

**EPA'S IRIS PROGRAM:  
EVALUATING THE SCIENCE AND PROCESS  
BEHIND CHEMICAL RISK ASSESSMENT**

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**HEARING**  
BEFORE THE  
SUBCOMMITTEE ON INVESTIGATIONS AND  
OVERSIGHT  
COMMITTEE ON SCIENCE, SPACE, AND  
TECHNOLOGY  
HOUSE OF REPRESENTATIVES  
ONE HUNDRED TWELFTH CONGRESS

FIRST SESSION

THURSDAY, JULY 14, 2011

**Serial No. 112-30**

Printed for the use of the Committee on Science, Space, and Technology



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RISK ASSESSMENT**

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**EPA'S IRIS PROGRAM:  
EVALUATING THE SCIENCE AND PROCESS  
BEHIND CHEMICAL RISK ASSESSMENT**

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**THURSDAY, JULY 14, 2011**

HOUSE OF REPRESENTATIVES,  
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT,  
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY,  
*Washington, DC.*

The Subcommittee met, pursuant to call, at 10:04 a.m., in Room 2318 of the Rayburn House Office Building, Hon. Paul C. Broun [Chairman of the Subcommittee] presiding.

RALPH HALL, TEXAS  
CHAIRMAN

EDDIE BERNICE JOHNSON, TEXAS  
RANKING MEMBER

U.S. HOUSE OF REPRESENTATIVES  
**COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY**  
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Subcommittee on Investigations and Oversight  
Hearing on

***EPA's IRIS Program: Evaluating the Science and Process Behind Chemical Risk Assessment***

Thursday, July 14, 2011  
10:00 a.m.-12:00 p.m.  
2318 Rayburn House Office Building

**Witnesses**

**Panel 1**

**The Honorable Paul Anastas**

Assistant Administrator, Office of Research and Development, U.S. Environmental Protection Agency

**Mr. David Trimble**

Director, Natural Resources and Environment, U.S. Government Accountability Office

**Dr. Jonathan M. Samet, MD, MS**

Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine,  
University of Southern California; Chair, Committee to Review EPA's Draft IRIS Assessment of  
Formaldehyde, National Research Council, The National Academies

**Panel 2**

**The Honorable Calvin Dooley**

President and Chief Executive Officer, American Chemistry Council

**Ms. Rena Steinzor**

Professor, University of Maryland School of Law, and President, Center for Progressive Reform

**Dr. Gail Charnley**

Principal, HealthRisk Strategies

**The Honorable J. Christian Bollwage**

Mayor, City of Elizabeth, New Jersey

## HEARING CHARTER

**COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY  
U.S. HOUSE OF REPRESENTATIVES  
SUBCOMMITTEE ON INVESTIGATIONS & OVERSIGHT**

**EPA's IRIS Program: Evaluating the Science  
and Process Behind Chemical Risk Assessment**

THURSDAY, JULY 14, 2011  
10:00 A.M. TO 12:00 P.M.  
2318 RAYBURN HOUSE OFFICE BUILDING

**Purpose**

On July 14, 2011, the Subcommittee on Investigations and Oversight will hold a hearing on the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS). There will be two panels at the hearing; the first panel will comprise of witnesses from EPA, the U.S. Government Accountability Office (GAO), and the National Academies' National Research Council. The second panel will include individuals and experts who will talk about their perspectives on IRIS.

In March of 2008, GAO reported that "the IRIS database was at serious risk of becoming obsolete because EPA had not been able to routinely complete timely, credible assessments. After subsequent reports, in January 2009 [GAO] added EPA's processes for assessing and controlling toxic chemicals to [its] list of areas at high risk for waste, fraud, abuse, and mismanagement or in need of broad-based transformation."<sup>1</sup>

As a result, the Subcommittee held several hearings on this subject. On May 21, 2008, the Subcommittee took testimony from Dr. George Gray, the then-Assistant Administrator for Research and Development at EPA, and Ms. Susan Dudley, the then-Administrator of the Office of Information and Regulatory Affairs (OIRA). Additionally, Mr. John Stephenson of GAO testified on findings regarding the lack of productivity in the IRIS process.

On June 12, 2008, the Subcommittee received testimony from Mr. Jerry Enslinger (U.S.M.C., retired), Mr. Lenny Seigel (Executive Director, Center for Public Environmental Oversight), and Dr. Linda Greer (Director of the Health Program at the Natural Resources Defense Council).

In 2009, the Subcommittee heard from Mr. John Stephenson again, and Dr. Kevin Teichman, the Deputy Assistant Administrator for Science at EPA's Office of Research and Development. They testified about the current IRIS process announced by EPA Administrator Lisa Jackson on May 21, 2009.

These prior IRIS hearings focused on the IRIS interagency review process, and delved into the role of the White House and other agencies, to determine the extent of their involvement in IRIS' chemical risk assessments. Today's hearing, prompted in part by the National Academies' National Research Council report on EPA's formaldehyde assessment, focuses on the process EPA uses to initially develop draft IRIS assessments, which is separate from the overall process that includes the multiple layers of review. The National Academy of Sciences' (NAS) report dedicated an entire chapter that reiterated several previous criticisms of EPA's IRIS process. In light of those criticisms, and recognizing that this is not the first time NAS has articulated them, the committee's goal is to better understand the process behind the development of IRIS' chemical risk assessments, whether EPA plans on adopting the NAS' recommendations, and whether or not EPA assessments are based on the best available evidence and evaluated in accordance with established protocols.

**Background**

IRIS was established in the 1980s as an internal EPA database to provide a single source of information on the risks associated with exposure to chemicals. The IRIS

<sup>1</sup>David Trimble, Director, Natural Resources and Environment, Testimony before the Subcommittee on Investigations and Oversight, Committee on Science, Space, and Technology, July 14, 2011

database provides a hazard identification and dose-response analysis, scientific information that when combined with estimates of exposure allow regulatory agencies to produce a risk assessment. Historically, entries to the database were the result of extensive in-house development by the science staff at EPA, peer review processes with experts from outside the agency, and opportunities for public input and comment.

By the early 1990s, the chemical database contained information on roughly 500 chemicals. However, as IRIS grew and gained more influence, EPA decided to restructure the IRIS process, which unfortunately led to the demise of the heretofore successful collaborative platform. This restructuring ultimately led to several reorganizations of the IRIS process (*see Appendix B*), with the most recent one announced by EPA Administrator Lisa Jackson on May 21, 2009.

In 2009, GAO testified before this Subcommittee that EPA “has not been able to complete timely, credible chemical assessments or decrease its backlog of 70 [as of 2008] ongoing assessments.”<sup>2</sup> Further, GAO reported, “because EPA staff time was dedicated to completing assessments in the backlog, EPA’s ability to both keep the more than 540 existing assessments up to date and initiate new assessments was limited. We found that 48 of the 70 assessments being conducted as of December 2007 had been in process for more than 5 years-and 12 of those, for more than nine years. These time frames have lengthened. Currently, of those 70 assessments, 58 have now been ongoing for more than 5 years-and 31 of those for more than 9 years.”<sup>3</sup>

The IRIS database currently includes 554 chemicals. Since GAO last reported, EPA completed six assessments in 2009 and ten assessments in 2010. These numbers are far below the twenty assessments EPA planned to finalize in 2010.<sup>4</sup> Moreover, 70 chemicals continue to remain in various stages of review.

Further compounding the problem, EPA line offices are no longer required to concur with IRIS assessments and internal EPA comments are still not transparent. The quality of assessments being produced also continues to be an issue. Since 2005, five assessments have been referred to the National Academies’ for evaluation. All of the NAS reviews have severely criticized EPA’s assessments, and offered numerous recommendations, which EPA has yet to implement.

## Issues

### NAS: “Review of the Environmental Protection Agency’s Draft IRIS Assessment of Formaldehyde”

On April 8 of this year, NAS published its long-awaited study on EPA’s formaldehyde assessment. While NAS “strongly questioned EPA claims that exposure to formaldehyde can result in increased risk of a leukemia and other cancers that had not previously been associated with formaldehyde, asthma, and reproductive toxicity,”<sup>5</sup> that is not the most compelling part of the document for the purposes of this hearing. Of interest is that the NAS panel “strongly faulted EPA’s methodology in crafting its draft assessment, warning of a pattern of problems in how the agency crafts assessments for its Integrated Risk Information System (IRIS) database that could continue to hamper future risk studies. The committee is concerned about the persistence of problems encountered with IRIS assessments over the years, especially given the multiple groups that have highlighted them . . . If the methodologic issues are not addressed, future assessments may still have the same general and avoidable problems that are highlighted here.”<sup>6</sup>

In the summary of the report, the panel commented on the similarities in some of the problems with the IRIS assessment on formaldehyde, and those identified in other reports published by previous NAS panels:

“Overall, the committee noted some recurring methodologic problems in the draft IRIS assessment of formaldehyde. Many of the problems are similar to those which have been reported over the last decade by other NRC committees tasked with re-

<sup>2</sup>John B. Stephenson, Director, Natural Resources and Environment, Testimony before the Subcommittee on Investigations and Oversight, Committee on Science and Technology, June 11, 2009

<sup>3</sup>Ibid.

<sup>4</sup>“Update on Integrated Risk Information System (IRIS) Program Activities,” EPA, Office of Research and Development, National Center for Environmental Assessment (NCEA) (hereinafter NCEA IRIS document)

<sup>5</sup>Maria Hegstad, “NAS Sets Back EPA Proposal For Strict Formaldehyde Risk Assessment,” Environmental NewsStand, April 8, 2011

<sup>6</sup>Ibid.

viewing EPA's IRIS assessments for other chemicals. Problems with clarity and transparency of the methods appear to be a repeating theme over the years, even though the documents appear to have grown considerably in length. In the roughly 1,000-page draft reviewed by the present committee, little beyond a brief introductory chapter could be found on the methods for conducting the assessment. Numerous EPA guidelines are cited, but their role in the preparation of the assessment is not clear. In general, the committee found that the draft was not prepared in a consistent fashion; it lacks clear links to an underlying conceptual framework; and 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."<sup>7</sup>

*Please see Appendix A for detailed recommendations from the NAS report.*

#### NAS: "Science and Decisions: Advancing Risk Assessment"<sup>8</sup>

Dr. Thomas Burke, associate dean of The Johns Hopkins Bloomberg School of Public Health, recently chaired an NAS panel on "ways to improve EPA risk assessments."<sup>9</sup> At a joint meeting of EPA's Science Advisory Board and EPA's Board of Scientific Counselors, Dr. Burke said, "The sleeping giant is that EPA science is on the rocks . . . if you fail, you become irrelevant, and that is kind of a crisis."<sup>10</sup> Referring to EPA's risk assessment process as the agency's "Achilles heel,"<sup>11</sup> Dr. Burke's NAS panel suggested steps on how EPA could improve that process in a 2009 report titled, "Science and Decisions: Advancing Risk Assessment." This report carries added weight in light of the NAS report on formaldehyde issued earlier this year with its chapter critical of EPA's IRIS process.

#### NTP's RoC

The Department of Health and Human Services' (HHS) National Toxicology Program (NTP) publishes a report every Congress called the Report on Carcinogens (RoC).<sup>12</sup> On June 10 of this year, the Twelfth RoC was released, and it elevated its classification of formaldehyde from 'reasonably anticipated to be a human carcinogen' to 'known to be a human carcinogen.' The report was published despite the NAS review. This is important because according to an analytic paper, NTP has:

"been reviewing the scientific data for formaldehyde in preparation for a listing decision in the 12th Report on Carcinogens (RoC). EPA and the NTP have had available, reviewed and relied upon the same studies, reports and underlying data in conducting their respective hazard evaluations of the possible relationship between formaldehyde exposure and leukemia and other lymphohematopoietic malignancies. **Therefore, the NRC committee's review of and conclusions concerning the draft EPA IRIS report are, with respect to lymphohematopoietic malignancies (including myeloid leukemia), directly applicable to the NTP's own review and conclusions—precisely because the draft EPA and NTP reports involve the same studies and data sets.**"<sup>13</sup>

Further:

<sup>7</sup>"Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde," National Research Council of the National Academies, April 8, 2011 (hereinafter NAS Formaldehyde Report)

<sup>8</sup>"Science and Decisions: Advancing Risk Assessment," National Research Council of the National Academies, 2009

<sup>9</sup>"Key Advisor Warns EPA to Improve Agency Science or Face a —Crisis," InsideEPA.com, July 8, 2011

<sup>10</sup>Ibid.

<sup>11</sup>Ibid.

<sup>12</sup>Maria Hegstad, "NAS Critique of EPA Formaldehyde Study Hampers HHS —Cancer' Report," Environmental NewsStand, April 26, 2011. "Congress directed the program to prepare the report every other year, but due to concerns over the review process for the document, the last RoC was published in 2005. The RoC provides information on chemicals that NTP deems carcinogenic or reasonably anticipates to be human carcinogens, along with people's potential for exposure to them."

<sup>13</sup>"National Research Council Report on Scientific Evidence Pertaining to the Relationship Between Formaldehyde Exposure and Leukemia: Implications for the National Toxicology Program's Listing of Formaldehyde in the 12th Report on Carcinogens," Environ International Corporation, April 22, 2011 (emphasis in original text)

“The NRC committee’s opinion was that EPA’s review of the scientific literature as presented in the draft IRIS assessment does not provide a sufficient scientific basis for concluding that there is a causal link between formaldehyde exposure and leukemia. The NRC committee’s conclusions concerning EPA’s assessment of leukemia apply as well to application of the ‘listing criteria’ for formaldehyde in the NTP’s 12th RoC. **In particular, there is no reasonable basis for the NTP to conclude that formaldehyde should be listed in the 12th RoC as being either ‘known’ or ‘reasonably anticipated’ to cause myeloid leukemia or any other lymphohematopoietic malignancy.**”<sup>14</sup>

The RoC’s more serious listing of formaldehyde could possibly influence EPA’s own assessment relating to formaldehyde and leukemia, despite NAS’ comments. Conversely, if EPA reassesses its formaldehyde review and comes to a different conclusion, then that raises questions about conflicting information from two different government entities, which may cause confusion downstream as risk managers and regulators try to understand which determination is more reliable.

### EPA’s SAB

Under the current process, EPA’s Science Advisory Board (SAB) is responsible for peer reviewing EPA’s IRIS assessments. However, “there have been questions in the past, including some raised by [EPA’s] Inspector General about the independence of the SAB panels.”<sup>15</sup> (Second footnote from passage)<sup>16</sup>The charge questions that lead SAB peer reviews are “written by the EPA office requesting the review and which industry says can narrow the focus of the reviews. Sources also say the panels do not include a broad-enough roster of experts. For example, the SAB panel that recently reviewed EPA’s IRIS assessment for inorganic arsenic\* \* \*did not include a statistician or a cancer modeling expert and only one epidemiologist.”<sup>17</sup>

### IRIS Assessments are not Insulated from Risk Management

In the NAS’ 1983 report, “Risk Assessment in the Federal Government: Managing the Process,” the National Research Council panel identified four components of a complete risk assessment:

- hazard identification;
- dose-response evaluation;
- exposure assessment; and
- risk characterization.<sup>18</sup>

IRIS reflects science that addresses the first two conditions. In discussing the difference between risk assessment and risk management, the Academy panel wrote:

“Risk assessment is the use of the factual base to define the health effects of exposure of individuals or populations to hazardous materials and situations. Risk management is the process of weighing policy alternatives and selecting the most appropriate regulatory action, integrating the results of risk assessment with engineering data and with social, economic and political concerns to reach a decision.”<sup>19</sup>

This distinction is commonly cited when IRIS assessments are criticized. When assessments make determinations that safe levels are below background levels, the IRIS program can reasonably claim that such factors can be weighed later in the risk management process. In reality, IRIS assessments are usually adopted with no further consideration. “[S]ome customers use IRIS because it is a useful source of information; while for other customers IRIS is mandatory, and those customers include state agencies. Customers who use IRIS for general information often rely upon other databases to complement an IRIS assessment. Other databases exist, which can provide some help, but for domestic regulatory purposes there is no satis-

<sup>14</sup> Ibid. (emphasis in original text)

<sup>15</sup> Aaron Lovell, “Rebuffed by EPA, Industry Asks OMB, GOP to Fix Chemical Study Process,” Environmental NewsStand.com, June 22, 2011 (hereinafter Lovell Article)

<sup>16</sup> U.S. EPA Office of Inspector General, “EPA can Improve its Process for Establishing Peer Review Panels,” Evaluation Report No. 09–P-0147, April 29, 2009

<sup>17</sup> Lovell Article, *supra*, note 11

<sup>18</sup> National Research Council, National Academy of Sciences, “Risk Assessment in the Federal Government: Managing the Process,” 1983

<sup>19</sup> Ibid.



factory alternative to IRIS. And using an IRIS file as the scientific basis for a regulatory decision is expected and seldom challenged.”<sup>20</sup>

## Witnesses

### PANEL 1

- *The Honorable Paul Anastas*, Assistant Administrator, Office of Research and Development, U.S. Environmental Protection Agency. Dr. Anastas will talk about EPA’s efforts to implement the most recent revised IRIS process, provide a status of assessments, and discuss EPA’s efforts to implement NAS’ and GAO’s recommendations.
- *Mr. David Trimble*, Director, Natural Resources and Environment, U.S. Government Accountability Office. Mr. Trimble will provide an overview of IRIS, highlight previous GAO work on IRIS, and evaluate EPA’s efforts to implement GAO’s recommendations.
- *Dr. Jonathan M. Samet*, MD, MS, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine, University of Southern California; and Chair, Committee to Review EPA’s Draft IRIS Assessment of Formaldehyde, National Research Council, The National Academies. Dr. Samet will highlight the NAS’ recent work on IRIS, and detail NAS’ recommendations contained in chapter seven of their recently release report on formaldehyde.

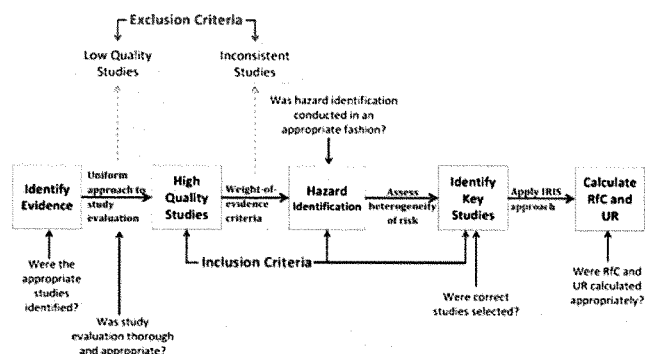
### PANEL 2

- *The Honorable Calvin Dooley*, President and Chief Executive Officer, American Chemistry Council. Mr. Dooley will talk about IRIS and industry’s perspective on the IRIS process.
- *Ms. Rena Steinzor*, Professor, University of Maryland School of Law, and President, Center for Progressive Reform. Ms. Steinzor will talk about IRIS, and offer suggestions on how to improve it and remove it from GAO’s high risk series.
- *Dr. Gail Charnley*, Principal, HealthRisk Strategies. Dr. Charnley will talk about IRIS, offer suggestions on how to improve it and remove it from GAO’s high risk series, and discuss the NAS’ recommendations.
- *The Honorable J. Christian Bollwage*, Mayor, City of Elizabeth, New Jersey. Mayor Bollwage will talk about how IRIS assessments impact local communities, particularly Elizabeth, New Jersey.

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<sup>20</sup>Jim Solyst, “Eyeballing IRIS,” The Environmental Forum, March/April 2009, Vol 26, No.

## Appendix A<sup>21</sup>



**FIGURE 7-2** Elements of the key steps in the development of a draft IRIS assessment. Abbreviations: IRIS, Integrated Risk Information System; RfC, reference concentration; and UR, unit risk.

### Reframing the Development of the IRIS Assessment

The committee was given the broad charge of reviewing the formaldehyde draft IRIS assessment and also asked to consider some specific questions. In addressing those questions, the committee found, as documented in Chapter 2, that some problems with the draft arose because of the processes and methods used to develop the assessment. Other committees have noted some of the same problems. Accordingly, the committee suggests here steps that EPA could take to improve IRIS assessment through the implementation of methods that would better reflect current practices. The committee offers a roadmap for changes in the development process if EPA concludes that such changes are needed. The term *roadmap* is used because the topics that need to be addressed are set out, but detailed guidance is not provided because that is seen as beyond the committee's charge. The committee's discussion of a reframing of the IRIS development process is based on its generic representation provided in Figure 7-2. The committee recognizes that the changes suggested would involve a multiyear process and extensive effort by the staff of the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others. The recent revision of the NAAQS review process provides an example of an overhauling of an EPA evidence-review and risk-assessment process that took about 2 years.

In the judgment of the present and past committees, consideration needs to be given to how each step of the process could be improved and gains made in transparency and efficiency. Models for conducting IRIS reviews more effectively and efficiently are available. For each of the various components (Figure 7-2), methods have been developed, and there are exemplary approaches in

<sup>21</sup> NAS Formaldehyde Report, *supra*, note 7. The following information is available in Chapter 7 of the report.

assessments carried out elsewhere in EPA and by other organizations. In addition, there are relevant examples of evidence-based algorithms that EPA could draw on. Guidelines and protocols for the conduct of evidence-based reviews are available, as are guidelines for inference as to the strength of evidence of association and causation. Thus, EPA may be able to make changes in the assessment process relatively quickly by drawing on appropriate experts and selecting and adapting existing approaches.

One major, overarching issue is the use of weight of evidence in hazard identification. The committee recognizes that the terminology is embedded in various EPA guidelines (see Appendix B) and has proved useful. The determination of weight of evidence relies heavily on expert judgment. As called for by others, EPA might direct effort at better understanding how weight-of-evidence determinations are made with a goal of improving the process (White et al. 2009).

The committee highlights below what it considers critical for the development of a scientifically sound IRIS assessment. Although many elements are basic and have been addressed in the numerous EPA guidelines, implementation does not appear to be systematic or uniform in the development of the IRIS assessments.

#### **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; for example, include standard approaches for reviews of various types of studies to ensure uniformity.
- Assess disciplinary structure of teams needed to conduct the assessments.

#### **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, 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**

- 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.

#### **Weight-of-Evidence Evaluation: Synthesis of Evidence for Hazard Identification**

- Review use of existing weight-of-evidence guidelines.
- Standardize approach to using weight-of-evidence guidelines.
- Conduct agency workshops on approaches to implementing weight-of-evidence guidelines.

- Develop uniform language to describe strength of evidence on noncancer effects.
- Expand and harmonize the approach for characterizing uncertainty and variability.
- To the extent possible, unify consideration of outcomes around common modes of action rather than considering multiple outcomes separately.

#### **Selection of Studies for Derivation of Reference Values and Unit Risks**

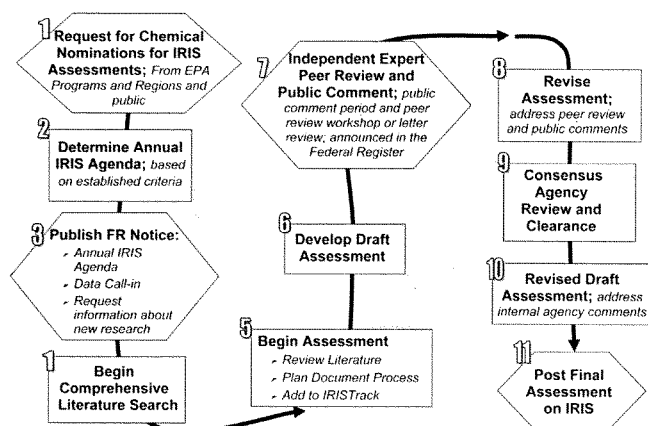
- Establish clear guidelines for study selection.
  - Balance strengths and weaknesses.
  - Weigh human vs experimental evidence.
  - Determine whether combining estimates among studies is warranted.

#### **Calculation of Reference Values and Unit Risks**

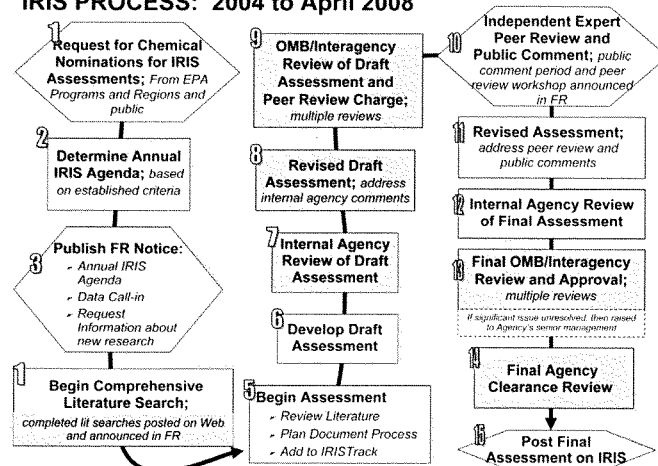
- Describe and justify assumptions and models used. This step includes review of dosimetry models and the implications of the models for uncertainty factors; determination of appropriate points of departure (such as benchmark dose, no-observed-adverse-effect level, and lowest observed-adverse-effect level), and assessment of the analyses that underlie the points of departure.
- 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.
- 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.
- 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.

## Appendix B<sup>22</sup>

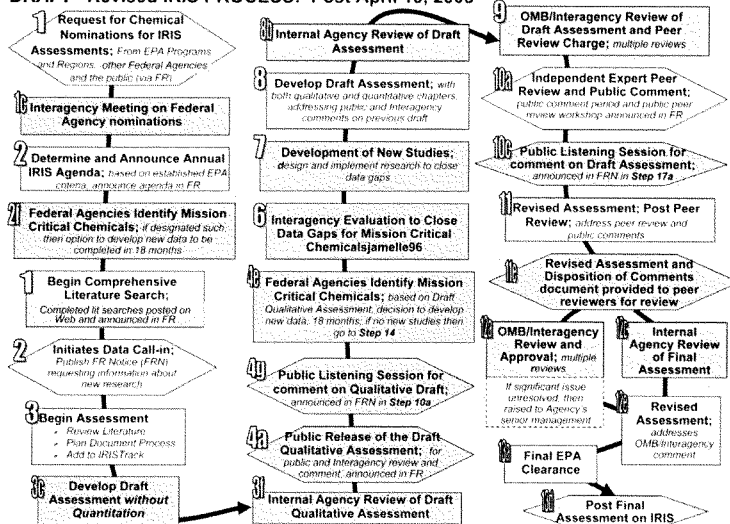
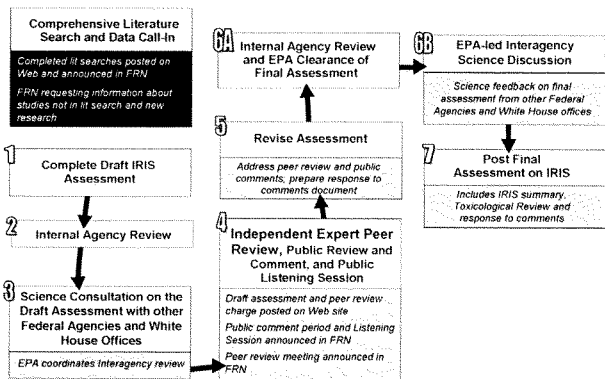
### IRIS PROCESS: Pre-2004



### IRIS PROCESS: 2004 to April 2008



<sup>22</sup> These figures are from EPA.

**DRAFT Revised IRIS PROCESS: Post April 10, 2008****Assessment Development Process for New IRIS**

Appendix C<sup>23</sup>Recently Completed Health  
Assessments

## FY2009

- Nitrobenzene
- Cerium
- Chlordecone
- 2-hexanone
- 1,2,3-trichloropropane
- Thallium



## FY2010

- Acrylamide
- Carbon tetrachloride
- EGBE
- 1,4-dioxane
- Hydrogen cyanide
- Cis- and trans-1,2-dichloroethylene
- 1,1,2,2-tetrachloroethane
- Pentachlorophenol
- Chloroprene

<sup>23</sup> NCEA IRIS document, *supra*, note 4

Appendix D<sup>24</sup>

## Active Chemicals on the IRIS Agenda

- |                      |                                   |                                    |
|----------------------|-----------------------------------|------------------------------------|
| •Acetaldehyde        | •Dibutyl phthalate                | •MTBE                              |
| •Acrylonitrile       | •1,2-, 1,3-, 1,4-dichlorobenzenes | •Naphthalene                       |
| •Arsenic (cancer)    | •Dichloromethane                  | •Nickel                            |
| •Arsenic (noncancer) | •Disobutyl phthalate              | •PAH mixtures                      |
| •Asbestos (Libby)    | •Disononyl phthalate              | •PCBs (noncancer)                  |
| •BBP                 | •Diethyl phthalate                | •Phthalate cumulative assessment   |
| •Benzo[a]pyrene      | •1,4 dioxane (inhalation)         | •Platinum                          |
| •Beryllium (cancer)  | •Dioxin                           | •RDX                               |
| •Biphenyl            | •Dipentyl phthalate               | •Tetrachloroethylene               |
| •N-butanol           | •ETBE                             | •Tetrahydrofuran                   |
| •T-butanol           | •Ethylene oxide (cancer)          | •Trichloroacetic acid              |
| •Cadmium             | •Formaldehyde                     | •Trichloroethylene                 |
| •Chloroform          | •Hexabromocyclododecane           | •1,2,4- and 1,3,5-trimethylbenzene |
| •Chromium VI         | •Hexachlorobutadiene              | •Uranium                           |
| •Cobalt              | •Hexachloroethane                 | •Urea                              |
| •Copper              | •Methanol                         | •Vanadium pentoxide                |
| •DEHA                | •Mirex                            | •Vinyl acetate                     |
| •DEHP                |                                   |                                    |

<sup>24</sup> Ibid.



**Appendix E**<sup>25</sup>

### Selected Major Upcoming Assessment Products

Chemical	Step in IRIS Process	Target Date for Posting
Arsenic (cancer)	Focused 2 <sup>nd</sup> external peer review (SAB) report received Feb 2011	Aug 2011
Chromium VI	External peer review (independent panel meets May 2011)	Sep 2011
Dioxin	External peer review (SAB)	Dec 2011
Formaldehyde	External peer review (NAS)	TBD
Halogenated Platinum Salts	Agency/interagency review	Sep 2011
Libby amphibole asbestos	Agency review	Sep 2012
PCBs (noncancer)	Draft development	Sep 2012
Phthalates cumulative assessment	Draft development	Sep 2012
Polycyclic aromatic hydrocarbon (PAH) mixtures	External peer review (SAB) report received Mar 2011	Dec 2011
Tetrachloroethylene (perc)	External peer review (NAS)	Jul 2011
Trichloroethylene (TCE)	External peer review (SAB)	Sep 2011

10

<sup>25</sup> Ibid.

Appendix F<sup>26</sup>

## Key Terms

- **Reference Concentration (RfC):** an estimate of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments.
- **Reference Dose (RfD):** An estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments.
- **Inhalation Unit Risk (IUR):** The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1  $\mu\text{g}/\text{m}^3$  in air. The interpretation of inhalation unit risk would be as follows: if unit risk =  $2 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3$ , 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1  $\mu\text{g}$  of the chemical per  $\text{m}^3$  of air.
- **Oral slope factor (OSF):** An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime oral exposure to an agent. This estimate is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100.

<sup>26</sup> Ibid.

Chairman BROWN. The Subcommittee on Investigations and Oversight will come to order. Good morning, everyone. Welcome to today's hearing titled EPA's IRIS Program: Evaluating the Science and Process Behind Chemical Risk Assessment. You will find in front of you packets containing our witnesses'—our witness panels' written testimony, biographies, and truth in testimony disclosure.

I recognize myself for five minutes for an opening statement.

Good morning. I want to welcome our witnesses here today.

This hearing continues the committee's work on EPA's Integrated Risk Information System or IRIS. The committee has held a number of hearings over the last few years on IRIS's ability to produce risk assessments associated with exposure to chemicals. In 2009, GAO placed the program on its High Risk Series because EPA was unable to complete timely, credible chemical assessments or decrease its backlog of ongoing assessments.

