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# The National Research Council's IRIS Report

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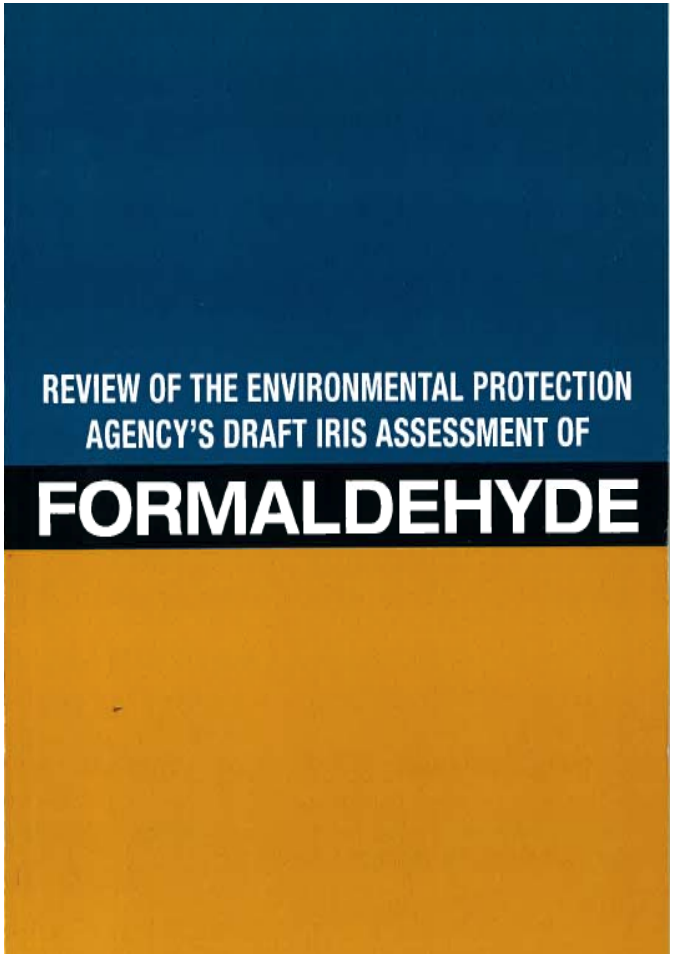
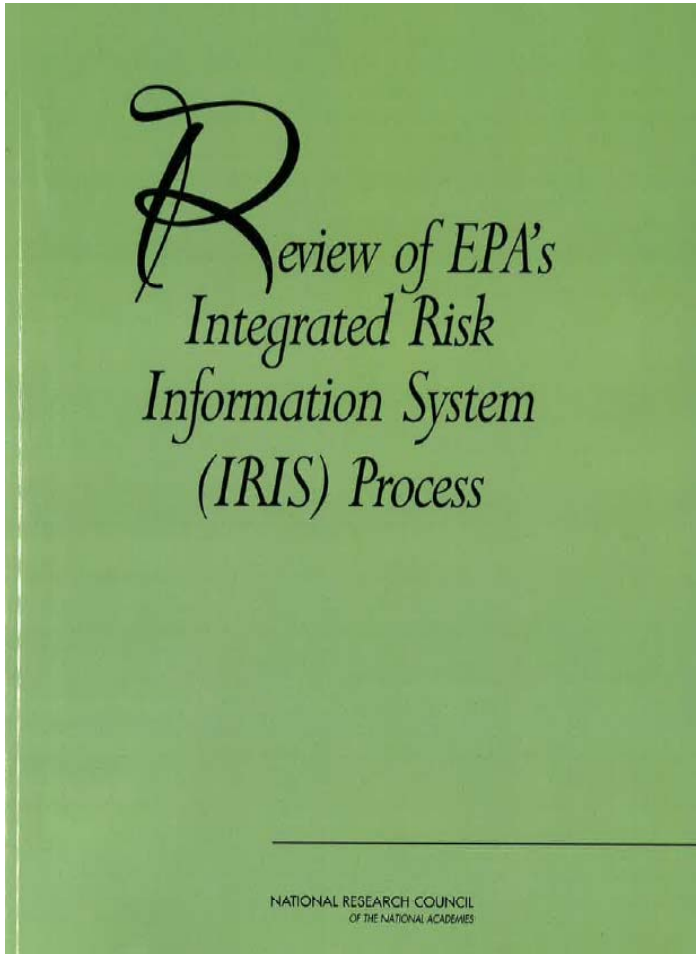
**Society of Toxicology, National Capital Area Chapter**

