

**Presentation to the CAAC Subcommittee, Science
Advisory Board, US EPA**

**NRC Committees to Review the IRIS
Draft Formaldehyde Assessment
and the IRIS Process**

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April 2, 2013

The Two Committees

IRIS HCHO Assessment

- Charge: review of draft HCHO assessment
- Report published 4/11
- Review of HCHO draft in-depth with comments for revision.
- Last chapter commented generally on IRIS and need for revisions.
- “Roadmap for revision”

IRIS Process Review

- Charge: review changes to IRIS process
- Committee has had 3 meetings and workshop
- Report anticipated in 2014
- Broad committee expertise



BEST

Board on Environmental Studies and Toxicology

**Review of the Environmental Protection Agency's
Draft IRIS Assessment of Formaldehyde**

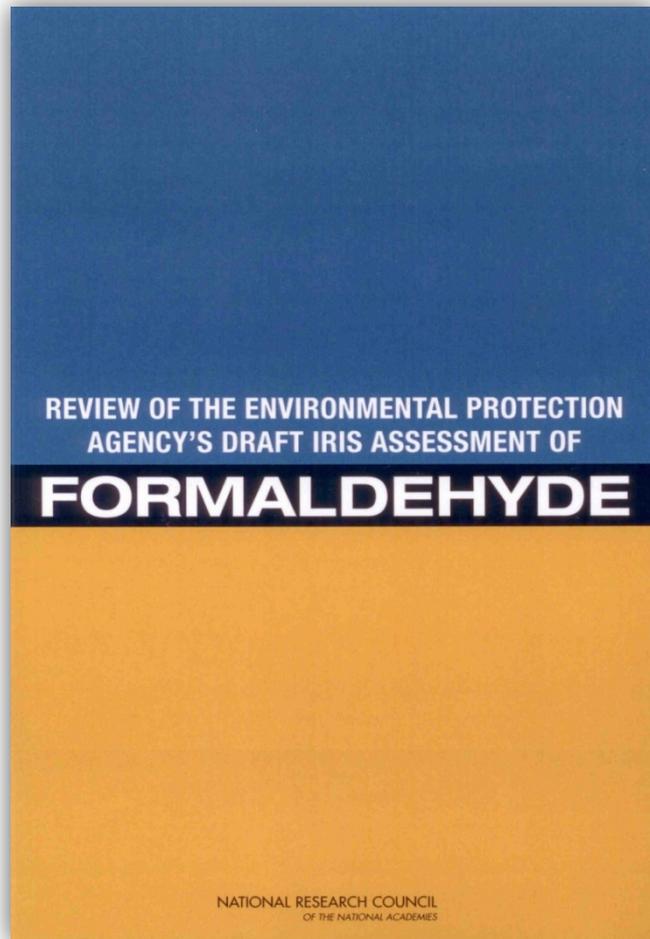
**Committee to Review EPA's Draft IRIS Assessment of
Formaldehyde**

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

National Research Council

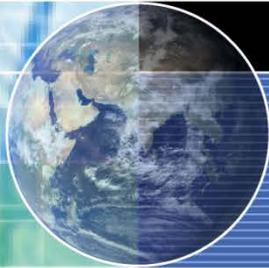
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Formaldehyde and IRIS: A Long Story

National Academies' National Research Council (NRC), April 2011

Available from: <http://dels.nas.edu/Report/Review-Environmental-Protection-Agency/13142>



History of EPA Formaldehyde Assessment

September 1990
May 1991

Oral
RfD
posted
online

May 1991

Cancer
assessment
posted online

January 1998

Reassessment of
noncancer and
cancer risks begun
by IRIS program

October 2004

Development of
draft IRIS
assessment begun

July 2009

Draft IRIS
assessment
undergoes
agency review

January 2010

Draft IRIS assessment
undergoes interagency
review

June 2010

Draft IRIS assessment
provided to NRC and
released to public

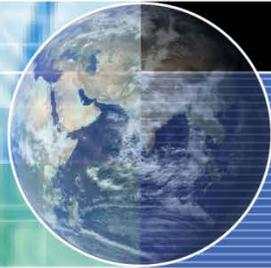
Draft Assessment

- Four volumes with 8 appendices
- 1000 pages in length



Statement of Task

- Review EPA's draft IRIS assessment and answer questions concerning the following:
 - identification of potential adverse noncancer health effects
 - selection of the points of departure for those health effects
 - basis for the determination of uncertainty factors used to derive the reference concentrations
- Comment on the scientific rationale provided for the cancer assessment and the quantified estimates derived.
- Committee's report requested nine months from committee's receipt of the draft IRIS assessment.