Over the last decade, the IRIS Program has gone through a number of changes, particularly to the process by which its assessments are reviewed. These changes were meant to address the inappropriate influence of the White House, regulated agencies, and industry on the IRIS process; the argument being that these entities were preventing assessments from being finalized. Despite these changes, the process implemented by EPA in 2009 still allows for White House input, and the program still has a backlog of over 70 assessments, unchanged from the previous Administration.

While EPA seems to be taking steps to adopt the recommendations of GAO regarding outside review, they have uniformly ignored the recommendations of another body, the National Academy of Sciences. For several years now they, too, have offered recommendations related to IRIS. These recommendations, however, did not focus on the review process but rather on how EPA develops the draft assessments in the first place. Time and time again, draft assessments were sent to the NAS for review, only to be severely criticized. Rather than adopting the recommendations of the Academy and updating their processes, EPA continued to churn out assessments that were summarily rebuked.

As I stated at our 2009 hearing, "The competing priorities of issuing assessments in a timely manner and producing assessments that are scientifically credible are central to the problems we face today." That statement remains just as true today as it did two years ago. Up until now, EPA has blamed outside forces for the failures of the program. In reality, they, too, are to blame. The program's credibility is threatened when it continually puts forth assessments that fail to address fundamental issues raised by reviewers. If, as the old adage goes, the definition of insanity is doing the same thing over and over and expecting a different result, then this program needs some therapy.

Adopting the NAS recommendations is the first step to restoring the program's credibility. EPA's announcement 2 days ago is a step in the right direction, but the program's success hinges on its implementation. As the Academy noted in its formaldehyde report, many of the concepts and approaches they recommended are elementary and already exist in EPA's guidelines. They went on to state, "The current state of the formaldehyde draft IRIS assessment suggests that there might be a problem with the practical im-

plementation of the guidelines in completing the IRIS assessments.”

Following through is the key here. It is up to the EPA to not only adopt the NAS recommendations but to also follow its own existing guidelines. This committee will continue its oversight of the IRIS program to ensure that EPA not only adopts the NAS recommendations, but that it follows guidelines already in existence and continuously seeks to employ the most modern, credible methods and protocols to assess chemical risks.

I have a lot of questions about this program and where it is headed. As GAO stated in their testimony in 2009, “EPA needs to hold itself more accountable to the public and Congress for carrying out this important component of its mission, especially since the IRIS program is discretionary.”

As a physician myself, I understand the stakes that we are dealing with, particularly for sensitive populations such as children, pregnant women, and the elderly. I want to make sure that they are protected from undue harm. I also am aware of the damage caused by overly-conservative measures that scare our citizens without reason, ultimately doing nothing to advance safety. The opening line of the NAS’s report titled, “Science and Decisions,” stated, “Virtually every aspect of life involves risk.” It is how we assess and manage that risk that ensures our safety.

[The prepared statement of Mr. Broun follows:]

#### PREPARED STATEMENT OF CHAIRMAN PAUL BROUN

Good morning. I want to welcome our witnesses here today.

This hearing continues the committee’s work on the EPA’s Integrated Risk Information System, or “IRIS.” The Committee has held a number of hearings over the last few years on IRIS’s ability to produce risk assessments associated with exposure to chemicals. In 2009, GAO placed the program on its High Risk Series because EPA was unable to complete timely, credible chemical assessments or decrease its backlog of ongoing assessments.

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While EPA seems to be taking steps to adopt the recommendations of GAO regarding outside review, they have uniformly ignored the recommendations of another body - the National Academy of Sciences. For several years now, they too have offered recommendations related to IRIS. These recommendations, however, did not focus on the review process, but rather on how EPA develops the draft assessments in the first place. Time-and-time-again, draft assessments were sent to the NAS for review, only to be severely criticized. Rather than adopting the recommendations of the Academy, and updating their processes, EPA continued to churn out assessments that were summarily rebuked.

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As a physician myself, I understand the stakes we are dealing with—particularly for sensitive populations such as children, pregnant women, and the elderly. I want to make sure they are protected from undue harm. I also am aware of the damage caused by overly conservative measures that scare our citizens without reason, ultimately doing nothing to advance safety. The opening line of the NAS's report titled Science and Decisions stated, "[v]irtually every aspect of life involves risk." It is how we assess and manage that risk that ensures our safety.

I now recognize the Ranking Member from Maryland for her opening statement.

Chairman BROWN. Now I recognize the Ranking Member from Maryland for her opening statement. I recognize Ms. Edwards for five minutes.

Ms. EDWARDS. Good morning, and thank you, Mr. Chairman.

For 50 years the tobacco industry has waged an organized campaign to cast doubt on the health risks of smoking cigarettes. They invented the effort to use science to fight science, to harness industry-funded research and public relations efforts, and to use friendly, public officials and FORA to point to these manufactured uncertainties in opposing any effort to protect the public.

During that entire time public health experts have known absolutely that smoking causes cancer and that smoking remains in the words of the surgeon general, "the single most important preventable cause of death in our society." This model of industry-funded science is being used to generate uncertainty and postpone even minor regulatory steps, regardless of the effects on public health and repeated with gusto by other industries.

A similar campaign is being waged by the fossil fuel industry to cast doubt on the science of climate change, and today we are going to see some of this unfolding, surrounding EPA's science-based efforts to develop risk assessments related to health consequences of chemicals that Americans are exposed to commonly.

Industry tends to push for two things in the realm of science and regulation. First they demand that we must have certainty before any action can be taken, and second, they point to studies that suggest there is uncertainty. What they don't mention quite so prominently is that the industry funds the production of studies designed to so doubt. That manufactured doubt is then used to justify inaction because obviously, there is no certainty. The result is gridlock. The country ends up in an endless loop of science, research, science, research that is expensive and counterproductive and making it almost impossible to ever make a statement about the harm of anything.

With enough money and enough willing researchers, there is always money and there are always willing payees. Industry can be certain that there is always another study just around the corner, no matter the chemical or the consensus regarding its harm with the industry, generally hoping that the study will show no harm.

In this world the scientists being paid say 325 bucks an hour, by the way, who work for industry, are not working to understand a problem but to provide answers that their clients want to use for their public relations campaigns. In 1983, the National Academy of Science has issued a red book on risk assessment. For almost 3 decades that has been the Bible on how to conduct a risk assessment. The report was motivated in part by a desire to try to set the science of assessing risk outside the political environment that surrounded decisions about what to do about those risks.

But deep pockets readily use the report to see science as a fertile ground for fighting regulation. Industry learned that they can forestall any movement out of the realm of risk assessment and into the realm of risk management by manufacturing doubt, a process institutionalized by the NAS book. Not by NAS but by those who used it.

Now the Academy has marched again into a situation that they may not have fully anticipated. The NAS report on EPA's draft formaldehyde assessment contains a very useful roadmap for how EPA should undertake reorganizing their IRIS assessments to make them more comprehensible and transparent, and though Dr. Anastas has embraced those recommendations, embraced the recommendations, the industries that most worry about IRIS assessments has seized on the language of the NAS report to try to claim that EPA cannot be trusted to do the science. That is not the message of the NAS report not the intention of the Academy panel.

Under the Bush Administration that so crippled the EPA through a broken program with interference by OMB, that agency was able to finalize only a couple of IRIS assessments a year. EPA Administrator Lisa Jackson put in place a new process that severely cut back on OMB and polluting agency interference.

So today we are going to hear from industry prescribers that go back to this kind of OMB-dominated system in which there is a suggestion that no assessment can ever be finalized without the Academy peer review of the draft assessment and then another peer review of the redrafted assessment.

Instead I suggest that we follow the National Academy's advice. All the EPA the time to institute the kind of changes proposed in the formaldehyde review. Dr. Anastas has already proposed an initiative tied to the Academy roadmap that appears to be responsive and robust. It seems clear to me that to allow EPA to do their job with the advice from the Academy and not get captured by the endless science of the doubt machine is the direction that we should go.

I look forward to hearing from our witnesses today to cast light on this process and to ensure that we have agencies that are actually working in the public interest and not in the private interest.

Thank you, and I yield.

[The prepared statement of Ms. Edwards follows:]

## PREPARED STATEMENT OF RANKING MEMBER DONNA F. EDWARDS

For fifty years the tobacco industry has fought a campaign to cast doubt on the health risks of smoking cigarettes. They invented the effort to use “science” to fight science; to harness industry-funded research for public relations campaigns; and to use friendly public officials to point to these manufactured uncertainties in opposing any effort to protect the public.

And during that entire time, public health experts have absolutely known that smoking causes cancer, and that smoking remains—in the words of the Surgeon General—“the single most important preventable cause of death in our society.”

That model of industry-funded science being used to generate uncertainty and postpone even minor regulatory steps—regardless of the effects on public health—has been taken up with gusto by other industries. A similar campaign is being waged by the fossil fuel industry to cast doubt on the science of climate change. And today we are going to see some of this unfold surrounding EPA’s science-based efforts to develop risk assessments of the health consequences of chemicals to which Americans are commonly exposed.

Industry tends to push for two things in the realm of science and regulation: first they demand that we must have certainty before any action can be taken, and, second, they point to studies that suggest there is uncertainty. What they don’t mention quite so prominently is that they fund the production of studies designed to create doubt. That manufactured doubt is then used to justify inaction because, obviously, there is no certainty.

The country ends up in an endless science loop that makes it almost impossible to ever make a statement about the harm of anything. If an agency tries to take a position, industry argues that there is “another study” just around the bend for which the agency should wait. With enough money and willing researchers, industry can guarantee that there is always another study just around the corner no matter the evidence regarding its harm.

Of course the science that industry funds is specifically aimed at producing studies that show no harm from their products. In this world, the scientists who work for industry are not working to honestly understand a problem, but to provide answers that their clients want to use for their public relations campaigns. And make no mistake, no one pays you \$325 an hour to produce science that isn’t useful to their interests.

The National Academy of Sciences has not been blind to this development in America’s science and regulatory landscape. In 1983, the National Academy of Sciences issued the “red book” on Risk Assessment. For almost three decades that has been the bible on how to conduct a risk assessment. The report was motivated, in part, by a desire to try to set the science of assessing risks outside the political environment that surrounded decisions about what to do about those risks—a process they labeled risk management. The Academy, perhaps naively, hoped that all the struggles over regulatory decisions would be focused on risk management.

What the Academy did not anticipate was how readily those with deep pockets would see science as fertile ground for fighting regulation. Industry learned that they can stall any movement out of the realm of risk assessment by manufacturing doubt, and the NAS red book helped institutionalize this system.

And now the Academy has again marched into a situation that they may not have fully anticipated. The NAS report on EPA’s draft formaldehyde assessment contains a very useful “roadmap” for how EPA should undertake reorganizing their IRIS assessments to make them more comprehensible and transparent. To his credit, Dr. Anastas has embraced those recommendations. But the industries that most worry about IRIS assessments have seized on the language of the NAS report to try to claim that EPA cannot be trusted to do science.

That is not the message of the NAS report nor the intention of the Academy panel.

- If the Academy panel thought EPA could not institute effective changes, they would not have suggested EPA undertake them.
- If the NAS panel did not think IRIS assessments were needed or could be produced to a high quality, they would not have advised EPA to continue to put out those assessments even as they work to incorporate changes to that process as recommended by the Academy.
- If the panel did not trust EPA’s ability to make appropriate changes to the draft-formaldehyde assessment, they could have recommended that EPA return to the Academy for a second review of that assessment. They did not make such a recommendation.

Yet we will have testimony today from an industry-funded scientist that goes so far as to say that in light of the Academy study, the IRIS program should be killed.

The IRIS program was a broken program during the Bush Administration. By 2006–2007, interference by OMB and endless science challenges by industry and polluting agencies that did not want to clean-up their messes—such as those documented at Camp LeJeune—had so crippled EPA that they were able to finalize only a couple of IRIS assessments a year.

Pressure from this Subcommittee helped inspire GAO to put IRIS on their high risk watch list and inspired the new Administrator of EPA, Lisa Jackson, to put in place a new process that severely cut back on the opportunities for OMB and polluting agencies to interfere with EPA's production of IRIS assessments.

It is too soon to know whether these steps will bear fruit, but we do know this: every IRIS assessment that the Academy has reviewed in the last half-dozen years, including the formaldehyde assessment, was largely a result of that broken process whereby OMB dictated to EPA much of the content and organization of those assessments. I would suggest that if the reports lacked coherence or clear communications perhaps it is because they were heavily interfered with by these non-EPA parties who insisted on new chapters, new sections, new issues and new articles being added.

And the cure that industry prescribes for improving IRIS reports? Why, go back to the OMB-dominated system that produced them in the first place! Mr. Dooley sent a letter making just such a suggestion to Jack Lew. They further advocate that no assessment ever be finalized without an Academy peer review of the draft assessment and then another peer review of the redrafted assessment.

Could the intent to slow roll action be any more transparent? And in the years between Academy reviews, just imagine how many new industry-funded studies might be created to throw up ever more science chaff in the path of EPA? These are not cures that will heal the IRIS program, but are designed to bleed it to death.

Instead, I suggest that we follow the National Academy's advice. Allow EPA the time to institute the kinds of changes proposed in the formaldehyde review. Dr. Anastas has already proposed an initiative tied to the Academy roadmap that appears responsive and robust. And there is a new director of the IRIS program, Dr. Coglianò, who has been recruited to do for IRIS what he did for the International Agency for Research on Cancer risk process.

*We have good people in place and good advice from the Academy. Let us allow them to do their job and not get captured by the endless science doubt machine.*

Chairman BROWN. Thank you, Ms. Edwards. If there are Members who wish to submit additional opening statements, your statements will be added to the record at this point.

Now, before we begin, let me note that, again, testimony from the EPA was not received within the timeframe established in our committee rules. Testimony was not received until 2:47 p.m. yesterday, with additional supplements trickling in at 5:45 p.m. yesterday.

Committee rule 7(B)(1) states that, "Insofar as is practicable, no later than 48 hours in advance of his or her appearance each witness who is to appear before the committee shall file in printed copy and in electronic form a written statement of his or her proposed testimony and the curriculum vitae. Late testimony inhibits the committee's ability to fully evaluate the matter before it. Late delivery of testimony could set the stage for the committee to refuse to accept the written testimony of or hear from a witness."

In this instance it is imperative that EPA testify, but EPA has once again obstructed the committee's ability to conduct legitimate oversight. EPA provided late testimony to the fiscal year 2012 budget hearing on March 10, late testimony to the May 11 hearing on hydraulic fracturing, and late testimony for the E-15 hearing on July the 7th.

Additionally, questions for the record from the fiscal year 2012 budget hearing were due on March 24, yet the committee only received responses 2 days ago, almost 4 months late.



This is intolerable. The committee provided EPA a heads up on this hearing almost 2 months ago, providing ample time for OMB to review EPA's testimony. Dr. Anastas, this is unacceptable, and I expect EPA's testimony to be on time so that this committee can execute its responsibilities, and I hope in the future that we can count on you to do so and other officials with EPA to do so, and I would appreciate a very prompt response to our request.

At this time I would like to introduce our first panel of witnesses. Dr. Paul Anastas, Assistant Administrator for the Office of Research and Development at the U.S. Environmental Protection Agency. Mr. David Trimble is the Director of Natural Resources and Environment at the U.S. Government Accountability Office. Dr. Jonathan Samet, is that correct? Samet. Okay. Samet, MD, served as Chair of the National Research Council's committee to review EPA's draft IRIS assessment of formaldehyde. Dr. Samet also previously chaired the National Research Council's Board on Environmental Studies and Toxicology, where he evaluated the EPA's reassessment of dioxin and related compounds.

As our witnesses should know, spoken testimony is limited to five minutes each, after which the Members of the committee will have five minutes each to ask questions. Your written testimony will be included in the record of the hearing. It is the practice of the Subcommittee on Investigations and Oversight to receive testimony under oath. Do any of you have any objection to taking an oath?

Let the record reflect that all witnesses are willing to take an oath. They indicated that by shaking their head from side to side, even though we heard no rattles. I saw it.

You all may also be represented by counsel. Do any of y'all have counsel here today? Y'all is Southern for you all.

Let the record reflect that none of the witnesses have counsel. They again indicated by the shake of their head, indicating no. If all of you would please stand now and raise your right hand, do you solemnly swear or affirm to tell whole truth and nothing but the truth, so help you God?

Let the record reflect that all witnesses participating have taken the oath. Please take your seat.

Now I recognize our first witness, Dr. Anastas.

**TESTIMONY OF THE HONORABLE PAUL ANASTAS,  
ASSISTANT ADMINISTRATOR, OFFICE OF RESEARCH  
AND DEVELOPMENT, U.S. ENVIRONMENTAL PROTECTION  
AGENCY**

Dr. ANASTAS. Good morning, Chairman Broun, Ranking Member Edwards, and other Members of the committee. I am Paul Anastas. I am the Assistant Administrator for the Office of Research and Development at the U.S. Environmental Protection Agency and the Agency's Science Advisor.

Before I begin let me make a personal statement to this committee, and I think this committee appreciates the amount of respect that I have for this committee, and I want to give a personal apology to this for the tardiness of today's testimony. I do believe it was prepared promptly, and my apologies for the clearance proc-

ess that may have delayed that. So that is something that I think is important and that I take seriously personally.

Chairman BROWN. Accepted and I greatly appreciate that. We look forward to having the testimony presented in a timely manner in the future. Thank you, and I am going to expect that, and I think you are a man of your word, and I appreciate that assurance that we can have that. Thank you.

Dr. ANASTAS. Thank you, and thank you for the opportunity to be with you here today to discuss the EPA Integrated Risk Information System, otherwise known as IRIS. EPA plays a critical role in providing high quality health information on chemicals of concern. The agency's IRIS Assessment Program is a key part of this effort. It includes human health assessments on more than 540 chemical substances. These assessments provide the sound scientific basis for EPA decisions and are widely used by risk assessors, health professionals, state and local governments, as well as international governments.

EPA is committed to upholding the highest standard of scientific integrity in all of its activities. This means constantly seeking to improve, strengthen, and enhance our scientific work to reflect the best available information. Continuous improvement of the IRIS Program is an important part of this effort.

The EPA recently announced changes to the IRIS Program that will ensure we continue to use the best and most transparent science to pursue our mission of protecting human health and the environment. The new changes build upon the significant improvements initiated by Administrator Lisa Jackson in 2009.

For example, since 2009, EPA has completed 16 IRIS assessments, more than the total number of assessments that were completed in the previous four years. We have cut down the average timeframe for completing assessments from between 3 and four years to within two years, and reduced the backlog of assessments in the pipeline, and yes, new assessments have been added to that pipeline, so that may be why the number looks to be the same.

These improvements have been accompanied by a strong and continued emphasis on independent peer review of the IRIS Program. In April of this year EPA received a report from the National Academy of Sciences on their review of EPA's draft IRIS assessment on formaldehyde. EPA welcomes and accepts the recommendations of the NAS on the formaldehyde assessment and will incorporate these recommendations in the revision of the assessment.

In the report the NAS also suggested ways to improve the IRIS process in two primary areas; accessibility and transparency. Because EPA is constantly seeking feedback from credible, independent scientific sources, we welcome these suggestions and are incorporating them fully into the IRIS Program.

The new IRIS assessment documents will be shorter, clearer, more concise, and more transparent. IRIS users can expect to see a reduced volume of text and increased clarity and transparency of data, methods, and decision criteria. IRIS documents will rigorously be edited to eliminate any inconsistencies and redundancies and will include more graphical and tabular representations of the data.

Related discussions will be consolidated into concise, narrative descriptions, and references to all studies used in the assessment development will be posted online. To make the scientific rationale of IRIS assessments as transparent as possible, the EPA will evaluate the strengths and weaknesses of critical studies in a more uniform way. We will also clearly indicate which criteria were most influential in weighing scientific evidence, supporting its choice of toxicity values. EPA is working closely with the Agency's Science Advisory Board to focus its expertise on how to best respond to the NAS suggestions.

In addition, we continue to be committed to full consultation with scientists throughout the government and carefully consider and respond to their input. We will add a peer consultation step to the early stages of major IRIS assessments to assure that the scientific community can provide input as we make critical design decisions for individual assessments.

These changes will be implemented over the coming months in a tiered approach, with the most extensive changes applied to those assessments in the earlier stages of development. These improvements are part of the natural evolution that accompanies all rigorous scientific work. We will continue to consider information and perspectives from independent scientific sources and pursue improvements in an ongoing basis.

Thank you. I will be happy to answer any questions at the appropriate time as the chair directs.

[The prepared statement of Mr. Anastas follows:]

PREPARED STATEMENT OF THE HONORABLE PAUL ANASTAS, ASSISTANT ADMINISTRATOR, OFFICE OF RESEARCH AND DEVELOPMENT, U.S. ENVIRONMENTAL PROTECTION AGENCY

Good morning Chairman Broun, Ranking Member Edwards and other Members of the Committee. My name is Paul Anastas. I am the Assistant Administrator for Research and Development (ORD) at the Environmental Protection Agency and the Agency's Science Advisor. It is a pleasure to be here with you this morning to discuss EPA's Integrated Risk Information System (IRIS).

#### **Background and Description of IRIS Program**

EPA recognizes the critical role we play in disseminating timely, high-quality and accessible human health risk information on environmental contaminants that may endanger the health of the American public. Central to this aspect of EPA's mission is its Integrated Risk Information System, commonly called the IRIS program, which 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 products. IRIS assessments provide a scientific foundation for EPA decisions to protect public health across EPA's programs and regions under an array of environmental laws. While not regulations, IRIS assessments are critical to many Agency decisions. IRIS is also a resource for risk assessors and environmental and health professionals in state and local governments and other countries. After becoming Administrator in early 2009, Administrator Jackson reviewed the IRIS program and asked the Office of Research and Development (ORD) in May 2009 to implement a new IRIS process that would revitalize the program and make it more responsive to the needs of the Agency. The aim of the new process was to ensure the highest level of scientific quality, integrity, transparency, and timeliness.

#### **EPA's Actions to Implement the 2009 IRIS Process**

EPA undertook several actions to implement the new IRIS process in 2009. EPA regularly solicits public comments on the IRIS agenda, and ORD works directly with program and regional offices to ensure that IRIS assessments meet their needs. To ensure that IRIS assessments are focused on the highest priority needs, EPA ex-

panded the role of the program and regional offices in nominating and prioritizing chemicals for assessment.

EPA also has increased efforts to work with other agencies to share data and avoid duplication of effort. For example, ORD has a new Memoranda of Understanding with the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment in addition to an existing Memoranda of Understanding with the Agency for Toxic Substances and Disease Registry. These efforts help to increase efficiency and assessment output. The Agency is also working closely with its Science Advisory Board on how to bring to bear its expertise on an ongoing basis to focus on the quality, transparency, and scientific rigor of IRIS assessments and guide EPA's response to the NAS recommendations. We will add a peer consultation step to the early stages of major IRIS assessments to assure that the scientific community can provide input as we make critical design decisions for individual assessments. The Agency also created an IRIS logistics team to coordinate all administrative support to improve efficiency and place increased emphasis on the scientific quality of assessments by allowing scientific staff to focus on the science. In addition, EPA developed the Health and Environmental Research Online database, referred to as HERO, which promotes transparency in risk assessments by capturing the literature used in EPA's health and environmental assessments and making the scientific studies used to develop assessments available to the public. The HERO database is web-based and accessible to everyone.

These actions, collectively, have led to improved results in the IRIS process. Specifically, EPA has completed 16 assessments since 2009, more than the number of assessments that were completed in the previous four years. EPA has reduced the IRIS backlog and is currently working on over 70 assessments. In 2010, EPA released nine assessments, seven of which were major assessments, for external peer review and public comment. Overall the new 2009 process resulted in greater involvement of EPA scientists and the public in the process.

In summary, there have been many improvements to the IRIS program since 2009 to provide high quality assessments in a timely fashion. Assessment development time was shortened to 23 months for most assessments, which will speed the availability of IRIS assessments for use by the risk assessment community and public. The IRIS program is now entirely managed by EPA and EPA strives to ensure that all of its science assessments undergo rigorous, open and independent external peer review and that multiple opportunities exist for public review and comment. Additionally, changes in IRIS assessments that occur during the interagency and public process are documented and explained, ensuring a transparent final product.

### **IRIS Process and the NAS Review**

In April 2011, the NAS released its review report of EPA's draft IRIS risk assessment of formaldehyde and included comments and recommendations to improve the IRIS process. EPA welcomes those recommendations and will be addressing all of them in a phased-in fashion. We note that the NAS specifically focused their comments on the development of draft IRIS assessments and did not recommend changes to the steps that occur later in the process. Additionally, the NAS recognized that EPA's implementation of their suggested changes would require a multiyear process. A summary of the NAS overall recommendations and EPA's responses to them are described below.<sup>1</sup>

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<sup>1</sup> Full text from p. 152 of the final published NAS report.

- To enhance the clarity of the document, the draft IRIS assessment needs rigorous editing to reduce the volume of text substantially and address redundancy and inconsistency. Long descriptions of particular studies, for example, should be replaced with informative evidence tables. When study details are appropriate, they could be provided in appendixes.
- 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 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 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.
- 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.
- 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. The present chapter provides general guidance on approaches to reviewing the critical types of evidence.
- 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.
- 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.

**1. NAS recommended that EPA rigorously edit documents to reduce the text volume and address redundancies and inconsistencies.**

To respond to this recommendation, EPA is rigorously editing our assessment documents to substantially reduce the volume of text and address redundancies and inconsistencies; building on the existing IRIS guidelines and process to enhance the clarity and transparency of data evaluation and the presentation of findings and conclusions; consolidating related discussions to eliminate redundancies; increasing the use of tables and figures to improve communication of information; and providing reference information on the IRIS website for all studies considered.

**2. NAS recommended that EPA include a fuller discussion of methods and develop concise statements of the criteria used to exclude, include and advance studies for hazard evaluation and derivation of toxicity values.**

In response to this recommendation, EPA is providing a fuller discussion of the methods used in our assessments, along with concise statements of the criteria used to exclude, include, and focus on the highest quality studies for hazard assessment and for derivation of toxicity values.

**3. NAS recommended standardized evidence tables for all health outcomes.**

EPA is working towards replacing text descriptions of the studies with standardized evidence tables that provide the methods and results of each study for all health outcomes; and including text that will accompany evidence tables to present the criteria used to include or exclude studies.

**4. NAS recommended that EPA provide a clearer articulation of the rationale and criteria for screening studies.**

To accomplish this, EPA is enhancing our sequential approach for progressively focusing on the most pertinent information, including: searching the literature, identifying the pertinent studies, and evaluating study characteristics; evaluating the overall weight of evidence for each health outcome; identifying plausible approaches for developing toxicity values; selecting the most pertinent data and developing toxicity values for each health hazard; and portraying toxicity information graphically.

**5. NAS recommended that EPA use uniform approaches to thoroughly evaluate the strengths and weaknesses of critical studies, summarize findings in tables, and clearly articulate the rationale for the studies used to calculate toxicity values.**

To respond to these two suggestions EPA is streamlining IRIS assessment documents and more fully document our approach for assembling and evaluating the range of scientific data. As the NAS report indicated, we have already made similar changes to how we present the scientific evidence on the criteria air pollutants in our Integrated Science Assessments, and we are confident we can make comparable improvements in how we present our analysis of health study findings for chemicals evaluated in the IRIS program. EPA is also implementing a more uniform approach to our evaluation of the strengths and weaknesses of critical studies to increase the clarity of the rationale for selecting the studies used to calculate toxicity values. Lastly, we are increasing the use of evidence tables that summarize the factual details of pertinent studies for each health hazard and developing standardized language to describe study strengths and limitations.

**6. NAS recommended that EPA provide descriptions to indicate various determinants of weight of evidence to promote understanding of what elements were emphasized in synthesizing the evidence.**

In response, EPA is augmenting its current analysis of data to indicate which criteria were most influential in evaluating the weight of evidence.

### **Timeline for Responding to NAS Recommendations**

EPA's overarching goal is to continually improve our IRIS assessments, recognizing that these improvements will have a greater impact on our new assessments as opposed to those already in the pipeline. It is important to note that the NAS report viewed the implementation of their recommendations as a multi-year process. For example, the NAS stated 'it is not recommending that EPA delay the revision of the formaldehyde assessment to implement a new approach.' To that end, EPA is doing the following:

- *Assessments that have already been peer-reviewed or released for peer review:* We are revising these assessments to address peer review comments, especially those that call for increased transparency of study selection and evidence evaluation.
- *Assessments currently under development but not yet released for peer review:* We are re-examining these assessments to ensure that the rationale for study selection and evidence evaluation is clear. These assessments will also be edited to reduce redundancy.
- *New assessments that have not yet been started:* We will fully implement the NAS recommendations for new assessments, including a tighter document structure, evidence tables to summarize details from pertinent studies, greater transparency in study selection and evaluation criteria, and greater emphasis on clear analysis and synthesis.

The standards to which IRIS assessments are held, including the rigorous independent external peer review of every draft IRIS assessment, are among the best in the federal government and the scientific community. Over the coming months, the IRIS program will fully implement the NAS recommendations and continue to improve the IRIS process to reflect the highest standards of scientific integrity and credibility. Strengthening and streamlining the IRIS process is a continuing and ongoing priority for EPA. Thank you for the invitation to share my thoughts on this important topic. I will gladly answer any questions you have.

Chairman BROWN. Thank you, Dr. Anastas.  
I now recognize our next witness, Mr. Trimble.

**TESTIMONY OF DAVID TRIMBLE,  
DIRECTOR, NATURAL RESOURCES AND ENVIRONMENT,  
U.S. GOVERNMENT ACCOUNTABILITY OFFICE**

Mr. TRIMBLE. Chairman Brown, Ranking Member Edwards, and Members of the Subcommittee, I am pleased to be here today to discuss our prior work and recommendations on EPA's Integrated Risk Information System. As you know, the IRIS database contains EPA's scientific position on the potential human health effects of exposure to more than 540 chemicals in the environment. IRIS assessments are a critical component of EPA's capacity to support scientifically-sound risk management decisions, policies, and regulations.

In March 2008, we reported that the IRIS Program was at serious risk of becoming obsolete because the Agency has not been able to complete timely, credible chemical assessments or decrease its backlog of 70 ongoing assessments. We found that the timeframes for completing assessments were unacceptably long, often taking over a decade. In many cases assessments became obsolete before they could be finalized and were stuck in an endless loop of assessment and reassessment.

In April 2008, EPA revised the IRIS process, but the changes made were not responsive to our recommendations. The new process was actually worse than the one it replaced, institutionalizing a process that resulted in frequent delays by enabling OMB to determine when an IRIS assessment could move forward. Further, this process effectively excluded the content of OMB's comments to EPA and those from the other interested federal agencies from the public record.

Concerned with these problems and the agency's lack of responsiveness, we added EPA's process for assessing and controlling toxic chemicals to our January, 2009, report on government-wide high-risk areas in need of increased attention by executive agencies and Congress.

In May 2009, the EPA made significant changes to the IRIS process. In June of that year we testified before this Subcommittee that these changes, if implemented and managed effectively, would be largely responsive to the recommendations we made in our March 2008 report. Let me highlight three of these key changes.

First, the IRIS process would be managed by EPA rather than OMB as the former process was, restoring independence to EPA. Second, it required that all written comments provided by OMB and other federal agencies on draft IRIS assessments be part of the public record, adding transparency and credibility to the process. Third, the new process consolidated and eliminated steps, streamlining the process.

Notably, the new process eliminated the step under which other federal agencies could have IRIS assessments suspended indefinitely to conduct additional research. As we have reported, we understand that there may be exceptional circumstances under which it may be appropriate to wait for the results of an important ongoing study. However, as a general rule, we believe the IRIS assessments that are based on the best available science is a standard that would best support the goal of completing assessments within reasonable time periods and minimizing the need to conduct wasteful rework.

While the May, 2009 IRIS process changes reflect a significant improvement that can help EPA restore the integrity and productivity of the IRIS Program, EPA still faces significant management challenges as it seeks to complete timely, credible IRIS assessments.

First, the EPA must continue to balance the need for using the best available science with completing IRIS assessments in a timely manner. As we have reported, even one delay can have a domino affect, requiring the process to essentially be repeated to incorporate changing science.

