EPA's Integrated Risk Information System Program

Progress Report and Report to Congress

U.S. Environmental Protection Agency: Office of Research and Development

Integrated Risk Information System Program Progress Report

I. Executive Summary

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) Program provides health effects information on chemicals to which the public may be exposed, providing a critical part of the scientific foundation for EPA's decisions to protect public health. EPA has made several changes to this important Program over the past few years, streamlining the assessment development process, improving transparency, and creating efficiencies within the Program. In April 2011, the National Research Council (NRC) made several recommendations to EPA for improving the development of IRIS assessments. The NRC's recommendations were focused on the development of draft assessments, and the NRC was clear that their intent was not to delay assessments.

EPA has made progress in implementing these recommendations. Consistent with the advice of the NRC, EPA is implementing these recommendations using a phased approach and is making the most extensive changes to documents that are in the earlier steps of the assessment development process. For assessments that are in the later stages of development, including assessments that have been posted on the IRIS database since the release of the NRC report, EPA is implementing the recommendations as feasible without taking the assessments backwards to earlier steps of the process. Phase 1 of implementing the NRC recommendations has focused on editing and streamlining documents and using more tables, figures, and appendices. EPA is now in Phase 2 of implementing the NRC recommendations and will soon publicly release two draft IRIS assessments that represent a major advancement in implementing the NRC recommendations. EPA is using a new document structure for these draft assessments, including an Executive Summary presenting major conclusions, a Preamble describing methods used to develop the assessment, distinct sections on Hazard Identification and Dose-Response Analysis, and more tables and figures to clearly present data. Additionally as part of

Phase 2, EPA is addressing all of the short-term recommendations provided by the NRC. As part of this effort, EPA will make several changes to IRIS assessments. Highlights include: evaluating and describing the strengths and weaknesses of critical studies in a more uniform way; including toxicity values for multiple effects associated with the chemical, if applicable and where the data allow; routinely considering the use of multiple data sets of combined multiple responses in deriving toxicity values, where appropriate; and evaluating existing guidelines to establish clearer criteria for study selection. Phase 3 of implementation will incorporate the longer-term scientific recommendations made by the NRC.

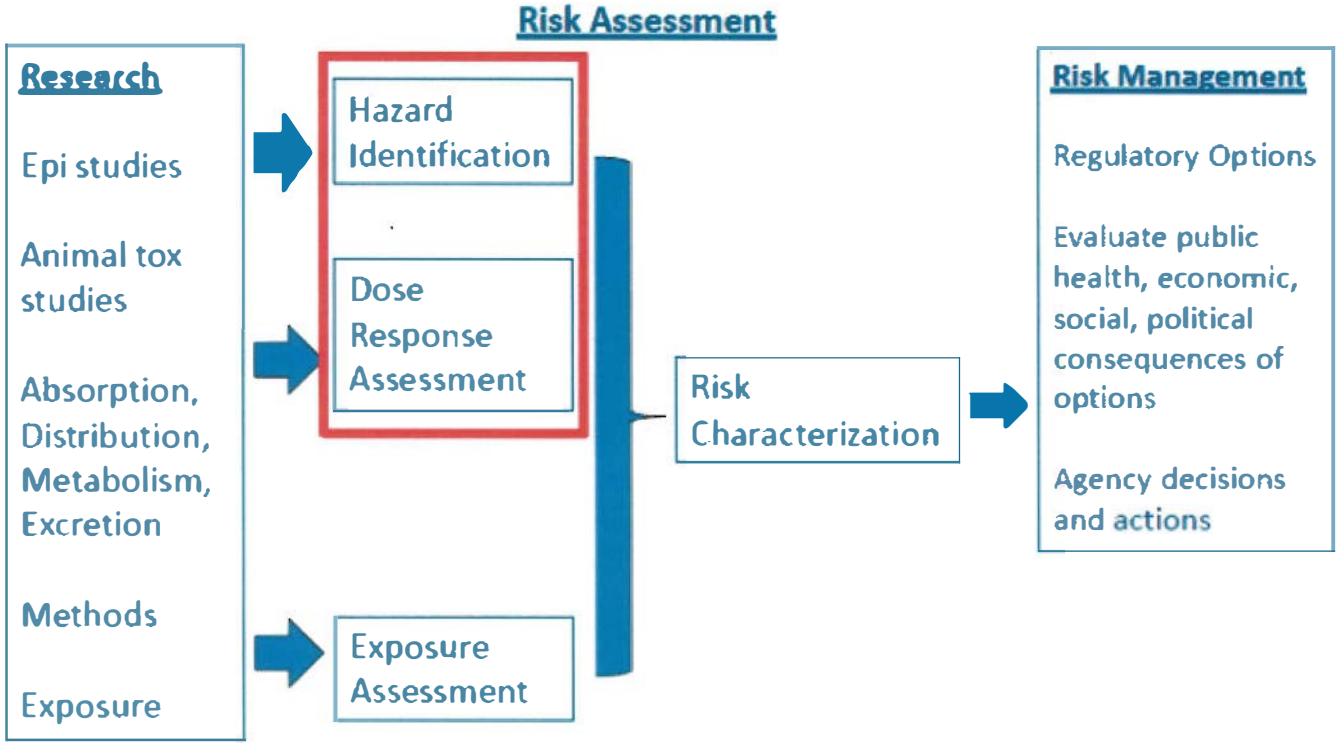
The U.S. Congress has directed EPA to issue a progress report to the House and Senate Committees on Appropriations and relevant Congressional authorizing committees to describe EPA's implementation of the NRC recommendations. This report provides Congress, stakeholders, and the public with an update on the IRIS Program and EPA's progress toward implementing the NRC recommendations and improving the Program.

II. Introduction

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) Program provides health effects information on chemicals to which the public may be exposed from releases to air, water, and land and through the use and disposal of chemicals. IRIS human health assessments provide a critical part of the scientific foundation for decisions to protect public health across EPA's programs and regions under an array of environmental laws. IRIS assessments are not regulations, but they are critical to Agency decisions. IRIS assessments may include reference doses, reference concentrations, cancer slope factors, and inhalation unit risks that can be combined with exposure information to characterize the public health risks of chemical substances. This information is used by EPA, together with other considerations, to make risk management decisions, including regulations. IRIS also is a resource for risk assessors and environmental and health professionals in state and local governments and other countries.

IRIS assessments are scientific reports that provide information on a chemical's hazard as well as quantitative dose-response information. These are developed from the evaluation of research studies on health effects combined with judgments regarding issues such as appropriate study choice, characterization of effects, and uncertainty factors, among others. When combined with specific exposure information, EPA's program and regional offices and stakeholders can use IRIS assessments to help characterize the public health risks of chemical substances in various situations. During the risk management phase, other information may also be considered, such as statutory and legal requirements, cost/benefit information, technological feasibility, and economic factors. Figure 1 illustrates the risk assessment and risk management paradigm and where IRIS assessments contribute information.

Figure 1. Risk Assessment Risk Management Paradigm (adapted from the National Research Council's paradigm, 1983). The red box shows the information included in IRIS assessments.



Adapted from the National Research Council risk assessment risk management paradigm (NRC 1983).

Because of the critical importance of IRIS for the Agency and beyond, a strong, vital and scientifically sound Program is key to providing needed health risk information. Over the past two years, EPA has worked to strengthen and streamline the IRIS Program, improving transparency and increasing the number of final assessments added to the IRIS database. Continually improving IRIS is a priority for the Agency, and efforts are underway to further strengthen and streamline this important Program.