Committee

Jonathan Samet, (Chair), University of Southern California, Los Angeles

Andrew Olshan, (Vice-Chair), University of North Carolina, Chapel Hill

A. John Bailer, Miami University, Oxford, OH

Sandra Baird, Massachusetts Department of Environmental Protection, Boston

Harvey Checkoway, University of Washington School of Public Health and
Community Medicine, Seattle

Richard Corley, Pacific Northwest National Laboratory, Richland, WA

David Dorman, North Carolina State University, Raleigh

Charles Hobbs, Lovelace Respiratory Research Institute, Albuquerque, NM

Michael Laiosa, University of Wisconsin, Milwaukee

Ivan Rusyn, University of North Carolina, Chapel Hill

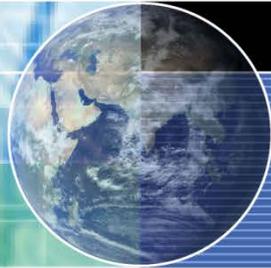
Mary Alice Smith, University of Georgia, Athens

Leslie Stayner, University of Illinois, Chicago

Helen Suh, Harvard School of Public Health, Boston, MA

Yiliang Zhu, University of South Florida, Tampa

Patrick Zweidler-Mckay, The University of Texas M. D. Anderson Cancer
Center, Houston



Committee's Approach to Its Task

- The committee did ***not*** perform its own assessment.
- Thus, it did ***not*** conduct its own literature searches, review all relevant evidence, systematically formulate its own conclusions regarding causality, or recommend values for the RfC and unit risk.
- The committee reviewed the draft IRIS assessment and key literature and determined whether EPA's conclusions were supported on the basis of that assessment and the literature reviewed.



Overview of the Report

- Chapter 1: Introduction
- Chapter 2: General Comments on Methods
- Chapter 3: Toxicokinetics and MOA
- Chapter 4: Portal-of-entry effects
- Chapter 5: Systemic effects
- Chapter 6: RfC and Unit Risk
- Chapter 7: Conclusions and Path Forward

- General problems identified by present committee are not unique to the formaldehyde assessment. Previous BEST committees have made similar observations.
- **The draft assessment was not prepared in a consistent fashion and lacks clear links to an underlying framework.**
- **It does not contain sufficient documentation on methods and criteria for identifying evidence from epidemiologic and experimental studies, for critically evaluating individual studies, for assessing the weight of evidence, and for selecting studies for derivation of the RfCs and unit risk estimates.**



Toxicokinetics – Key Issues

Committee focused on several key issues:

- Implications of endogenous formaldehyde.
- Fate of inhaled formaldehyde.
- Systemic availability of formaldehyde.
- Ability of formaldehyde to cause systemic genotoxic effects.
- Usefulness of various physiological and dose models.



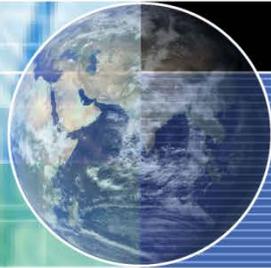
Endogenous Formaldehyde

- Formaldehyde is normally present at low concentrations in all tissues, cells, and bodily fluids as a result of normal metabolism.
- **The endogenous production of formaldehyde complicates the assessment of the risk associated with formaldehyde inhalation and remains an important uncertainty in assessing the additional dose received by inhalation, particularly at sites beyond the respiratory tract.**



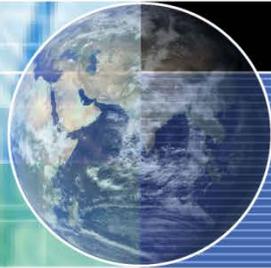
Fate of Inhaled Formaldehyde

- Formaldehyde is a highly water-soluble, reactive chemical that has a short biologic half-life.
- Formaldehyde is absorbed primarily at the site of first contact where it undergoes extensive local metabolism and reactions with macromolecules.
- The net result is that inhaled formaldehyde remains predominantly in the respiratory epithelium that lines the airways.