Second, EPA faces long-standing difficulties in completing assessments of chemicals of key concerns; those that are both widespread and likely to cause significant health issues. We believe that EPA must continue to focus on the best available science, attaining credible expert review and finalizing IRIS assessments.

Third, EPA must be disciplined in keeping to timelines, even in the absence of statutory deadlines for completing IRIS assessments.

Lastly, we believe that to produce timely, credible IRIS assessments over a sustained period of time, it will be imperative for EPA to maintain a stable consistent process going forward.

We are currently reviewing EPA's implementation of its revised 2009 IRIS assessment process and its response to our previous recommendations. As part of this review, we will be examining EPA's response to NAS's recommendations for improvements to the IRIS process. We plan to issue a report later this year.

That concludes the summary of my statement. I will be happy to answer any questions that you or the Members of the committee may have.

[The prepared statement of Mr. Trimble follows:]



PREPARED STATEMENT OF MR. DAVID TRIMBLE, DIRECTOR, NATURAL RESOURCES AND ENVIRONMENT, U.S. GOVERNMENT ACCOUNTABILITY OFFICE

United States Government Accountability Office

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Testimony  
Before the Subcommittee on  
Investigations and Oversight, Committee  
on Science, Space, and Technology,  
House of Representatives

For Release on Delivery  
Expected at 10:00 a.m. EDT  
Thursday, July 14, 2011

# EPA HEALTH RISK ASSESSMENTS

## Sustained Management and Oversight Key to Overcoming Challenges

Statement of David Trimble, Director  
Natural Resources and Environment



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Chairman Broun, Ranking Member Edwards, and Members of the Subcommittee:

I am pleased to be here today to discuss our prior work on the Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) program and database. As you know, IRIS is one of the most significant tools that EPA has developed to support its mission to protect people and the environment from harmful chemical exposures. The IRIS database contains EPA's scientific position on the potential human health effects that may result from exposure to more than 540 chemicals in the environment and is a critical component of EPA's capacity to support its mission.

EPA created IRIS in 1985 to help the agency develop consensus opinions within the agency about the health effects from chronic exposure to chemicals. Over time, the importance of the program has increased as EPA program offices, state and local environmental programs, and some international regulatory bodies have increasingly relied on IRIS health risk assessment information to support risk-based decision making to protect public health and the environment. As the IRIS database became more widely used and accepted, EPA took steps, beginning in the early 1990s, to improve and maintain the IRIS program and database. Over the years, the agency has implemented a variety of new operational procedures aimed at improving the IRIS program and database—with the most recent change to its IRIS assessment process occurring in May 2009.

Because of the potential for EPA's health risk assessments to lead to regulations that can significantly affect certain industries or federal agencies, IRIS assessments have frequently received considerable attention. For example, in recent months, much attention has been focused on EPA's draft health risk assessment of formaldehyde and the National Academies' review of the draft assessment.<sup>1</sup> In addition to reviewing the draft assessment of formaldehyde, the National Academies' report also offered some suggestions for improving the preparation and presentation of draft health risk assessments in general. Our work to date has not focused on these aspects of IRIS assessments.

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<sup>1</sup>The National Academies comprises four organizations: the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine, and the National Research Council.

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Instead, our body of work on the IRIS program has more broadly evaluated the overall IRIS assessment process and the challenges the program has faced in implementing it. In March 2008, we reported that the IRIS database was at serious risk of becoming obsolete because EPA had not been able to routinely complete timely, credible assessments.<sup>2</sup> After subsequent reports,<sup>3</sup> in January 2009 we added EPA's processes for assessing and controlling toxic chemicals to our list of areas at high risk for waste, fraud, abuse, and mismanagement or in need of broad-based transformation.<sup>4</sup> We are currently undertaking a review of EPA's revised 2009 IRIS assessment process and the agency's progress in implementing it and plan to issue a report later this year.

In this context, my testimony today discusses our past work on (1) the timeliness and credibility of IRIS assessments and (2) EPA's May 2009 IRIS assessment process. We conducted the performance audit work that supports this statement in accordance with generally accepted government auditing standards. Additional information on our scope and methodology is available in each issued product.

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## Summary

From March through September 2008, we reported on shortcomings in EPA's IRIS process that limited the agency's ability to complete timely and credible IRIS assessments. For example, the Office of Management and Budget (OMB) required and managed interagency reviews of IRIS assessments, and OMB determined when assessments could proceed to the next process step, frequently resulting in delayed IRIS assessments. Such shortcomings contributed to our decision to designate the IRIS program as a high-risk area in January 2009. In June 2009, we testified

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<sup>2</sup>GAO, *Chemical Assessments: Low Productivity and New Interagency Review Process Limit the Usefulness and Credibility of EPA's Integrated Risk Information System*, GAO-08-440 (Washington, D.C.: Mar. 7, 2008).

<sup>3</sup>GAO, *Toxic Chemicals: EPA's New Assessment Process Will Increase Challenges EPA Faces in Evaluating and Regulating Chemicals*, GAO-08-743T (Washington, D.C.: Apr. 29, 2008); *Chemical Assessments: EPA's New Assessment Process Will Further Limit the Productivity and Credibility of Its Integrated Risk Information System*, GAO-08-810T (Washington, D.C.: May 21, 2008); and *EPA Science: New Assessment Process Further Limits the Credibility and Timeliness of EPA's Assessments of Toxic Chemicals*, GAO-08-1168T (Washington, D.C.: Sept. 18, 2008).

<sup>4</sup>GAO, *High-Risk Series: An Update*, GAO-09-271 (Washington, D.C.: January 2009). This high-risk area addresses EPA's implementation of the IRIS program as well as implementation of the Toxic Substances Control Act (TSCA).

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that EPA's May 2009 IRIS assessment process reforms, if implemented effectively, would represent a significant improvement over the previous IRIS process by restoring EPA control, establishing transparency, and streamlining the process. We are currently undertaking a review of EPA's revised 2009 IRIS assessment process and the agency's progress in implementing it and plan to issue a report later this year.

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**EPA's Inability to  
Complete Timely,  
Credible IRIS  
Assessments  
Contributed to the  
Program's High-Risk  
Designation**

From March through September 2008, we reported on shortcomings in EPA's IRIS process that limited the agency's ability to complete timely and credible IRIS assessments.<sup>5</sup> These shortcomings contributed to our decision to designate the IRIS program as a high-risk area. Specifically, beginning in 2004, OMB began requiring and managing two interagency reviews of IRIS assessments by OMB and other federal agencies with an interest in these assessments, such as the Departments of Defense and Energy. These reviews contributed to concerns about the timeliness and credibility of IRIS assessments. In particular, EPA was not allowed to move forward with an assessment until OMB determined that EPA had satisfactorily addressed all OMB and other federal agency comments. As a result, IRIS assessments were frequently delayed. In addition, the content of the OMB-required reviews was not publicly available, thus limiting the transparency and the credibility of IRIS assessments. The credibility of the assessments was further limited by the involvement of other federal agencies that could be affected by the assessments if they led to regulatory actions. That is, if EPA issued an IRIS assessment that resulted in a decision to regulate a chemical to protect the public, some of the agencies participating in these reviews, such as the Department of Defense, could face increased cleanup costs and other legal liabilities.

In addition, some EPA management decisions to suspend ongoing IRIS assessments to wait for new and ongoing scientific studies to be completed also limited the timeliness of IRIS assessments. In fact, EPA's decisions to await the results of new and ongoing studies before completing some IRIS assessments resulted, in some cases, in delaying them for years. We understand that there may be exceptional circumstances under which it may be appropriate to wait for the results of an important ongoing study, such as a major epidemiological study that will provide new, critical data for an assessment. However, as a general

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<sup>5</sup>GAO-08-440, GAO-08-743T, GAO-08-810T, and GAO-08-1168T.

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rule, requiring that IRIS assessments be based on the best science available at the time of the assessment is a standard that would best support a goal of completing assessments within reasonable time periods and minimizing the need to conduct significant levels of rework, as we reported in March 2008.

Moreover, in April 2008, EPA revised its IRIS assessment process, but the revised process did not address the issues we raised in our March 2008 report.<sup>6</sup> More specifically, our report contained recommendations for EPA to reevaluate its proposed revisions to the IRIS assessment process and to streamline the process to better ensure that EPA had the ability to develop transparent, credible assessments. However, in April 2008, EPA issued a revised IRIS assessment process that was largely the same as the proposed revisions that we had evaluated and had taken issue with during our review.

As a result of these and other issues, in January 2009 we added transforming EPA's processes for assessing and controlling toxic chemicals to our list of high-risk areas.

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<sup>6</sup>GAO-08-440.

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**EPA's May 2009 IRIS Assessment Process Reforms Appeared to Represent Significant Improvement, but the Viability of the IRIS Program Will Depend on Effective and Sustained Management and Oversight**

As we testified before the House Subcommittee on Investigations and Oversight in June 2009,<sup>7</sup> the IRIS assessment process reforms instituted by EPA in May 2009 appeared to represent a significant improvement over the previous IRIS process and, if implemented effectively, with sustained management and oversight, could help EPA restore the credibility and increase the timeliness of this important program. The reforms included the following:

- *Restored EPA control.* The new process and the memorandum announcing it indicated that the IRIS assessment process would be entirely managed by EPA, including the interagency science consultations (formerly called interagency reviews). Under EPA's prior process, these two interagency reviews were required and managed by OMB, and OMB determined when assessments could proceed to the next process step. The control restored to EPA under the new process is critical in ensuring that EPA has the ability to develop transparent, credible IRIS chemical assessments that the agency and other IRIS users, such as state and local environmental agencies, need to develop adequate protections for human health and the environment.
- *Established transparency.* The new process addressed a key transparency concern highlighted in our 2008 report and subsequent testimonies. As we recommended, the new process expressly required that all written comments on draft IRIS assessments provided during interagency science consultations by other federal agencies and OMB be part of the public record.
- *Streamlined process.* The new process streamlined the previous one by consolidating and eliminating some steps. Importantly, EPA eliminated the step under which other federal agencies could cause IRIS assessments to be suspended in order to conduct additional research, thus returning to EPA's practice in the 1990s of developing assessments on the basis of the best available science. As noted previously, long delays to await the results of new scientific research do not support a goal of completing assessments within reasonable time periods and minimizing the need to conduct significant levels of rework.

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<sup>7</sup>GAO, *EPA Chemical Assessments: Process Reforms Offer the Potential to Address Key Problems*, GAO-09-774T (Washington, D.C.: June 11, 2009).

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Although EPA's May 2009 IRIS assessment process appeared to represent a significant improvement over the previous IRIS process, we testified in June 2009 that the viability of the IRIS program would depend on effective and sustained management and oversight. We identified the following factors that collectively could present significant management challenges to EPA's ability to complete timely, credible IRIS assessments.

- Unlike a number of other EPA programs with statutory deadlines for completing various activities, no enforceable deadlines apply to the IRIS program. We believe the absence of statutory deadlines may contribute to EPA's failure to complete timely IRIS assessments. For example, assessment schedules can easily be extended—and frequently are. Chronic delays in completing IRIS assessments have detrimental consequences for EPA's ability to develop timely and scientifically sound decisions, policies, and regulations.
- Because science and methodologies are constantly changing, there will always be a tension between assessing the best available science and waiting for more information. The IRIS program will remain viable only if it continues to use the best science available at the time of its assessments and plans for periodic updates of assessments to identify the need for revisions.
- An overarching factor that affects EPA's ability to complete IRIS assessments in a timely manner is the compounding effect of delays—even one delay can have a domino effect, requiring the process to essentially be repeated to incorporate changing science. For example, delays often require repeating reviews of the scientific literature on a chemical to take into account the time that has passed since the literature review was completed; this, in turn, may require detailed analyses of any new studies found to be relevant.
- Long-standing difficulties in completing assessments of chemicals of key concern—those that are both widespread and likely to cause significant health issues—stem in part from challenges by external parties, including those that may be affected by EPA regulation of chemicals should an assessment lead to such action. Such challenges are to be expected and can be best addressed by EPA's focusing on the best available science, obtaining credible expert review, and completing the assessments.
- IRIS process reforms, such as those issued in May 2009, are not established in regulation or statute and thus can easily be altered. As

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we have reported, continuous changes to the process have presented a challenge to the chemical managers who undertake the assessments.<sup>6</sup> To produce timely, credible IRIS assessments over a sustained period of time, it will be important for EPA to maintain a stable, consistent process going forward.

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Chairman Broun, Ranking Member Edwards, and Members of the Subcommittee, this concludes my prepared statement. I would be happy to respond to any questions that you or other Members of the Subcommittee may have at this time.

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**GAO Contact and  
Staff  
Acknowledgments**

For further information on this statement, please contact David Trimble at (202) 512-3841 or [trimbled@gao.gov](mailto:trimbled@gao.gov). Contact points for our Congressional Relations and Public Affairs offices may be found on the last page of this statement. Other staff that made key contributions to this testimony include Diane LoFaro, Assistant Director; Summer Lingard; Christine Fishkin; Nancy Crothers; Richard P. Johnson; Kiki Theodoropoulos; Robert Grace; and Jennifer Cheung.

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<sup>6</sup>GAO-09-774T.



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## Related GAO Products

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*High-Risk Series: An Update.* GAO-11-278. Washington, D.C.: February 2011.

*EPA Chemical Assessments: Process Reforms Offer the Potential to Address Key Problems.* GAO-09-774T. Washington, D.C.: June 11, 2009.

*Scientific Integrity: EPA's Efforts to Enhance the Credibility and Transparency of Its Scientific Processes.* GAO-09-773T. Washington, D.C.: June 9, 2009.

*High-Risk Series: An Update.* GAO-09-271. Washington, D.C.: January 2009.

*EPA Science: New Assessment Process Further Limits the Credibility and Timeliness of EPA's Assessments of Toxic Chemicals.* GAO-08-1168T. Washington, D.C.: September 18, 2008.

*Chemical Assessments: EPA's New Assessment Process Will Further Limit the Productivity and Credibility of Its Integrated Risk Information System.* GAO-08-810T. Washington, D.C.: May 21, 2008.

*Toxic Chemicals: EPA's New Assessment Process Will Increase Challenges EPA Faces in Evaluating and Regulating Chemicals.* GAO-08-743T. Washington, D.C.: April 29, 2008.

*Chemical Assessments: Low Productivity and New Interagency Review Process Limit the Usefulness and Credibility of EPA's Integrated Risk Information System.* GAO-08-440. Washington, D.C.: March 7, 2008.

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Please Print on Recycled Paper

Chairman BROWN. Thank you, Mr. Trimble.  
I know recognize for five minutes our next witness, Dr. Samet.

**TESTIMONY OF JONATHAN M. SAMET, MD, MS,  
PROFESSOR AND FLORA L. THORNTON CHAIR,  
DEPARTMENT OF PREVENTATIVE MEDICINE,  
KECK SCHOOL OF MEDICINE, UNIVERSITY OF SOUTHERN  
CALIFORNIA, AND CHAIR, COMMITTEE TO REVIEW  
EPA'S DRAFT IRIS ASSESSMENT OF FORMALDEHYDE,  
NATIONAL RESEARCH COUNCIL, THE NATIONAL ACADEMIES.**

Dr. SAMET. Good morning, Mr. Chairman and Members of the Subcommittee. I am Jonathan Samet from the University of Southern California. As noted, I chaired the National Research Council committee that reviewed the EPA's draft IRIS formaldehyde assessment. I also currently chair the Clean Air Scientific Advisory Committee of the Agency.

The draft, our review of the draft assessment was written by a 15-member committee that had a wide range of scientific expertise needed for the task. Our charge focused primarily on specific questions related to the Agency's approach to the IRIS assessment. But beyond these charge questions, the committee assessed the processes underlying the development of the draft and made suggestions about the process generally followed by EPA in developing the IRIS assessments. We were not charged or constituted to carry out an independent review of the evidence on formaldehyde.

To do its job we reviewed the 1,000 page, approximately, draft assessment and key literature and determined whether EPA's conclusions were supported on the basis of that assessment and the literature reviewed. Much of our report is directed at providing constructive comments and recommendations on improving this draft specifically following our charge.

That said, we felt that we could not address our charge without considering the methods and structure of the document as a whole and in responding to its charge questions, the committee found some recurring methodological problems that are cut across components of its charge.

Consequently, we commented on the general methodology of the assessment in our second chapter and offered general suggestions in chapter seven with regard to the processes used by EPA. The general problems that we identified were not unique and have been reported by other committees. I think those problems have already received some comment. We found relatively little documentation of methods and insufficient clarity and transparency in how the evidence reviewed in the report was related back to the weight of evidence guidelines.

We offered six specific recommendations with regard to how the present draft could be completed and moved forward satisfactorily. I will not go through these. They are listed in chapter seven of our report. They are straightforward and could be followed to bring the report to completion.

I will turn to our general comments and suggestions on IRIS. As noted, we found general problems that we thought had been persistent in looking at NRC reviews of other IRIS reports. On the basis of lessons learned from the formaldehyde assessment, we offered our suggestions for changes in the IRIS development process

that might help EPA improve its approach. We recognized that EPA had already implemented the plan discussed, released, and covered in the memorandum of 2009 from Administrator Jackson.

We put together our own view of the underlying development process and offered a several-page roadmap for changes in the development process. The term roadmap was used because the topics that need to be addressed are set out, but we did not give detailed guidance. Each topic, in fact, would speak—would need to be developed in further detail.

For each of the critical steps in the roadmaps there are underlying processes that would need to be examined and reconsidered. Our report provides further detail. We think that change in the IRIS development process, the process by which the drafts are developed, is feasible. We note as one example of the largely-successful overhaul of the process used for the National Ambient Air Quality Standards as an example. I have personally watched the revision of that process and noted its benefits.

In conclusion, thank you for the opportunity to speak with you today, and I look forward to answering your questions.

[The prepared statement of Dr. Samet follows:]

PREPARED STATEMENT OF DR. JONATHAN M. SAMET, MD, MS, PROFESSOR AND FLORA L. THORNTON CHAIR, DEPARTMENT OF PREVENTIVE MEDICINE, KECK SCHOOL OF MEDICINE, UNIVERSITY OF SOUTHERN CALIFORNIA; AND CHAIR, COMMITTEE TO REVIEW EPA'S DRAFT IRIS ASSESSMENT OF FORMALDEHYDE, NATIONAL RESEARCH COUNCIL, THE NATIONAL ACADEMIES

Good morning, Mr. Chairman and members of the subcommittee. My name is Jonathan Samet. I am Flora L. Thornton Chair and Professor in the Department of Preventive Medicine at the Keck School of Medicine of the University of Southern California. I am a pulmonary physician and epidemiologist and I have carried out population studies on the health effects of environmental pollutants for over three decades. I served as chair of the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, a committee of the National Research Council (NRC). The NRC is the operating arm of the National Academy of Sciences and the National Academy of Engineering. I also chair the Clean Air Scientific Advisory Committee (CASAC) of the EPA.

I am pleased to appear before you today to discuss our committee's recent report, *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*, which was released on April 8, 2011. As stated in the policies of the National Academies, the purpose of report review in general is to assist the authors in making their report as accurate and effective as possible, enhancing the clarity, cogency, and credibility of the final document. Our review of the draft assessment was written by a 15-member committee that had a wide range of scientific expertise, appropriate to the task. Our charge primarily focused on specific questions related to the EPA's derivation of reference concentrations (RfCs) for noncancer effects and of unit risk estimates for cancer. Beyond these specific questions, the committee assessed the processes underlying the development of the draft and made suggestions about the process generally followed by EPA in developing the IRIS assessments. Our committee was not charged or constituted to carry out an independent review on the strength of evidence for causation of non-cancer effects and cancer by formaldehyde. We have provided a copy of the report for the Subcommittee and the Executive Summary is attached.

Formaldehyde is widely used and exposure to formaldehyde is ubiquitous, both indoors and outdoors. Consequently, the health effects of formaldehyde exposure have been a topic of research for decades. Past concerns arose because of exposures to people from various indoor sources and because of findings

of worker studies showing increased risks of nasopharyngeal cancer. Recently, one concern has been adverse health effects reported by people displaced by hurricanes who were relocated into trailers provided by the Federal Emergency Management Agency. Published research has also reported an association between leukemia and formaldehyde exposure.

The U.S. Environmental Protection Agency (EPA) has been working to update its assessment of formaldehyde for its Integrated Risk Information System (IRIS) for a number of years. The large amount of new research data on formaldehyde since its original assessment in the early 1990s has made the task challenging and lengthy. Given the complex nature of the IRIS assessment and the knowledge that the assessment will be used as the basis of regulatory decisions, the NRC was asked to conduct an independent scientific review of the draft IRIS assessment. Specifically, the committee was asked to answer questions concerning the EPA's identification of potential noncancer health effects, the toxicological basis for those health effects, and the basis of the determination of uncertainty factors used to derive the reference concentrations (RfCs). The committee was also asked specifically to comment on the scientific rationale provided for the cancer assessment and the quantified risk estimates derived.

To address its task, 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. The committee was not charged or constituted to perform its own assessment and therefore 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. Furthermore, given the committee's statement of task, the committee focused on reviewing and critiquing the draft IRIS assessment, and the majority of the committee's report is directed at providing constructive comments and recommendations on improving specifically the draft IRIS assessment of formaldehyde

That said, the committee found that it could not address its charge without considering the methods and structure of the document as a whole, and in responding to its charge questions, the committee found some recurring methodologic problems that cut across components of its charge. Consequently, the committee commented on the general methodology of the assessment in Chapter 2 of the report and offered general suggestions in Chapter 7 with regard to the processes used by EPA to develop IRIS assessments. It did not review the IRIS Program itself, but rather focused on "lessons learned" from the formaldehyde assessment.

The general problems identified by the present committee are not unique and have been reported over the last decade by other NRC committees tasked with reviewing EPA's IRIS assessments for other chemicals. Problems with clarity and transparency of the methods appear to be a repeating theme over the years, even though some of the documents are very lengthy. In the roughly 1,000-page formaldehyde draft reviewed by the present committee, little beyond a brief (two page) introductory chapter could be found on the methods for conducting the assessment. In fact, the introductory chapter of formaldehyde is nearly identical to that used in other IRIS assessments. Numerous EPA guidelines are cited, but their role in the preparation of the assessment is not clear. In general, the committee found that the draft was not prepared in a consistent fashion; it lacks clear links to an underlying conceptual framework; and 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. The critical summary sections that synthesize the evidence are variable and too often brief or not present, and strength of evidence is not characterized with standardized descriptors.

As noted, the committee's report provides many comments and recommendations specific to topics of its charge; additionally, the committee offered six concluding recommendations that were considered as critical to completion of the draft IRIS assessment. First, 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. Second, Chapter 1 of the draft assessment needs to discuss more fully the methods used to develop the assessment. The committee is not recommending 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. Third, 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. Fourth, 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. Fifth, the rationales for selection of studies that are used to calculate RfCs and unit risks need to be articulated clearly. Sixth, the weight-of-evidence descriptions need to indicate the various determinants of "weight." Readers of the draft need to be able to understand what elements (such as consistency) were emphasized in synthesizing the evidence.

The committee's review of the EPA's draft IRIS assessment of formaldehyde identified both specific and general problems with the document. The persistence of the problems encountered with the IRIS assessment methods and reports concerned the committee, particularly in light of the continued evolution of risk-assessment methods and the growing societal and legislative needs to evaluate many more chemicals in an expedient manner. On the basis of the "lessons learned" from the formaldehyde assessment, the committee offered some suggestions for changes in the IRIS development process that might help EPA improve its approach. The committee recognized that EPA has initiated a plan to revise the overall IRIS process and that it issued a memorandum in 2009 giving a brief description of the steps. However, the focus of the revision as indicated in the 2009 memorandum appears to be on the steps taken after the assessment has been generated (that is, the multiple layers of review). The committee's focus was on the completion of the draft IRIS assessment (that is, the development phase).



The committee offered a several-page roadmap for changes in the development process. The term *roadmap* was used because the topics that need to be addressed are set out, but detailed guidance was not provided because that was seen as beyond the committee's charge. Thus, the committee provided general guidance for the overall process and some more specific guidance on the specific steps of evidence identification, evidence review and evaluation, weight-of-evidence evaluation, selection of studies for derivation of RfCs and unit risk, and calculation of RfCs and unit risks. For each of these steps, there are underlying processes that would need to be examined and reconsidered. The report provides further detail.

The committee recognized that any revision of the approach would involve an extensive effort by EPA staff and others and consequently, it did not recommend that EPA delay the revision of the formaldehyde assessment while revisions of the approach are undertaken. In fact, we provided specific guidance as to the steps needed to revise the existing draft. Models for conducting IRIS assessments more effectively and efficiently are available, and the committee provided several examples in the present report. Thus, EPA might be able to make changes in its process relatively quickly by selecting and adapting existing approaches, as it moves towards a more state-of-art process.

Chairman BROUN. I want to thank the panel, all of you.

Reminding Members the committee rules limit questioning to five minutes each. The chair at this point will open the round of questions.

The chair recognizes himself for five minutes.

EPA announced changes to the IRIS process 2 days ago. In that announcement EPA indicated that it signed an MOU with the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment to—in order to cooperate in the development of health assessments to encourage data sharing, avoid duplication of effort.

Dr. Anastas, as a Georgian why should I be subject to California's risk assessments? If states are doing this work, why do we need IRIS? If IRIS assessments are better than state assessment, why have California do assessments for EPA? If IRIS isn't sufficient, why not rely on one own state assessment. Why just rely on one own state assessment? Please explain this to me why this isn't a backdoor attempt to implement California's risk assessment policies on the rest of the Nation.

Dr. Anastas.

Dr. ANASTAS. Thank you very much, Mr. Chairman. I am very happy that you asked that question because it gives the opportunity to explain some misconceptions about what IRIS is.

IRIS assessments are not risk assessments. They are not risk management actions. They are not regulations. They are scientific assessments to understand the hazard, the underlying toxicity of substances. So the information that would be being shared between California and EPA is simply the underlying scientific basis, the assessments that are done by using the open scientific literature that is the basis of the science, but in no way would these assessments be risk assessments, California risk assessments, California regulations. These are only the underlying scientific bases that would be shared and the basis of these health hazard assessments.

Chairman BROUN. Well, I have got some follow-up questions to that that I will give you in writing to go forward, but just in the sake of time, Dr. Samet, as chair of the National Research Council committee that reviewed the EPA's draft IRIS assessment on formaldehyde, the committee decided to devote an entire chapter entitled, "Roadmap for Revision." That highlighted specific changes to improve the formaldehyde IRIS assessment but also went a step further and offered recommendation for improving the IRIS process in general.

Why did the committee decide to offer additional recommendations to improve the IRIS process? What letter grade would you give EPA for its formaldehyde assessment, A being excellent and F being a failure? And how about for the four other assessments that NAS has reviewed since 2005?

Dr. SAMET. The committee in its chapter seven wanted to give very specific guidance to the Agency on how to bring the formaldehyde assessment to completion. That was the six recommendations. The document, the draft assessment involves a number of underlying processes that have a generality to them, pulling together all the evidence, reviewing it, and evaluating it. And as we looked at

the assessment, we found weaknesses which we documented in how those processes had been put into place and carried out.

We felt that it was important to give the specific suggestions but also to provide general guidance on what needed to be done to help improve not only this IRIS assessment but hopefully future ones. As you noted, the National Research Council has reviewed other major IRIS assessments in the last decade and have found deficiencies in those documents.

Now, I will say the committee was not asked to give a letter grade. I certainly couldn't give an A. I probably would be, Paul, sorry, a little pressed to give a B, and let us say we would certainly give—we will give a passing grade here, and I am not sure, and if I give a too-low grade, I know they will come back and ask me to revise it.

Chairman BROWN. Okay. Thank you, Dr. Samet.

My time has just about expired, so I will recognize Ms. Edwards for five minutes.

Ms. EDWARDS. Thank you, Mr. Chairman, and thank you to our witnesses this morning.

Dr. Samet, your panel laid out certain challenges for EPA to take up to make the formaldehyde assessment stronger. Your panel did not recommend, however, that EPA bring that revised assessment back to the Academy for another round of review but to finish it and finalize it.

Do you have confidence that EPA can successfully address the issues raised by your panel regarding how to strengthen and clarify the formaldehyde assessment?

Dr. SAMET. As a first comment, of course, an Academy panel can't recommend that something be brought back to the Academy, and I think however the document is revised I suspect that EPA will undertake further review. I think we were careful in chapter seven to say specifically what should be done. These changes as I noted in my testimony should be feasible, and they are changes that—and revisions that the agency should be able to make successfully.

Ms. EDWARDS. And Dr. Anastas, do you have confidence that you will be able to make that assessment given the analysis by the Academy?

Dr. ANASTAS. Yes. I think the important thing is we seek out the type of input that we received from the National Academy, we seek out from scientific experts, and we are very confident that getting the kind of input, the kind of recommendations, that we are able to follow through and incorporate those suggestions.

Ms. EDWARDS. Thank you, and to follow on then, Dr. Samet, the Subcommittee has received some testimony for this hearing that suggests that the Academy should review every IRIS assessment, then review every revised assessment after changes are made following the NAS report. Would this be a difficult thing for the Academy to take on, and what effort would it require to review 20 IRIS assessments a year?

Dr. SAMET. Well, I, you know, certainly I am now speaking as chair of the committee and not in general with the Academy, which I can't do. I think there are many ways to have successful peer review. The Science Advisory Board of the EPA, which I serve on,

being one. The Academy being another. I will say that now speaking individually, the effort involved in completing this review was substantial as I have mentioned. A 15-member committee of volunteers working in four meetings in 8 months and producing a, you know, a report over 100 pages.

So substantial effort would be involved, and I think if the full load of peer review were somehow placed before the Academy, I am certain that that would stress the community of scientists who carry out such reviews.

Ms. EDWARDS. Yes. I suspect that would be pretty impracticable.

I wonder, Dr. Samet, you also provided a roadmap for EPA on how you think the IRIS process could be improved, and your panel apparently believed that EPA is actually capable of implementing those changes that the agency decides make sense.

As chair of the Clean Air Science Advisory Committee at EPA you have had such changes take place and then I will just use the acronym, in the NAAQS process, and also as chair of CASAC and those assessment processes, are there lessons that might be learned here for IRIS?

Dr. SAMET. Well, I think if you look at chapter seven of our report we provided a case study of the revisions that were made, and having participated in reviews of NAAQS standards now for several decades and I think the process has become much clearer, must more transparent, and much more efficient, and I think it has worked. It took some time on the part of the Agency and some interactions with CASAC, but I think an improved process resulted.

Ms. EDWARDS. And I just want to be clear. Your report contained examples of where your panel felt that the EPA got the science wrong or failed to adequately communicate how they evaluated studies and came to conclusions, but I couldn't find anyplace where you imply that EPA purposely distorted the science or their findings. Did you find any evidence at all of purposeful deception or intentional manipulation on the part of EPA?

Dr. SAMET. Well, certainly as we addressed our charge, we look carefully at how studies were selected and reviewed. I think we certainly found many examples where we felt that EPA had not communicated well or we could not follow their methodology but nothing that I would regard as purposeful to use your words.

Ms. EDWARDS. Thank you, and then lastly, we will hear testimony today that argues that the Science Advisory Board lacks independence because it depends on EPA staff. Doesn't the CASAC also depend on EPA staff for its work?

Dr. SAMET. Well, EPA, I am sorry, CASAC certainly is supported by EPA staff. Our deliberations and discussions are fully public, and I certainly don't see them as influenced by EPA staff as we carry them out in the complete open.

Ms. EDWARDS. Does either CASAC or the Science Advisory Board have, do you have any reason to believe that they lack any kind of independence because they rely somewhat on EPA staff?

Dr. SAMET. Not in my experience. No.

Ms. EDWARDS. Thank you very much, and with that I yield.

Mr. HULTGREN. [Presiding] I am going to yield myself five minutes for some questions as well. So, Mr. Trimble, if I could start

with you, what would it take to remove the IRIS Program from GAO's high-risk series?

Mr. TRIMBLE. That is a challenging question. We are in the process of working with the agency and OMB to discuss what sort of steps we would like to see along that process. I think there is no simple answer that is X and Y and Z. I think that we have got a little bit more work to figure out all the steps.