The purpose of this progress report is to provide Congress, stakeholders, and the public with an update on the IRIS Program and EPA's progress toward implementing the NRC recommendations. This report provides an overview of improvements made to the IRIS Program over the past several years, with an emphasis on the most recent improvements.

III. The Consolidated Appropriations Act, 2012

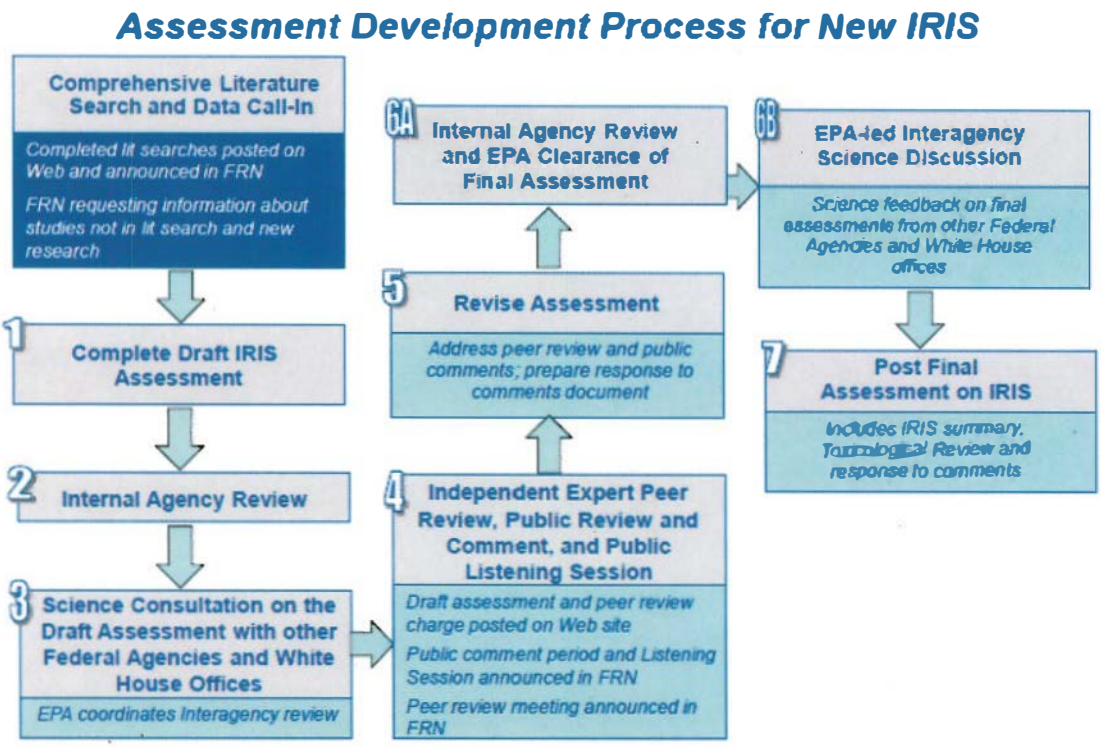
On December 23, 2011, "The Consolidated Appropriations Act, 2012" was signed into law. The report language included direction to EPA for the IRIS Program related to recommendations provided by the National Research Council (NRC) in their review of EPA's draft IRIS assessment for formaldehyde. The NRC's recommendations, provided in Chapter 7 of their review report, offered suggestions for improving the development of IRIS assessments (see Tables 1 and 2). The report language directs EPA to incorporate, "as appropriate, based on chemical-specific datasets and biological effects," the NRC recommendations into the IRIS process. The report language also directs EPA to include documentation, in draft assessments released in fiscal year 2012, describing how the NRC recommendations were implemented. Further, the report language directs EPA to issue a progress report to the House and Senate Committees on Appropriations and relevant Congressional authorizing committees to describe implementation of the NRC recommendations for ongoing and new IRIS assessments.[1] The full report language is provided in Appendix 1.

IV. Background

In May 2009, EPA Administrator Lisa Jackson announced a new IRIS assessment development process (Figure 2) designed to streamline, strengthen and improve transparency within the IRIS Program while ensuring the highest level of scientific quality and integrity and a renewed commitment to rigorous independent peer review.[2]

[1] Pub. L. No. 112-74, Consolidated Appropriations Act, 2012
[2] http://yosemite.epa.gov/opa/admpress.nsf/48f0fa7dd51f9e9885257359003f5342/065e2c61afea09178525 75bd0064c9db!OpenDocument

Figure 2. May 2009 IRIS Assessment Development Process[3]



This new process was announced after a thorough review of the IRIS Program and in response to investigations by the Government Accountability Office (GAO) conducted in 2008. The GAO found that the IRIS database was at risk of becoming obsolete because EPA has not been able to routinely complete timely, credible assessments.[4] The May 2009 IRIS process included the following key features:[5,6]

[3] http://www.epa.gov/iris/pdfs/IRIS_PROCESS_FLOW_CHART.PDF

[4] Government Accountability Office, 2008. *Chemical Assessments-Low Productivity and New Interagency Review Process Limit the Usefulness and Credibility of EPA's Integrated Risk Information System.*

[5] IRIS Progress Report, July 2011. http://www.epa.gov/iris/pdfs/irisprogressreport2011.pdf

[6] http://www.epa.gov/iris/pdfs/IRIS_PROCESS_MEMO.5.21.09.PDF

- EPA would manage the IRIS Program and have final responsibility for the content of all IRIS assessments;
- The assessment development time was shortened to 23 months, a reduction of more than half the estimated time for an assessment to be developed under the previous process;
- The number of steps in the assessment development process was reduced from 14 to 7;
- Other federal agencies and White House offices would have the opportunity to provide scientific input at two points in the assessment development process, and the comments would be made publicly available;
- The assessment development process would include the opportunity for public comment and rely on an open, rigorous and independent external peer review;
- A public listening session would be offered for each chemical assessment; and
- Changes in EPA's scientific judgments during the process would be clearly documented and explained.

EPA has remained strongly committed to scientific integrity, public involvement, rigorous independent external peer review, and consultation with scientists at White House offices and other federal agencies. Opportunities for public involvement throughout the IRIS process include:

- Public nominations of substances to be considered for an assessment or reassessment through the IRIS Program.
- Public availability and opportunity to comment on a completed literature review for chemicals at the beginning of the assessment development process.
- Public availability of draft IRIS assessment documents and interagency comments for review and comment.
- Listening session, where the public can make comments or present information related to the draft assessment.
- Independent expert peer review meeting, which is open to the public and where members of the public may make formal comments and presentations.

V. Overview of Improvements from May 2009 to April 2011

Since the new process was instituted in 2009, and as of the writing of this report, EPA has completed 24 assessments. In fiscal year 2009, EPA completed six final IRIS assessments after the new process was implemented. In fiscal year 2010, EPA completed 10 IRIS assessments and released nine for external peer review and public comment. In fiscal year 2011, EPA completed four assessments, including the long-awaited assessment for trichloroethylene (TCE). Thus far in fiscal year 2012, EPA has completed the final IRIS assessments for dichloromethane, tetrahydrofuran, tetrachloroethylene (perc) and the non-cancer assessment for dioxin. EPA remains strongly committed to continually improving the IRIS Program. From May 2009 to April 2011, EPA:

- Expanded the role of EPA's program and regional offices in nominating and prioritizing chemicals for assessment development to ensure that the IRIS Program is responsive to the most critical Agency needs;
- Hosted regular meetings between the IRIS Program and EPA's programs and regions to discuss individual IRIS assessments and the IRIS process;
- Created an IRIS logistics team to help create further efficiencies in the assessment development process; this team is charged with coordinating all administrative support, freeing up scientific staff to focus on the science of the assessments; and
- Developed the web-based Health and Environmental Research Online (HERO) database (www.epa.gov/hero), which promotes transparency by capturing and making available to the public the references and abstracts to scientific studies used in Agency health and environmental assessments.