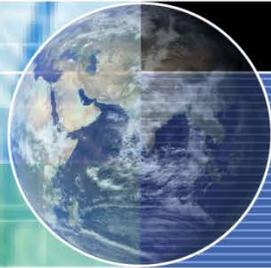
Systemic Availability of Formaldehyde

- The issue of whether inhaled formaldehyde can reach the systemic circulation is important in assessing the risk of adverse effects at nonrespiratory sites.
- **Direct evidence of systemic delivery of formaldehyde is generally lacking.**
- Furthermore, experimental data provide compelling evidence that hydration of formaldehyde does not enhance delivery beyond the portal of entry to distal tissues.



Systemic Genotoxic Effects of Formaldehyde Exposure

- **The draft IRIS assessment correctly concludes that formaldehyde is a genotoxic (DNA-reactive) chemical that causes cytogenetic effects, such as mutations.**
- Furthermore, the overall body of evidence suggests that inhaled formaldehyde has a cytogenetic effect that can be detected in peripheral (circulating) blood lymphocytes.
- **However, the committee concludes that data are insufficient to conclude definitively that formaldehyde itself is causing cytogenetic effects at distant sites.**



Usefulness of Various Models: CFD Model

- Computational fluid dynamics (CFD) models have been developed to help predict the dose to nasal tissues from inhaled formaldehyde.
- EPA fairly evaluated the CFD models and sources of uncertainty but did not use the models to extrapolate to low concentrations.
- **The committee concludes that the models would be useful for that purpose and recommends that EPA use the CFD models to extrapolate to low concentrations, include the results in the revised IRIS assessment, and explain clearly its use of CFD modeling approaches.**



Usefulness of Various Models: BBDR Models

- On the basis of various extrapolations, EPA decided not to use the biologically based dose-response (BBDR) models that have been developed for formaldehyde in its assessment.
- **Given that the BBDR models are some of the best-developed to date, the positive attributes of BBDR models generally, and the limitations of the human data, the committee recommends that EPA use the BBDR models for formaldehyde in its cancer assessment, compare the results with those described in the draft assessment, and discuss the strengths and weaknesses of each approach.**



Mode of Action

- EPA based its approach to its cancer assessment primarily on the conclusion that formaldehyde is a genotoxic chemical that causes mutations (a mutagenic mode of action).
- However, for nasal tumors attributed to formaldehyde exposure, animal data also support a mode of action characterized by regenerative cellular proliferation that results from cytotoxicity.
- **The committee recommends that EPA provide additional calculations that factor in regenerative cellular proliferation as a mode of action.**



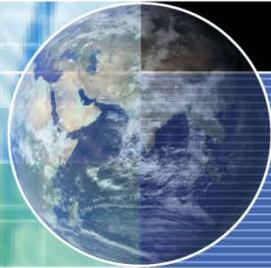
Mode of Action

- Little is known about a potential mode of action for hematopoietic cancers, such as leukemias, that have been attributed to formaldehyde exposure.
- **The draft assessment provides several hypotheses on how formaldehyde could cause hematopoietic cancers. However, experimental evidence is either lacking or contradictory to what has been proposed.**



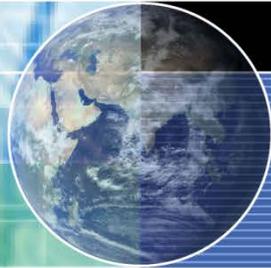
Health Effects Evaluated in IRIS Assessment

- EPA evaluated a wide array of health outcomes, which the committee characterized as either portal-of-entry or systemic effects.
- Portal-of-entry effects were defined as effects that arise from direct interaction of inhaled formaldehyde with the airways or from the direct contact of airborne formaldehyde with eyes or other tissues.
- Systemic effects were defined as effects that occur outside those systems.



Portal-of-Entry Health Effects

- EPA evaluated the following “portal-of-entry” health effects: irritation, decreased pulmonary function, respiratory tract pathology, asthma, and respiratory tract cancers.
- **Overall, the committee found that the noted outcomes were appropriate to evaluate.**
- EPA identified relevant studies for its assessment, and on the basis of the committee’s familiarity with the scientific literature, it does not appear to have overlooked any important study.