Clearly from our prior work some of the steps they have taken has moved the ball along in terms of restoring independence, adding some transparency to the process, but clearly a lot of work needs to be done in terms of being able to address the large backlog that still remains, as well as to be able to move ongoing assessments forward in a timely manner.

I think there is also the issue that is still lurking out there regarding sort of the pent-up backlog of IRIS assessments that the Office of Water and other parts of the EPA have not put in requests because they know there is such a logjam currently. So there are a lot of other hidden issues that we haven't addressed yet, but we are in the process of planning work.

Mr. HULTGREN. Do you have any estimate on the timeline on that?

Mr. TRIMBLE. Well, we have meetings scheduled I believe this fall with the Agency and OMB to sort of do a status report, and you know, I am not, I don't have a timeline at this stage.

Mr. HULTGREN. Dr. Anastas, let me read one part of Dr. Samet's testimony where he says, "In the roughly 1,000 page formaldehyde draft reviewed by the present committee, little beyond a brief two-page introductory chapter could be found on the methods for conducting the assessment. In fact, the introductory chapter of formaldehyde is nearly identical to that used in the IRIS assessments. Numerous EPA guidelines are cited, but their role in the preparation of the assessment is not clear. In general, the committee found that the draft was not prepared in a consistent fashion. It lacked clear links to an underlying conceptual framework, and 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. The critical summary sections that synthesized the evidence are variable and too often brief or not present, and strength of evidence is not characterized with standardized descriptors."

How do you respond to that?

Dr. ANASTAS. The reason that the Environmental Protection Agency seeks out the type of peer review, expert peer review from whether it is our Science Advisory Board or the National Academies is to get that exact type of review, that exact type of input. We take those recommendations extremely seriously. We think that those improvements are absolutely essential to improving and finalizing this draft assessment. That is why we seek it out. That is why we fully accept them. That is why we are integrating them into our revision of the formaldehyde assessment.

Mr. HULTGREN. So what is your intention, I guess, with, I mean, this is pretty significant what they have said, you know, that it

sounds like there was a pretty significant failure here in the processes. What will happen to address those recognized failures?

Dr. ANASTAS. I guess I look at it a little bit differently. I view that as a success in the process. We seek out this exact type of peer review in order to continuously improve this draft document. When we write a draft document, we want that type of input so that the final version that gets posted and is available to the American public and beyond is of the highest quality. That is why we accept those recommendations, and that is why we will build them into our revision.

Mr. HULTGREN. Okay. Dr. Samet, with my last remaining minute here, in her testimony Ms. Steinzor takes exception to your scolding of EPA staff in the April formaldehyde report by saying, "I wish that the NRC Committee had not adopted such a haughty tone in scolding EPA staff."

In responding to her observation can you provide us with some context of how many reviews the Academy has done of other IRIS assessments and how often you or other chairs repeated the suggestions and recommendations that ultimately led to chapter seven of the formaldehyde report?

Dr. SAMET. Well, I guess I had not read the testimony or seen the term, scolding. I think that our comments in chapter seven are provided as recommendations and as positive help to the Agency in trying to improve the process as Dr. Anastas mentioned. I think probably, and I can look to my left and get a little help, but this is probably the fifth review in the last decade by a National Research Council committee of an IRIS assessment. These have been the larger, more complicated assessments, and I think in all of them there have been one or more general comments about methodology and some specific chapters on aspects of methodology with concerns expressed.

Mr. HULTGREN. Thank you. My time is up.

I yield five minutes to Mr. McNerney.

Mr. MCNERNEY. Thank you, Mr. Chairman. I thank the panel for stepping forward this morning. I appreciate, Dr. Anastas, the attitude that you have about looking for input from independent sources. That is very important. As a scientist I appreciate that, and I understand that the Office of Research and Development relies on a board of scientific counselors to help provide an independent evaluation of your programs. That board did an assessment in 2008, and then again in 2010.

Later this morning we are going to hear that the IRIS assessments are considered irrelevant and the department weak in science. Can you tell us a little bit about the board and what sort of people serve on it, their independence, and summarize their observations for us, please?

Dr. ANASTAS. Yes. A number of years ago we sought to establish the Board of Scientific Counselors to give us independent reviews of our general performance, how we are performing on the wide range of activities that the Office of Research and Development undertakes. Specifically we asked them to review the IRIS process, and these Members who are of the highest quality from industry, academia, a broad spectrum of people, looked at the IRIS Program

and gave us tremendous feedback, both constructive recommendations, as well as recognizing the strengths.

Some of the quotes from the Board of Scientific Counselors include, "Internationally IRIS assessments are considered to be of the highest quality and reliability." Another quote is, "IRIS assessments are among the most heavily-peer-reviewed documents produced by scientists anywhere."

So there are tremendous strengths to the IRIS Program, but we also need to recognize that even strong programs can and must improve. I come from Boston where the Boston Red Sox happen to be in first place right now, but they are always seeking to improve. We will always engage in continuous improvement because that is what scientists do.

Mr. MCNERNEY. Was the Board's recommendations or are their recommendations aligned more or less with the recommendations from the National Academy?

Dr. ANASTAS. Yes.

Mr. MCNERNEY. Thank you. Dr. Samet, why did the National Academy undertake the assessment in the first place, and who paid for that effort?

Dr. SAMET. Well, the National Research Council was asked by the Agency to carry out this review. I think there is a somewhat long and complicated history about that request that you are likely aware of, but the support for the review to the Academies came from the Environmental Protection Agency.

Mr. MCNERNEY. Did the National Academy feel that their recommendations or that your recommendations should be mandatory and enacted by the end of this year? Was that the intent?

Dr. SAMET. Well, the Academy, of course, makes—our report provides its recommendations. These have no binding requirements for the Agency. They are really peer review and suggestions and comments that we make in the spirit that we hope they will prove to be useful to the Agency as it revises the document or if it chooses to undertake revisions to the IRIS process itself.

Mr. MCNERNEY. So, I mean, they weren't initially given as, hey, you need to do this by the end of this year, or this is a big problem. That wasn't the intent then, was it?

Dr. SAMET. Well, an Academy committee would not make recommendations in that spirit. I mean, again, the Academy is an advisory to the government.

Mr. MCNERNEY. Thank you. Mr. Trimble, you reported this morning that the assessment, the IRIS assessment was unresponsive. I think that is the word I heard a number of times. What do you believe is the underlying cause for that assessment for your unresponsive assessment?

Mr. TRIMBLE. I believe the unresponsiveness I was referring to was in response to our 2008 report where we made recommendations to improve the process and then later in 2008, they made changes formalizing the process which was essentially no change. They institutionalized the things we had identified as problematic. That process was then changed in 2009.

So the lack of responsiveness is to our prior recommendations and one of the reasons we put the area on our high-risk list.

Mr. MCNERNEY. I mean, you didn't answer my question. What do you think the underlying causes of that unresponsiveness?

Mr. TRIMBLE. Well, at that time I believe OMB and the EPA were committed to the procedures they had in place, and they were—their position was that the OMB's comments and other agencies' comments were deliberative and should not be put in the public domain.

Mr. MCNERNEY. Okay. My time has expired, but you never really answered the question. Thank you.

Mr. HULTGREN. I recognize Dr. Benishek for five minutes.

Dr. BENISHEK. Thank you, Mr. Chairman. Distinguished Members of the panel, thank you for your time today. I know we are here to talk about chemicals, and as a physician I have a bit of experience with chemicals.

I would like to talk today about a chemical called acrylonitrile or AN. It kind of has a funny name, and you probably never heard of it, but we all come in contact with it. As a physician I really haven't been aware that I was using the compound, but it is around in medicine a lot. It is found in everything from dialysis tubing to cell phones to computers and golf clubs.

Recently the EPA released an IRIS assessment for AN with a 60-day comment period, and based on initial review of the draft it doesn't seem to have a comprehensive objective review of the science. The draft completely ignores many of the articles published in reputable peer review journals, many with opposing views.

I am concerned that the assessment will lead to burdensome regulations in a variety of industries, you know, especially in my district, plastics and boating industry, medical equipment. I find it troubling that the Agency seems to spend a lot of time and money accusing us in Congress to not—to ignoring science but fails to follow some of its own advice.

Is the EPA's objective to review all critical published scientific information when preparing these assessments, whether or not the Agency agrees with the position? Dr. Anastas.

Dr. ANASTAS. Thank you very much for the question. The short answer to your question is yes. We—an essential part of all of our analyses, speaking generally across all of the IRIS assessments, is understanding the relevant, credible scientific information and composing its assessments. Those assessments, and I am speaking specifically to acrylonitrile right now, go into an external peer review process where we get the reaction to this draft assessment.

So if there are concerns about particular studies that may not have been identified, considered, that those are caught during this period in the peer review process.

Dr. BENISHEK. Well, the reason I am asking this is, you know, apparently what this is, acrylonitrile review, there is no mention of several other publications. I am looking at one here. The International Agency for Research on Cancer, part of the World Health Organization published a review that wasn't cited. There is a review on AN in North Carolina Scientific Advisory Board that wasn't cited. There was a review by an independent peer review panel organized by TERA, the Toxicology for Excellence and Risk Assessment. There are several conflicting sources of information that aren't cited in the review and I just want to understand how



the committee decides which studies to include in the review and which studies not to include.

I mean——

Dr. ANASTAS. That is an excellent question. The process by which studies are selected based on their relevance, their credibility is something that as we have spoken about, is always something that we are seeking to make clear, transparent with these public meetings, with this public external peer review. All of these comments are considered. That is why this draft is going out for this public peer review.

I do want to clarify one thing that I mentioned earlier. These assessments are not regulations. These assessments are not risk assessments. These are the underlying scientific characterization of the hazard.

Dr. BENISHEK. Well, it doesn't seem to me to, you know, I have read the papers where you may have like 100 citations, and just not having all the citations that are available doesn't seem to make any sense to me. You know what I mean? Why some are not listed I just don't get it, because, I mean, you just put another citation in there. It makes sense to have comments on both sides of the issue.

Dr. ANASTAS. Absolutely and that is why we have these public sessions to consider all scientifically-sound, credible information be part of these assessments.

Dr. BENISHEK. And yet these things that I cited weren't included. So I just don't understand why not.

Dr. ANASTAS. If there were any scientific, credible, independent studies that were not included, then this is the process to ensure that all of them are included. This is why we go to the external public peer review.

Dr. BENISHEK. So then are we going to include these studies that I had mentioned to you in the future or reevaluate the situation or what?

Dr. ANASTAS. Any literature, any study that is relevant, sound, independent, scientifically credible. Anything that is—that meets those criteria would certainly be included.

Dr. BENISHEK. Well, great. Then we will have the committee forward these studies to you, but maybe they can be included in your evaluation.

Dr. ANASTAS. And the timing is excellent, because this is the external peer review and public assessment comment.

Dr. BENISHEK. All right. Thanks.

I yield back my time.

Chairman BROWN. The gentleman's time is expired.

Now I recognize Mr. Miller for five minutes.

Mr. MILLER. Thank you. This is an issue, the IRIS System, that this Subcommittee considered when I was chair of the Subcommittee. We have thousands of chemicals that are in widespread use. We really do not know what the public health consequences are of exposure to those chemicals. We have about 700 new chemicals entering the marketplace every year. We have no idea what most of those do to anybody. We have got cancer clusters and clusters of birth defects all over the country we know have got to be the result of exposure to something, and we don't know what, and

the IRIS System is supposed to be how we assess the risk of exposure to chemicals.

But despite all that because of the system that was in place there are only about three new or revised assessments being issued a year, and there was ample evidence of political interference and a great deal of influence by the industries that made those chemicals or use those chemicals.

I have three charts I would like to show, and I believe somebody is, yes, standing by, and I hope the witnesses can see these.

[Chart]

This is actually a schematic of the process that the Bush Administration inherited from the Clinton Administration. Well, I believe it was in effect for most of the Bush Administration, and then a step or supposedly this was streamlined.

Can we show the second?

[Chart]

Yeah. That is the streamlined version. Now, at the time I said that I was reminded of Chico Marx quote, "Who are you going to believe, me or your own eyes," that that was a streamlined version of the process that had existed before. What that did, however, was put OIRA in the middle of the whole process.

Now, Dr. Anastas, when Chairman Broun scolded you for not getting your testimony in on time, he said you had completed it, but you had to get it reviewed. Was that a review by OMB?

Dr. ANASTAS. All testimony is reviewed by OMB.

Mr. MILLER. Okay, and that is where the holdup was? Well, I know you don't want to criticize OMB. Is OIRA a part of OMB?

Dr. ANASTAS. Yes.

Mr. MILLER. Okay. Thank you, and that is the system that slowed it, that appeared to slowed it down greatly. Now, Mr. Trimble, the GAO has been in—very involved in all this in reviewing the IRIS System, and you were not suggesting—well, let us now go to the third slide.

[Slide]

And that is the slide that supposedly is streamlined, and actually it appears that you could believe your own eyes that that is streamlined. You are not suggesting we go from that back to the previous system, are you?

Mr. TRIMBLE. No, sir. The opposite.

Mr. MILLER. Okay. The opposite. All right.

Dr. Samet, you reviewed a lot of OIRA's assessments. You looked at, let us see, formaldehyde, perchlorate, dioxin, trichloroethylene. I am not on of the committee's doctors. And tetrachloroethylene.

Which of those systems were those assessments done under?

Dr. SAMET. I would, I can't exactly answer that. I mean, I would have to look at the timing of each of those and when they were done. They were mostly done over the last 5 or six years, so I guess that would be back with your 2004, 2008 slide.

Mr. MILLER. Well, Dr. Anastas, can you answer that question? Were any of these assessments that the academies have found fault with been performed under that system?

Dr. ANASTAS. No.

Mr. MILLER. They were all under the previous systems?

Dr. ANASTAS. Correct.

Mr. MILLER. The streamlined previous systems?

Dr. ANASTAS. Correct.

Mr. MILLER. All right, and, again, although Susan Dudley, who headed OIRA at the time, sat right there, raised her hand, right hand, took the same oath that you all had, and said that there was never any—they never really substituted their judgment on science for EPA. There was a huge amount of evidence that that happened routinely.

The impression from that period and from our hearings before is that the work EPA was doing to get a risk assessment through this streamlined process was one performed under fire, under hostile fire from the industries that produced the chemicals and from the industries and the agencies of government that used the chemicals. Is that correct?

Dr. ANASTAS. Was that the characterization?

Mr. MILLER. Yes, sir.

Dr. ANASTAS. That was the characterization.

Mr. MILLER. Okay, and is it possible that some of the fault that the academies have found with EPA's work in this is the result of the fact that the people performing the work felt they were under fire and were trying to anticipate every possible criticism?

Dr. ANASTAS. There are those who have characterized that that way. Yes.

Mr. MILLER. Okay. Would you be one of those who characterizes it that way?

Dr. ANASTAS. I think the excellent scientists who dedicate their professional lives to this have felt under a tremendous amount of pressure from different sources. Correct.

Mr. MILLER. Okay. My time has expired, Mr. Chairman.

Chairman BROWN. Thank you, Mr. Miller. Nice seeing you stay within five minutes. No, I said that in all sincerity.

Now the Chairman recognizes Mr. Rohrabacher for five minutes.

Mr. ROHRABACHER. Thank you very much, Mr. Chairman.

Yeah. I guess we have seen lots of examples where scientists have been put under pressure, especially during this investigation of global warming and such issues where our scientists were denied grants because they did not believe in global warming's theory, which we heard reports of across the board for years in this committee.

So we know that there are certain advocacy elements within the scientific community that are willing to pressure other people within the scientific community. It is sort of like tenure in college for the college professors, of course, would never think about trying to control what type of people are hired onto their departments, but we all know that happens, don't we?

I would like to ask in terms of how this affects the scientific questions that we are dealing with today, is—and I certainly would—I will take you, I will address you, you are the head man. Are the scientists who are involved with this risk assessment program, are they—are steps taken to make sure that they have not been part of advocacy groups prior to their involvement with this program?

Dr. ANASTAS. I can't say that I do not investigate the backgrounds of scientists.

Mr. ROHRABACHER. Okay. So there is no background check to see if a scientist has been involved with an advocacy program or actually been hired, perhaps, by an advocacy organization prior to him getting involved and his decision making being trusted by your organization?

Dr. ANASTAS. The only background check that would be done is for the scientific excellence.

Mr. ROHRABACHER. Okay. So you could have someone who is very etiological, very, very etiological and even being hired by groups that are just adamant about what they believe, and that person could still be someone who you are relying on for their judgment not to be impaired.

Dr. ANASTAS. I can only say that we hire people for their excellence in science, that demonstrated excellence in science.

Mr. ROHRABACHER. Uh-huh, and you don't take into consideration if that person had been involved in an organization that perhaps that organization is so committed to a position that it reflects anyone who could associate. You know, there are certain groups that have a position, whether they are against what you believe or for what you believe, but they are so adamant that we know that that might indicate the person doesn't have an open mind towards certain issues.

But that is not taken into consideration for hiring someone?

Dr. ANASTAS. You raise an excellent point, Congressman, because at the essence of scientific excellence is objectivity.

Mr. ROHRABACHER. Correct.

Dr. ANASTAS. And so when I use the words, scientific excellence, embedded in that definition would be objectivity.

Mr. ROHRABACHER. Okay, and however, someone's affiliation with certain advocacy groups is not something that you would look at to determine their objectivity?

Dr. ANASTAS. If a person skewed their science in order to meet ideological ends, that would be antithetical to scientific excellence.

Mr. ROHRABACHER. And there is no organizations that you believe that just an association with that organization would say, well, maybe that person is just too much involved with advocating a position to be able to come on board?

Dr. ANASTAS. I would only say that we need to evaluate the scientific excellence and the objectivity and other litmus tests, background checks—

Mr. ROHRABACHER. Right.

Dr. ANASTAS. —or—

Mr. ROHRABACHER. Now, what we have seen too much of is scientific excellence is dependent on whether someone agrees with me or not, and that is what we have seen over and over and over again by the liberal establishment here in this city in dealing with scientific issues. And I certainly would think that if we have certain people that are committed to a position and they are involved with organizations that are committed, that that should be taken into consideration when giving them responsibility to assess whether or not something is scientifically viable or not.

Let me ask you another thing.

Chairman BROWN. The Chairman's time has expired.

Mr. ROHRABACHER. Oh. Pardon me.

Chairman BROWN. Thank you, Mr. Rohrabacher.

I now recognize Mr. Clarke for five minutes.

Mr. CLARKE. Thank you, Mr. Chairman. My question is more than likely for Dr. Anastas about anyone else could feel free to answer. It is really a basic one.

I just wanted to get clarification again between the difference between an IRIS scientific assessment and a complete risk assessment, if there are certain elements in a risk assessment that the IRIS assessment does not address. And then ultimately how you would compare the IRIS assessment in time development and in substance to the ultimate regulatory proposal that is issue?

Dr. ANASTAS. Certainly and thank you very much for the question.

The information that is provided in an IRIS assessment is an essential and key part that feeds into a risk assessment. However, there is the hazard characterization. In order to come up with the risk assessment, the risk probability, you need exposure data. So the exposure of an individual to the substance through a variety of routes, whether it is children, it is breathing in air, it is ingested in the water, that—those components coming together are part of the risk assessment process, which then feeds into the risk management alternatives. Those are the regulatory determinations that are carried out by our program offices, our Office of Water, our Office of Air, to take into account a wide variety of other factors, including everything from socio, economic, other considerations, technological feasibility of various risk management options.

And so while the IRIS assessments and the information they provide is a critical piece, it is significantly removed from the regulatory process.

Chairman BROWN. Thank you, Mr. Clarke.

Now recognize the full committee Chairman, Mr. Hall, for five minutes.

Chairman HALL. Thank you, Mr. Chairman. Inasmuch as I don't know what questions have been asked or answers elicited and as much as I probably wouldn't believe anything any of the three of you say, I will yield back my time.

Chairman BROWN. I can't believe it. Okay.

Mr. Sarbanes is still down there. I yield Mr. Sarbanes five minutes.

Mr. SARBANES. Thank you, Mr. Chairman. I appreciate it. Thank you for your testimony.

I always start these hearings, these hearings being ones that are about chemicals and the risks that chemicals pose out there and our efforts to try to get a handle on that and get more information by observing it, if the average member of the public understood how little information and knowledge we have about the chemicals that are being put out there in the stream of commerce, in the natural streams, and so forth, they would be amazed and appalled. I think they have the expectation that our level of knowledge is much, much higher than it is, and a lot of the delay that we see in the kind of regulation and oversight and assessment is something they wouldn't imagine would be happening in the United States of America in the 21st century. So I don't know who is

watching this hearing out there in the public, but I hope they spread the word on this.

I was looking at this silver book, as it is so called, and on the back it talks about how risk assessment has become a dominant public policy tool for making choices based on limited resources to protect public health and the environment. So we talked a lot about that.

However, risk assessment is at a crossroads, it says. Despite advances in the field risk assessment faces a number of significant challenges including lengthy delays in completing complex risk assessments, lack of data leading to significant uncertainty in risk assessments, and many chemicals in the marketplace that have not been evaluated, and emerging agents requiring assessment, which is a pretty good encapsulation of the testimony and exchange that we have been having here this morning.

I think you all recognize that, and I see the three of you working in concert to try to improve the process, improve the reliability of the risk assessment process, and Dr. Anastas, I appreciate your lack of defensiveness with respect to the assessments and evaluations that have been done that you invite in terms of the IRIS process, and you are getting some good constructive input.

Then commenting on the silver book, this—the back flap here says, “Science and decisions,” which is the name of the silver book, “makes practical scientific and technical recommendations to address these challenges,” i.e., the ones just referred to.

Can you speak to the value of this? This is a follow up on an earlier framework known as the red book, as I understand it it complements it, but can you speak to the value of this, and then Dr. Samet, I would like to get your perspective on it as well. Thank you.

Dr. ANASTAS. Thank you very much, Congressman, for the question because the so-called silver book was carried out by the National Research Council and chaired by a very well-respected professor at Johns Hopkins University named Tom Burke and provided some excellent framework for how we need to continuously improve our risk assessment processes, how we need to think more broadly if we are going to ensure that the risk framework is as strong as it needs to be.

As Science Advisor of the Agency, I have the honor of chairing the Science Technology and Policy Council. Adopting the recommendations in the science book is something that is going on in real time, moving ahead so that across the Agency the findings of the silver book are able to be incorporated.

Mr. SARBANES. Thank you. Dr. Samet.

Dr. SAMET. I think the silver book was an important updating and broadening of the concepts that were in the so-called red book.

I would also bring your attention to one other report that came out from the National Research Council around the same time, Toxicity Testing for the 21st Century, which laid out, I am sorry to use the word again, but a roadmap or a blueprint for how to address the problem highlighted in the comments on the back of the silver book. We need to have a way to test with validity the many chemicals coming into the marketplace. And the proposal in that document is how do we use our new science to try and address this

question with some certainty, dealing with the hundreds of chemicals whose risks we are uncertain about as they come into the marketplace, using the best science possible.

So I think that together those two reports do set out a, hopefully a new approach for the future.

Mr. SARBANES. Thank you. I yield back.

Chairman BROUN. The gentleman's time has expired. Thank you so much, Mr. Sarbanes.

I want to thank the panel for you all's testimony and your answering questions, particularly in an expeditious manner, and I want to thank the committee Members for also asking their questions in an expeditious manner.

You will be excused. Members may desire to submit written questions, and I trust that we will get replies in a timely manner from you all, so you all are excused, and thank you for your testimony today.

And if the second panel will expeditiously also take their seats.

At this time I would like to welcome and introduce our final panel of witnesses. First is the Honorable Calvin Dooley. He is President and CEO of the American Chemistry Council. Congressman Dooley previously represented the 20th Congressional District in California. We have Ms. Rena Steinzor, who is Professor at the University of Maryland School of Law and Founder and President of the Center for Progressive Reform. We have Dr. Gail Charnley, is Principal at HealthRisk Strategies. Dr. Charnley is an internationally-recognized scientist who has served on several advisory committees, including peer review panels for the EPA and FDA, the Presidential Congressional Commission on Risk Assessment and Risk Management, and is currently on the National Academy of Sciences Board on Environmental Studies in Toxicology. The Honorable Chris Bollwage is Mayor for the City of Elizabeth, New Jersey, a position he has held for the past 18 years. I am sorry. You have got one of the hardest jobs in politics. Mayor Bollwage also serves as Chair of the Conference of Mayors Brownfields Task Force.

As our witnesses should know, spoken testimony is limited to five minutes each, and please try to maintain that five minutes. After which Members of the committee will have five minutes to ask each questions. I ask the committee Members to please be mindful of the time. Your written testimony will be included in the record of the hearing. It is the practice of the Subcommittee on Investigations and Oversight to receive testimony under oath. Do any of you have objections to taking an oath?

Let the record reflect that all witnesses are willing to take an oath.

You also may be represented by counsel. Do any of you have counsel here today?

Let the record reflect that none of the witnesses have counsel. I think Congressman Dooley, you indicated you do not. Okay. That is great. If all of you would please now stand and raise your right hand. Do you solemnly swear or affirm to tell the whole truth and nothing but the truth, so help you God?

Thank you, and you may be seated. Let the record reflect that all the witnesses participating have taken the oath.

I now recognize our first witness, Congressman Dooley, for five minutes.

**TESTIMONY OF CALVIN DOOLEY,  
PRESIDENT AND CHIEF EXECUTIVE OFFICER,  
AMERICAN CHEMISTRY COUNCIL**

Mr. DOOLEY. Good morning Mr. Chairman and Members of the committee. I appreciate the opportunity to be here today to speak to the pressing need to fix the Environmental Protection Agency's Integrated Risk Information System or IRIS.

IRIS is one of the most important programs that EPA uses to assess the safety of chemicals. But in recent years, IRIS frequently has been criticized for failing to meet high standards of scientific inquiry, transparency, and quality.

I have outlined several examples of flawed IRIS assessments in my written testimony, but the recent peer review of formaldehyde is perhaps the most telling. After EPA's draft IRIS review of formaldehyde was scrutinized, EPA asked the independent experts at the National Academy of Sciences, NAS, to review its findings.

The NAS review questioned the evidence IRIS used to support its conclusions that a link exists between the exposure to formaldehyde and certain types of leukemia, stating, "Conclusions appear to be based on a subjective view of the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data, and the lack of mechanistic data."

The NAS report also devoted an entire chapter to needed program improvements. NAS summed it up by saying, "The committee is concerned about the persistence of problems encountered with IRIS assessments over the years, especially given the multiple groups that have highlighted them. If the methodologic issues are not addressed, future assessments may still have the same general and avoidable problems that they highlighted in their report."

While IRIS is a complex program that examines complex issues, the problems can be boiled down to two things. First, IRIS does not reflect modern scientific methods or 21st century knowledge about how chemicals interact in the body at different levels of exposure. Rather, IRIS continues to rely too heavily on outdated assumptions that were formulated in the 1970s.

Second, there is little independence in the program's peer review process. EPA controls each step of the review process and ultimately decides which recommendations from peer review groups to act upon and which to ignore.

IRIS needs a comprehensive overhaul to ensure that assessments are based on proven scientific data and modern scientific understanding. The peer review process must be enhanced so there is an honest broker to ensure that IRIS assessments are reviewed independently and recommendations from peer reviews and public comments are adequately incorporated.

While EPA announced some process changes earlier this week and we are pleased that EPA has done so and that they recognize the program must be reformed, we remain concerned about the lack of a truly independent peer review process. ACC continues to believe that NAS should review all pending IRIS assessments to



ensure their quality until the systematic problems with the program are fixed. And I will stress that. Until we have the confidence that the systematic problems are fixed.

If the improvements announced this week are effective, that will validate—be validated by NAS reviews. Anyone who looks at the evidence, whether you are a state regulator, a public health official, or a furniture maker can see that the IRIS Program is broken. Getting it right is in the interest of us all. The current deficiencies and the lack of confidence in the program cause delays and unnecessary costs. Flawed assessments create public confusion, unwarranted alarm, unnecessary product de-selection, and litigation, all of which can put jobs and innovation at risk without a sound scientific basis.

By making needed changes to IRIS we can minimize delays and provide answers to the public, public health professionals, and industry in a far-more credible and timely way.

Thank you very much for the opportunity to testify, and I look forward to taking your questions.

[The prepared statement of Mr. Dooley follows:]

PREPARED STATEMENT OF THE HONORABLE CALVIN DOOLEY, PRESIDENT AND CHIEF  
EXECUTIVE OFFICER, AMERICAN CHEMISTRY COUNCIL

Mr. Chairman and Members of the Committee. I am Cal Dooley, president and CEO of the American Chemistry Council. I appreciate the opportunity to be here today to speak to the pressing need to fix the Environmental Protection Agency's (EPA) Integrated Risk Information System, or IRIS.

Shortly after taking office, President Obama committed that science and the scientific process would guide decisions of his Administration. We at the American Chemistry Council (ACC) welcomed this pledge, because we agree that credible, accurate, modern science must form the foundation of regulatory decisions.

Three years later, though, our confidence in the Administration's commitment to scientific integrity in the regulatory process has eroded. This is in large part due to troubling inconsistencies, inefficiencies and lack of transparency in the federal system for assessing the safety of chemicals.

IRIS is one of the most important programs EPA uses to assess chemical safety. It serves as a leading source of health risk information for other federal, state, and international regulatory bodies. But over the years, the program has been repeatedly criticized for failing to consistently meet high standards of scientific inquiry, transparency and quality.

It is time to fix the IRIS program to protect health, safety and the environment and preserve the ability of American industry to innovate, compete and create jobs.

Several examples illustrate the shortcomings of the IRIS program:

#### Formaldehyde

Perhaps the most telling example can be found in the recent case of formaldehyde. Formaldehyde has been the subject of scientific study for years. Numerous organizations including the World Health Organization have concluded that a large body of evidence shows that the levels of formaldehyde most people encounter do not cause adverse health effects. Despite this, EPA completed its IRIS review of formaldehyde in 2010, asserting that a link exists between exposure to formaldehyde and certain types of leukemia. EPA's conclusions quickly came under scrutiny. To provide clarity, EPA asked the National Academies of Science (NAS) to convene an expert Committee to review its findings.

The NAS Committee issued its report earlier this spring and in it, they questioned the evidence EPA used to support its conclusion. In the report NAS stated:

**"Conclusions appear to be based on a subjective view of the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data and the lack of mechanistic data."**

In the report, the NAS Committee also offered a harsh critique of the IRIS program in general. In fact, the expert committee felt so strongly that they included

an entire chapter devoted to the program improvements that they saw as “critical for the development of a scientifically sound IRIS assessment.” The NAS report stated:

**“The committee is concerned about the persistence of problems encountered with IRIS assessments over the years, especially given the multiple groups that have highlighted them. If the methodologic issues are not addressed, future assessments may still have the same general and avoidable problems that are highlighted here.”**

### Hexavalent Chromium

In 2009, industry undertook a multi-million dollar mode-of-action research program to develop new data that EPA could use to assess the risk that Cr6 poses from low-level, environmentally-relevant exposure through drinking water. The research was directly responsive to the data needs of the Agency, and EPA staff was consulted during the process of developing the research plan.

Despite the pending research, due later this year, the agency significantly accelerated its timetable for the hexavalent chromium IRIS assessment, publishing a draft in late 2010. EPA’s independent peer review group expressed significant concerns about the scientific quality of the draft assessment, citing knowledge gaps, including those that could be filled by the industry research. EPA still intends to finalize the IRIS assessment by the end of September, about the same time that the new research should be completed.

With this intensive schedule, we are concerned that EPA will not fully incorporate the extensive comments from EPA’s peer review group. Failure to address the peer review comments and include the new research findings will result in a risk assessment that will be out-dated and inaccurate as soon as it is released.

### Dioxin

The IRIS program first published its draft assessment of dioxin in the mid nineteen-eighties, but it remains a point of contention today. Specifically, both EPA’s own Science Advisory Board (SAB) and the NAS criticized the model that EPA used in the IRIS assessment to evaluate cancer risk.

In 1995, the Scientific Advisory Board told the IRIS program that it was inappropriate to extrapolate using a linear low dose method to estimate cancer risk to humans. EPA revised the assessment, but failed to follow the SAB directive.