VI. Overview of EPA's Roadmap to Revisions

In April 2011, the National Research Council (NRC) released its "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde." In addition to offering comments specifically about EPA's draft formaldehyde assessment, the NRC included comments and

recommendations to improve IRIS documents generally. A summary of the general recommendations is provided in Tables 1 (short-term) and 2 (long-term).

Table 1. National Research Council recommendations that EPA is implementing in the short-term[7]

General recommendations for completing the IRIS formaldehyde assessment that EPA will adopt for all IRIS assessments (p. 152)
1. To enhance the clarity of the document, the draft IRIS assessment needs rigorous editing to reduce the volume of text substantially and address redundancies and inconsistencies. Long descriptions of particular studies should be replaced with informative evidence tables. When study details are appropriate, they could be provided in appendices.
2. Chapter 1 needs to be expanded to describe more fully the methods of the assessment, including a description of search strategies used to identify studies with the exclusion and inclusion criteria articulated and a better description of the outcomes of the searches and clear descriptions of the weight-of-evidence approaches used for the various non-cancer outcomes. The committee emphasizes that it is not recommending the addition of long descriptions of EPA guidelines to the introduction, but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.
3. Standardized evidence tables for all health outcomes need to be developed. If there were appropriate tables, long text descriptions of studies could be moved to an appendix or deleted.
4. All critical studies need to be thoroughly evaluated with standardized approaches that are clearly formulated and based on the type of research, for example, observational epidemiologic or animal bioassays. The findings of the reviews might be presented in tables to ensure transparency.
5. The rationales for the selection of the studies that are advanced for consideration in calculating the RfCs and unit risks need to be expanded. All candidate RfCs should be evaluated together with the aid of graphic displays that incorporate selected information on attributes relevant to the database.
6. Strengthened, more integrative, and more transparent discussions of weight of evidence are needed. The discussions would benefit from more rigorous and systematic coverage of the various determinants of weight of evidence, such as consistency.
General Guidance for the Overall Process (p. 164)
7. Elaborate an overall, documented, and quality-controlled process for IRIS assessments.
8. Ensure standardization of review and evaluation approaches among contributors and teams of contributors; for example, include standard approaches for reviews of various types of studies to ensure uniformity.
9. Assess disciplinary structure of teams needed to conduct the assessments.
Evidence Identification: Literature Collection and Collation Phase (p. 164)
10. Select outcomes on the basis of available evidence and understanding of mode of action.
11. Establish standard protocols for evidence identification.
12. Develop a template for description of the search approach.
13. Use a database, such as the Health and Environmental Research Online (HERO) database, to capture study information and relevant quantitative data.
Evidence Evaluation: Hazard Identification and Dose-Response Modeling (p. 165)
14. 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.
15. Develop templates for evidence tables, forest plots, or other displays.

[7] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

16. Establish protocols for review of major types of studies, such as epidemiologic and bioassay.
Selection of Studies for Derivation of Reference Values and Unit Risks (p. 165)
17. Establish clear guidelines for study selection.
18. Balance strengths and weaknesses.
19. Weigh human vs. experimental evidence.
20. Determine whether combining estimates among studies is warranted.
Calculation of Reference Values and Unit Risks (pp. 165-166)
21. Describe and justify assumptions and models used. This step includes review of dosimetry models and the implications of the models for uncertainty factors; determination of appropriate points of departure (such as benchmark dose, no-observed-adverse-effect level, and lowest observed-adverse-effect level), and assessment of the analyses that underlie the points of departure.
22. Provide explanation of the risk-estimation modeling processes (for example, a statistical or biologic model fit to the data) that are used to develop a unit risk estimate.
23. Provide adequate documentation for conclusions and estimation of reference values and unit risks. As noted by the committee throughout the present report, sufficient support for conclusions in the formaldehyde draft IRIS assessment is often lacking. Given that the development of specific IRIS assessments and their conclusions are of interest to many stakeholders, it is important that they provide sufficient references and supporting documentation for their conclusions. Detailed appendixes, which might be made available only electronically, should be provided, when appropriate.

Table 2. National Research Council recommendations that EPA is implementing in the long-term[8]

Weight-of-Evidence Evaluation: Synthesis of Evidence for Hazard Identification (p. 165)
24. Review use of existing weight-of-evidence guidelines.
25. Standardize approach to using weight-of-evidence guidelines.
26. Conduct agency workshops on approaches to implementing weight-of-evidence guidelines.
27. Develop uniform language to describe strength of evidence on noncancer effects.
28. Expand and harmonize the approach for characterizing uncertainty and variability.
29. To the extent possible, unify consideration of outcomes around common modes of action rather than considering multiple outcomes separately.
Calculation of Reference Values and Unit Risks (pp. 165-166)
30. Assess the sensitivity of derived estimates to model assumptions and end points selected. This step should include appropriate tabular and graphic displays to illustrate the range of the estimates and the effect of uncertainty factors on the estimates.

EPA agrees with the NRC's recommendations for the development of IRIS assessments and is fully implementing them consistent with the NRC's "Roadmap for Revision," which viewed the full implementation of their recommendations as a multi-year process. In July 2011, EPA announced plans

[8] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

to further improve the IRIS Program, both as part of an ongoing effort to strengthen IRIS and also in response to the NRC recommendations.[9] At that time, EPA announced that it would implement the NRC recommendations using a phased approach. As such, EPA is making the most extensive changes to documents that are in the earlier steps of the assessment development process. For assessments that are in the later stages of development, EPA is implementing the recommendations, as feasible, without taking the assessments backwards to earlier steps of the process. Appendix 2 provides a figure illustrating the timing of implementing Phases 1, 2, and 3, and a description of these Phases is provided below.

Phase 1 of implementation focused on a subset of the short-term recommendations, such as editing and streamlining documents, increasing transparency and clarity, and using more tables, figures, and appendices to present information and data in assessments. Phase 1 also focused on assessments near the end of the development process and close to final posting. EPA is now in Phase 2 of implementation, which addresses all of the short-term recommendations from Table 1. EPA is implementing all of these recommendations but recognizes that achieving full and robust implementation of certain recommendations will be an evolving process with input and feedback from the public, stakeholders, and external peer review committees. EPA will soon publicly release two draft IRIS assessments that represent a major advancement in implementing the short-term NRC recommendations (recommendations from Table 1). Phase 3 of implementation will incorporate the longer-term recommendations made by the NRC (recommendations from Table 2).

This phased approach is consistent with the NRC's "Roadmap for Revision" as described in Chapter 7 of the formaldehyde review report. The NRC stated that "the committee recognizes that the changes suggested would involve a multi-year process and extensive effort by the staff at the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others."[10]

To respond to the NRC recommendations, and as part of Phase 2 of implementing them, draft IRIS assessments released in fiscal year 2012 will be:

[9] http://yosemite.epa.gov/opa/admpress.nsf/d0cf6618525a9efb85257359003fb69d/a3fcd60838197067852578cb00666c4d!OpenDocument
[10] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

- Shorter, more concise and visual, with more graphs and tables used to represent data.
- Clearer and more transparent with respect to data, methods, and decision criteria used.
- More rigorously edited to eliminate inconsistencies and redundancies.