Portal-of-Entry Health Effects

- For a few outcomes (irritation, asthma), EPA did not discuss or evaluate literature on mode of action that could have supported its conclusions.
- **Although EPA adequately described the studies, critical evaluations of the strengths and weaknesses of the studies were generally deficient, and clear rationales for many conclusions were not provided.**
- **In several cases (irritation, decreased pulmonary function, respiratory tract pathology, asthma), the committee would not have advanced a particular study or would have advanced other studies to calculate the candidate RfCs.**



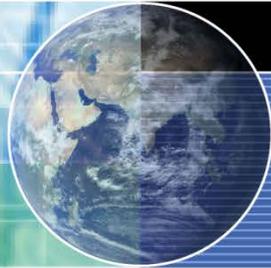
Respiratory Tract Cancers

- The respiratory tract is considered to be a plausible location of formaldehyde-induced cancers in humans because these cancers occur at the site of first contact and because studies have shown an increased incidence of nasal tumors in rats and mice exposed to formaldehyde.
- **However, the draft IRIS assessment does not present a clear framework for causal determinations and presents several conflicting statements that need to be resolved regarding the evidence of a causal association between formaldehyde and respiratory tract cancers.**



Respiratory Tract Cancers

- **The committee agrees that there is sufficient evidence of a causal association between formaldehyde and cancers of the nose, nasal cavity, and nasopharynx.**
- **It disagrees with the EPA conclusion that the evidence regarding other sites in the respiratory tract is sufficient.**
- **The committee agrees with EPA that the study by Hauptmann et al. (2004) is the most appropriate for deriving a unit risk value but notes that this study is being updated.**



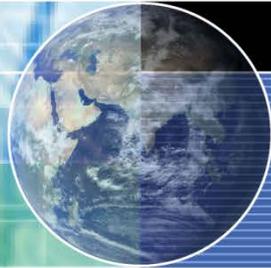
Systemic Health Effects

- As noted, high reactivity and extensive nasal absorption of formaldehyde restrict systemic delivery of inhaled formaldehyde beyond the upper respiratory tract and major conducting airways of the lung
- So, systemic responses are unlikely to arise from the direct delivery of formaldehyde (or its hydrated form, methanediol) to a distant site in the body.
- However, a distinction needs to be made between systemic delivery and systemic effects.



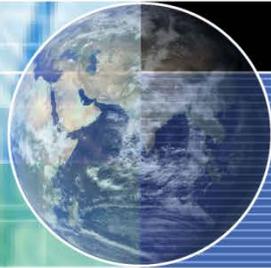
Systemic Health Effects

- The possibility remains that systemic delivery of formaldehyde is not a prerequisite for some of the reported systemic effects seen after formaldehyde exposure.
- Those effects may result from indirect modes of action associated with local effects, such as irritation, inflammation, and stress.
- Therefore, the committee reviewed EPA's evaluation of the systemic effects and determined whether the evidence presented supported EPA's conclusions.



Systemic Health Effects

- The systemic effects evaluated by EPA include immunotoxicity, neurotoxicity, reproductive and developmental toxicity, and lymphohematopoietic cancers.
- **As in the evaluation of the portal-of-entry effects, the committee concluded that EPA identified relevant literature and adequately described the studies selected.**
- **However, critical evaluations of study strengths and weaknesses were generally lacking, and clear rationales for conclusions were often not provided. As a result, some narratives did not support the conclusions stated.**



Systemic Health Effects

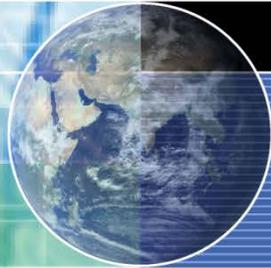
The committee differed with EPA's analysis for several outcomes.

- **EPA overstated the evidence to deem formaldehyde neurotoxic; the human data are insufficient, and the candidate animal studies deviate substantially from testing guidelines and common practice.**
- **The totality of the epidemiologic evidence for reproductive and developmental toxicity should be described as “suggestive” rather than “convincing.”**



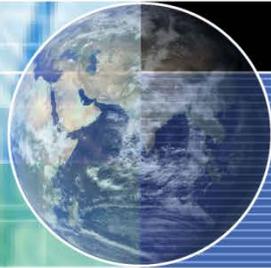
Lymphohematopoietic Cancers

- **Although EPA provided an exhaustive description of the studies and speculated extensively on possible modes of action, the causal determinations are not supported by the narrative provided in the draft IRIS assessment.**
- **Accordingly, the committee recommends that EPA revisit arguments that support determinations of causality for specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality.**