In 2006, after reviewing EPA’s 2003 reassessment of dioxin, the NAS concluded—unanimously—that a non-linear method (as opposed to a linear dose-response model) should be used to extrapolate for estimating cancer risk to humans.

Despite the National Academy’s 2006 recommendation, EPA’s reanalysis of key issues in the dioxin assessment again used a linear dose-response model.

Sixteen years after EPA was given a clear recommendation by the SAB peer review to use a model that reflects knowledge of mode of action in the dioxin IRIS assessment, IRIS continues to push an out-dated risk assessment model for dioxin. Based on the expert review in 1995 and 2006, IRIS has no scientific justification for doing so.

### Inorganic Arsenic

In a case similar to dioxin, EPA defaulted to a linear no-threshold model in its draft IRIS assessment of inorganic arsenic, disregarding the 2005 EPA peer review panel recommendation to consider a threshold model. This is critical because applying the proposed model would result in naturally occurring levels in many soil and water supplies around the country being considered “unacceptable” by EPA guidelines.

If this draft IRIS assessment stands, it could lead to confusion, undue concern and unnecessary costly modifications to water treatment systems, the abandonment of water sources, and the forced identification of alternative water supplies. And it could create the impression that typical arsenic levels in foodstuffs such as rice, fish, grapes, and other common foods could be cancer-causing.

These examples clearly demonstrate that IRIS has failed to evolve with the significant progress that has been made in the science and technology of chemical risk assessment.

Over the years, researchers and health professionals have gained a greater scientific understanding of the human body; the ways chemicals can interact with the body at different levels of exposures; and how that knowledge applies to determine

the safety of chemical uses. However, IRIS risk assessments lag behind these advances and rely too heavily on outdated assumptions formulated in the 1970s.

For example, IRIS assessments of carcinogenic responses in high-dose animal studies typically take the most conservative default approach, rather than applying relevant mode of action and real world exposure information to more accurately show the risk to humans.

In effect, IRIS has clung to risk assessment approaches that assume that there is no safe dose or threshold—even when experts tell the program otherwise—as was the case with dioxin and inorganic arsenic. IRIS's failure to integrate this information into program decisions undermines the development of new science-based risk assessment practices, wastes investments in research and undercuts effective public health science policy.

Not only has IRIS failed to keep pace with modern science, the program lacks the scientific accountability needed to be considered objective and credible.

There is little independence in the IRIS program's standard peer review process: the IRIS office controls the development of the assessment, the design of the peer review charge questions, and the evaluation of the peer review findings. Ultimately, the IRIS program itself decides which recommendations from peer review groups to act upon and which to ignore. As we have seen in the case of dioxin, the IRIS office has exhibited steadfast reluctance to upgrade the assessments in response to the demands of independent peer reviewers.

To restore credibility to the program, there must be an honest broker to ensure that EPA adequately considers and incorporates changes from peer reviews and public comments. That is why ACC has called for the NAS to review all pending IRIS assessments. Unfortunately, EPA dismissed this suggestion saying, "IRIS is a model for openness, transparency, scientific integrity and scientific quality."

Anyone who looks at the evidence, whether you are a state regulator, a public health official or a furniture maker, can see that the IRIS program is broken and fails to effectively support EPA's mission to protect public health and the environment.

EPA's refusal to fully acknowledge and rectify the many problems with the IRIS program calls for Congress to step in.

EPA must be required to take immediate steps that will ensure pending IRIS assessments meet the highest standards of accuracy and scientific integrity:

- IRIS assessments in progress should incorporate the recommendations described in Chapter 7 of the NAS panel formaldehyde scientific peer review report where they are applicable;
- IRIS assessments that are currently in draft form (or that will be issued as draft for public comment and peer review in 2011 and 2012) should be submitted to the NAS for independent scientific peer review; and,
- Revised IRIS assessments developed by the Agency must be evaluated (preferably by the same NAS panel that conducted the initial peer review) to ensure that the peer review panel's findings and recommendations have been adequately and transparently addressed.

While NAS review of pending assessments will help improve the program in the interim, EPA must also initiate a comprehensive overhaul of the program to make IRIS effective and efficient in the future:

- Assessments must rely on proven scientific data instead of outdated assumptions;
- EPA must establish consistent data evaluation methods;
- EPA must adopt a consistent weight of evidence framework, based on transparent, rigorous evaluation methods, so that all available data can be taken into account, with the best and most relevant science given the greatest weight;
- Assessments should be based on 21st century knowledge of how chemicals interact with the human body;
- EPA must adopt proven approaches for evaluating cause, effect and uncertainty as part of IRIS assessments; and,
- EPA must enhance public comment and independent scientific peer review processes.

The IRIS program is a critical part of our chemical regulatory system, and it must be improved. The current deficiencies and lack of confidence in the program are resulting in delays and unnecessary costs as the frequent shortcomings in draft assessments are addressed. Flawed assessments have significant consequences in and

of themselves. They create public confusion, unwarranted alarm, unnecessary product de-selection and litigation, all of which ultimately can put jobs at risk without sound scientific basis.

To be clear, ACC is not suggesting that IRIS assessments be suspended or delayed. We are proposing concrete ways to make pending and future reviews more accurate and more credible. Making the necessary changes will ensure that the program completes assessments more efficiently and provides answers to the public, public health professionals and industry in a far more timely way. Thank you very much for the opportunity to testify. I look forward to taking your questions.

Chairman BROWN. Thank you, Congressman.

Now I now recognize our next witness, Ms. Steinzor. You are recognized for five minutes.

**TESTIMONY OF RENA STEINZOR,  
PROFESSOR, UNIVERSITY OF MARYLAND SCHOOL  
OF LAW AND PRESIDENT, CENTER FOR PROGRESSIVE  
REFORM**

Ms. STEINZOR. I appreciate the opportunity to testify on one of EPA's most important and foundational programs. These days the more important a public health program, the more likely it is to be the subject of relentless, intemperate, and unjustified attacks. IRIS is no exception. The program is a serious, well-informed, and carefully-conducted scientific effort to synthesize existing research in order to set reference doses for the worst toxic chemicals. But industry lobbyists have mischaracterized it as an anti-scientific effort to demonize such ostensibly benign substances as arsenic, formaldehyde, and dioxin. Arsenic, formaldehyde, dioxin. Really?

Without IRIS EPA would be hard pressed to develop standards for the control of emissions of toxic chemicals that cause brain damage, cardiovascular illness, reproductive dysfunction, cancer, and a range of other diseases. Delaying IRIS profiles has and will endanger public health, an intolerable outcome that this committee must not allow to happen.

The simple fact is that everyone attending this hearing would be hard pressed to come up with more than a handful of toxic chemicals that were exonerated by additional research. The overwhelmingly powerful historical trend moves in the opposite direction. As the research accumulates, chemicals prove to be more toxic than we first imagined, often by several orders of magnitude.

From the American public's perspective the central and urgent problem with IRIS is not that it rushes to judgment on toxic chemicals. Far from it. The problem is that repeated rounds of redundant peer review and interagency comment allow, in fact, invite chemical manufacturers to slow the program to a crawl. Because of these delays IRIS is woefully incomplete.

Profiles are missing for at least 255 high-priority chemicals. The 2008 GAO report warned that the Bush Administration's approach to IRIS left the database at risk of becoming obsolete. To its credit, the Obama Administration reviewed IRIS in an effort to speed the production of assessments. Although these changes are a definite improvement, the rate of production is still slow enough that EPA will not catch up with its existing backlog for another 55 years.

Chemical manufacturers and their allies, most notably federal agencies like the Department of Defense and NASA, have targeted IRIS as a chokepoint for regulation. Anyone who has followed the IRIS Program closely for many years cannot help but find their re-

cent denunciations of the program disingenuous and surreal. They have been in the thick of the action since IRIS began, making their case to IRIS staff, more senior EPA officials, sympathetic federal agencies and departments, and the White House Office of Information and Regulatory Affairs. In fact, the reason why IRIS profiles have ballooned into unmanageable length is the reaction of EPA staff to constant harassment by industry participants.

The remedies proposed by the chemical industry will make these problems worse, not better. One of the most intemperate proposals is that OIRA increase its oversight of the program. OIRA is staffed almost exclusively by economists who have no better idea of what constitutes a good RfD than any other layperson.

A second demand is that the NRDC be brought in to review—NRD be brought in to review all IRIS assessments. The academic scientists who serve on NRC review committees receive compensation that does not nearly pay for their time. Instead, they are motivated by a commitment to public service and the prestige of serving on a panel to consider cutting-edge scientific issues. Using NRC to run around double-checking routine government work would disrupt this delicate balance, damaging the National Academies as well as EPA.

The final example of overreaction is the rider proposed for EPA's appropriations bill that would bar EPA from moving forward with future assessments until all existing assessments had been revised to conform to the NRC's advice about the formaldehyde assessment. This proposal would paralyze the IRIS Program for the foreseeable future by forcing its staff to engage in a massive round of paper shuffling.

The chemicals we are talking about here are the worst of the worst, produced in amounts of millions of pounds annually. The victims of further IRIS delays are neither the companies that makes these chemicals, nor the scientists engaged in the endless research, but rather Americans and their health.

Thank you.

[The prepared statement of Ms. Steinzor follows:]

PREPARED STATEMENT OF MS. RENA STEINZOR, PROFESSOR, UNIVERSITY OF MARYLAND SCHOOL OF LAW, AND PRESIDENT, CENTER FOR PROGRESSIVE REFORM

Mr. Chairman, Ranking Member Edwards, and Members of the Subcommittee, I appreciate the opportunity to testify before you today on one of the Environmental Protection Agency's (EPA) most important and foundational programs, the Integrated Risk Information System (IRIS). Let me get straight to the point. These days, the more important a public health program, the more likely it is to be the subject of relentless, intemperate, and unjustified attacks. IRIS is no exception. What is in fact a sober, well-informed, and carefully conducted scientific effort to synthesize existing research in order to set reference doses for the most toxic chemicals is portrayed by industry lobbyists as an anti-scientific effort to "demonize" such ostensibly benign substances as arsenic, formaldehyde, and dioxin. This deliberate misreading of the science by industry lobbyists is intended to prolong Americans' exposure to dangerous substances in the service of corporate profit, while at the same time immobilizing the federal agency best qualified to protect public health, the EPA.

The truth is that everyone attending this hearing would be hard-pressed to come up with more than a dozen examples of toxic chemicals that have been found to be significantly less harmful than we originally thought when additional research was done. The powerful historic trend moves strongly in the opposite direction: as the research has accumulated, chemicals like dioxin, arsenic, formaldehyde, cadmium, mercury, and lead prove to be *more* toxic than we first imagined. Endless efforts to deconstruct individual studies should not obscure this trend, as the chemical in-

dustry was well aware until the current backlash against regulation offered it new opportunities to defeat safeguards that protect public health by distorting EPA's track record.

IRIS started as an internal EPA database used to develop toxicological profiles for common chemicals. These profiles set the reference dose, or RfD, for a given chemical on the basis of existing scientific literature. An RfD is the amount below which human exposure is deemed unlikely to cause adverse health effects. Over time, IRIS has become an invaluable resource: It receives some 2,000 internet visits a day, testament to its importance as among the best, most comprehensive databases for this kind of baseline information. And, although IRIS itself most definitely is *not* a regulatory program, it provides a strong scientific foundation for much of the rest of the agency's work. Without the scientific determinations IRIS contains, EPA would be hard-pressed to develop standards for the control of emissions of toxic chemicals that cause brain damage, cardiovascular illness, reproductive dysfunction, cancer, and a range of other diseases. Delaying the production of IRIS profiles costs lives and endangers public health, an intolerable outcome that this Committee must not allow to happen.

My testimony today makes four points about the future of the IRIS program:

- *From the American public's perspective, the central and urgent problem with IRIS is not that it rushes to judgment on toxic chemicals. Far from it. The problem is that repeated rounds of redundant "peer review" and interagency comment allow—in fact, invite—chemical manufacturers, the Department of Defense, and other self-interested parties to slow the program to a crawl.* Because these delays help to ensure that dangerous chemicals are left in commerce for years longer than necessary, people suffer avoidable diseases and irrevocable neurological and reproductive damage. The Government Accountability Office (GAO) has repeatedly warned Congress about the negative implications of these delays. See, e.g., GAO-08-6743T, EPA's New Assessment Process Will Increase Challenges EPA Faces in Evaluating and Regulating Chemicals (April 29, 2008) and GAO-09-271, HIGH-RISK SERIES, An Update (January 2009). GAO has placed the EPA chemicals program in the "high risk" category reserved for a small number of the most troubled programs in government. It made this important decision in part because IRIS updates are so slow that the data base risks becoming obsolete. It did not make any reference to the distorted critique of EPA science that the chemical industry has developed.
- *Given that IRIS is constantly struggling to avoid capture by the chemical industry and, if anything, gives manufacturers far too many opportunities to befuddle final assessments, the chemical industry's sudden discovery of its flaws is as opportunistic as it is incredible.*
- *The National Research Council's (NRC) report on formaldehyde does not justify the radical changes sought by the industry. In fact, the NRC explicitly endorsed the program's continuation and improvement.* Its critique of the formaldehyde assessment constitutes robust peer review, not an outright condemnation of the program and EPA science as industry witnesses would have you believe. I wish that the NRC committee had not adopted such a haughty tone in scolding EPA staff. But that tone was the product of political naiveté regarding how its report would be exploited in the existing political climate. It cannot fairly be characterized as a recommendation that IRIS stop or even slow its critical work.
- *The remedies sought by the American Chemistry Council (ACC) are designed to run IRIS off the road, further undermining EPA's mission to protect public health. I urge the Committee to side with the public, not the manufacturers of toxic chemicals long overdue for assessment and control.*

I am a law professor at the University of Maryland School of Law and the President of the Center for Progressive Reform (CPR) (<http://www.progressivereform.org/>). Founded in 2002, CPR is a 501(c)(3) nonprofit research and educational organization comprising a network of sixty scholars across the nation who are dedicated to protecting health, safety, and the environment through analysis and commentary. I joined academia mid-career, after seven years as an attorney at the Federal Trade Commission, five years as staff counsel to the House Energy and Commerce Committee, and seven years representing small and mid-sized electric utilities. My work on environmental regulation includes four books, and over twenty-seven articles (as author or co-author). My most recent book, published by the University of Chicago Press, is *The People's Agents and the Battle to Protect the American Public: Special Interests, Government, and Threats to Health, Safety, and the Environment*, which I co-authored with Professor Sidney Shapiro of Wake Forest University's School of

Law, analyzes the state of the regulatory system that protects public health, worker and consumer safety, and natural resources, concluding that these agencies are under-funded, lack adequate legal authority, and are undermined by political pressure motivated by special interests. I have served as a consultant to EPA and have testified previously before Congress on regulatory subjects on numerous occasions.

### **Saving IRIS**

Since 2005, Member Scholars at the Center for Progressive Reform (CPR) have researched and written five white papers regarding IRIS and the need to streamline the process for developing toxicological profiles and several letters to decision makers concerned about the program's future. They are available here: <http://www.progressivereform.org/IRIS.cfm>, and I have attached the two most recent reports, *Corrective Lenses for IRIS* and *Setting Priorities for IRIS* to this testimony. Our key findings include:

1. IRIS is woefully incomplete. EPA is many years behind in completing profiles of at least 255 chemicals. Some 109 chemical profiles that EPA was required by the Clean Air Act Amendments of 1990 to have completed by 2008 are either included in IRIS but missing critical elements, or entirely absent from the database. A similarly sad situation afflicts the agency's efforts to carry out the statutory mandates of the Safe Drinking Water Act. Every five years, EPA generates a new Contaminant Candidate List (CCL). The lists contain recommendations both for chemicals and microbiological contaminants. Since 1996, EPA has published three CCLs that contain 156 distinct chemical substances. IRIS profiles are missing for 64 (41 percent) of these substances.
2. So severe are the delays in the IRIS process that a 2008 GAO report warned that the Bush Administration's approach to IRIS, which resulted in just *two completed profiles per year*, left the database at risk of becoming obsolete. (The report is available at <http://www.gao.gov/new.items/d08743t.pdf>.) To its credit, the Obama Administration revised the IRIS process in an effort to speed the production of assessments, and has managed to increase the number of completed profiles to nine annually. But although this performance is a definite improvement, the rate of production is still slow enough that, if nothing else is done to improve the pace of IRIS, EPA will not catch up with its existing backlog for another *55 years*.
3. One area of particular concern is that the Obama Administration's new IRIS process left in place many of the roadblocks GAO had previously identified, including interagency review of individual assessments, multiple reviews by outside science panels, and prioritization of a few high-profile assessments at the expense of faster assessments. Potentially regulated parties, including other federal agencies like the Department of Defense and National Aeronautics and Space Administration, have targeted IRIS as a choke point for regulation. The labyrinthine process they have demanded, diagrammed on page 9 of the *Corrective Lenses* report, contains multiple rounds of peer review, public comment, and interagency review that are as redundant as they are time-consuming. In effect, the program suffers from the problem of "information capture"—a phenomenon where potentially regulated industries and their federal agency clients submit so much irrelevant data to EPA, and do so with such frequency, that new assessments become mired in never-ending controversy.
4. To close data gaps and reestablish IRIS's credibility as a cutting-edge database, EPA needs to make four changes. First, EPA should reduce the procedural burdens that were formalized during the Bush administration. Second, EPA must articulate clear, statute-driven priorities about which assessments to complete to ensure that data gaps in statutory mandates would be more quickly addressed. Third, the IRIS process must be restructured to allow for timely assessments to be written on the basis of the weight of available evidence at the time an assessment is undertaken. Fourth, EPA must have adequate resources and use those resources efficiently—to complete a much larger number of assessments.

One additional point is worth making. The chemicals we are talking about here are the worst of the worst, produced in amounts of millions of pounds annually. As just one example, chromium compounds, which are categorized in the worst ten percent of all toxic chemicals and are among the hazardous air pollutants missing from IRIS, are emitted in amounts exceeding 58 million pounds annually. Unsafe exposure to chromium compounds causes cancer, suppresses immune systems, and harms kidney and respiratory functions. Over the last several years, industry has

sponsored several studies of chromium. When a study documents adverse effects at common levels of exposure, the sponsors commission a second study designed to rip apart the first. Unfortunately, the victims of this endless treadmill are neither the sponsors, nor the scientists engaged in chasing each other's tails, but rather the public's health.

### Industry Influence over IRIS

Anyone who has observed IRIS for many years cannot help but find the chemical industry's recent denunciations of the program disingenuous, even surreal. Far from being helpless bystanders in the process, industry Members have been in the thick of the action since the database was initiated, submitting the research they think most important and repeatedly advocating their view of the research to IRIS staff, more senior EPA officials, sympathetic federal agencies and departments, and the White House Office of Information and Regulatory Affairs (OIRA). To whatever extent that IRIS science is flawed, the people complaining about those flaws are full partners in its development. In fact, one reason why IRIS profiles have ballooned into unmanageable length is the reaction of EPA staff to constant harassment by industry participants.

### The Formaldehyde Review

The NRC conducted a robust peer review of the draft IRIS formaldehyde assessment. The report is written in the detailed language of one group of scientists giving another group of scientists an unvarnished assessment of how a scientific finding could be revised and bolstered. Its work will undoubtedly improve the IRIS process, and EPA is already taking its recommendations to heart.

Unfortunately, the NRC reviewers also succumbed to the fatal attraction of reiterating their professional superiority, using tough, even haughty language to critique EPA's work, and exhibiting a remarkable level of insensitivity to how their comments would be interpreted in the over-heated political atmosphere that afflicts the nation's Capitol these days. Clearly, the NRC committee was trying to help IRIS staff to do better, not to immobilize the program. Consider the following direct quotes from the NRC report:

The draft IRIS assessment *correctly concludes* that formaldehyde is a genotoxic (DNA-reactive) chemical that causes cytogenetic effects, such as mutations. (emphasis added) (p. 4)

The committee recognizes that revision of the 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, models for conducting IRIS assessments more effectively and efficiently are available, and the committee provides several examples in the present report. Thus, EPA might be able to make changes in its process relatively quickly by selecting and adapting existing approaches. (emphasis added) (p. 11)

As a person who teaches for a living, I would urge future NRC panels to keep in mind how much self-important scolding can interfere with a student's learning process—we all know that truth in our academic lives but may forget it when we enter the policymaking world. Regardless, Congress would make a grave error if, at the behest of self-interested chemical manufacturers, it ignored the stated goals of the NRC's review.

### Excessive Remedies

The remedies proposed by the chemical industry representatives here today confuse and distort the core purposes of IRIS. For example, one of the most intemperate proposals advanced by the American Chemistry Council is that the OIRA increase its oversight of the program. OIRA is the division within the White House that checks agency cost-benefit analyses. It is staffed almost exclusively by economists who have no better idea of what constitutes a good RfD than any other lay person. Two scientists work at OIRA, in comparison to the dozens of well-qualified scientists representing multiple disciplines who work at EPA. The recommendation that OIRA be put in charge of IRIS is not designed to improve the program's scientific validity, but rather is intended to give chemical manufacturers a sympathetic forum where they can tie IRIS in knots more easily.

A second industry demand voiced by ACC is that NRC be brought in to review all IRIS assessments. NRC is the gold standard for peer review and, as I mentioned earlier, its critiques are always interesting. On the other hand, the academic sci-



entists who serve on NRC review committees receive compensation that does not nearly pay for their time. Instead, they are motivated by a commitment to public service, the pleasure of engaging with bright and sophisticated colleagues, and the prestige of serving by invitation on a panel convened by the finest scientific institution in the nation. Using NRC to run around double-checking government work would corrode this delicate balance, ultimately rendering it unworkable. Not incidentally, it would also add unreasonable delay to an already dangerously slow process. I hope that the NRC recognizes the insidious implications of this recommendation and strongly opposes it.

The invocation of NRC, and the National Academies as a whole, has become a common practice for potentially regulated parties who hope to slow down EPA decision making. The little-recognized hypocrisy of this practice is that when NRC ratifies EPA's judgments without qualification, aggrieved industry participants simply ignore its findings and proceed with their campaign against the agency. So, for example, NRC issued a report on mercury that was fully supportive of the RfD that EPA had set for the substance. (The NRC report is available at <http://www.nap.edu/openbook.php?isbn=0309071402>.) The electric utilities fighting EPA's regulatory efforts simply ignored the NRC report as if it had never been completed, continuing their attacks on the research underlying the agency's decision. Far from serving as an umpire in heated disputes, NRC was exploited as a tool to delay final action and then promptly cast aside.

The final, penultimate example of overreaction that will endanger public health is the rider now pending in the House Appropriations Committee. It would bar EPA from moving forward with future assessments until all existing assessments had been revised to conform to the NRC's advice about the formaldehyde assessment. This proposal would paralyze the IRIS program for the foreseeable future by forcing its staff to engage in a massive round of paper shuffling.

In a surprisingly successful effort to obscure the real motivations behind these radical suggestions, regulated industries have portrayed them as essential to job creation, and therefore of direct benefit to the average American. Fundamental to this set of claims is the notion that regulatory excesses in these times of economic recession have hit industry so hard that its Members cannot afford to expand their businesses and put people back to work. But some quick research on the percentage increase in profits from 2009 to 2010 for some of the ACC's largest Members yielded surprising results.

Company	Fortune 500 Rank	Increase in Profit 2009 to 2010
Dow	45	19.4%
Dupont	84	19.98%
PPG Industries	181	9.7%
Praxair	241	13.0%
Air Products & Chemicals	271	7.7%
Ashland	272	11.2%
Eastman Chemical	348	32.6%
Avery Dennison	356	9.4%
Celanese	388	16.5%
Lubrizol	423	18.1%

Source: CNN Money, Issue date: May 23, 2011,

<http://money.cnn.com/magazines/fortune/fortune500/2011/industries/7/index.html>

Rules to protect public health and the environment most definitely do not have the effect of sweeping money into a pile and setting it on fire. Rather, they save the lives of millions of people, prevent many more millions from getting sick or becoming sicker, and preserve the irreplaceable natural resources without which human life would be impossible.

For example, Clean Air Act regulations are uniformly recognized as a wonderful economic bargain by honest experts from all points on the political spectrum. According to EPA's very conservative numbers, which dramatically *understate* benefits and *overstate* costs, clean air rules saved 164,300 adult lives in 2010, and will save 237,000 lives annually by 2020. EPA estimates that the economic value of Clean Air Act regulatory controls will be \$2 trillion annually by 2020; costs of compliance in that year will be \$65 billion. Air pollution controls saved 13 million days of work loss and 3.2 million days of school loss in 2010. By 2020, they will save 17 million work loss days and 5.4 million school loss days. I emphasize that EPA's cost estimates are based on extraordinarily conservative assumptions regarding regulatory benefits. For example, EPA says that a non-fatal heart attack in a person 0–24 years old is worth only \$84,000 and that an emergency room visit to treat an asthma attack is worth only \$363 per incident-hospitalizations don't give you a plastic ID bracelet for that little.

And according to OIRA, which houses the staff of economists so embraced by ACC, "the estimated annual benefits of major federal regulations are in the aggregate between \$132 billion and \$655 billion, while the estimated annual costs are in the aggregate between \$44 billion and \$62 billion." (See <http://www.whitehouse.gov/sites/default/files/omb/inforeg/2011—cb/2011—cba—report.pdf>.)

Thank you, Mr. Chairman and Ranking Member Edwards. I would be happy to answer any questions you may have.

Attachments:

1. *CPR Report, Corrective Lenses for IRIS*
2. *CPR Report, Setting Priorities for IRIS*



## **Corrective Lenses for IRIS:**

**Additional Reforms to Improve EPA's  
Integrated Risk Information System**

**By CPR Member Scholars Rena Steinzor  
and Wendy Wagner and CPR Policy  
Analysts Lena Pons and Matthew Shultz**



Attachment 1

## Center for Progressive Reform

CENTER FOR  
PROGRESSIVE REFORM  
WHITE PAPER #1009

October 2010

## About the Center for Progressive Reform

Founded in 2002, the Center for Progressive Reform (CPR) is a 501(c)(3) nonprofit research and educational organization comprising a network of scholars across the nation dedicated to protecting health, safety, and the environment through analysis and commentary. CPR believes that sensible safeguards in these areas serve important shared values, including doing the best we can to prevent harm to people and the environment, distributing environmental harms and benefits fairly, and protecting the earth for future generations. CPR rejects the view that the economic efficiency of private markets should be the only value used to guide government action. Rather, CPR supports thoughtful government action and reform to advance the well-being of human life and the environment. Additionally, CPR believes that people play a crucial role in ensuring both private and public sector decisions that result in improved protection of consumers, public health and safety, and the environment. Accordingly, CPR supports ready public access to the courts, enhanced public participation, and improved public access to information. CPR is grateful to The John Merck Fund for funding this white paper, as well as to the Deer Creek Foundation, the Bauman Foundation, and the Open Society Institute for their generous support of its work in general.

This white paper is a collaborative effort of the following Member Scholars and Staff of the Center for Progressive Reform: **Rena Steinzor** is a Professor of Law at the University of Maryland School of Law, with a secondary appointment at the University of Maryland Medical School's Department of Epidemiology and Preventive Medicine, and the President of the Center for Progressive Reform; **Wendy Wagner** is the Joe A. Worsham Centennial Professor at the University of Texas School of Law, Austin Texas, and a Member Scholar of the Center for Progressive Reform; **Lena Pons** is a Policy Analyst and **Matthew Shudtz** is a Senior Policy Analyst with the Center for Progressive Reform.

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View of the Seattle Skyline through glasses courtesy of WikiCommons.

**Corrective Lenses for IRIS: Reforms to Improve EPA's Integrated Risk Information System**

## Executive Summary

The Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) is the most important toxicological database in the world. Not only is it the single most comprehensive database of human health information about toxic substances, it also serves as a gateway to regulation, as well as to a range of public and private sector efforts to protect against toxic substances. IRIS "profiles" of individual substances include a number of scientific assessments of the substance's toxicity to humans by various means of exposure -- by inhalation, contact with the skin, and so on. Federal regulators rely on the assessments to do their important work protecting the public, as do state and local environmental protection authorities, and industry itself.

For EPA, the assessments conducted to complete profiles of particular toxic substances for IRIS provide the authoritative underpinnings for a wide range of regulatory actions under the Clean Air Act (CAA), the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), and the Safe Drinking Water Act (SDWA). At the state and local level, IRIS profiles are the basis for regulation of toxic substances. For example, the Oregon Department of Environmental Quality used IRIS values in its Portland Air Toxics Assessment, conducted in 2006.<sup>1</sup> The Portland Air Toxics Assessment modeled ambient air concentrations of 12 pollutants at a highly localized level. Rather than having to rely on EPA's county-level assessment of toxic air pollutants, Oregon officials can now estimate exposure and risk at a neighborhood level and set permit allowances accordingly. In the private sector, IRIS information may be used in toxic tort suits, or by individuals or public interest groups to advocate for lower permissible permit levels under Title V of the CAA.

Unfortunately, IRIS is woefully incomplete. EPA is many years behind in meeting statutory mandates for completing profiles of at least 255 chemicals, and as a result regulatory and enforcement action related to those chemicals has been stalled. Some chemical profiles in IRIS are missing information essential to regulatory action. In addition, 77 of the hazardous air pollutants (HAPs) listed in IRIS are missing the most important piece of information -- an assessment of how much of the substance may be safely inhaled. In all, some 109 chemical profiles that EPA was required by the Clean Air Act Amendments of 1990 to have completed by 2008 are either included in IRIS but missing critical elements, or entirely absent from the database. So severe is the delay in the IRIS process that a 2008 Government Accountability Office (GAO) report warned that the Bush Administration's approach to IRIS, which resulted in just two completed profiles per year, left the database at risk of becoming obsolete.<sup>2</sup>

In May 2009, newly appointed EPA Administrator Lisa Jackson introduced reforms she predicted would improve EPA's performance with respect to IRIS that included making it harder for other agencies of the federal government to slow down or exert undue influence over EPA's assessment of the environmental health effects of substances listed in IRIS. The Administrator's stated goal was to ensure completion of new assessments in 23 months, but she made no promises about how many assessments EPA would complete in a year. Neither

did she present any plan for clearing the backlog of the 478 assessments that are in process, nor mention that EPA has long since been required by statute to complete, or have been identified as out of date by EPA staff.<sup>3</sup>

In the year since the new process has been in effect, EPA has made only modest progress completing assessments, finishing nine assessments in 2009 – up from the Bush pace of two per year – but still slow enough that, if it does nothing to improve its performance, EPA will not catch up with its backlog for another 55 years. Moreover, it is not clear from information available to the public whether the agency is fulfilling Jackson's 23-month pledge on individual IRIS assessments.

One area of particular concern is that the Administrator's new IRIS process left in place many of the roadblocks GAO had previously identified, including interagency review of individual assessments, multiple reviews by outside science panels, and prioritization of a few high-profile assessments at the expense of faster assessments.<sup>4</sup> The consequence is that significant data gaps are still a serious problem.

Specifically, the IRIS database is missing important human health information about the toxicological effects of HAPs, drinking water contaminants, and chemicals commonly found in Superfund toxic waste sites.

- **Thirty-two HAPs regulated under the CAA are not listed in IRIS at all, and 77 HAPs lack inhalation values, hampering the air office's ability to do the "residual risk assessments" that ensure technology-based standards provide an "ample margin of safety."<sup>5</sup>**

#### The Human Consequence of the IRIS Breakdown

The ramifications of the large-scale breakdown of the IRIS process are very real. For example, residents of the Marine Corps Base Camp Lejeune have been exposed to high levels of trichloroethylene for decades. A Navy-funded study of increased cancer risk for children born at Camp Lejeune found 14 cases of Acute Lymphocytic Leukemia in a cohort of 10,000-12,000 births, or more than 100 times the expected rate.

EPA drafted an updated IRIS assessment of trichloroethylene in 2001, but it was challenged by the Department of Defense (DOD). Under pressure from DOD, EPA commissioned a National Academy of Sciences Review of trichloroethylene. In 2007, five Senators introduced a bill instructing EPA to complete the trichloroethylene assessment and issue a drinking water standard for trichloroethylene. The bill was reported in the Senate, but has not passed in either chamber.