These assessments also will include a template for description of the literature search approach and will be linked to the Health and Environmental Research Online (HERO) database, to capture study information and relevant quantitative data.

Additionally, these assessments will:

- Evaluate and describe the strengths and weaknesses of critical studies in a more uniform way.
- Include toxicity values for multiple effects associated with the chemical, if applicable, and where there are suitable epidemiologic or experimental studies available.
- Take into account the Hill criteria in assessing evidence from epidemiological studies.
- Weigh the epidemiologic and experimental studies pertinent to each effect in a more consistent and integrative manner and make a clear statement about the strength of the evidence for the effect.
- Provide graphical presentations that synthesize related effects from multiple studies.
- Routinely consider the use of multiple data sets or combine multiple responses in deriving toxicity values, where appropriate.
- Indicate which criteria were most influential in selecting critical studies and toxicity endpoints.
- Describe and justify assumptions and models used to calculate toxicity values, with adequate documentation, including explanations of the risk estimation modeling processes.

Additionally, as part of Phase 2, EPA is evaluating existing guidelines to establish clearer criteria for study selection that will:

- Identify the strengths and weaknesses of studies for quantitative analysis.
- Describe criteria for selecting approaches to deriving toxicity values.
- Consider the possibility of combining multiple studies or effects for deriving toxicity values.

EPA also is developing graphic aids that will illustrate the range of concentrations evaluated in each study selected for quantitative assessment. This will help EPA to identify clusters of studies and low or high reference values that may be inconsistent with the larger body of literature.

Finally, EPA has created Chemical Assessment Support Teams to formalize an internal process to provide additional overall quality control for the development of IRIS assessments. This initiative uses a team approach to making timely, consistent decisions about the development of IRIS assessments across the Program. These teams will help ensure that the necessary disciplinary expertise is available when developing draft assessments, and they will provide a forum for identifying and addressing key issues prior to peer review. These teams also will help EPA objectively monitor progress in implementing the NRC recommendations on an assessment-by-assessment basis. As part of Phase 3, EPA is evaluating existing weight-of-evidence approaches and will adopt an approach or develop a new approach to consistently evaluate weight-of-evidence in IRIS assessments. EPA also will further work to develop systematic approaches to quantify uncertainty and variation. These actions respond to the long-term recommendations in Table 2.

The NRC recognized that a number of past IRIS assessments meet their expectations related to certain recommendations they provided. For example, in their report reviewing EPA's draft IRIS assessment for formaldehyde, the NRC endorsed an approach for presenting and deriving proposed RfC values that was used in the recent IRIS assessments for tetrachloroethylene and trichloroethylene, noting that "the approach described and illustrated in Figure 6-2 has been used in recent EPA assessments of tetrachloroethylene (EPA 2008b) and trichloroethylene (EPA 2009b)."[11]

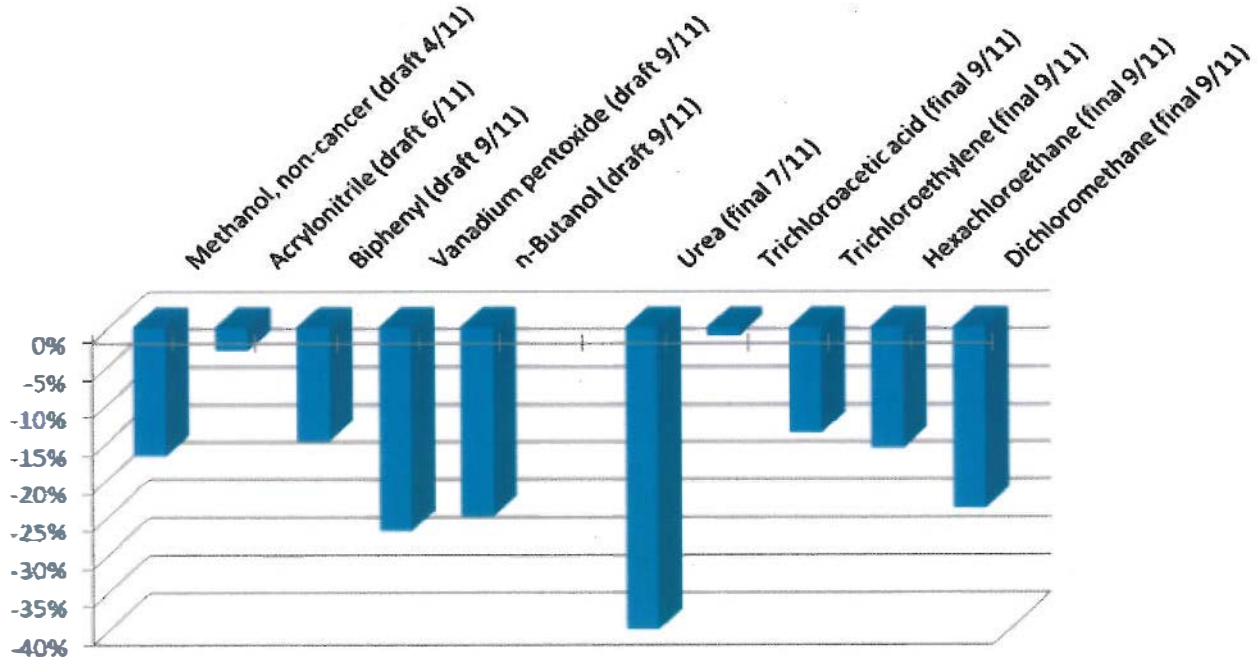
Since April 2011, EPA has been making strong progress toward implementing the NRC's recommendations to streamline assessments, making them more concise and readable, and using appendices. In a recent review of the IRIS Program, the Government Accountability Office (GAO) noted that, while challenges remained, they had reviewed two IRIS assessments that reflect changes made in response to the NRC suggestions. In reviewing the assessment of urea, which was finalized in July 2011, GAO stated that "EPA streamlined the report by moving sections of text from the body to an appendix, which shortened the body of the assessment from 89 to 57 pages, making it more concise."

[11] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

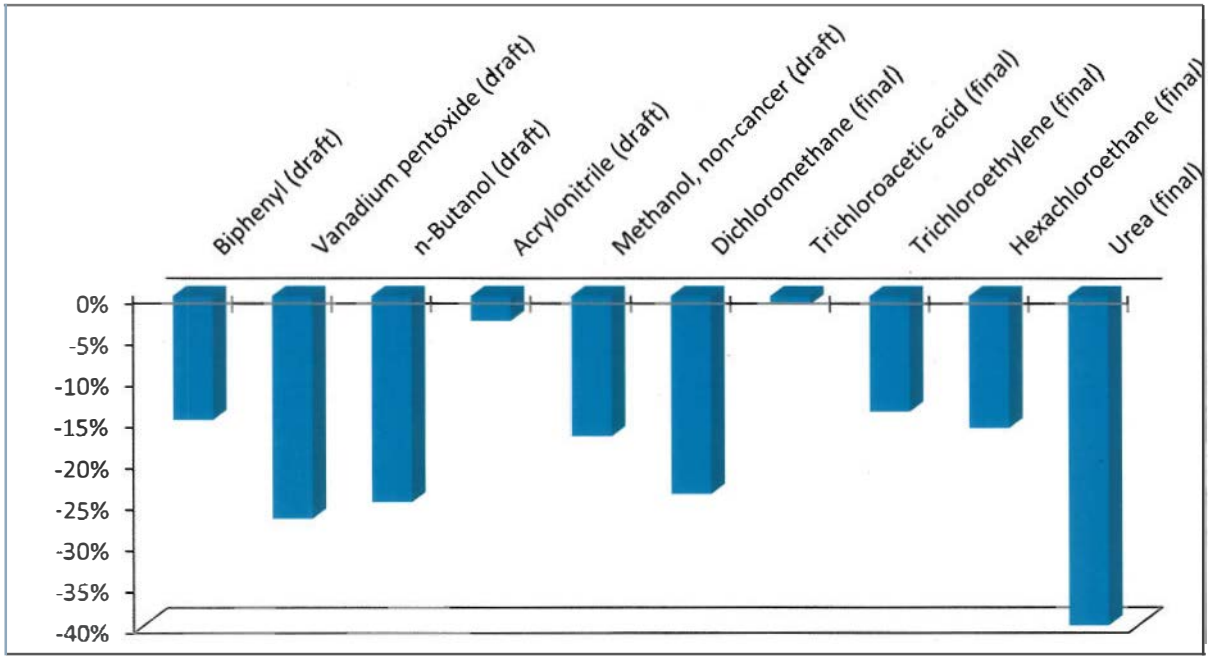
GAO also reviewed the draft IRIS assessment of diisobutyl phthalate (DIBP), which was undergoing Agency review (Step 2) when EPA provided it to GAO, noting that it includes "(1) descriptive and pictorial explanations of the study selection methods used; (2) tables that, among other things, give side-by-side comparisons of studies considered in determining the oral reference dose for the chemical; and (3) brief descriptions of the strengths and weaknesses of various studies considered." GAO further noted that, for these two assessments, "it appears that EPA has begun to enhance the readability of its assessments by making changes that appear to be in line with the suggestions made by the National Academies."[12]