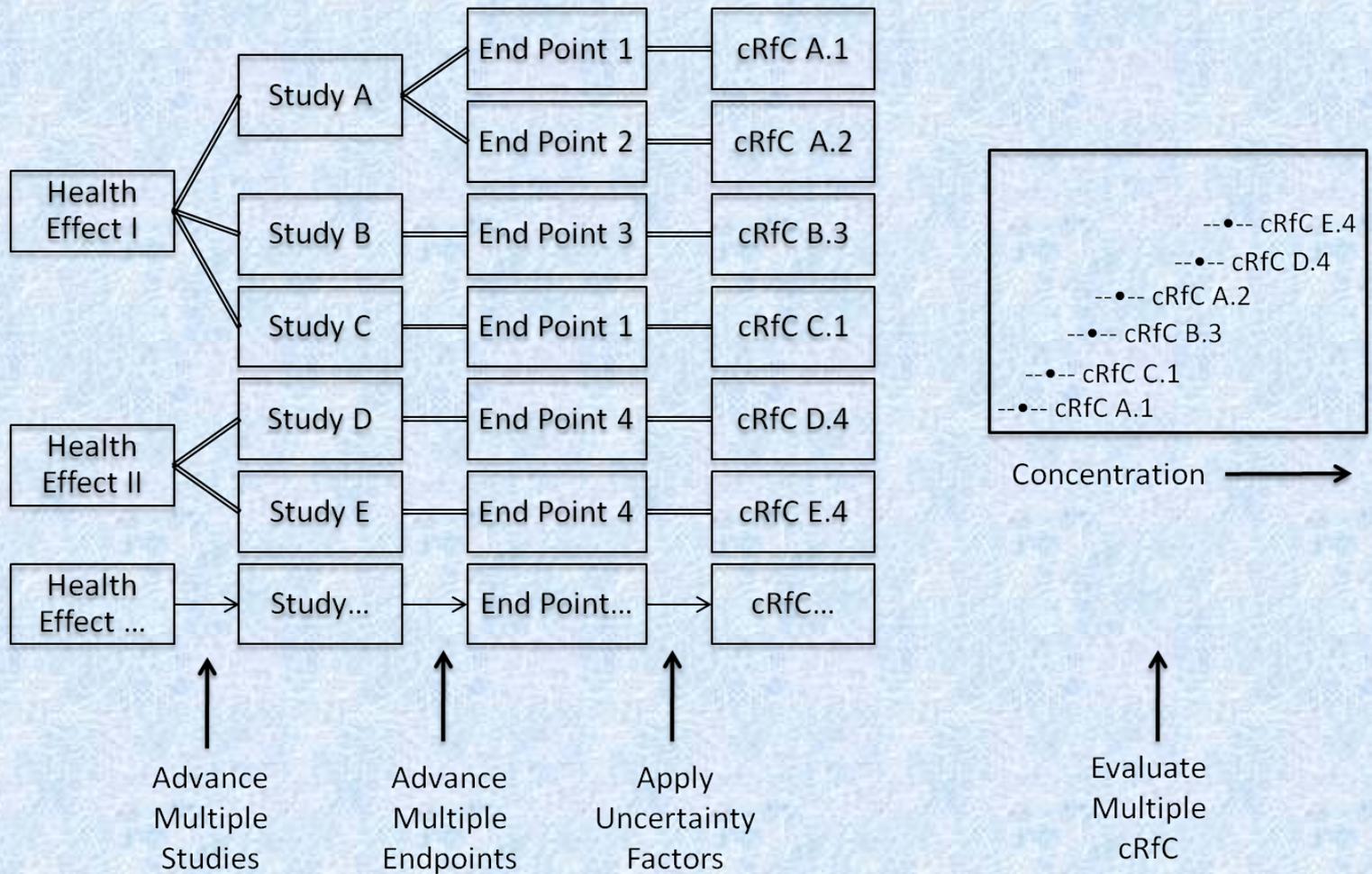


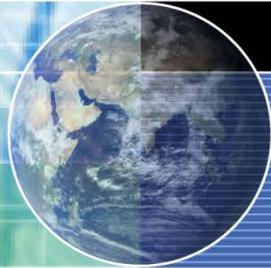
Derivation of Reference Concentrations

- **Overall, the committee is troubled by the presentation and derivation of the proposed RfC values.**
- **Appropriate graphics may identify a central value, isolate especially low or high RfC values that might not be consistent with the literature, and ultimately improve the ability of the assessment to make a compelling case that the RfC proposed is appropriate.**