The Department of Defense objects to lowering the exposure limit for trichloroethylene because of the resulting

increased cleanup costs. DOD estimates it would cost \$5 billion more to clean up trichloroethylene if the drinking water standard went from five parts per billion to one part per billion.

Toward that end, DOD submitted 72 pages of comments to EPA's Nov. 2009 draft assessment of trichloroethylene. The new draft assessment will undergo review by the Science Advisory Board in 2010.

Meanwhile, EPA's IRIS assessment of trichloroethylene is still pending. Residents of Camp Lejeune continue to be exposed to high levels of trichloroethylene in drinking water, and cannot successfully prove these levels are harmful until EPA finishes this work.

— House of Representatives Committee on Science and Technology. Toxic Communities: How EPA's IRIS Program Fails the Public. (Jun. 12, 2008).

— Department of Defense. Comments on the Review of Trichloroethylene. (Aug. 25, 2009).

- Three of 71 contaminants regulated under the SDWA are not listed, and an additional 64 of 156 substances nominated to the Contaminant Candidate List, slowing EPA's ability to develop enforceable standards for drinking water contaminants.
- Of the 275 substances the Agency for Toxic Substances and Disease Registry has identified as "high profile" based on their frequency of occurrence at Superfund sites, toxicity, and potential for human exposure, 87 (32 percent) are not listed.<sup>6</sup>

The sources of delay have not changed: priority treatment of complex, high-profile assessments at the expense of other needed assessments; excessive interagency review; involvement of the Office of Information and Regulatory Affairs (OIRA); industry interference; and recursive, formalized outside review continue to contribute to the small number of IRIS assessments completed each year.

The interagency review process is one of the largest sources of delay. It provides agencies, which are often also potentially regulated entities, with multiple opportunities to influence and soften EPA's risk assessments and reduce future regulatory burdens. Even under the new process, federal agencies, coordinated by OIRA, have two special opportunities to comment on draft IRIS assessments. EPA has the discretion to terminate the interagency review process, which is unusual and would not be tolerated at other agencies. The DOD, for example, would not allow EPA to comment on decisions about training because of concerns about hazardous pollution.

To close data gaps and reestablish IRIS's credibility as a cutting-edge database, EPA needs to make four changes. First, EPA should reduce the procedural burdens that were formalized during the Bush administration. Second, EPA must articulate clear, statute-driven priorities about which assessments to complete to ensure that data gaps in statutory mandates would be more quickly addressed. Third, the IRIS process must be restructured to allow for timely assessments made based on the weight-of-the-evidence at the time an assessment is undertaken. Fourth, EPA must also have adequate resources and make better use of its resources to complete a much larger number of assessments than it is currently finishing each year.

Administrator Jackson has repeatedly emphasized her commitment to use EPA's chemical management program to reinvigorate the agency's public health responsibility.<sup>7</sup> The IRIS program has featured prominently in her discussion of these efforts. EPA has substantial latitude to reform the program and remove these obstacles to make it more productive. For Administrator Jackson to be successful with chemical management, she will need to impose further reforms on the IRIS process.

Tables 1 and 2: Hundreds of millions of pounds of highly toxic chemicals are released each year without IRIS numbers that would allow EPA, state and local officials, the media, and community groups to gauge public health hazards.

Chemical	Total Air Releases (lbs)
Chromium compounds	58,875,719
Ethylene oxide	19,326,422
Chloroprene	6,917,570
Diethanolamine	5,292,937
Ethyl acrylate	4,536,125
Cobalt compounds	4,502,987
Titanium tetrachloride	3,603,494
Cadmium compounds	1,736,020
O-Toluidine	626,844
Hydrogen fluoride	526,486
<b>Total</b>	<b>105,944,603</b>

Chemical	Total Air Releases (lbs)
Methanol	112,091,055
Carbonyl sulfide	353,389
Formaldehyde	313,659
Chlorine	270,468
Dichloromethane	205,328
Phenol	53,622
Trichloroethylene	48,130
Tetrachloroethylene	40,888
Lead compounds	14,478
Chloroform	12,191
<b>Total</b>	<b>113,413,298</b>

Figure 1, 2, & 3: Hearing on Fixing EPA's Broken Integrated Risk Information System, Before the Subcommittee on Oversight and Investigation of the U.S. House on Science and Technology (Jun. 11, 2009).

### Corrective Lenses for IRIS: Reforms to Improve EPA's Integrated Risk Information System

## Introduction

The IRIS database provides a number of important pieces of information about the human health effects of specific toxic substances. These include specific oral and inhalation "reference doses," accounting for the effects of ingestion and inhalation of the substance, as well as a "cancer slope factor" that measures the risk of cancer associated with exposure to increasing concentrations of a substance. EPA relies on this information in developing regulations to protect Americans from a variety of risks, fulfilling its statutory mandate under several laws, including parts of the Clean Air Act (CAA), Safe Drinking Water Act (SDWA), Superfund and other statutes. IRIS is widely used, not just by EPA, but also by state, local, and international public health experts, as well as toxic tort attorneys. In all, the online version of IRIS receives approximately 20,000 hits per day.

Originally, IRIS was an internal EPA database, aggregating human health information collected by various offices within the agency. But the assessments grew to be so vital to the regulatory process and other risk-management decisions, that advocates for industry and the public interest began targeting IRIS assessments. In response, EPA has restructured the IRIS process three times since 2004. In doing so, EPA struggled to balance the need to complete IRIS assessments quickly with the desire to produce assessments that are so robust as to be immunized against criticism from outside interests.

EPA has failed to develop a process that can achieve this balance between providing information in a timely fashion so that the agency can get on with its work and attempting to generate definitive answers that demand a level of finality and precision that science cannot produce. The resulting IRIS assessment process has injected additional burdens, including interagency review coordinated by the White House Office of Information and Regulatory Affairs (OIRA) and recursive critique by outside scientists. These additional requirements slowed EPA productivity so significantly that although the IRIS program received increased funding from 2000 to 2007, the number of assessments completed in this period fell from an average of five per year to two per year.<sup>8</sup> After the Bush Administration's final round of reforms to the IRIS assessment process, congressional overseers estimated that it would take EPA six to eight years to clear all of the procedural hurdles between initiation of an assessment and its final posting in the public database.<sup>9</sup>

The Government Accountability Office (GAO) and the U.S. House of Representatives Committee on Science and Technology identified three primary problems with the Bush-era IRIS process: interagency review, multiple layers of science review, and EPA's choice to focus considerable resources on a few high profile assessments at the expense of progress on others.<sup>10</sup> In response, EPA Administrator Lisa Jackson announced a new IRIS process in May 2009. Jackson promised to regain control over interagency review and streamline each step so that assessments would be completed in 23 months. She explained that the new process would restore timely, transparent assessments in service of other actions to protect public health.<sup>11</sup> But Jackson's focus on completing assessments in 23 months rather than



whittling down the prodigious backlog of uncompleted assessments suggests that it might be decades before the agency meets current statutory requirements whose deadlines have long since passed.

Indeed, the new IRIS process has failed to meet these goals precisely because it retained many of the same features of the old process. Interagency review of individual assessments, industry efforts to hijack the process through Data Quality Act petitions, overuse of science advisory boards, and a focus on high profile and complex assessments have all prevented EPA from completing assessments in a timely and transparent way. For example, under the new process, EPA releases written comments provided in the interagency review process, but the documents do not provide a full picture of what transpires between the agencies because they do not provide a record of telephone calls and other communications. And EPA's agenda for IRIS assessments has become less transparent, with less information available about which substances will be assessed and the projected timeline for doing so.

With that in mind, this paper proposes five specific reforms to the IRIS process to make the program more productive and able to complete a greater number of assessments each year:

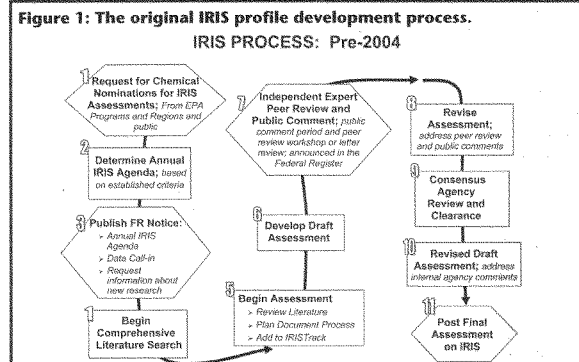
1. EPA should adopt a transparent, statute-driven process for selecting substances to be assessed.
2. EPA should eliminate the interagency review process, which has largely served to create additional opportunities for industry interference, without adding significantly to the scientific discussion that should be at the heart of EPA's regulatory decision-making.
3. EPA should put faith in its own scientific expertise and rely on outside science review only in the most complex cases.
4. EPA Administrator Lisa Jackson should advocate for adequate resources for IRIS and ensure they are used to the greatest possible effect.
5. EPA should announce these reforms in a memorandum that also sets out a streamlined six-step process for developing an IRIS profile: (1) publish a notice of assessment in the Federal Register; (2) open a docket for public to add studies during staff literature review; (3) draft an assessment; (4) publish the draft for public and agency comment; (5) revise the draft based on input during the public comment process, and; (6) publish the final assessment to IRIS.

It might be decades before the agency meets current statutory requirements whose deadlines have long since passed.

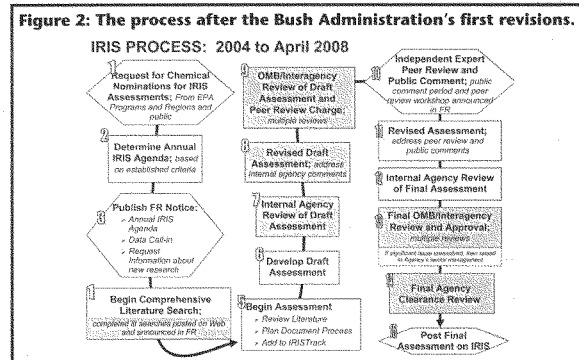
### History of the EPA's IRIS Process

EPA has restructured the IRIS process three times since 2004. During the Bush administration, additional steps were added that provided OMB and other federal agencies a special opportunity to influence the process. EPA's current IRIS process eliminates some steps; however, some of the steps in the new IRIS process are not contained in the chart. Under the current process, OMB and federal agencies still have an opportunity to review IRIS assessments before the public comment period.

**Figure 1: The original IRIS profile development process.**



**Figure 2: The process after the Bush Administration's first revisions.**



*Figures courtesy Environmental Protection Agency.*

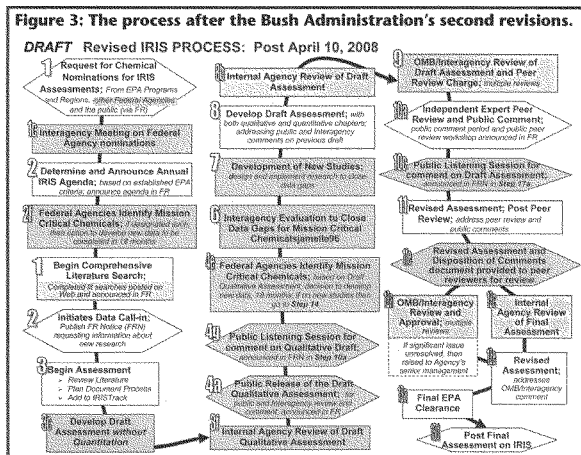


Figure 1, 2, & 3: Hearing on Fixing EPA's Broken Integrated Risk Information System, Before the Subcomm. on Oversight and Investigations of the H. Comm. on Science and Technology (Jun. 11, 2009).<sup>7</sup>

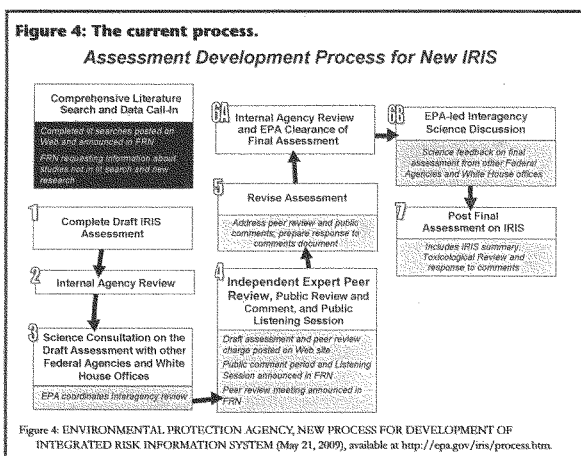


Figure 4: ENVIRONMENTAL PROTECTION AGENCY, NEW PROCESS FOR DEVELOPMENT OF INTEGRATED RISK INFORMATION SYSTEM (May 21, 2009), available at <http://epa.gov/iris/process.htm>.

### Improving the Process for Setting the IRIS Agenda

The principal purposes of the IRIS database are to identify hazards and help EPA and other agencies prioritize toxic substances that are of concern. The basic toxicology information contained in IRIS assessments along with other information collected by EPA, such as the Toxics Release Inventory, provide a basis for making decisions about chemical management. But the risk management process has its own set of procedural requirements for determining how best to protect the environment and public health from hazards related to toxic chemicals. These decisions are essentially separate from the risk assessment process, and need not be made during the IRIS process.

Given the gaping holes in the IRIS database, it is essential that EPA develop and pursue a well-considered process for completing the assessments necessary to complete IRIS profiles. That process ought to reflect communication and cooperation between IRIS staff and other EPA program officers, it ought to seek to balance of statutory needs and priorities of the program offices, and it ought to be transparent so that the public and various stakeholders will know what is under consideration. So far, however, EPA has focused on a few high-profile IRIS assessments, without offering up to the public any explanation for why these assessments have been chosen at the expense of others.

EPA program offices that regulate toxic substances rely heavily on IRIS assessments to help carry out their statutory responsibilities. The CAA's HAPs program regulates emissions of toxic substances.<sup>12</sup> Under the program, EPA establishes standards for sources of toxic air pollutants and then determines the residual risk associated with these substances once industry implements the regulations. EPA program staff makes residual risk determinations based on health hazard analyses, exposure data, and dose-response characterizations.<sup>13</sup>

The IRIS database should provide key information for those determinations, but it has critical data gaps. **Thirty-two of the 188 HAPs listed in the CAA have no IRIS assessment at all, and 77 pollutants are listed in IRIS but do not have inhalation risk information.** As a result, EPA cannot easily evaluate residual risk for 109 of 188 listed substances.

Similarly, EPA program staff's implementation of the SDWA relies on human health information for prioritizing substances to set primary drinking water standards. Their work is also dependent on public health information for health risk reduction and cost analysis in setting standards. Quantitative risk information is supposed to be included in IRIS, and, indeed, IRIS provides information on all but three substances currently regulated under the SDWA. In addition, 64 substances that have been nominated for regulatory consideration do not have IRIS assessments. Included in the most recent Contaminant Candidate List are a range of pesticides and estrogen-like hormones for which there are no IRIS profiles.<sup>14</sup> These missing assessments, as with HAPs, hinder EPA's work in implementing the SDWA.

IRIS is also critical in cleaning up Superfund sites. EPA guidance for using human health information in risk assessments for Superfund states that if an IRIS assessment is available, EPA need not seek out additional human health information.<sup>15</sup> Unfortunately, IRIS assessments are not available for 87 of the 275 high-priority substances the Agency for Toxic Substances and Disease Registry (ATSDR) identified in 2007. For these substances, EPA must look to other sources and make determinations about the quality of the information before a risk assessment can be completed. Risk assessments are used to determine whether cleanup action is warranted, to establish protective cleanup levels, and to estimate residual risk after cleanup.

The IRIS database should be a resource for other program offices. The IRIS staff should encourage open communication with other program offices to ensure that the IRIS database is most useful to the program offices. For example, the CAA Amendments of 1990 direct EPA to develop emissions standards for 188 specific HAPs, and then assess the "residual risk" posed by the pollutants after industry has instituted the pollution controls needed to meet the standards. The law provides only limited guidance to EPA on which assessments to undertake first. The Office of Air and Radiation should consult with IRIS staff to help develop such priorities.

EPA has generally provided lists of substances whose IRIS assessments had been completed in the previous year, new substances nominated for assessment in a specific year, and ongoing assessments that EPA expected to complete that year.<sup>16</sup> In 2009, EPA only provided information about substances for which literature searches had been completed.<sup>17</sup> EPA provides additional information about the progress of assessments through IRISTrack, but does not provide detailed information about how it has selected and prioritized assessments, nor does it explain its strategy or goals for working through the large number of assessments indicated by program offices.

The Obama administration has expressed a commitment to transparency through the Open Government Directive, which lays out several goals for improving transparency, including publishing information online, creating a culture of open government, and making legislative, budgetary and regulatory materials more accessible. EPA should explain its priorities for the IRIS program and account for data gaps on substances program offices need to carry out their missions. In effect, EPA is providing data without providing the underlying rationale for its decision-making, defeating the objective of the President's transparency initiative.

#### Recommendation

EPA should publish a clearly articulated IRIS agenda in the *Federal Register* each year. It should describe in its agenda how it plans to complete the large number of assessments needed to make the database current. When EPA develops this plan, it should give consideration, where possible, to conducting assessments of similar or related chemicals

at the same time. The agency should divide the assessments into groups based on factors related to how complex they will be to complete and use those groupings to divide the workload more evenly. EPA should also explain how it will complete high-profile assessments without preventing the agency from completing all the other assessments.

## Removing the Barrier of Interagency Review

The interagency review process is a significant contributor to delay of IRIS assessments. From 2003 to 2007, the number of full-time staff devoted to IRIS rose from 10 to 35. In this period, the number of draft assessments set for interagency review rose from zero to 15, but the number of completed assessments was relatively stagnant – with five assessments completed in 2003 but just two in 2007.<sup>18</sup>

Not only does the interagency review process contribute greatly to gumming up the works of IRIS assessments, it also gives agencies that are themselves potentially regulated entities the opportunity to assert undue influence or delay assessments by years or even decades. The Department of Defense (DOD), for example, is the nation's biggest polluter, yet the interagency review process affords it a preferred seat at the table in establishing standards by which it will be regulated, something no corporate polluter could even hope to achieve.

In her 2009 reforms, Administrator Jackson chose to keep in place two opportunities for interagency review. The first is what is labeled "Step 3" in the new process: "Science consultation on the draft assessments with other Federal Agencies and White House Offices."<sup>19</sup> In a 2009 report, GAO noted that EPA's use of the phrase, "White House offices," is vague, and does not provide sufficient information about what White House offices are to be involved in this process. But based on the interagency review comments available for substances assessed under the new process, the White House Office of Management and Budget (OMB) seems to be the main driver, notwithstanding the fact that it only employs two professional scientists. The second opportunity for interagency review in Administrator Jackson's 2009 process is labeled, "Step 6B," "EPA-led Interagency Science Discussion." In brief, with this reform, Jackson asserted EPA control over the interagency review process, where previously OMB coordinated interagency review through OIRA.

The core problem with interagency review is that it provides agencies that may have conflicts of interest an opportunity to influence and delay risk assessments under the IRIS process. One example is the reassessment of trichloroethylene, long-term exposure to which has been linked to liver and kidney cancer and nerve damage. The substance is used as an industrial degreaser by many industries, as well as by the DOD, Department of Energy (DOE) and National Aeronautics and Space Administration (NASA). In 2004, EPA commissioned a joint study from the National Academy of Sciences (NAS) with DOD, DOE, and NASA on human health effects of trichloroethylene.<sup>20</sup> In response to the NAS report, NASA released a bulletin discussing the potential impact of regulatory actions related to trichloroethylene, including clean-up action.<sup>21</sup> NASA and other agencies were then given an opportunity to comment on the trichloroethylene draft assessment, a plain conflict of interest for the agencies, since the agencies themselves, and their contractors, are subject to the eventual regulation. Of course, public and private polluters are entitled to offer their views and provide information to regulators during the public comment period. The issue here is whether polluters should be given an up-front opportunity to comment on EPA scientists' findings about the hazards of the pollutants they discharge.

Interagency review not only slows IRIS assessments, it also lets agencies that are potentially regulated push for favorable standards and cause delay.

As that example demonstrates, the interagency review process provides other federal agencies with a disruptive opportunity to inject policy considerations into the scientific assessments developed under IRIS. For example, this year, OMB submitted comments to the 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) reassessment expressing its disappointment that EPA did not calculate a "margin of exposure" in proposing a reference dose (RfD) for dioxin.<sup>22</sup> OMB argued: "Because the exposures of a proportion of the U.S. population would be above any RfD, it would have been useful for EPA to define the nature and magnitude of the risks at different levels of intake, the groups of the population most at risk, and the major sources of exposure for any at-risk groups." But decisions about whether and how to subdivide the exposed population for purposes of an IRIS assessment are science policy choices that do not belong in the IRIS process. These decisions should be made through the regulatory process, based on the strength of data and other factors without influence from potentially regulated parties, whose policy views are likely more informed by potential cleanup costs than by unbiased scientific considerations.

By retaining this interagency review process, EPA signaled that it continues to support the treatment of IRIS assessments as if they were themselves regulatory actions, rather than the scientific underpinnings for subsequent regulatory actions. For example, interagency review panels often call for additional explanation of factors related to regulatory action. In comments on the draft dioxin assessment, agencies asked for EPA to provide additional support for toxicity equivalent factors, which EPA explained were not used for the purposes of making IRIS assessments, but would be useful for future regulatory applications.<sup>23</sup> EPA leadership of the interagency science review process should have resulted in better balancing of EPA's interests with those of other federal agencies, but since the new IRIS process took effect, interagency comments have still resulted in delay, additional layers of analysis and calls for more and more science review.<sup>24</sup> The additional information supplied by federal agencies could be provided during a public comment period, so the delay created by interagency review does not justify the value of additional information shared by agencies.

A second problem with interagency review is that it provides additional avenues for industry interests to influence or delay the IRIS process. Industry interests commonly devote substantial resources to exploiting procedural opportunities to slow the process. And indeed, delay is at least a partial victory for industry, because assessments often provide significant basis for future regulations on toxic substances. As long as an industry can produce the appearance of a controversy around a substance, it can delay any regulatory action, and put off the day when it will have to conform to stricter regulation.

Industry tactics for delaying IRIS assessments are the product of years of experience fighting regulations. The guiding principle for delaying regulations and any government action that would protect people from hazards is to create a public perception of uncertainty in the link between chemical exposure and adverse effects. Industry has used this strategy for decades to delay regulations, win less stringent controls, and generate skepticism about



science from the agencies, including EPA.<sup>25</sup> Although industry manufactures this sense of doubt in many ways, at the core, each tactic is related to the overarching strategy of delay.

Recent actions by the American Forest and Paper Association (AF&PA) and the Methanol Institute exemplify how industry can manipulate the interagency review process to sow doubt and promote regulatory delay. EPA posted its original IRIS profile for methanol in 1988. The agency updated the profile in 1993, however it still lacks the two most critical data points for a CAA HAP—an inhalation reference concentration and a cancer slope factor. In 2002, EPA began the process of developing these numbers, and by 2009 had come up with a draft of a new profile. At that point, AF&PA and the Methanol Institute instituted a coordinated attack on EPA's draft. AF&PA attacked the individual studies EPA used to support the new inhalation reference concentration and the new cancer slope factor.<sup>26</sup> The Methanol Institute took on the studies that EPA used to support the overall conclusion that methanol is likely to be a human carcinogen.<sup>27</sup> Those studies were conducted by the Ramazzini Institute, an Italian lab that specializes in long-term carcinogenesis studies that industry believes overestimate chemicals' carcinogenic potential. In its comments attacking the Ramazzini methanol studies, the Methanol Institute went so far as to demand an audit of the lab. Soon thereafter, the National Toxicology Program (NTP), an interagency program housed in the Department of Health and Human Services, made a visit to the Ramazzini labs and issued a report that was critical of the labs' pathology practices.<sup>28</sup> The report also suggested that EPA conduct additional review of the Ramazzini results used in various IRIS profiles. Immediately after receiving the report, EPA announced it would suspend its assessment of methanol and three other chemicals currently under review in the IRIS program.<sup>29</sup>

The delay brought on by NTP's review of the Ramazzini labs may be evidence of a shrewd manipulation of the interagency review process by affected industry. At the very least, it will provide them with the opportunity to dump additional studies that they have funded into the docket. For instance, AF&PA hired a consulting company to conduct a review of EPA's draft IRIS assessment for methanol. The company, Exponent, has a long history of science for hire that stretches back to tobacco industry efforts to generate research to discredit the connection between smoking and cancer.<sup>30</sup> Since then, Exponent has been involved in a number of high-profile, industry-sponsored efforts to create a public perception that research linking products to hazards is controversial, including tests of laminated glass for Ford, which the company uses in litigation.<sup>31</sup> Such industry-sponsored studies are not subject to the guidelines set by the agencies and OMB for "quality, objectivity, utility, and integrity." Indeed, regulated industry has significant incentives to pay for studies that challenge agency results that recommend regulation. Such studies affect the IRIS process in two major ways—they slow it by requiring agencies to respond to petitions for correction of information, and they foster a perception of scientific disagreement. Industry interests have several opportunities to critique and discredit government science, but agencies are not provided with the same capacity to critique and re-analyze research presented from outside entities.

The agency could devote more resources to completing assessments if IRIS staff was not developing draft assessments to clear interagency hurdles.

Public access to federally funded research is much greater than privately funded research. Under the Data Access Act, federally funded research is subject to the Freedom of Information Act, giving private entities the opportunity to request underlying data and other information about federally funded studies. But privately funded studies are subject to no such disclosure requirements. As a result, industry-funded studies like the one conducted by Exponent for the AF&PA are effectively shielded from scrutiny by the media, the public, public interest organizations, and even the agencies themselves.

Without such checks on their work, there can be little assurance that industry-funded research meets the high standards of quality, objectivity, and independence required for use in the IRIS program. For instance, AF&PA also attached to its comments a study critical of EPA's assessment published in the journal *Regulatory Toxicology and Pathology*. The journal is sponsored by the industry-funded International Society of Regulatory Toxicology and Pharmacology, and has been criticized by a group of toxicologists for lacking transparency and editorial independence.<sup>32</sup>

One straightforward way to reduce the likelihood that bought-and-paid-for research finds its way into the IRIS process is to require a simple conflict disclosure, modeled after existing conflict disclosures adopted by scientific journals. Conflict disclosure would allow EPA, other agencies, and outside observers to quickly and easily consider potential conflicts of interest and account for any bias that might be built into industry-sponsored studies.<sup>33</sup> Apart from the problem of conflicts of interest, industry's ability to delay the regulatory process using research that is difficult to verify undermines EPA's ability to do its job in a timely manner.

In short, the interagency review process delays assessments without contributing to the IRIS process in a productive way. EPA expends resources in responding to interagency review comments and refining assessments multiple times before they are made available to a broader public for further comment. The agency could devote more resources to completing assessments if IRIS staff was not developing draft assessments to clear interagency hurdles—concerns that are often motivated by risk management concerns that are more appropriately raised during the development of actual regulations, rather than the development of a scientific assessment of possible harms. In addition, because EPA divides the review process into multiple steps, each of which requires EPA to wait and then re-evaluate its assessment, the agency sometimes is forced to respond to the same objections more than once.

#### Recommendations

The interagency review process should be eliminated and agencies should be given an opportunity to comment during a public comment period that is made equally available to all stakeholders. If significant science issues are raised in these public comments, EPA could then choose to initiate a more formal process for agencies to share information and resolve disputes.

In addition, EPA should assert more authority to question or re-analyze industry-sponsored research or at least to be able to take conflicts of interest into account when considering weight-of-the-evidence determinations about toxic substances. A conflict disclosure requirement that provides information about identity of sponsors, what kind of support they provided, the role of the sponsor in the research process, and the sponsors' level of control over the study and data, would enable EPA to make such assessments.

### Limiting Redundant Review

In her 2009 memo announcing the new IRIS process, Administrator Jackson wrote that EPA would occasionally seek outside scientific review from the NAS and EPA's Science Advisory Board (SAB), but only in high-profile assessments of major importance.<sup>34</sup> Since then, however, EPA has chosen to focus the bulk of its IRIS energies on a handful of high-profile assessments, with the result that six assessments expected to be completed this year have been recommended for SAB review: dioxin, arsenic (inorganic), arsenic (non-cancer effects), trichloroethylene, polycyclic aromatic hydrocarbons, and methanol. Half of these assessments have already been reviewed by at least one outside panel of scientific experts: inorganic arsenic, dioxin and trichloroethylene have had SAB reviews previously. Inorganic arsenic was previously reviewed by the SAB from 2005-2006. Dioxin was previously reviewed by SAB in 1995 and by NAS in 2006. Trichloroethylene was previously reviewed by SAB in 2001 and by NAS in 2006. Often OMB encourages these science advisory board meetings during the interagency review process.<sup>35</sup>

To be sure, NAS and SAB review can add an additional layer of scientific expertise to the process. But it is a process that has already incorporated the expertise of EPA scientists, who are, among other things, assessing existing scientific literature based on expert research. In addition, the extra layer of review comes at the cost of greatly slowing down the process, sometimes by years. In the case of trichloroethylene, the two SAB reviews have taken nine years – the first SAB review was initiated in 2001, and the second SAB review has not yet been completed.

Between the outside peer review process, public comments and additional reviews of EPA's scientific judgment delay assessments by focusing on details that may not be relevant to the risk assessment task at hand, and contribute to cascading delays, making delay of assessments so lengthy that new research emerges in the interim, requiring EPA to start again from the beginning. All scientific questions can be studied virtually indefinitely. At some point, assessments must be entered into the IRIS database so that regulators can get to work protecting the public from harm. While it is important that IRIS assessments provide the best available scientific information, the science advisory process furthers the myth that IRIS assessments can be static answers about human health effects. EPA's decision to wait for unassailable answers undermines the goal of IRIS to be broadly informative. In addition, redundant layers of review can have a demoralizing effect on EPA staff that prompts them to rely only on the most deeply entrenched studies preventing them from incorporating new research.

EPA could easily incorporate more expert advice without halting the process to wait for additional SAB and NAS review, by inviting additional experts to comment on individual assessments as part of the public comment period. Instead of asking these experts to come to a consensus opinion, as NAS and the SAB do, EPA could simply solicit opinions and comments on any problems with EPA's draft. This would keep the assessment process

moving forward and would prevent peer review from delaying the process. Including such comments in the public comment process would also promote transparency of the peer review process. Comments from outside experts would be published to a docket for the assessment and therefore could be reviewed by all interested parties.

### Recommendations

EPA should attempt to limit SAB review to the greatest extent possible. There will be difficult and complicated assessments, where input from the SAB may add value, reduce conflicts and provide EPA staff with needed oversight and outside expertise. But EPA should strive to avoid multiple reviews by SAB and NAS. Further, EPA should make decisions about how and when it will consult outside scientific expertise, not OMB. One place where outside science review could add genuine value is when broader scientific questions are raised, such as the development of toxicity equivalence factors, which compare the relative toxicity of individual chemicals within a family of similar chemicals, or review of classes of chemicals. In these cases, the expert opinions and additional guidance to EPA provides clear added value, as such determinations are complex and may require additional scrutiny, particularly in cases where EPA is evaluating techniques or approaches it has not used previously.

If and when EPA program offices act on IRIS information and propose a regulatory action, specific procedures under the Administrative Procedure Act, executive orders governing review of regulatory actions, and statutory requirements under each specific statute should govern the promulgation of regulations. This process is well-developed and provides regulated industry and other stakeholders with ample opportunity to evaluate EPA's proposal and present information and perspectives to the process. EPA should forgo outside science review aimed at resolving questions that are related to potential regulatory actions or risk management decisions, rather than to the science underlying those decisions.

A nimbler IRIS process would also make it easier for EPA to revise assessments if new research becomes available. In fact, EPA staff undertook the task in 2003 of identifying assessments in the IRIS database that should be revised because of new research.<sup>19</sup> At its best, the IRIS database should be responsive to new information, and be flexible enough that that EPA can incorporate new information to existing assessments relatively quickly. Because other program offices rely so heavily on information in the IRIS database, EPA should err on the side of information and provide the greatest possible amount of information that is scientifically credible.