Figure 3 illustrates one aspect of EPA's efforts for Phase 1 of implementing the NRC recommendations. This figure provides assessment-specific information related to streamlining IRIS assessments by developing shorter, clearer and more concise documents with a reduced volume of text and a greater use of appendices for presenting certain types of information.

Figure 3. Percent change in number of pages in recent IRIS assessments (not including appendices) between prior and most recent version of assessments



[12] Government Accountability Office, 2011. Chemical Assessments: Challenges Remain with EPA's Integrated Risk Information System Program.



VII. Revision Initiatives

In addition to the actions described above, EPA has developed several initiatives that are key aspects of EPA's plans to further improving the IRIS Program. Unless otherwise noted, these initiatives are part of EPA's response to the recommendations in Table 1.

EPA has presented these initiatives to various stakeholders at professional society meetings and has received positive feedback.

A. New Document Structure

As part of Phase 2 of implementing the NRC recommendations, EPA is improving the IRIS assessment template to substantially reduce the volume of text and address redundancies and inconsistencies in assessments. The new template provides a clear explanation of the literature review search strategy, study selection criteria, and methods used to develop the assessment. It also provides clear descriptions of the decision-making process that EPA uses in developing hazard identification and dose-response modeling.

The new document structure includes an *Executive Summary* in the beginning of each assessment that provides a concise summary of the major conclusions of the assessment related to hazard characterization and dose response analyses. Additionally, a newly developed *Preamble* describes the methods used to develop the assessment. Each assessment will include information on the literature search strategy used to develop the document, as well as the evaluation criteria and rationale used to make decisions about including and excluding studies in the assessment. Additional details about the *Preamble* and literature search strategy are found in Sections VII B and C of this report.

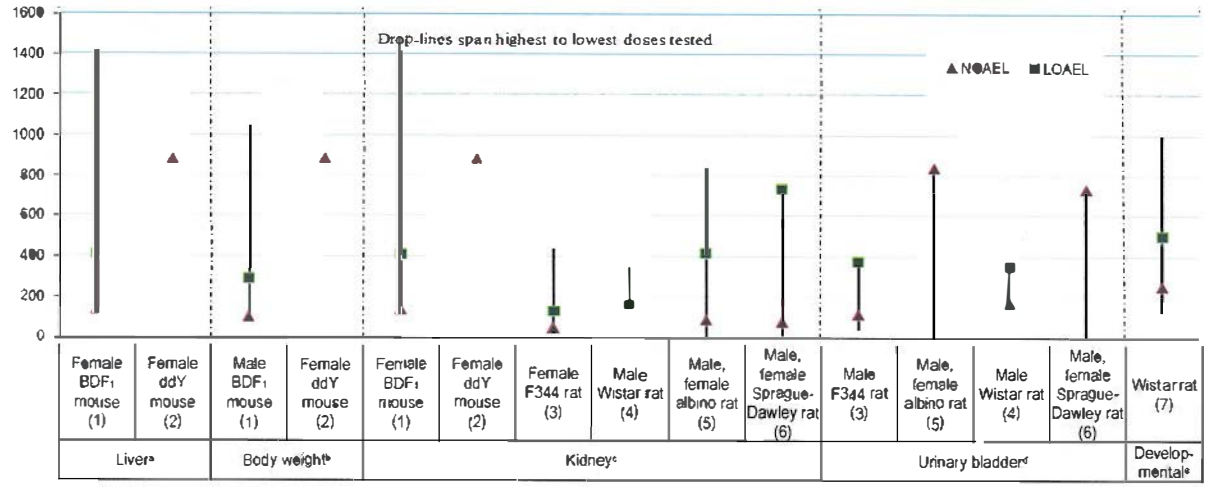
As part of the new document structure, EPA is reorganizing the main body of the assessment into two sections, *Hazard Identification* and *Dose-Response Analysis*, to help further reduce the volume of text and redundancies. Information on chemical and physical properties and toxicokinetics is being moved to a supplemental materials appendix which will improve the flow of the document.

In the *Hazard Identification* chapter of the new document template, EPA will use evidence tables to present the key study findings that support how toxicological hazards are identified. Exposure-response arrays will be used as visual tools to inform the analysis. This chapter will provide a strengthened and more integrated and transparent discussion of the weight of the available evidence supporting the findings related to the chemical's hazard and toxicity. EPA also is developing standardized study summary tables, which will be included in the supplemental materials appendices, to present more detailed study summary information and key study characteristics.

EPA has used several of these approaches in the past in developing IRIS assessments and the IRIS Program will use these approaches consistently moving forward. For example, EPA's draft IRIS Toxicological Review of Biphenyl, which was released for public comment and external peer review in September 2011, includes exposure-response arrays to provide a visual representation of points of departure for various effect endpoints resulting from exposure to the chemical. These arrays support EPA's decision-making in developing the toxicity analysis (e.g., identifying doses associated with specific effects; selecting critical studies and effects; etc.). Figure 4, below, provides an example of an exposure-response array presented in the draft IRIS Toxicological Review of Biphenyl.[13]

[13] US Environmental Protection Agency. Draft Toxicological Review of Biphenyl. EPA/635/R-11/005A. September 2011.

Figure 4. Exposure-response array, External Peer Review Draft IRIS Toxicological Review of Biphenyl



[a]Increased plasma liver enzymes in BDF_1 mice.
[b]Decreased body weight (>10% lower than controls) in BDF_1 mice.
[c]Increased incidences of kidney lesions including: mineralization in outer medulla in BDF_1 mice; renal pelvis transitional cell hyperplasia and hemosiderin deposits in F344 rats; kidney stone formation in Wistar rats; renal tubular atrophy in albino rats; renal tubular dilatation in Sprague-Dawley rats.
[d]Increased incidences of urinary bladder calculi or stones and hyperplasia in F344 rats and Wistar rats.
[e]Increased number of litters with fetal skeletal anomalies in Wistar rats.

