyde report. EPA has progressed in assessing the quality of observation studies in humans and animal toxicology studies.

Further recommendations include:

- Formulate the specific question that will be addressed (problem formulation)
- Develop literature search strategy protocols
- Engage information specialists trained in systematic-review methods
- Explicitly identify factors that can lead to bias
- Develop standards for evaluating studies
- Select a method that is transparent, reproducible, and scientifically defensible
- Describe approaches and report results

Summary

- IRIS is implementing systematic review methods to improve scientific integrity and transparency
- Methods will continue to evolve
- Approaches will be strengthened by experience and feedback
- Full implementation is expected to be an iterative process
  - Progress will be made in successive assessments
  - Methods will be improved through testing and review
- NRC, following its review of IRIS, noted that if the Program continues on its current trajectories, addresses recommendations, and maintains implementation objectives, it will become a much more effective and efficient program
- IRIS is following advice from the NRC and SAB, and getting feedback from stakeholders to ensure transparency and use of the best available science in IRIS assessments