In short, expert peer review can be an important tool for supporting the findings of EPA, but the agency should strive to keep redundant reviews of IRIS assessments by outside science advisory boards to an absolute minimum.

While it is important that IRIS assessments provide the best available scientific information, the science advisory process furthers the myth that IRIS assessments can be static answers about human health effects.

### Putting EPA's Resources to the Greatest Effect

EPA's IRISTrack program paints a compelling portrait of just how much work remains before IRIS is truly current. A compilation of status reports on EPA's IRIS assessments currently in progress, IRISTrack shows that 67 IRIS assessments are currently in process, while 255 substances need assessments for EPA program offices to fulfill statutory mandates, and 169 substances currently listed in the database have been identified by EPA staff as being in need of updating to account for new information. EPA must complete a significantly greater number of assessments each year to quickly clear the backlog of assessments. If EPA were to complete these assessments in five years, it would have to complete approximately 84 assessments each year – nine times the number of assessments per year that it completed in the past year. Assessments cost money, and even if EPA streamlines its process along the lines recommended in this paper, the agency will require an increase in its IRIS budget from its current level of \$14.5 million to approximately \$100 million, with a commensurate increase in the number of full time staff to allow EPA to complete enough assessments for the database to stay current.

Although the IRIS program has received increases in funding and staff since 2000, it has not been able to complete enough assessments to meet the needs of EPA program officers and other users of the database. The low level of productivity of the IRIS program was the subject of House Science Committee hearings in 2009. The briefing memo for the hearing suggested that 20 assessments per year was the bare minimum level of productivity for the IRIS database to be relevant.<sup>37</sup> Even that is, in all likelihood, an understatement of what is needed. To complete the 478 assessments listed above at the rate of 20 per year would take 24 years. If the schedule includes the 77 HAPs listed but still missing inhalation values, it would take EPA 25 years to complete all the statutorily-indicated assessments, without taking on any new assessments. By contrast, at EPA's current pace of nine assessments per year, it will take 55 years for the IRIS program just to clear its backlog.

Simply dumping more money into the IRIS program will not fix the problem. EPA must make more effective use of its resources. In fiscal year 2010, the IRIS program received \$5 million additional dollars and 10 additional staff to carry out its work.<sup>38</sup> In 2010, six assessments were referred for interagency review, eight are expected to complete the draft development phase, and EPA expects to complete nine assessments this year.<sup>39</sup>

The unfortunate reality is that EPA's new process for completing IRIS assessments has not addressed root causes of delay: the interagency review process, interference from regulated industry, excessive and redundant science review and inadequate strategic planning. Ideally, EPA would strive to reduce burdens on the assessment development process by focusing on a smaller number of key goals: reviewing toxicology information on toxic substances and providing an opportunity for peer review and public comment on the agency's assessment. Reducing these burdens would ensure that interested parties would have an opportunity to participate in the assessment development process and provide key oversight consistent with the requirements of the scientific community.

**Recommendations**

EPA should pursue two principal budget objectives with respect to IRIS. First, it should devote a limited amount of resources to high-profile IRIS assessments. Doing so would ensure that these high-profile or complex assessments are completed, but that they do not interfere with EPA's completion of other, easier-to-assess substances. The fraction of IRIS program resources devoted to high-profile chemicals should have a firm cap, so as to put an end to the current dynamic, in which EPA works on just a handful of the most difficult-to-complete assessments.

Second, EPA should develop a budget request that relies on a determination of what would actually be required to complete a target number of assessments. It should then add funding for ongoing assessments of high-profile substances. Such an approach would ensure that EPA would continue to complete assessments at a pace to keep the database up to date without high-profile assessments cannibalizing resources.

Administrator Jackson has an important opportunity to back up her assertion that the IRIS program is a key part of her chemical management strategy. The program needs sufficient resources and support so that the database can support the work of other program offices at EPA. Streamlining and simplifying the IRIS process would allow EPA to devote more of the agency's resources to completing assessments rather than responding to interagency comments and submitting to outside science review. If the agency divided priorities between a few high-profile assessments and a larger number of assessments that could be completed more quickly, EPA could complete more assessments while still making progress on the small number of high-profile assessments.

Finally, Congress should provide the IRIS program with the resources necessary to make sure IRIS is able to meet the needs of the program offices, and to keep the database up to date.

## Conclusion

The reforms to the IRIS program implemented by EPA in May 2009 have not made the IRIS program productive enough to support EPA's statutory responsibilities with respect to IRIS, or to the regulatory programs that rely on it so that they can do the important work of protecting Americans from toxic substances. In particular, by prioritizing a small number of high-profile assessments, retaining interagency review, and overusing NAS and SAB review, EPA has fallen into the trap of continuing the appallingly low completion rate for IRIS assessments.

EPA has the authority to implement all of these changes recommended in this paper, with the exception of funding requests that will require appropriation by Congress. EPA's principles for chemical management state that "[c]lear, enforceable and practicable deadlines applicable to the Agency and industry should be set for completion of chemical reviews, in particular those that might impact sensitive sub-populations."<sup>40</sup> Under the EPA's current IRIS process, there is no way to set a clear or enforceable deadline for chemical review. If Administrator Jackson wants to achieve a better, more protective chemical management strategy, it is imperative that the IRIS program become nimbler and better able to fulfill the needs of other offices at EPA to carry out their statutory responsibilities.



## Endnotes

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- <sup>4</sup> U.S. GOV'T ACCOUNTABILITY OFFICE, *Chemical Assessments: Low Productivity and New Interagency Review Process Limit the Usefulness and Credibility of EPA's Integrated Risk Information System*, GAO-08-440 (2008) [hereinafter GAO, *Chemical Assessments*].
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*Setting Priorities for IRIS:*

*47 Chemicals that Should  
Move to the Head  
of the Risk-Assessment Line*

by CPR Member Scholar Rena Steinzor and  
CPR Policy Analysts Matthew Shudtz and Lena Pons



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*Setting Priorities for IRIS: 47 Chemicals that Should Move to  
the Head of the Risk-Assessment Line*

**Executive Summary**

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EPA's Integrated Risk Information System (IRIS) is the starting point for new regulations under the Clean Air Act (CAA), Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) and the Safe Drinking Water Act (SDWA). Scientists in the IRIS office produce risk assessments of individual chemicals, which regulatory staff then combine with exposure data and statute-based policy choices to write new emissions limits and cleanup standards. In previous reports, the Center for Progressive Reform (CPR) has described massive gaps in the IRIS database, including more than 250 chemicals for which EPA's air, drinking water, and Superfund offices need robust risk assessments.<sup>1</sup> In this white paper, we describe how EPA should prioritize the work it will take to close those data gaps. We have developed a list of 47 chemicals that IRIS staff should move to the top of its list of priorities, based on the air toxics, drinking water, and Superfund program offices' most pressing needs.

Toxicology is predicated on the axiom that the dose makes the poison. IRIS profiles provide EPA, state and local public health officials, and the public with information about the relevant doses for hundreds of toxic substances. We recommend EPA improve its priority-setting process for IRIS by taking a two-step approach to deciding which data gaps to fill first. As a first step, EPA must foster better cooperation and communication between IRIS staff and their colleagues in the air, drinking water and Superfund program offices, to ensure that the priorities of risk assessors in the IRIS office parallel the priorities of risk managers in the program offices. Second, EPA should take environmental justice into consideration and determine whether there are patterns of unknown chemicals being emitted in large quantities in disadvantaged communities.

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<sup>1</sup> CENTER FOR PROGRESSIVE REFORM, *Corrective Lenses for IRIS: Additional Reforms to Improve EPA's Integrated Risk Information System* (Oct. 2010), available at [http://www.progressivereform.org/articles/IRIS\\_1009.pdf](http://www.progressivereform.org/articles/IRIS_1009.pdf) [hereinafter CPR, *Corrective Lenses for IRIS*].

Table 1: Priority Chemicals List				
<i>Air toxins</i>	<i>Superfund pollutants</i>	<i>Drinking water contaminants</i>	<i>Multi-media threats</i>	<i>Environmental justice concerns</i>
Cadmium compounds	Polycyclic aromatic hydrocarbons	1,2-Diphenylhydrazine	Acetamide <sup>1,3</sup>	1,1,2-Trichloroethane <sup>1,2,4,5</sup>
Carbonyl sulfide	Arochlor 1260	1,3-Dinitrobenzene	4-Aminobiphenyl <sup>1,2</sup>	1,2-Dichloroethane <sup>1,2,3,4</sup>
Formaldehyde	Arochlor 1242	Acetochlor ethanesulfonic acid	Arochlors <sup>1,2</sup>	Chlorobenzene <sup>4,5</sup>
Hydrogen fluoride	Arochlor 1221	Acetochlor oxanilic acid	Chromium <sup>2,3</sup>	Diaminotoluene <sup>4</sup>
Lead compounds	Cobalt	Alachlor ethanesulfonic acid	Cobalt <sup>2,3</sup>	Hexachlorobenzene <sup>4,5</sup>
Mercury compounds	DDT, O,P'	Alachlor oxanilic acid	Ethylene oxide <sup>1,3</sup>	Hexachloroethane <sup>1,3,4,5</sup>
Methanol	Nickel	Diazinon	2,3,7,8-Tetrachlorodibenzo-p-dioxin <sup>1,2</sup>	Methyl iodide <sup>5</sup>
Methylene chloride	Endrin ketone	N-Nitrosodimethylamine (NDMA)	Vanadium <sup>2,3</sup>	Phthalic anhydride <sup>2,3</sup>
Nickel compounds	Chromium(VI) oxide	N-Nitrosodiethylamine (NDEA)		Quinone <sup>2</sup>
Phenol	Methane	N-nitroso-di-n-propylamine (NDPA)		Urethane <sup>3</sup>
		Terbufos		

<sup>1</sup>Air, <sup>2</sup>Superfund,  
<sup>3</sup>Drinking water

Chemicals above are released in the following ZIP codes: <sup>1</sup>70734, <sup>2</sup>70805, <sup>3</sup>71730, <sup>4</sup>77541, <sup>5</sup>77571

In CPR's last paper on IRIS's information gaps, we identified 253 unique substances that need new or updated IRIS assessments.<sup>2</sup> In this paper, we selected the 47 substances from that list that EPA should move to the front of the line. The IRIS program staff are currently working on new assessments for just 17 of these 47 substances,<sup>3</sup> underscoring our concern that statutory priorities are not sufficiently factored into the IRIS agenda. The 47 unique substances listed in

<sup>2</sup> CPR, *Corrective Lenses for IRIS*, *supra* note 1, at 2-3.

<sup>3</sup> ENVIRONMENTAL PROTECTION AGENCY, *Integrated Risk Information System (IRIS): Request for Chemical Substance Nominations for 2011 Program*, 75 Fed. Reg. 63,827 (Oct. 18, 2010).

Table 1 include: ten hazardous air pollutants (HAPs) in the greatest number of upcoming air toxics standards; the ten highest-scoring Superfund priority substances; 11 substances listed on the drinking water Contaminant Candidate List; eight substances that appear on more than one list; and the ten highest-emitting HAPs in areas with environmental justice concerns.

## Introduction

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EPA's three key statutes for regulating toxic chemicals in commerce are the Clean Air Act (CAA), the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), and the Safe Drinking Water Act (SDWA). These statutes share two characteristics that make environmental regulation complex: they are media-specific, which balkanizes the regulatory landscape; and they require EPA to quantify the risks of individual chemicals before setting regulations.

At present, EPA takes nominations for new chemical risk assessments from Deputy Assistant Administrators, Deputy Regional Administrators, federal agencies that participate in reviews of draft IRIS assessments, and the public, then uses six criteria to select chemicals for IRIS assessments from among the nominations. But this process has not been sufficient to push the IRIS office to complete assessments in time for EPA program offices to regulate toxic substances.

The priority setting process functions like a black box: We know the criteria EPA applies and we know which IRIS profiles are completed, but we do not know how EPA applies these criteria to the un-assessed and under-assessed substances to set IRIS priorities. Based on the large number of chemicals identified by program offices that have not been assessed, we can infer that EPA's current process is not prioritizing assessments to meet the program offices' needs.

In this paper, we propose a two-step process for prioritizing new chemical reviews in the IRIS program: first, risk assessors from the IRIS office and risk managers from the regulatory offices need to work together to develop a complete list of chemicals in need of IRIS assessments; second, the chemicals should be prioritized in terms of the existing regulatory agenda and environmental justice concerns.

EPA program offices provide public information about chemicals considered for regulation, which we have parsed to develop a list of 253 substances that could be the starting point for discussions between IRIS risk assessors and regulatory risk managers. The CAA HAPs have been public since the Clean Air Act Amendments of 1990 were made law; the Agency for Toxic Substances and Disease Registry (ATSDR), a program under CERCLA, periodically publishes a list of priority chemicals; and, under the SDWA, the Office of Water must publish a Contaminant Candidate List (CCL) every five years. This information gives the IRIS staff guidance about chemicals of concern to EPA, but does not help them to prioritize their work.



Since IRIS staff cannot tackle all 253 substances at once, a more robust effort at coordination is necessary, including regular meetings between the staff and managers of all offices to set short- and long-term priorities. Those priorities should be informed by environmental justice concerns. Specifically, EPA should prioritize the assessment of chemicals that lack IRIS profiles and are emitted in large quantities in communities with significant populations of poor and minority residents and in localities where a large number of un-assessed chemicals are emitted together. In this white paper, we profile five communities that bear the burden of numerous un-assessed HAPs and multiple Superfund sites.

Improving priority-setting policies will put the IRIS staff on the right path, but the database will remain outdated without reforms to the assessment process. Potentially regulated parties, particularly industry and other federal agencies like the Department of Defense and National Aeronautics and Space Administration, have isolated IRIS as a choke point for regulation. Their opposition has resulted in an IRIS program that can neither keep up with the demands that have already been made, nor incorporate information about new substances. IRIS staff must consider new ways to avoid the problem of “information capture,” whereby potentially regulated parties dump so much new data on the agency – and do so with such frequency – that new assessments become mired in continuous controversy.

### **Setting Priorities, Step One: Improving Communication between Regulatory Office and IRIS Staff**

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EPA program offices have specific deadlines and plans to complete regulatory actions on toxic chemicals. The IRIS staff should be well-attuned to the deadlines and priorities of the program offices, and strive to provide program offices with the best available risk assessment information in a timely manner to support regulatory decisions. There should be regular communication and interaction between the program office staff and IRIS staff to facilitate priority-setting and ensure that priorities are consistent with the needs of the program offices.

The next three sections provide some additional details about the three programs and some thoughts on prioritizing chemicals that are important to each program.

#### ***Hazardous Air Pollutants***

The CAA Amendments of 1990 specify 188 toxic air pollutants that EPA must regulate through a two-step process. First, EPA must issue “technology-based” standards for all major sources of HAPs. At this stage, EPA staff simply determine emissions limitations based on the average emission limitation of the best performing 12 percent of existing sources. EPA has issued 96

technology standards covering 174 “major” and “area” sources.<sup>4</sup> In the second step of the HAPs regulations, EPA must evaluate “residual risks” associated with air pollutants eight years after the technology-based standards are promulgated, in an effort to determine whether the technology-based standards protect public health with “an ample margin of safety.”<sup>5</sup>

IRIS profiles are integral to the residual risk determinations. EPA considers an ample margin of safety to be exposures below the reference concentration (RfC or inhalation value) listed in IRIS for non-carcinogens, and the level at which added cancer risk does not exceed one in one million.<sup>6</sup> But the IRIS database is missing assessments or inhalation values for 107 of 188 HAPs, slowing progress toward completion of residual risk standards. In fact, EPA’s Science Advisory Board (SAB) reviewed the Office of Air and Radiation’s (OAR) methodology for completing two residual risk evaluations and implored EPA to complete IRIS profiles for all HAPs in a timelier manner.<sup>7</sup> They said that EPA’s alternate method of determining risk was too simplistic, and recommended that EPA elaborate on the proposed method. But they stressed that the best course of action was to complete IRIS profiles for all the HAPs.

Data gaps in IRIS’s HAPs coverage stymie public health efforts led by state and local agencies, too. In 2005, the Mayor of Houston, Bill White, ordered a task force on air pollution in the area. Houston’s Ship Channel is home to large number of petrochemical refineries and other chemical plants, and has high concentrations of a broad range of HAPs. The Task Force focused on 176 HAPs listed in EPA’s 1999 National Air Toxics Assessment that were present in the 10 counties that comprise the greater Houston area. The researchers expressed difficulty in developing risk characterizations for Houston-area HAPs: “The intrinsic challenges of comparing HAPs-related health risks are illustrated by the fact that 118 (67%) of the 176 HAPs examined by the Task Force were assigned to the uncertain risk category. This decision was based on their collective judgment that there is insufficient evidence on hand to ascertain whether these substances currently pose a significant threat to the health and well being of Houston residents.” Of the 118 HAPs placed in the uncertain risk category, 63 are missing IRIS profiles or lack inhalation values.

EPA completed the last of the technology-based standards in 2006, so it must issue all residual risk standards by 2014. With that deadline in mind, and with input from OAR, IRIS staff should set an agenda for completing risk assessments on all HAPs in an order that will pave the way for

<sup>4</sup> ENVIRONMENTAL PROTECTION AGENCY, OFFICE OF INSPECTOR GENERAL, EVALUATION REPORT: KEY ACTIVITIES IN EPA’S INTEGRATED URBAN AIR TOXICS STRATEGY REMAIN UNIMPLEMENTED, Report No. 10-P-0154, (2010).

<sup>5</sup> 42 U.S.C. § 7412(f).

<sup>6</sup> See, e.g., ENVIRONMENTAL PROTECTION AGENCY, *National Emission Standards for Coke Oven Batteries*, 70 Fed. Reg. 19,993 (Apr. 15, 2005).

<sup>7</sup> ENVIRONMENTAL PROTECTION AGENCY, SCIENCE ADVISORY BOARD, *Review of EPA’s draft entitled, “Risk and Technology Review (RTR) Risk Assessment Methodologies: For Review by the EPA’s Science Advisory Board with Case Studies – MACT I Petroleum Refining Sources and Portland Cement Manufacturing,”* SAB-10-007, at 5 (May 7, 2010) [hereinafter EPA, RTR Methodology].

OAR's regulatory agenda. EPA has already finalized 16 residual risk standards and proposed or requested comment on 17 others. IRIS and OAR staff should work together to determine how the 13 HAPs covered by proposed standards but lacking key IRIS data could be assessed in time to meet OAR's regulatory timeline. A recent consent decree prompted by a Sierra Club lawsuit sets deadlines for 16 more residual risk standards that cover 114 HAPs—43 of which lack inhalation values in the IRIS database and should also be prioritized for review by IRIS staff.

CPR reviewed EPA's proposed rules and the 16 other standards which EPA must propose under the consent decree, and identified 123 HAPs in these upcoming standards.<sup>8</sup> Table 2 highlights the top 10 of those 123 HAPs, based on the number of upcoming rules in which they appear. The Appendix (Table A2) provides a longer list—all 46 HAPs that appear in upcoming standards but lack inhalation values or do not have IRIS values. Input from OAR would be valuable in improving the usefulness of this priority list. OAR needs IRIS profiles for HAPs to complete the residual risk standards, and OAR should share its needs with ORD, so IRIS profiles can be completed in a timely manner.

<b>Table 2: Hazardous Air Pollutants with Insufficient IRIS Information in Upcoming Residual Risk Rules</b>
<i>Chemical</i>
Cadmium compounds*
Carbonyl sulfide
Formaldehyde
Hydrogen fluoride*
Lead compounds
Mercury compounds
Methanol
Methylene chloride
Nickel compounds
Phenol
* No IRIS profile information.

*Human Health Effects: Cadmium compounds*

Cadmium compounds have been linked to kidney disease, lung damage, cancer, and fragile bones.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY, ToxFAQ for CADMIUM, (Sept. 2008), available at <http://www.atsdr.cdc.gov/tfacts5.pdf> (accessed Oct. 21, 2010).

<sup>8</sup> ENVIRONMENTAL PROTECTION AGENCY, *Risk and Technology Review, Phase II, Group 2*, 72 Fed. Reg. 14,741-14,744 (Mar. 29, 2007); ENVIRONMENTAL PROTECTION AGENCY, *National Emission Standards for Hazardous Air Pollutant Emissions: Group I Polymers and Resins*, 73 Fed. Reg. 60,437-60,440 (Oct. 8, 2008).

### ***Superfund Pollutants***

Superfund is a critical part of EPA's overall mission. The Superfund program has a budget of \$1.3 billion; it makes up 12 percent of EPA's total budget.<sup>9</sup> Cleanup standards for Superfund inform other waste management programs, including the Resource Conservation and Recovery Act and private-sector cleanup efforts. IRIS profiles are the first step in setting Superfund standards and initiating work that radiates beyond Superfund.

Superfund sites are places of significant soil and groundwater pollution, often by multiple contaminants. EPA prioritizes cleanup efforts based on whether contaminants pose an immediate hazard or a longer-term cleanup effort. Sites that are not marked for emergency response are added to the National Priorities List (NPL). After a site has been added to the NPL, it undergoes a seven-step process through which EPA oversees the remediation of a site, a process that begins with risk assessment.

The CERCLA requires ATSDR to periodically compile a list of "high priority" substances.<sup>10</sup> ATSDR generates this list from substances that are found in sites on the NPL. The list is placed in a weighted priority order that takes into account the frequency with which substances are found at sites on the NPL, the toxicity of the substance, and the likelihood of human exposure to the substance at a site. ATSDR provides the IRIS staff with quite a bit of useful information to make determinations about how to prioritize substances for IRIS assessment. ATSDR updates the list periodically, with new substances being added and others removed as the sites on the NPL change.<sup>11</sup> Nonetheless, many substances remain on the list for years, because they are common industrial chemicals, or are persistent environmental toxics. Even the longstanding high priority chemicals lack sufficient coverage in IRIS – 17 substances that have been on ATSDR's list since 1997 do not have IRIS profiles (*See* Appendix, Table A4).

#### ***Why ATSDR?***

Dividing responsibilities across multiple agencies is one strategy to avoid agency capture. Congress created the ATSDR in 1986, after the integrity of EPA's Superfund program had been called into question by the actions of Reagan administration officials in charge of the program.

ATSDR's list, like the CAA's list of HAPs, provides an obvious indication of an EPA regulatory office's needs. But similar to its treatment of HAPs data gaps, EPA's IRIS agenda does not explain how it will address data gaps for substances on the ATSDR high priority list. There is no formal relationship between the ATSDR list and the IRIS agenda process. Research conducted

<sup>9</sup> ENVIRONMENTAL PROTECTION AGENCY, FY 2010 EPA BUDGET IN BRIEF, 2, 6 (Apr. 2009) available at <http://www.epa.gov/budget/2010/2010bib.pdf> (accessed Dec. 15, 2010).

<sup>10</sup> 42 U.S.C. § 9604(i).

<sup>11</sup> AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY, CERCLA PRIORITY LIST OF HAZARDOUS SUBSTANCES, lists are available for 1997, 1999, 2001, 2003, 2005 and 2007, available at <http://www.atsdr.cdc.gov/cercla/07list.html> (accessed Sept. 16, 2010) [hereinafter ATSDR, CERCLA PRIORITY LIST].

by ATSDR should flow freely between ATSDR and the IRIS program – indeed IRIS was created when EPA combined several disparate databases of human health information maintained by various program offices at EPA. The Superfund program should support IRIS to the extent that ATSDR is able to assist the IRIS program in completing assessments, identifying key studies, and making judgments about weight-of-the-evidence evaluations of toxic chemicals.

Table 3: Top Ten ATSDR Priority Chemicals not Listed in IRIS <sup>12</sup>		Human Health Effects: Nickel
Chemical	ATSDR points <sup>13</sup>	
Polycyclic aromatic hydrocarbons	1316.98	<p>Exposure to nickel dust has been linked to respiratory problems including bronchitis and reduced lung function. Occupational exposures have been linked to lung and nasal cancer.</p> <p>AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY, TOXFAQ FOR NICKEL, (Aug. 2005), available at <a href="http://www.atsdr.cdc.gov/tfacts15.pdf">http://www.atsdr.cdc.gov/tfacts15.pdf</a> (accessed Oct. 21, 2010).</p>
Aroclor 1260	1177.77	
Aroclor 1242	1093.14	
Aroclor 1221	1018.41	
Cobalt	1015.57	
DDT, O,P'	1014.71	
Nickel	1005.4	
Endrin ketone	978.99	
Chromium(VI)oxide	969.58	
Methane	959.78	

### Drinking Water Contaminants

The Safe Drinking Water Act (SDWA) requires EPA to set standards for limits on drinking water contaminants. Unlike HAPs, which were specified by Congress, EPA is responsible for identifying water contaminants. EPA identifies additional water contaminants that might be candidates for regulation every five years by generating a new Contaminant Candidate List (CCL).<sup>14</sup> The lists contain recommendations both for chemicals and microbiological contaminants. Since 1996, EPA has published three CCLs that contain 156 distinct chemical substances.<sup>15</sup> IRIS profiles are missing for 64 (41 percent) of these substances. Absence of an IRIS profile hinders regulation of drinking water contaminants because the Water Office uses health risk information to prioritize unregulated substances to monitor, as well as determine what order to regulate water contaminants.

<sup>12</sup> ATSDR, CERCLA PRIORITY LIST, *supra* note 11.

<sup>13</sup> Points are assigned by ATSDR is based on an algorithm that utilizes the following three components: frequency of occurrence at NPL sites, toxicity, and potential for human exposure to the substances found at NPL sites. See AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY, CERCLA PRIORITY LIST OF HAZARDOUS SUBSTANCES, WHAT IS THE CERCLA LIST, available at <http://www.atsdr.cdc.gov/cercla/index.asp> (accessed Sept. 19, 2010) [hereinafter ATSDR, WHAT IS THE CERCLA LIST].

<sup>14</sup> 42 U.S.C. § 300g-1(b)(1)(B)(i).

<sup>15</sup> ENVIRONMENTAL PROTECTION AGENCY, *Announcement of the Drinking Water Contaminant Candidate List; Notice*, 63 Fed. Reg. 10,273 (Mar. 2, 1998); ENVIRONMENTAL PROTECTION AGENCY, *Drinking Water Contaminant Candidate List 2; Final Notice*, 70 Fed. Reg. 9,071 (Feb. 24, 2005); ENVIRONMENTAL PROTECTION AGENCY, *Drinking Water Contaminant Candidate List 3 – Final*, 74 Fed. Reg. 51,850 (Oct. 8, 2009).

The SDWA requires the EPA Administrator to make a public health finding about a contaminant before EPA moves to regulate the substance. The public health finding requires three determinations: first, EPA must establish that the contaminant may have an adverse effect on human health; second, the agency must determine that the contaminant is known or likely to occur in public water systems; and third, EPA must determine that regulation through SDWA presents a meaningful opportunity for reducing public health risks.<sup>16</sup> Reference doses contained in IRIS profiles are exactly relevant to the first determination. The IRIS program has not kept up with demand to provide information about CCL substances, which makes it more difficult for EPA to make the health risk related determinations required under SDWA.

Table 4 lists 11 of the 64 substances that appear in the CCLs that do not have IRIS profiles, culled from the larger list because they are also tracked under the Unregulated Contaminant Monitoring program. In the Appendix (Table A5), we identify nine additional substances EPA tracks under the Unregulated Contaminant Monitoring program that do not appear on the Contaminant Candidate Lists, but are missing IRIS profiles.

<b>Table 4: UCMR Listed Substances also on CCL without IRIS profiles</b>	
<i>Chemical</i>	<i>Human Health Effects: Ethylene Oxide</i>
1,2-diphenylhydrazine	Ethylene oxide has been linked to miscarriage, respiratory and nervous system effects.
1,3-Dinitrobenzene	
Acetochlor ethanesulfonic acid	Ethylene oxide is listed of programmatic importance both for safe drinking water and as a HAP.
Acetochlor oxanilic acid	
Alachlor ethanesulfonic acid	AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY, ToxFAQ FOR ETHYLENE OXIDE, (Jul. 1999), available at <a href="http://www.atsdr.cdc.gov/tfacts137.pdf">http://www.atsdr.cdc.gov/tfacts137.pdf</a> (accessed Oct. 21, 2010).
Alachlor oxanilic acid	
Diazinon	
N-nitrosodiethylamine (NDEA)	
N-nitrosodimethylamine (NDMA)	
N-nitroso-di-n-propylamine (NDPA)	
Terbufos	

<sup>16</sup> 42 U.S.C. §300g-1(b)(1)(A).

## Setting Priorities, Step Two: Considering Environmental Justice

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IRIS staff can use the regulatory offices' legal obligations and administrative priorities to start the process of choosing which chemicals need new or updated assessments, but those two factors will still leave them with a substantial list. IRIS staff should further prioritize new assessments by taking into consideration environmental justice concerns.

Environmental justice, as defined by EPA, means "fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies."<sup>17</sup> In practice, EPA's policy for ensuring environmental justice places an obligation on EPA staff to consider first, whether their actions disproportionately impact any group(s) of people, and second, whether all affected groups have a meaningful opportunity for involvement in the regulatory process.

In the IRIS assessment priority-setting context, IRIS staff could take into account the potential for disproportionate impacts by analyzing emissions and exposure data for the unassessed HAPs, CERCLA priority chemicals, and drinking water contaminants to determine where clusters of those unassessed chemicals can be found. Over the next few pages, we profile five communities where HAPs that have insufficient profiles are released in significant quantities. These five communities were chosen because they are sites with a large diversity of toxic air pollutants and have the largest number of HAPs without IRIS profiles. In addition to considering HAPs, we also looked at the presence of Superfund sites, and toxic chemical releases listed in EPA's Toxic Release Inventory (TRI). After we selected the communities, we probed basic demographic information from the 2000 Census, which is listed in the community profiles.

Our methodology is but one way that IRIS staff might take environmental justice into account when prioritizing new assessments. These communities are subject to diverse exposure to toxic chemicals through multiple pathways. We selected them based on the presence of the largest number of exposures to substances that are missing IRIS profiles, but these communities are also exposed to an even larger diversity of toxins.

One of EPA's long-term goals is to better understand the cumulative impacts of multiple toxins.<sup>18</sup> Chemical-by-chemical information contained in IRIS – oral exposure limits, inhalation values – is exactly the kind of toxicology information needed to complete cumulative risk

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<sup>17</sup> ENVIRONMENTAL PROTECTION AGENCY, OFFICE OF POLICY, ECONOMICS AND INNOVATION, EPA'S ACTION DEVELOPMENT PROCESS: INTERIM GUIDANCE ON CONSIDERING ENVIRONMENTAL JUSTICE DURING THE DEVELOPMENT OF AN ACTION (2010) available at <http://epa.gov/compliance/ej/resources/policy/considering-ej-in-rulemaking-guide-07-2010.pdf> (accessed Nov. 2, 2010).

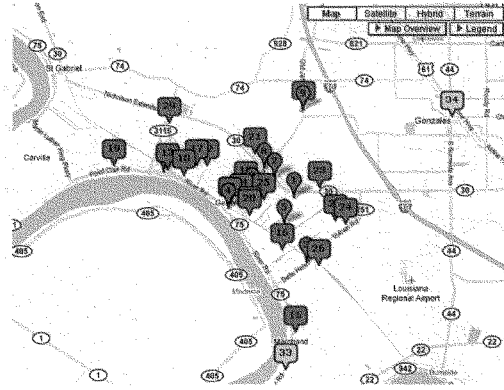
<sup>18</sup> See, e.g., Thomas Burke, *Overview of Cumulative Risk, presentation before Environmental Protection Agency, Mid-Atlantic Cumulative Risk Workshop* (2003), available at [http://www.epa.gov/region3/environmental\\_justice/cumriskwkskshop.htm](http://www.epa.gov/region3/environmental_justice/cumriskwkskshop.htm) (accessed Dec. 1, 2010).

analysis. Cumulative risk assessments are highly dependent on toxicology information about each of the various toxic substances and exposure pathways. If toxicology information is not present, then the evaluation cannot be credibly completed. Cumulative risk assessments become less credible as the number of data gaps increase. EPA must identify both where there is a large diversity of exposure to toxic substances, and which toxic substances that appear in these areas are missing critical toxicology information. The IRIS office should then strive to prioritize substances that hinder cumulative risk assessment.