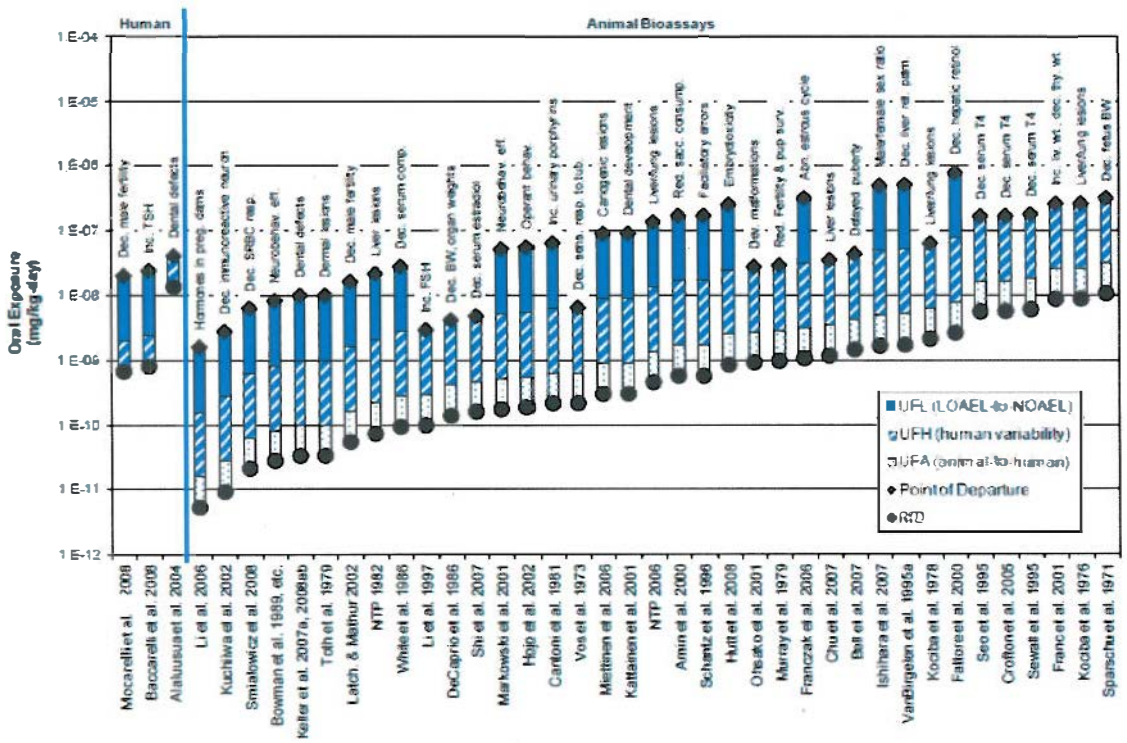
(1) = Umeda et al., 2005; (2) = Imai et al., 1983; (3) = Umeda et al., 2002; (4) = Shiraiwa et al., 1989; (5) = Ambrose et al., 1960; (6) = Dow Chemical Co., 1953; (7) = Khera et al., 1979

The *Dose-Response Analysis* section of the new document structure provides a clear explanation of the rationale used to select and advance studies for consideration in calculating toxicity values. Key data supporting the dose-response analysis are reported and the methodology and derivation of toxicity values are described. In addition, details of the dose-response analysis, including the data, models, methods, and software, are provided in an appendix and described in sufficient detail to allow for independent replication and verification. The section also includes figures showing candidate reference values for comparison across studies and endpoints. Finally, the *Dose-Response Analysis* section of the new document structure includes clear documentation of the conclusions and estimation of the toxicity values.

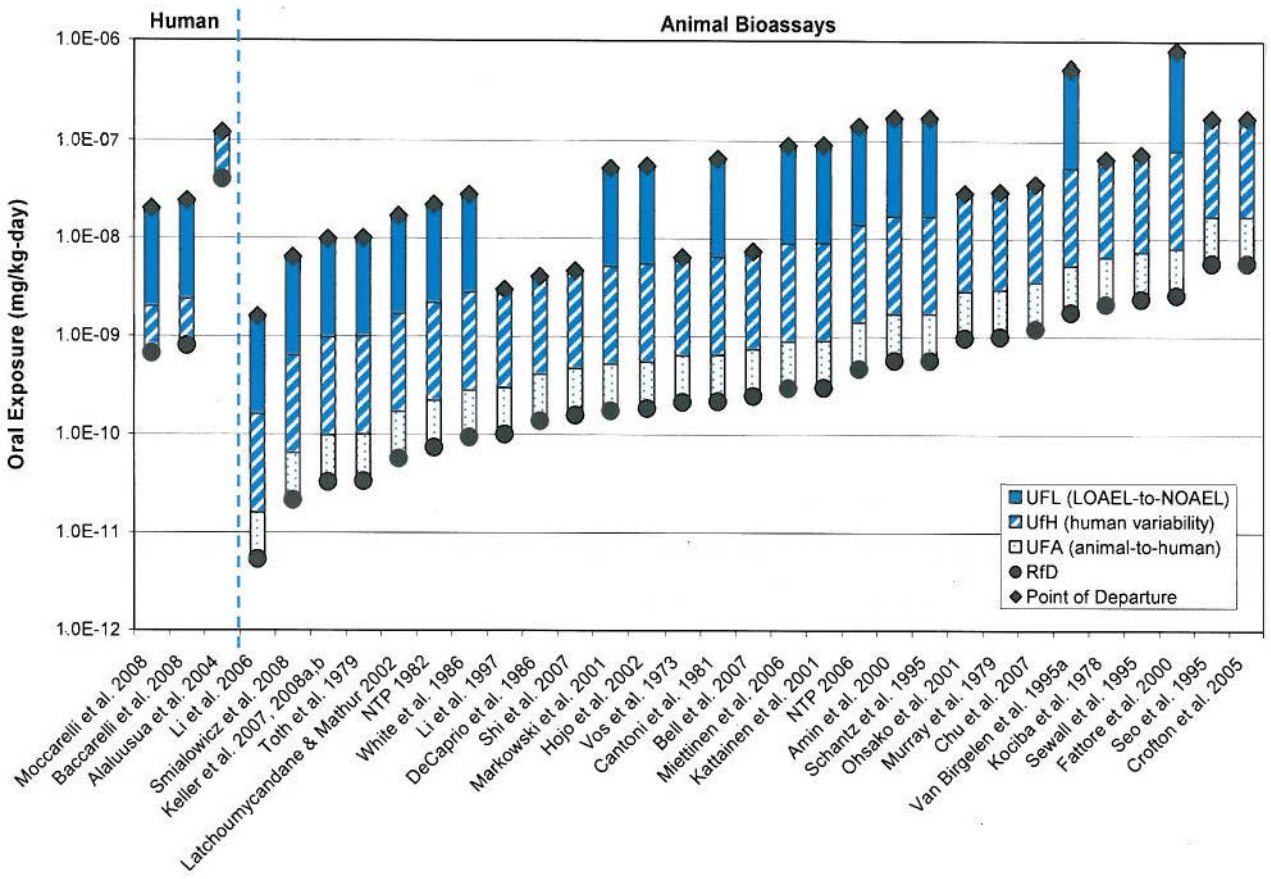
EPA has used reference value arrays in the past and has received positive feedback from independent reviewers on this approach. These types of arrays will be used on a routine basis in the future where the data allow. For example, EPA's 2010 draft "Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments" (dioxin reanalysis) provided an array of candidate reference doses. This

is illustrated in Figure 5. The Science Advisory Board (SAB), in their review of the draft dioxin reanalysis, noted that "Figures 4.3 and 4.4 in the Report show quantitative comparisons across the RfDs and benchmark dose lower bounds calculated from the animal and epidemiological studies. These figures are useful in understanding the quantitative similarities...in these calculations."[14]

Figure 5. Reference value array from EPA's 2010 draft "Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments"



[14] U.S. Environmental Protection Agency Science Advisory Board, EPA-SAB-011-014. SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (May 2010). August 2011.