Derivation of Reference Concentrations





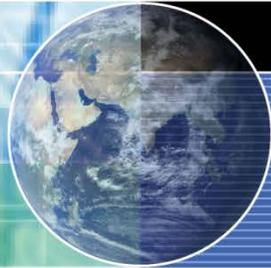
Derivation of Cancer Unit Risks

- EPA used the National Cancer Institute (NCI) cohort to derive unit cancer risks for nasopharyngeal cancer, Hodgkin lymphoma, and leukemia.
- **The committee agrees that the NCI studies are a reasonable choice because they are the only ones with exposure and dose-response data sufficient for calculation of the unit risks.**
- **Although there are uncertainties regarding the causal relationship of formaldehyde exposure and the three kinds of cancer, EPA's decision to calculate unit risk values for them appears to be defensible on the basis of the agency's cancer guidelines.**



Derivation of Cancer Unit Risks

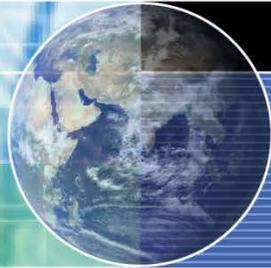
- **EPA should provide a clear description of the criteria that it used to select the specific cancers and demonstrate a systematic application of the criteria.**
- **The committee recommends that EPA conduct an independent analysis of the dose-response models to confirm the degree to which the models fit the data appropriately.**
- EPA is encouraged to consider the use of alternative extrapolation models for the analysis of the cancer data.



The Path Forward: What needs to be done

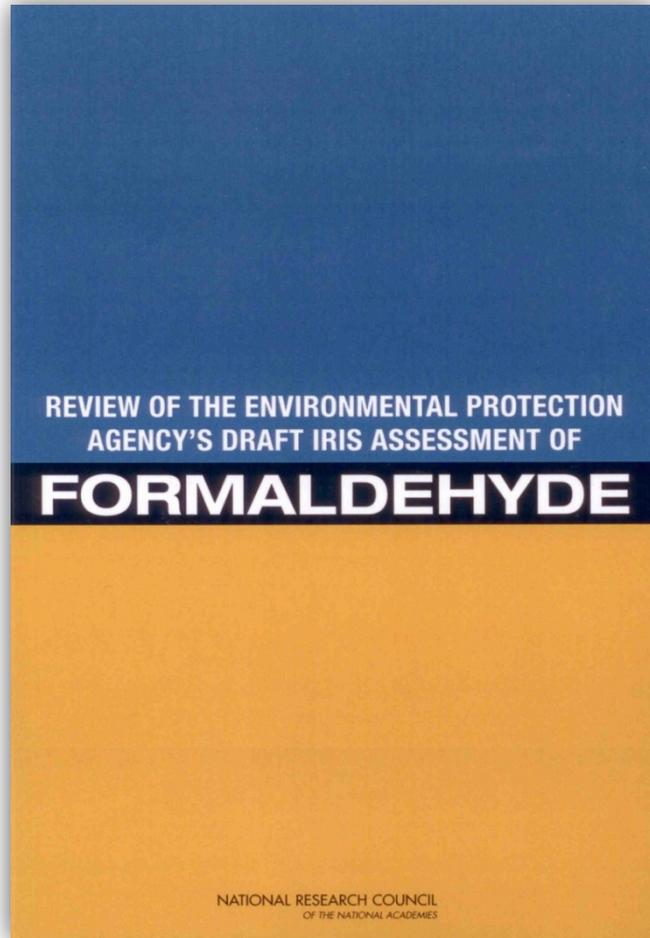
The committee concludes that the following six general recommendations are critical to address in the revision of the draft assessment.

- **Rigorous editing is needed to reduce the volume of the text substantially and address the redundancies and inconsistencies; reducing the text could greatly enhance the clarity of the document.**
- **Chapter 1 of the draft assessment needs to discuss more fully the methods of the assessment. The committee is recommending not the addition of long descriptions of EPA guidelines but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.**



The Path Forward: What needs to be done

- **Standardized evidence tables that provide the methods and results of each study are needed for all health outcomes; if appropriate tables were used, long descriptions of the studies could be moved to an appendix or deleted.**
- **All critical studies need to be thoroughly evaluated for strengths and weaknesses by using uniform approaches; the findings of these evaluations could be summarized in tables to ensure transparency.**
- **The rationales for selection of studies that are used to calculate RfCs and unit risks need to be articulated clearly.**
- **The weight-of-evidence descriptions need to indicate the various determinants of “weight.” The reader needs to be able to understand what elements (such as consistency) were emphasized in synthesizing the evidence.**