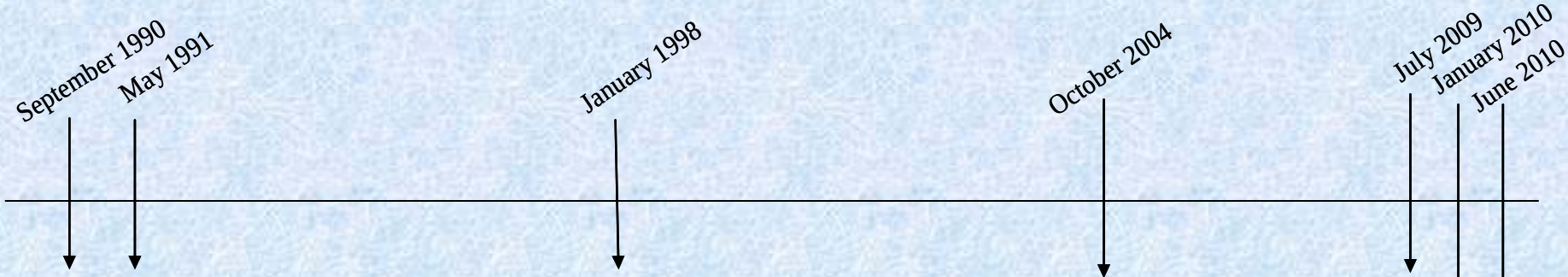
# Formaldehyde and IRIS Reports




**For PDF version or to order: http://www.nap.edu**

# History of EPA Formaldehyde Assessment




## Draft Assessment

- Four volumes with 8 appendices
- 1000 pages in length

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# Beyond Formaldehyde: Revising the IRIS Process

- The committee is concerned about the persistence of problems encountered with IRIS assessments over the years.
- The committee urges EPA to address the fundamental problems and provides some guidance, most of which focuses on current methods for conducting systematic reviews.
- The following few slides highlight some critical considerations for the development of a scientifically sound IRIS assessment.

BEST

Board on Environmental Studies and Toxicology

# Review of EPA's Integrated Risk Information System (IRIS) Process

## Committee to Review the IRIS Process

## Board on Environmental Studies and Toxicology

## Division on Earth and Life Studies

## National Research Council

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# Integrated Risk Information System

- EPA program responsible for developing toxicological assessments of environmental contaminants.
- IRIS assessments contain hazard identifications and dose-response assessments.


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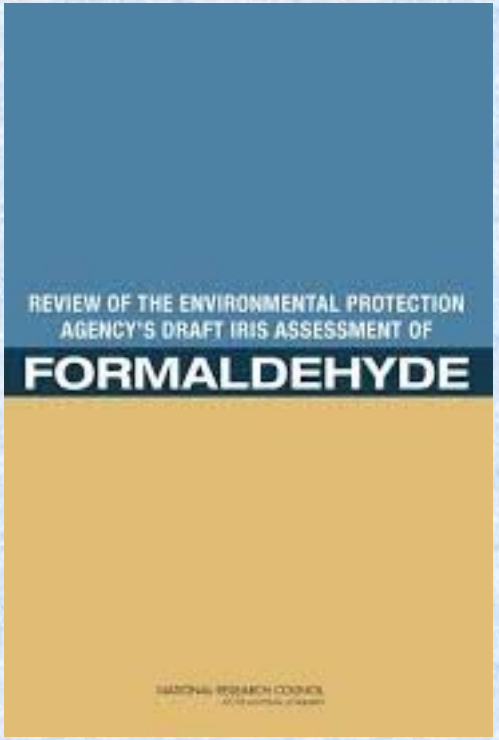
# Study Genesis

- Formaldehyde committee, like other NRC committees, identified deficiencies in the specific assessment, but also more broadly in EPA's general approaches and specific methods.

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# Congressional Response to Formaldehyde Report

- Congress held several hearings to examine the IRIS program.

- Congress directed EPA to implement NRC recommendations in Chapter 7 of the formaldehyde report into the IRIS process and asked NRC to assess the changes to IRIS program.

# Statement of Task

- Review the IRIS process and the changes being implemented or planned by EPA and recommend modifications or additional changes as appropriate to improve the scientific and technical performance of the IRIS program.

- Review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments.

# Committee

**JONATHAN M. SAMET** (*Chair*), University of Southern California
**SCOTT BARTELL**, University of California, Irvine
**LISA BERO**, University of California, San Francisco
**ANN BOSTROM**, University of Washington
**KAY DICKERSIN,** Johns Hopkins School of Public Health, MD
**DAVID C. DORMAN,** North Carolina State University
**DAVID L. EATON,** University of Washington
**JOE G. GARCIA**, University of Arizona
**MIGUEL HERNÁN**, Harvard School of Public Health, MA
**JAMES S. HOUSE**, University of Michigan
**MARGARET M. MACDONELL**, Argonne National Laboratory, IL
**RICHARD P. SCHEINES**, Carnegie Mellon University, PA
**LEONARD M. SIEGEL**, Center for Public Environmental Oversight, CA
**ROBERT B. WALLACE**, University of Iowa College of Public Health
**YILIANG ZHU**, University of South Florida