B. *IRIS Assessment Preamble*

In their review report, the NRC recommended that EPA expand Chapter 1 of IRIS assessments to "describe more fully the methods of the assessment, including a description of search strategies used to identify studies with the exclusion and inclusion criteria clearly articulated and a better description of the outcomes of the searches (a model for displaying the results of literature searches is provided later in this chapter) and clear descriptions of the weight-of-evidence approaches used for the various noncancer outcomes. The committee emphasizes that it is not recommending the addition of long descriptions of EPA guidelines to the introduction, but rather clear and concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates."[15]

In accordance with this NRC recommendation, and as part of Phase 2 of implementation, EPA is replacing Chapter 1 of IRIS assessments with a *Preamble* that will describe the application of existing

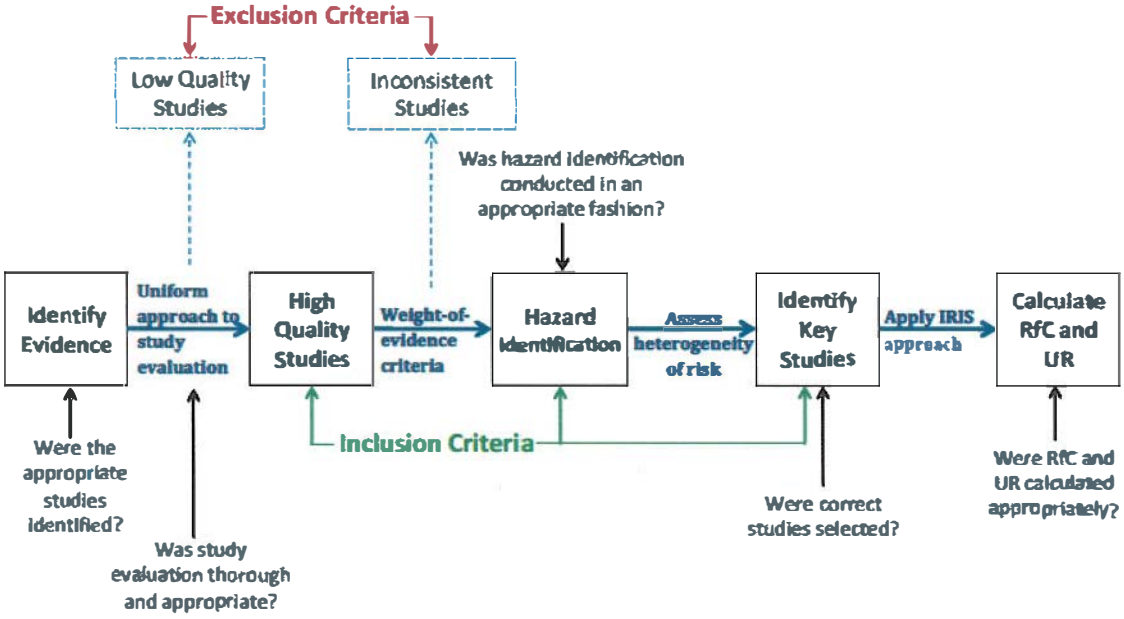
[15] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

EPA guidance and the methods and criteria used in developing the assessments. The term "*Preamble*" is used to emphasize that these methods and criteria are being applied consistently across IRIS assessments. The new *Preamble* includes discussions about the following topics:

- Identifying and selecting pertinent studies
- Evaluating the quality of individual studies
- Weighing the overall evidence of each effect
- Selecting studies for derivation of toxicity values
- Deriving toxicity values

These topics correspond to the five steps that the NRC identified in their review report, "Elements of the key steps in the development of a draft IRIS assessment,"[16] which is shown in Figure 6 below.

Figure 6. Elements of the key steps in the development of a draft IRIS assessment (Figure 7-2 of the NRC review report of formaldehyde)[17]



For each topic, the *Preamble* summarizes and cites EPA guidance while also incorporating other NRC recommendations. The new *Preamble*, for example, emphasizes the disclosure of literature search

[16] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.
[17] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

strategies, standardized study evaluation criteria based on the type of study, the use of evidence tables to summarize study details, strengthened and more transparent discussions of weight-of-evidence, and graphical displays of candidate toxicity values.

The *Preamble* will be included in all new IRIS assessments as they are released for external peer review. The *Preamble* will be discussed at the first public meeting of the new SAB panel that will be dedicated to reviewing IRIS assessments (additional details are provided in Section VII F).

C. *Literature Search Strategy*

EPA's new document structure includes a detailed description of the literature search strategy and study evaluation process that EPA uses to develop IRIS assessments. This description, which is part of Phase 2 of EPA's implementation of the NRC recommendations, will be included in new IRIS assessments as they are developed. In discussing the literature search strategy in IRIS assessments, EPA will describe how the scientific literature was gathered and emphasize how studies were selected to be included in the document, and, if applicable, explain the rationale for excluding potentially relevant studies from the assessment. This section of the new document structure will be specific to each chemical assessment. It is designed to provide enough information that an independent literature search would be able to replicate the results of the literature search used by EPA in developing the assessment. In this section, EPA will provide a link to an external database (www.epa.gov/hero) that contains the references that were cited in the document, along with those that were considered for inclusion in the assessment, but not cited.

D. *Weight of Evidence*

EPA is currently developing a formal framework to establish conclusions about the weight of evidence for health effects other than cancer. In the meantime, the Agency is using existing guidelines that address these issues to inform its assessments. In addition, EPA is taking a more systematic approach to analyze the available human and animal toxicity data in IRIS assessments. This is being done as part of Phase 2 of EPA's implementation of the NRC recommendations.

In conducting this analysis and developing the synthesis, EPA evaluates the data for the:

- strength of the relationship between the exposure and response and the presence of a dose-response relationship;
- specificity of the response to chemical exposure and whether the exposure precedes the effect;
- consistency of the association between the chemical exposure and response; and
- biological plausibility of the response or effect and its relevance to humans.

EPA uses this weight of evidence approach to identify the potential hazards associated with chemical exposure.

EPA recognizes the benefit of adopting a formal weight-of-evidence framework that includes standardized classification of causality. As part of Phase 3 of implementing the NRC recommendations, the Agency is planning and will convene a workshop on adapting weight-of-evidence procedures for effects other than cancer. The NRC discussed current approaches to hazard identification, which involves answering the question: Does the agent cause the adverse effect? [pp 159-160].[18] The NRC recommended that the answer to this question should be a clear statement on the strength of the evidence of causation, following a standardized classification to avoid ambiguity and to ensure comparability among different agents and outcomes. The NRC offered as examples the Surgeon General's 2004 report on smoking and the monographs of the International Agency for Research on Cancer and the U.S. National Toxicology Program.

During 2012, EPA will convene a workshop to discuss approaches to weight-of-evidence characterization. EPA will identify the various approaches that are currently in use and compare their strengths and limitations. The workshop will include scientists with expertise in the classification of chemicals for various health effects. The workshop will be open to the public, with opportunity for written and oral comments. EPA is currently discussing the workshop within the Agency and considering how it will be conducted. EPA will publicly announce details about the workshop in a Federal Register Notice and on the IRIS website (www.epa.gov/iris).