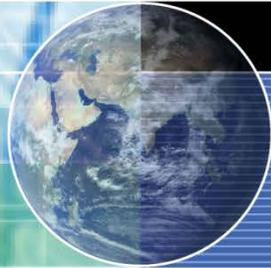
Chapter 7: A Roadmap for Revision

- **Need to fully reassess and revise the IRIS process**
- **Problems with formaldehyde noted in prior reviews**
- **State-of-Art processes not followed throughout**
- **Lack of transparency in review and evidence evaluation**
- **Weight of evidence analyses inadequate**



Roadmap for Revision

- 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.
- Models for conducting IRIS assessment more effectively and efficiently are available, and EPA might be able to make changes relatively quickly by selecting and adapting existing approaches.



Roadmap for Revision

- The committee recognizes that revision of the overall approach will involve an extensive effort by EPA staff and others, and it is not recommending that EPA delay the revision of the formaldehyde assessment to implement a new approach.
- **However, if the methodologic issues are not addressed, future assessments may still have the same general and avoidable problems that are highlighted in this report.**



Beyond Formaldehyde: Revising the IRIS Process

General Guidance for the Overall Process

- **Elaborate an overall, documented, and quality-controlled process for IRIS assessments.**
- **Ensure standardization of review and evaluation approaches among contributors and teams of contributors.**
- **Assess disciplinary structure of teams needed to conduct the assessments.**



Beyond Formaldehyde: Revising the IRIS Process

Evidence Identification: Literature Collection and Collation Phase

- **Select outcomes on the basis of available evidence and understanding of mode of action.**
- **Establish standard protocols for evidence identification.**
- **Develop a template for description of the search approach.**
- **Use a database to capture study information and relevant quantitative data.**



Beyond Formaldehyde: Revising the IRIS Process

Evidence Evaluation: Hazard ID and Dose-Response Modeling

- **Standardize the presentation of reviewed studies in tabular or graphic form to capture the key dimensions of study characteristics, weight of evidence, and utility as a basis for deriving reference values and unit risks.**
- **Develop templates for evidence tables, forest plots, or other displays.**
- **Establish protocols for review of major types of studies, such as epidemiologic and bioassay**



Beyond Formaldehyde: Revising the IRIS Process

Weight-of-Evidence Evaluation: Synthesis of Evidence for Hazard ID

- Review use of existing weight-of-evidence guidelines and standardize approach to using weight-of-evidence guidelines.
- Conduct agency workshops on approaches to implementing weight-of-evidence guidelines.
- Develop uniform language for strength of evidence on non-cancer effects.
- Expand and harmonize approach for characterizing uncertainty and variability.
- To the extent possible, unify consideration of outcomes around common modes of action rather than multiple outcomes separately.

Selection of Studies for Derivation of RfCs and Unit Risks

- **Establish clear guidelines for study selection.**
 - **Balance strengths and weaknesses.**
 - **Weigh human vs experimental evidence.**
 - **Determine whether combining estimates among studies is warranted.**



Beyond Formaldehyde: Revising the IRIS Process

Calculation of Reference Concentrations and Unit Risks

- **Describe and justify assumptions and models used.**
- **Provide explanation of the risk-estimation modeling processes that are used to develop a unit risk estimate.**
- **Assess the sensitivity of derived estimates to model assumptions and end points selected.**
- **Provide adequate documentation for conclusions and estimation of reference values and unit risks.**