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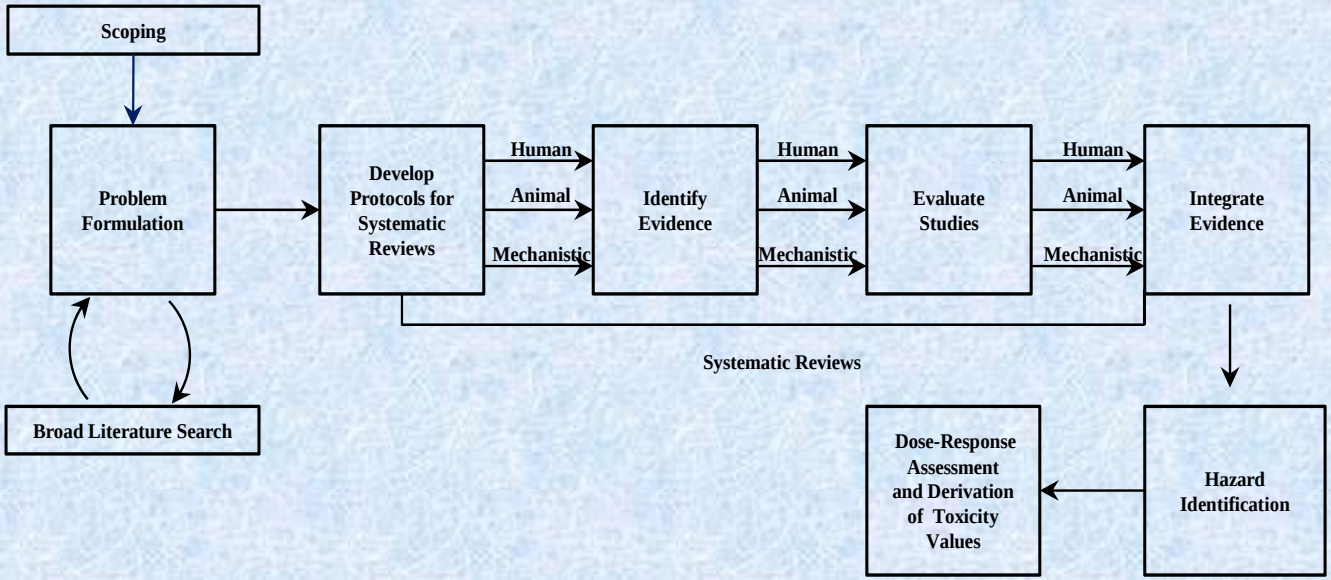
# The IRIS Process: A Framework

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# Systematic Review

- EPA is incorporating systematic-review principles as it implements changes in the IRIS process.

  - *Systematic review is "a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies."*

- The committee agrees with EPA that the systematic-review standards provide an approach that would substantially strengthen the IRIS process.

# EPA Response to General Recommendations from NRC Formaldehyde Report

***EPA has implemented new document structure*.**

- IRIS committee finds new document structure improves organization and streamlines assessments. Use of evidence tables and graphic displays reduces text and enhances clarity and transparency.

***EPA has added standard a preamble to all assessments.***

- IRIS committee finds the preamble to be a useful description of general principles. However, an overview is still needed that indicates how general principles are applied in a specific assessment.

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# EPA Response to General Recommendations from NRC Formaldehyde Report (cont.)

***EPA has drafted a handbook that provides a more detailed description of the IRIS process.***

- IRIS committee finds that the handbook is critical for providing consistency among the assessment teams and contributors, and the final version should be peer-reviewed to ensure that the document is on target and provides the needed guidance.

***EPA has formed chemical assessment support teams (CASTs) to oversee the assessment-development process.***

- IRIS committee is encouraged by efforts to strengthen overall expertise. However, experts from outside EPA and the government should be engaged when needed to fill gaps in expertise in specific areas and to conduct peer review of draft and final assessments.

## EPA Response to General Recommendations from NRC Formaldehyde Report (cont.)

***EPA has implemented several initiatives to increase stakeholder input in the IRIS process.***

- IRIS committee applauds EPA initiatives to involve stakeholders, but cautions that not all stakeholders have the same scientific and financial resources to provide timely comments and recommends that EPA consider ways to provide technical assistance to under-resourced stakeholders.

# Problem Formulation and Protocol Development

- Critical elements of conducting a systematic review include formulating the specific question that will be addressed (problem formulation) and developing the protocol that specifies the methods that will be used to address the question (protocol development).