[18] National Research Council, 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

EPA will consider the comments and discussions from the workshop to either adopt or adapt existing approaches to weight-of-evidence classification for use in subsequent IRIS assessments. These activities respond to recommendations 24-29 in Table 2.

E. Early Peer Consultation

In addition to the public listening session and public comment period that are already part of the IRIS assessment development process, EPA will increase the use of public peer consultation workshops to enhance the input of the scientific community as assessments are designed. These workshops will be open to the public with opportunity for oral and written comments. Information regarding specific peer consultation workshops will be announced to the public in advance of the meetings through a Federal Register Notice and on the IRIS website (www.epa.gov/iris). While not an explicitly stated recommendation of the NRC in the formaldehyde review report, early peer consultation workshops fit with the spirit of the NRC's overall group of recommendations. The goal of these workshops will vary. For example, the workshops may focus on the state-of-the-science for a particular chemical or provide a forum for discussion with experts about certain cross-cutting scientific issues that may impact the development of a scientifically complex assessment. The first of these peer consultation workshops will focus on mouse lung tumors as they relate to human cancer risk. This is an important issue for the IRIS assessments for naphthalene, styrene, and ethylbenzene. This workshop will be open to the public, with opportunity for oral and written comments. It is anticipated that the workshop will convene in summer 2012.

EPA has occasionally held these types of workshops in the past and the Agency plans to incorporate early peer consultation more frequently in the future. For example, in December 2010, EPA convened a peer consultation workshop, which included a panel of external independent experts, to discuss approaches to assessing the cumulative risks of mixtures of phthalates. The experts were asked to review recommendations provided by the NRC in their 2008 report, "Phthalates and Cumulative Risk: The Tasks Ahead," for evaluating the cumulative risk of mixtures of phthalates and to propose any additional methods or approaches, not captured in the NRC report, that could be appropriate to use for this type of cumulative assessment. The public was invited to register and attend the workshop as observers and give brief oral comments at the conclusion of each workshop day. Additionally, the

public was invited to provide written comments regarding the subject matter under discussion. EPA is using the comments and recommendations resulting from the workshop, including the public comments, to develop a draft cumulative assessment for six phthalates. EPA convened a similar peer consultation workshop for dioxin in 2009, hosting a public, three-day, scientific workshop to discuss key issues related to dioxin's toxicity. The results of this workshop informed EPA's development of EPA's 2010 draft "Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments."

F. Dedicated Chemical Assessment Advisory Committee

While the NRC focused their recommendations exclusively on the development of draft IRIS assessments, and did not specifically address peer review, EPA is seeking to make some changes in this area to further improve IRIS. Specifically, EPA has established a dedicated Chemical Assessment Advisory Committee, under the auspices of EPA's Science Advisory Board (SAB), to provide advice to EPA on draft IRIS Toxicological Reviews and the IRIS Program. In November 2011, EPA announced a request for the public to nominate potential panelists for a new, standing advisory panel including experts in the fields of public health, epidemiology, toxicology, modeling, biostatistics, and risk assessment.[19] The SAB will take public comment on the proposed nominated panel before assembling the final Chemical Assessment Advisory Committee.

EPA will send the first assessment to the new committee for a consultation as soon as it is established, followed by a face-to-face meeting in summer 2012. Two additional meetings with the panel are anticipated for later in the year. EPA will consult the panel for peer review of a range of IRIS assessments and seek advice on how the IRIS Program implements the NRC recommendations. A schedule for meetings and draft assessments to be reviewed is under development and will be announced to the public in a Federal Register Notice and on the IRIS website (www.epa.gov/iris).

The first assessments that will be sent to the new SAB Chemical Assessment Advisory Committee for review will be the draft IRIS assessments for ammonia and two trimethylbenzenes (1,2,4- and 1,3,5-). These draft assessments, which will be in the new document structure, will be the first released for public comment and external peer review that were developed during Phase 2 of implementation.

[19] http://www.gpo.gov/fdsys/pkg/FR-2011-11-18/pdf/2011-29916.pdf

These assessments represent a major advancement for the IRIS Program in implementing the NRC recommendations.

VIII. Conclusion

EPA's IRIS Program provides critically important health effects information on chemicals to which the public may be exposed from releases to air, water, and land and through the use and disposal of chemicals. IRIS assessments are critical to risk assessors and decision-makers at EPA and beyond. EPA's Board of Scientific Counselors (BOSC) has reviewed the IRIS Program on several occasions. They have recognized the importance and quality of the IRIS Program, noting that the IRIS website receives about 8 million visits annually, "a testament to the value of IRIS as a resource" and stating that "the comprehensiveness, transparency, and consistency of the IRIS approach have made it into the internationally recognized standard in hazard characterization."[20]

EPA recognizes and embraces this role, and understands that a strong, scientifically rigorous IRIS Program is of critical importance. Over the past two years, EPA has worked to strengthen and streamline the IRIS Program, improving transparency and increasing the number of final assessments added to the IRIS database while maintaining a firm commitment to public engagement and rigorous expert peer review. Continually improving the IRIS Program is a priority for the Agency. EPA will continue to pursue excellence in the IRIS Program, using the best science with integrity and efficiency in support of EPA's mission to protect the health of the American public.

[20] Board of Scientific Counselors Human Health Risk Assessment Research Program Review, April 2008. http://www.epa.gov/osp/bosc/pdf/hhra0804rpt.pdf

Appendix 1. Language from the "Consolidated Appropriations Act, 2012" report language[21]

Integrated Risk Information System (IRIS) – In lieu of the directives contained in H. Rept. 112-151 regarding the Integrated Risk Information System, the conferees agree to the following:

(1) Fundamental improvements to the policies and practices of this program are necessary to ensure that IRIS assessment reflect the highest standard of scientific integrity.

(2) The Agency shall incorporate, as appropriate, based on chemical-specific datasets and biological effects, the recommendations of Chapter 7 of the National Research Council's Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde into the IRIS process.

(3) The Agency shall issue a progress report to House and Senate Committees on Appropriations and relevant Congressional authorizing committees no later than March 1, 2012, describing its implementation of the National Research Council's Chapter 7 recommendations for ongoing and new assessments.

(4) For draft assessments released in fiscal year 2012, the Agency shall include documentation describing how the Chapter 7 recommendations of the National Academy of Science (NAS) have been implemented or addressed, including an explanation for why certain recommendations were not incorporated.

(5) The Agency shall contract with NAS to conduct up to three reviews of IRIS assessments that EPA seeks to make final. Reviews shall include an evaluation of whether the recommendations it made in previous reviews, including in Chapter 7 of the National Research Council's Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde, have been implemented. Reviews are not intended to unduly delay the Agency's risk assessment process. The conferees further direct NAS to complete any reviews authorized by this paragraph by no later than 18 months after the date that EPA and the NAS have agreed to the terms of the review. One of these NAS reviews shall be a study of the cancer and non-cancer hazards from oral exposure to inorganic arsenic. The NAS review of inorganic arsenic shall incorporate the direction provided in House Report 112-151 regarding parameters of the study. Additional

[21] Pub. L. No. 112-74, Consolidated Appropriations Act, 2012.

reviews will be chosen by NAS from a representational sample of IRIS assessments and NAS will notify Congress directly of these choices.

(6) Further, the conferees strongly believe any current and future IRIS assessments must not only be grounded in sound, objective, and peer-reviewed science and methodologies but should also provide risk managers with realistic values that will result in enhanced protection of human health.

Appendix 2. Timeline for Phases 1, 2, and 3 of implementing the NRC recommendations for IRIS