BEST

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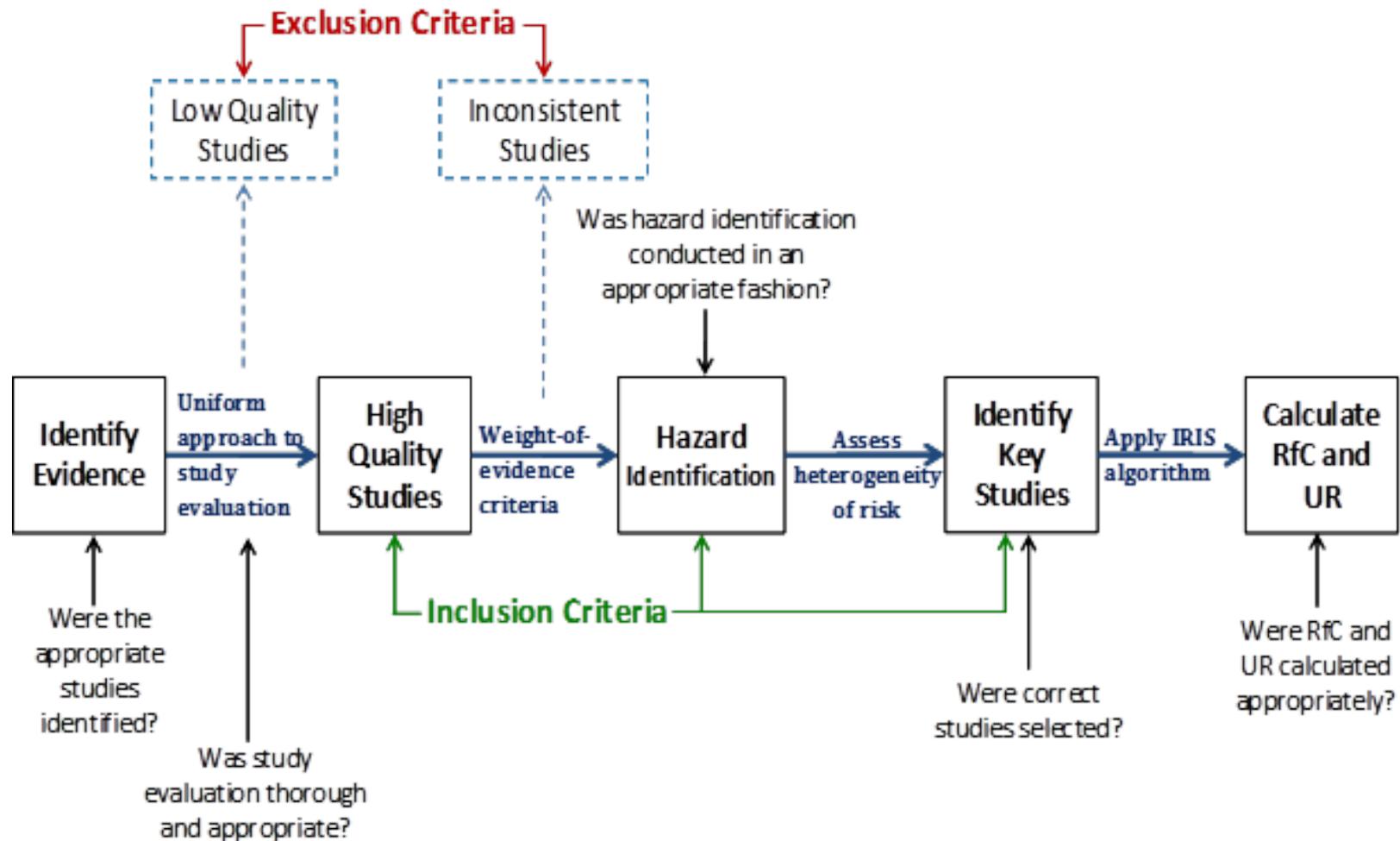
Review of the IRIS Process Committee Membership

Jonathan 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 Bloomberg School of Public Health
David C. Dorman	University of Washington
Joe G. Garcia	University of Illinois at Chicago
Miguel Hernan	Harvard School of Public Health
James S. House	University of Michigan
Margaret M. MacDonell	Argonne National Laboratory
Richard P. Scheines	Carnegie Mellon University
Leonard M. Siegel	Center for Public Environmental Oversight
Robert B. Wallace	The University of Iowa
Yiliang Zhu	University of South Florida

Statement of Task

A committee of the National Research Council (NRC) will assess the scientific, technical, and process changes being implemented by the U.S. Environmental Protection Agency (EPA) for its Integrated Risk Information System (IRIS). Specifically, the committee will review the IRIS process and the changes being implemented or planned by EPA and will recommend modifications or additional changes as appropriate to improve the scientific and technical performance of the IRIS program. The committee will focus on the development of the IRIS assessments rather than the review process that follows draft development. Because several reviews of IRIS assessments have expressed concerns about EPA's weight-of-evidence analyses, the committee will review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments.

Steps of IRIS Assessments



Committee Workshop Topics

- Assembling the evidence
- Mechanism and mode of action
- Integration of data
- Causality
- Characterizing and communicating uncertainty
- Use of expert judgment



Report of the Committee to Review the IRIS Process



Coming Attractions