- IRIS committee suggested a three-step process for problem formulation:
  - Perform broad literature search.
  - Construct table to guide formulation of specific questions.
  - Examine table to determine which outcomes warrant systematic review and how to define systematic-review questions.

# Problem Formulation and Protocol Development (cont.)

- After the systematic-review questions are specified, a protocol for each review should be developed.
- A protocol makes the methods and the process of the review transparent, can provide the opportunity for peer review of the methods, and stands as a record of the review.
- Any changes made after the protocol is in place should be transparent, and the rationale for each should be stated.
- The protocol should be included in the IRIS assessment—for example, as an appendix.

# Evidence Identification

Overall, the IRIS committee finds that EPA has substantially improved its approach to evidence identification. EPA is well on the way to adopting a more rigorous approach to evidence identification that, when fully implemented, should meet standards for systematic review.

# Evidence Identification (cont.)

***The IRIS committee emphasizes the following points:***

- Searching for and identifying evidence are important steps in a systematic review. Using a standardized search strategy and reporting format is essential for evidence identification.
- EPA should use an information specialist trained in systematic-review methods who reviews the proposed evidence-identification section of the protocol.
- EPA should use at least two reviewers who work independently to screen and select studies, pending an evaluation of validity and reliability to determine whether multiple reviewers are needed.

# Evidence Evaluation

- Risk of bias is related to the internal validity of a study and reflects study-design characteristics that can introduce a systematic error that might affect the magnitude and even the direction of the apparent effect.
- EPA correctly identifies important study attributes that can be used to judge study quality but does not describe how it will assess risk of bias in the identified studies.

# Evidence Evaluation (cont.)

- An assessment of risk of bias is a key element in systematic-review standards; potential biases must be assessed to determine how confidently conclusions can be drawn from the data.
- Thus, a risk-of-bias assessment should be conducted on studies that are used by EPA as primary data sources for the hazard identification and dose-response assessment.
- The assessment approach and the results should be fully described and reported in the IRIS assessment.

# Evidence Integration

- Several qualitative and quantitative options are available for overall evidence integration and are described in committee's report.
- EPA currently integrates evidence by using guided expert judgment but appears to be moving toward a structured approach.

# Evidence Integration (cont.)

- The committee does not recommend a particular approach but suggests that EPA consider which approach best fits its plans for the IRIS program.
- If it maintains its current guided-expert-judgment process, it needs to make its application more transparent.
- If it moves to a structured-evidence-integration process, it should pursue a customized GRADE-like approach along the lines that the National Toxicology Program has taken.
- Adopting a structured process would have the benefit of transparency.

# Evidence Integration (cont.)

- Quantitative approaches to integrating evidence will be increasingly needed and useful to EPA, and the agency should seriously consider expanding its ability to perform quantitative modeling for evidence integration.
- Regardless of the approach, EPA should develop templates for structured narrative justifications of the evidence-integration process and the conclusion reached.

# Calculation of Toxicity Values

- The committee is encouraged by the improvements that EPA has made in the IRIS process for deriving toxicity values, particularly the shift away from choosing one study as the "best" study for deriving a toxicity value and toward deriving and graphically presenting multiple candidate toxicity values.

- EPA should develop formal methods for combining the results of multiple studies and selecting the final IRIS values with an emphasis on achieving a transparent and replicable process.

# Calculation of Toxicity Values (cont.)

- EPA could also improve documentation of dose-response information by clearly presenting two dose-response values: a central estimate and a lower-bound estimate for a point of departure from which a final toxicity value is derived.
- Reporting both values provides information on statistical uncertainty, such as sampling variation, and makes available to the risk assessor the full range of information.
- EPA should develop guidelines for uncertainty analysis and communication in the context of IRIS to support the consistent and transparent treatment of uncertainties.

# Future Directions

- The committee expects EPA to complete its planned revisions in a timely way and expects the revisions to result in a transformation of the IRIS program.

- To ensure that the IRIS program provides the best assessments possible, the committee identified three broad areas on which EPA should focus attention.

# Future Directions (cont.)

- First, the assessment methods will need to be updated in a continuing, strategic fashion.
- Second, inefficiencies in the IRIS process need to be identified and addressed systematically.
- Third, EPA management needs to evaluate human and technologic resources that are needed to conduct IRIS assessments and support methodologic research and implementation of new approaches.

***If sufficient financial and staff resources are not available to EPA, it will not be able to continue to improve the IRIS program and keep pace with scientific advancements.***

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# Overall Conclusions of IRIS Committee

- It is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report.
- The changes that EPA has proposed and implemented in various degrees constitute substantial improvements in the IRIS process.
- If current trajectories are maintained, inconsistencies identified in the present report are addressed, and objectives still to be implemented are successfully completed, the IRIS process will become much more effective and efficient program.

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