EPA's environmental justice policies also require that staff consider whether all affected groups are able to meaningfully participate in program decisions. IRIS staff can help more groups participate more meaningfully in the regulatory process by finalizing new chemical profiles for toxins that appear in communities like those profiled below. These communities often have limited resources to devote to participation in the highly technical standard-setting and permitting decisions that affect the quality of their air, water, and soil. The existence of IRIS profiles for all relevant chemicals helps these communities advocate for themselves. The IRIS office should strive to support environmental justice by identifying unassessed chemicals from our list that appear in communities that are not adequately included in the decision making process.



**Geismer, LA 70734**  
**Ascension Parish**



Geismer, Louisiana is located about 30 miles south of Baton Rouge. It is home to a large number of petrochemical facilities, including the largest manufacturing facility for the chemical company BASF. According to EPA's Toxic Release Inventory, residents of Geismer are exposed to 94 toxic chemicals.

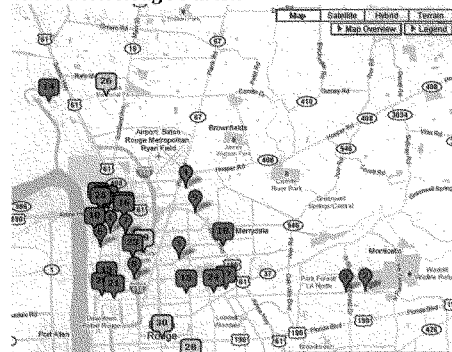
Blue markers represent sources of air pollution. Yellow markers are Superfund sites.

Toxics Release Inventory Information for 70734				
Total Releases (lbs)	Air Releases (lbs)	Water Releases (lbs)	Land Releases (lbs)	Transfers to Off-Site Treatment Works (lbs)
9,522,750	2,530,641	6,738,084	27,569	226,457

Sources of Toxic Substance Exposures for 70734 and Ascension Parish		
Air toxics not in IRIS	Superfund sites (70734)	Superfund sites (Ascension, LA)
14	2	5

Demographics Information for Geismer and Ascension Parish		
	70734	Ascension Parish
Race		
White	58.7%	77.6%
Black	36.9%	19.8%
Native American	0.0%	0.4%
Asian	1.6%	0.4%
Pacific Islander	0.0%	0.0%
Hispanic/Other	0.4%	0.9%
Median household income	\$39,336	\$44,288
% below poverty line	12.9%	12.8%

**Baton Rouge, LA 70734**  
**East Baton Rouge Parish**



Baton Rouge is the capital of Louisiana. It lies on the Mississippi River, about eighty miles west of New Orleans. Baton Rouge is home to a deepwater port connecting the Mississippi River to the Gulf of Mexico. Major industries in Baton Rouge include petrochemical production, plastic, rubber, and timber and paper products, which contribute to air and water pollution in the area. According to EPA's Toxics Release Inventory, residents of Baton Rouge are exposed to 116 different toxic chemicals.

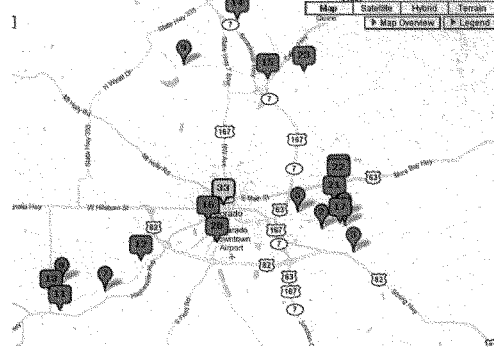
Blue markers represent sources of air pollution. Yellow markers are Superfund sites.

Toxics Release Inventory Information for 70805				
Total Releases (lbs)	Air Releases (lbs)	Water Releases (lbs)	Land Releases (lbs)	Transfers to Off-Site Treatment Works (lbs)
9,961,982	4,725,250	5,089,631	250	146,851

Sources of Toxic Substance Exposures for 70805 and East Baton Rouge Parish		
Air toxics not in IRIS	Superfund sites (70805)	Superfund sites (East Baton Rouge Parish)
12	1	18

Demographics Information for Baton Rouge and East Baton Rouge Parish		
	70805	East Baton Rouge Parish
Race		
White	10.7%	51.8%
Black	86.8%	44.5%
Native American	0.2%	0.3%
Asian	0.8%	2.5%
Pacific Islander	0.0%	0.0%
Hispanic/Other	0.5%	2.8%
Median household income	\$21,203	\$42,173
% below poverty line	34.2%	17.6%

**El Dorado, AR 71730**  
**Union County**



El Dorado, Arkansas is located in the southern part of the state, near the Louisiana border. It was once a site for oil extraction. More recently it is the home to a diversity of chemicals manufacturing, including agricultural chemicals, automotive chemicals, pesticides, bleaching agents and synthetic dyes. The town of El Dorado contains six Superfund sites. EPA estimates residents of El Dorado are exposed to 177 toxic chemicals.

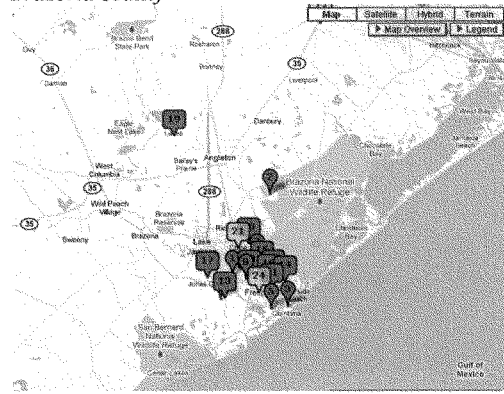
Blue markers represent sources of air pollution. Yellow markers are Superfund sites.

Toxics Release Inventory Information for 71730				
Total Releases (lbs)	Air Releases (lbs)	Water Releases (lbs)	Land Releases (lbs)	Transfers to Off-Site Treatment Works (lbs)
7,749,243	1,209,550	4,369,657	1,464,241	705,794

Sources of Toxic Substance Exposures for 71730 and Union County		
Air toxics not in IRIS	Superfund sites (71730)	Superfund sites (Union County)
14	6	7

Demographics Information for El Dorado, AR and Union County		
	71730	Union County
Race		
White	66.2%	64.8%
Black	31.6%	33.1%
Native American	0.3%	0.3%
Asian	0.4%	2.5%
Pacific Islander	0.0%	0.0%
Hispanic/Other	0.5%	2.8%
Median household income	\$30,565	\$37,120
% below poverty line	18.8%	18.6%

**Freeport, TX 77541**  
**Brazoria County**



Freeport, Texas is located on the Gulf of Mexico coast south of Houston. It is home to a deepwater port and large-scale petrochemical manufacturing. Freeport also maintains a liquefied natural gas terminal. These sites are major sources of air pollution in Freeport. EPA reports that residents of Freeport are exposed to 136 toxic chemicals.

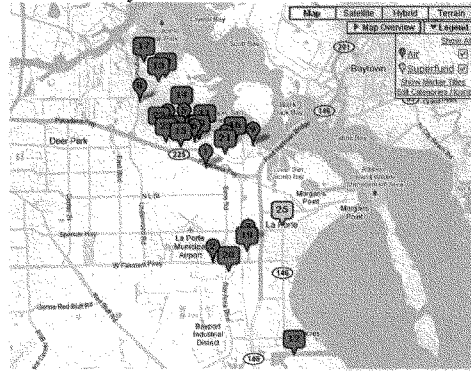
Blue markers represent sources of air pollution. Yellow markers are Superfund sites.

Toxics Release Inventory Information for 77541				
Total Releases (lbs)	Air Releases (lbs)	Water Releases (lbs)	Land Releases (lbs)	Transfers to Off-Site Treatment Works (lbs)
5,377,060	2,452,712	2,535,381	69,489	319,470

Sources of Toxic Substance Exposures for 77541 and Brazoria County		
<i>Air toxics not in IRIS</i>	<i>Superfund sites (77541)</i>	<i>Superfund sites (Brazoria County)</i>
9	2	10

Demographics Information for Freeport, TX and Brazoria County		
	77541	Brazoria County
<i>Race</i>		
White	83.5%	82.2%
Black	12.1%	11.2%
Native American	0.6%	0.6%
Asian	0.4%	4.6%
Pacific Islander	0.0%	0.0%
Hispanic/Other	19.8%	2.1%
<i>Median household income</i>	\$33,933	\$60,784
<i>% below poverty line</i>	23.5%	9.2%

**La Porte, TX 77571**  
**Harris County**



Blue markers represent sources of air pollution. Yellow markers are Superfund sites.

LaPorte, Texas is on Galveston Bay and is located in Houston's Ship Channel, which is home to a large number of petrochemical facilities. In 2005, the Mayor of Houston ordered a task force to investigate the effects of air pollution in the Houston area, including Harris County. Data gaps in IRIS hindered the task force's ability to assess health effects. In addition to air pollution, Harris County also contains 81 Superfund sites. According to EPA, residents of LaPorte are exposed to 279 toxic chemicals.

Toxics Release Inventory Information for 77571				
Total Releases (lbs)	Air Releases (lbs)	Water Releases (lbs)	Land Releases (lbs)	Transfers to Off-Site Treatment Works (lbs)
4,379,416	2,195,039	1,680,546	169,558	334,272

Sources of Toxic Substance Exposures for 77571 and Harris County		
Air toxics not in IRIS	Superfund sites (77571)	Superfund sites (Harris County)
16	1	81

Demographics Information for LaPorte, TX and Harris County		
	77571	Harris County
Race		
White	81.5%	73.5%
Black	6.7%	18.7%
Native American	0.6%	0.7%
Asian	0.7%	5.1%
Pacific Islander	0.0%	0.2%
Hispanic/Other	7.9%	1.3%
Median household income	\$56,552	\$42,598
% below poverty line	7.2%	15.9%

## Streamlining the Process

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Improving the priority-setting process for completing IRIS assessments is key to bringing the IRIS database up to date. But considering that EPA has such a large number of assessments to complete, it must also address how it manages its workload, and devise a process that allows the IRIS program to complete more assessments each year. EPA should streamline the process by setting goals for how many assessments to complete each year, drawing from substances of programmatic importance; eliminating the interagency review process; relying on outside science review only in the most complex cases; and preventing a few high-profile assessments from impeding progress on others by completing those assessments on a separate track with a separate budget.

In addition to structural problems with the IRIS process, regulatory agencies including EPA are plagued by information overload.<sup>19</sup> The regulatory process does not discourage—and actually encourages—interested parties to submit large volumes of unfiltered information to agencies. As a result, attention, not information, is in short supply in making regulatory decisions. The consequences of this overload of information include an increased cost of participation in the regulatory process – both to produce competing analyses and information and to review and understand information submitted by other interests. Industry interests, having more resources to participate in this process, dominate the process in terms of the amount of information submitted to agencies and critical evaluation of information submitted by other interests. This creates an echo chamber effect where agencies hear one perspective—industry’s—much more often than others, creating a perception that the dominant perspective is the correct one.

This drop-off in pluralistic participation is described as “information capture.”<sup>20</sup> By volume and frequency of participation, better-funded industry interests influence agencies in favor of the industry position. The IRIS program is subject to substantial information capture due to the complexity of the assessment process and the highly technical nature of its work. The IRIS office faces a prodigious backlog of assessments, and a stream of critique of its work. Industry has a strong incentive to flood the agency with more information than it can effectively process. Since there are no mechanisms in the regulatory process to limit interested parties from dumping raw data into the record, there is too much information for agency staff to read through. The agencies, battered by searching judicial review of their prior decisions, take it upon themselves to respond to the content of all the submissions made to the agency in the course of the regulatory process, in an attempt to insulate themselves against future litigation.

Although the IRIS process is not a regulatory process, it is subject to many of the same challenges in terms of information overload. ORD staff is inundated from the start with

<sup>19</sup> Wendy Wagner, *Administrative Law, Filter Failure, and Information Capture*, DUKE L. J. Vol. 59, (2010) [hereinafter Wagner, *Filter Failure*].

<sup>20</sup> *Id.*

information. Before a draft assessment is published, ORD staff comb through the literature and produce a “screening-level literature review,” which is then published in the *Federal Register* and opened for public comment. Industry and other interests, including other federal agencies, then submit additional studies and data that ORD staff must read and synthesize. Part of this process is motivated by industry’s efforts to generate the appearance of controversy, a deregulatory tactic that dates from the tobacco industry’s 1960s efforts to suppress and obfuscate the relationship between smoking and cancer.<sup>21</sup>

Information capture is not unique to the IRIS process. But with such a large backlog of assessments to complete, the IRIS process could be a good test case for strategies to reduce the influence of excessive information. Placing some manner of filtering requirement on interest groups, akin to limits placed by appellate courts on litigants, could provide some relief to agencies in addressing information overload.<sup>22</sup> Limits would encourage interested parties to point to specific studies or findings relevant to issues with IRIS assessments. EPA staff could then focus on a few problems and more quickly finish the weight-of-the-evidence determinations required for IRIS.

## Conclusion

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CPR’s research has identified 253 substances awaiting IRIS assessments, an unacceptably high number. EPA’s program offices need IRIS information to complete statutorily mandated tasks. EPA should set a goal for working through these assessments, and then submit a budget proposal that reflects the resources it would take to finish the work in that amount of time. Congress should then provide the IRIS program with adequate funding to complete the work. Although the current budget situation is such that many programs are being cut, our own back-of-the-envelope calculations estimate that the IRIS backlog could be cleared in five years for approximately \$100 million. In the context of the federal budget, this is not an unbearable request. Indeed, it would amount to 0.003 percent of the \$3.5 trillion in federal outlays from FY2009. The IRIS process should be reformed to remove roadblocks and reduce the amount of time it takes to complete assessments.

Moving forward, EPA should set priorities based on program office need, taking into consideration environmental justice factors. Some mechanism for setting the IRIS agenda based on expected needs of the program offices should be developed. The IRIS staff should determine how many assessments must be completed based on the need from the program offices, not based on the available budget. To the greatest extent feasible, program offices should give ORD advance notice of chemicals of interest, so the IRIS staff can integrate these substances into the

<sup>21</sup> DAVID MICHAELS, *DOUBT IS THEIR PRODUCT: HOW INDUSTRY’S ASSAULT ON SCIENCE THREATENS YOUR HEALTH* (OXFORD UNIVERSITY PRESS) (2008).

<sup>22</sup> Wagner, *Filter Failure*, *supra* note 19, at 1419.

agenda-setting process. EPA should analyze whether certain communities are disproportionately affected by chemicals for which there is no IRIS information and strive to prioritize these assessments as well.

IRIS should push the regulatory agencies forward. It should also screen the epidemiology literature for candidate substances and provide information that prods the program offices to act under statutory authority. The relationship between the program offices and IRIS should be symbiotic and reinforcing.



**Appendix: Additional Tables of Chemicals Indicated by Program Offices  
Not Listed in IRIS**

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<b>Table A1: Substances identified by CPR as CAA, SDWA, or Superfund data gaps that are being assessed by IRIS staff</b>	
<i>Chemical</i>	
Aroclors (polychlorinated biphenyls) <sup>1,2</sup>	
Cadmium <sup>1</sup>	
Carbonyl sulfide <sup>1</sup>	
Chloroform <sup>1</sup>	
Cobalt <sup>2,3</sup>	
1,2-Dichloroethane <sup>1</sup>	
1,4-Dioxane <sup>1</sup>	
Ethylene oxide <sup>1,3</sup>	
Formaldehyde <sup>1</sup>	
Methanol <sup>1</sup>	
Methyl <i>tert</i> -butyl ether <sup>3</sup>	
Methylene chloride <sup>1</sup>	
Nickel <sup>2</sup>	
Polycyclic aromatic hydrocarbons <sup>2</sup>	
2,3,7,8-Tetrachlorodibenzo-p-dioxin <sup>1,2</sup>	
Tetrachloroethylene <sup>1</sup>	
Trichloroethylene <sup>1</sup>	
<sup>1</sup> Air pollutants; <sup>2</sup> Superfund pollutants; <sup>3</sup> Drinking water contaminants	

Table A2: Hazardous Air Pollutants with Insufficient IRIS Information in Proposed or Mandated Residual Risk Rules	
<i>Chemical</i>	
Benzyl chloride	Hexachlorobenzene
Bis(chloromethyl) ether	Hexachloroethane
Bromoform	Hydrogen fluoride
Cadmium compounds	Isophorone
Carbonyl sulfide	Lead compounds
Chlorine	Lindane
Chlorobenzene	Mercury compounds
Chloroform	Methanol
Chloromethyl methyl ether	Methyl iodide
Cyanide compounds	Methyl isothiocyanate
2,4-D	N,N-Dimethylaniline
Dibenzofuran	Nickel compounds
1,2-Dichloroethane	o-Toluidine
Dichloromethane	Pentachloronitrobenzene
Diethyl sulfate	Phenol
Dimethyl carbamoyl chloride	Selenium
2,4-Dinitrophenol	Styrene oxide
2,4-Dinitrotoluene	1,1,2,2-Tetrachloroethane
1,4-Dioxane	Tetrachloroethylene
Dioxin and dioxin-like compounds	1,2,4-Trichlorobenzene
Ethyl acrylate	Trichloroethylene
Ethylene oxide	2,4,5-Trichlorophenol
Formaldehyde	2,4,6-Trichlorophenol

**Table A3: Hazardous Air Pollutants with Insufficient IRIS Information in the Hazardous Organic NESHP**

<i>Chemical</i>
Anthraquinone
Bromonaphthalene
Chloronaphthalene
Chrystene
Fluoranthene
Alpha-Naphthalene sulfonic acid
Beta-Naphthalene sulfonic acid
Alpha-Naphthol
Beta-Naphthol
Naphthol sulfonic acid
1-Naphthylamine
2-Naphthylamine
1,4-Naphthylamine sulfonic acid
1,2-Naphthylamine sulfonic acid
1-Nitronaphthalene
Tetrahydronaphthalene

*These chemicals are not listed in the Clean Air Act Amendments of 1990 with the other HAPs profiled in this paper, but they were regulated by EPA under the Hazardous Organic NESHP. We have included them because there is also insufficient IRIS information on these chemicals.*

**Table A4: ATSDR Priority Chemicals Listed for more than 10 years not in IRIS<sup>23</sup>**

<i>Chemical</i>	<i>ATSDR points<sup>24</sup></i>
Aroclor 1240	888.11
Radon-220	804.54
Tributyltin	802.61
Neptunium-237	802.13
Iodine-129	801.64
Gamma-chlordene	702.59
Americium	701.62
Carbon Monoxide	684.49
Chromium trioxide	610.85
Benzopyrene	603.00
Actinium-227	602.57
Ethoprop	602.13
Alpha-chlordene	601.94
Calcium arsenate	601.48
Hydrogen fluoride	588.03
Pentaerythritol tetranitrate	545.59
Carbazole	534.52

<sup>23</sup> ATSDR, CERCLA PRIORITY LIST, *supra* note 11.

<sup>24</sup> Points are assigned by ATSDR is based on an algorithm that utilizes the following three components: frequency of occurrence at NPL sites, toxicity, and potential for human exposure to the substances found at NPL sites. See ATSDR, WHAT IS THE CERCLA LIST, *supra* note 13.

<b>Table A5: Water Contaminants Tracked under Unregulated Contaminant Monitoring, not in the CCL lists, not in IRIS</b>
<i>Chemical</i>
2,2',4,4',5,5'-Hexabromobiphenyl
2,2,4,4',6-Pentabromodiphenyl ether
Dacthal di-acid degradate
Dacthal mono-acid degradate
Lead-210
Metolachlor ethane sulfonic acid
Metolachlor oxanilic acid
Polonium-210
Terbufos sulfone

### ***About the Center for Progressive Reform***

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Founded in 2002, the Center for Progressive Reform is a 501(c)(3) nonprofit research and educational organization comprising a network of scholars across the nation dedicated to protecting health, safety, and the environment through analysis and commentary. CPR believes sensible safeguards in these areas serve important shared values, including doing the best we can to prevent harm to people and the environment, distributing environmental harms and benefits fairly, and protecting the earth for future generations. CPR rejects the view that the economic efficiency of private markets should be the only value used to guide government action. Rather, CPR supports thoughtful government action and reform to advance the well-being of human life and the environment. Additionally, CPR believes people play a crucial role in ensuring both private and public sector decisions that result in improved protection of consumers, public health and safety, and the environment. Accordingly, CPR supports ready public access to the courts, enhanced public participation, and improved public access to information. The Center for Progressive Reform is grateful to the The John Merck Fund and the Bauman Foundation for funding this white paper. CPR also thanks the Public Welfare Foundation and the Deer Creek Foundation for their generous support of CPR's work on regulatory issues in general.

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Chairman BROWN. Thank you, Ms. Steinzor.

I now recognize our next witness, Dr. Charnley, for five minutes.  
Dr. Charnley.

**TESTIMONY OF GAIL CHARNLEY, PRINCIPAL, HEALTHRISK  
STRATEGIES**

Dr. CHARNLEY. Thank you, and good morning. I am a toxicologist, a human health risk analyst, and a toxicology consultant who has relied for many years on the information contained in the IRIS database for my work. I am speaking on the basis of my 30-year career as a scientist evaluating the relationship between chemical exposures and human health effects, and I am not representing any organization today.

The role and purpose of IRIS are good and well-intentioned, but over the years IRIS has lost its way, straying from science and veering towards advocacy. As a result it no longer has much scientific credibility outside the agency or, importantly, within the agency itself.

IRIS started out as a good idea, an advisory group of scientists that assessed chemical toxicity for the rest of EPA. The reach of IRIS goes way beyond EPA, however, as other federal agencies, state and local governments, both within the United States and in other countries, lacking their own resources to generate toxicity values, chemical toxicity values, have come to rely on those generated by IRIS. Because the influence of IRIS is so broad, the scientific quality and integrity of its reviews are critically important.

The problem is that IRIS toxicity evaluations do not follow a rigorous, objective, transparent, scientific weight of evidence process, instead, relying on what—in the absence of such a process—appears to be cherry-picking data in support of policy preferences as needed.

A true weight of evidence analysis should explicitly present the criteria for inclusion and exclusion of studies so that all relevant information is included and so that biases towards the inclusion of certain outcomes are avoided.

IRIS assessments fail to use a weight of evidence process despite the explicit direction to do so provided by EPA's own risk assessment guidance and repeatedly by various National Academy of Sciences committees. My written statement details some of the large body of EPA documentation stating that it is EPA policy to perform balanced weight of evidence analysis as part of chemical risk assessment, a policy that is clearly being ignored by IRIS.

I think the solution is not to try once more to tweak or revamp the existing process but to start over. Public health is not served by a broken, cumbersome, controversial process that lacks a rigorous scientific foundation and a transparent, replicable weight of evidence framework. Setting up a more effective process should follow the recommendations of a National Academy of Sciences committee convened for that purpose and should follow a weight of evidence procedure recommended by the Academy.

Chapter seven of the Academy's formaldehyde report provides helpful but general guidance toward that end, and, no, I am not advocating that NAS review all IRIS reviews.

EPA's recently proposed IRIS redesign relies on EPA's Science Advisory Board for, "independent review and oversight," instead of the Academy. However, the SAB is not independent. EPA officials select SAB Members, formulate charge questions, provide staff support for the review process, and oversee SAB deliberations and report drafting.

In contrast, the NAS process for selecting scientific panel Members and conducting reviews assures independence and objectivity along with appropriate expertise for which they are not compensated in any way.

Truly independent peer review is the only way to give stakeholders confidence in the credibility of the outcome. Stakeholders are likely to accept the outcome of an independent Academy committee and unlikely to accept the outcome of an EPA-administered committee.

In conclusion, the IRIS process is dysfunctional and attempts to tweak it have not resulted in meaningful improvements. Changes proposed this week are promising, but I believe that implementing those changes and implementing an improved, scientifically-based, transparent IRIS process would benefit greatly from National Academy of Science's guidance. The NAS is in a unique position to provide unbiased, credible, expert advice that, sadly, is so critically needed at this point if we are to move IRIS into a 21st century approach to assessing chemical toxicity effectively.

Thank you.

[The prepared statement of Ms. Charnley follows:]

PREPARED STATEMENT OF DR. GAIL CHARNLEY, PRINCIPAL, HEALTHRISK STRATEGIES

Good morning. I am speaking today as a toxicologist with a Ph.D. from MIT, as a human health risk analyst, and as a toxicology consultant to private clients who has relied for many years on the information contained in the IRIS database for my work. I am speaking on the basis of my 30-year career studying the relationship between chemical exposures and human health effects, as executive director of the bipartisan Presidential/Congressional Commission on Risk Assessment and Risk Management, as a member of the National Toxicology Program's Report on Carcinogens Committee, as a former senior program officer in the National Academy of Sciences' Toxicology and Risk Program, as a member of National Academy of Sciences committees, and as a member of the National Academy of Sciences Board on Environmental Studies and Toxicology. I am not representing any organization today, however, or being paid for my testimony.

The role and purpose of IRIS are good and well-intentioned, but over the years IRIS has lost its way. IRIS started out as a good idea—a scientific advisory group that assesses chemical toxicity for the rest of EPA so as to avoid every office having to do it themselves and generating potentially conflicting toxicity values. The reach of IRIS goes far beyond EPA, however, as other federal agencies and state and local governments in the U.S. and other countries lacking their own resources for generating chemical toxicity values have come to rely on those generated by IRIS. IRIS assessment can thus become a de facto component of regulatory decision-making without benefit of appropriate administrative process. Because the influence of IRIS is so broad, the scientific quality and integrity of its reviews are critically important.

Unfortunately, over time the IRIS process has become politicized and, as a result, it no longer has much scientific credibility outside the agency or, importantly, even within the agency. The process has strayed from science and veered towards advocacy. As you have heard from other speakers this morning, IRIS toxicity evaluations do not follow a rigorous, objective, transparent, scientific weight-of-evidence process, instead relying on cherry-picking data as needed to support policy preferences. Indeed, many of IRIS' recent conclusions appear to be based on what my colleagues and I refer to as "magical modes of action", that is, highly speculative biological explanations for toxicity.

IRIS assessments fail to evaluate potential human cancer and noncancer effects of chemical exposures using a weight-of-evidence analysis despite the direction to

do so provided by EPA's own risk assessment guidance documents and, repeatedly, by various National Academy of Sciences committees. For example, EPA's Information Quality Guidelines state that when EPA develops "influential" scientific risk assessments, it intends to use all relevant information and reach a position based on careful consideration of all such information, a process typically referred to as the "weight-of-evidence" approach.<sup>2</sup> EPA's Assessment Factors Handbook<sup>3</sup> states that a weight-of-evidence approach generally considers all relevant information in an integrative assessment and explains how the various types of evidence fit together. EPA's Risk Assessment Principles & Practices documentation asserts that risk assessment involves consideration of the weight of evidence provided by all available scientific data.<sup>4</sup> My point is that there is a large body of EPA documentation stating that it is EPA policy to perform balanced weight-of-evidence analysis as part of chemical risk assessment that is clearly being ignored—a glaring omission in light of EPA's own guidelines, policies, and NAS recommendations.

A weight-of-evidence analysis for any potential health effects, whether cancer or noncancer, should be more than a matter of describing a set of available studies with an array of results and then announcing one's overall subjective judgment. Because judgments made about potential risk will usually not be definitive, it is important to present the strengths and weaknesses of alternative judgments that could be made, giving the reader a picture of how strongly one or another interpretation is supported vis-à-vis alternative possible explanations. Instead, IRIS assessments preclude a weight-of-evidence analysis by selecting almost solely for studies that demonstrate a positive result and a dose-response relationship, typically excluding studies that demonstrate no effect and thereby effectively preventing a balanced consideration of available evidence supporting or refuting the biological plausibility and likelihood of effects.

A true weight-of-evidence analysis should explicitly present the criteria for inclusion and exclusion of studies so that all relevant information is included and so that biases toward inclusion of certain outcomes—such as only positive outcomes—are avoided. The goal should be to interpret possible reasons for disagreement, not to select the "best" study and rely on it even if it is contradicted by other study results. Omitting endpoints or studies that do not show a dose-response relationship in the direction EPA favors discounts valuable information, particularly information that could inform mode of action as well as dose-response.

I think the solution is not to try once more to tweak or revamp the existing process but to get rid of it entirely and start over. Public health is not served by a broken, cumbersome, controversial process that lacks a rigorous scientific foundation and a transparent, replicable weight-of-evidence framework. Setting up a more effective process should follow the recommendations of a National Academy of Sciences committee convened for that purpose and should follow a weight-of-evidence procedure recommended by the Academy. Chapter 7 of the Academy's formaldehyde report provides helpful guidance to that end.<sup>5</sup>

Some have proposed that IRIS rely on EPA's Science Advisory Board for independent external review and oversight instead of the Academy. However, the SAB review process is not independent. EPA officials select SAB Members, formulate the charge questions, provide staff support for the review process, and observe SAB deliberations and report drafting. According to the SAB web site, "The Staff Office manages EPA requests for scientific and technical advice and peer review. The Staff Office also provides policy, technical and administrative assistance to advisory committees in conducting meetings and preparing reports. The SAB Staff Office oversees the formation of advisory committees and panels . . ." and so forth. In contrast, the NAS process for selecting scientific panel Members and conducting reviews assures independence and objectivity along with appropriate expertise. Truly independent peer review is the only way to give stakeholders confidence in the credibility of the outcome. Stakeholders are likely to accept the outcome of an independent Academy peer review and unlikely to accept the outcome of an EPA-administered peer review. Then there's the problem of delay. Most of the recent controver-

<sup>2</sup> EPA (2002) Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency. EPA/260R-02-008. Office of Environmental Information, Washington, DC

<sup>3</sup> EPA (2003) A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information. EPA 100/B-03/001. Science Policy Council, Washington, DC

<sup>4</sup> EPA (2004) Risk Assessment Principles and Practices. EPA/100/B-04/001. Office of the Science Advisor, Washington, DC

<sup>5</sup> National Academy of Sciences/National Research Council. 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. National Academy Press. Washington, DC



sial IRIS assessments reviewed by the NAS had already been reviewed by the SAB, but ended up at the Academy anyway.

In conclusion, the IRIS process is dysfunctional and attempts to tweak it have not resulted in meaningful improvements. Developing an improved, scientifically based, transparent IRIS process would benefit greatly from National Academy of Sciences guidance. The NAS is in a unique position to provide unbiased, expert advice that, sadly, is so critically needed at this point if we are to move IRIS to a 21st century approach to assessing chemical toxicity effectively.

Chairman BROWN. Exactly five minutes. Exactly.

Mayor Bollwage, you are now recognized for five minutes.

**TESTIMONY OF J. CHRISTIAN BOLLWAGE, MAYOR, CITY OF  
ELIZABETH, NEW JERSEY**

Mr. BOLLWAGE. Thank you very much, Mr. Chairman and Members of the committee. I just want to say upfront that I am a mayor. I am not a scientist, so I talk about trying to create jobs, economic development. We work with our city councils, our department managers. We make decisions on the ground every day, but risk management is one of those areas where local elected officials must make decisions, and we always like to have the best available tools.

The IRIS System is a mix of scientific measure, expert guesswork, and surrounded by a high level of uncertainty with what might happen to humans if they are exposed to chemical substances. In the end from my position it is a tool, and we have learned through the experience of governing city that when you use a tool to guide decision making, you want to use the right tool, applied to the right problem, and use the tool in the right way. And the IRIS method has to yield the result that makes commonsense.

I have worked closely with the Conference of Mayors for 15 years in convincing the EPA and the Congress that not all contaminated sites in communities are the same. There are grossly contaminated sites called Superfund, but there are hundreds of thousands throughout our country less contaminated brownfield sites. I am very concerned with the public health in my community, and if that health threat can be dealt with and brownfield sites properly redeveloped, then it is a win-win for the community. Brownfield legislation has helped us remove that public health threat. We put these lands back to productive use creating jobs, urban redevelopment, new sources of revenues that are used to support public safety, public health, and maintain our physical infrastructure.

One of the greatest impediments to this type of progress was the way that the EPA and the press have over-characterized the risk to the public. This attached an unpardonable stigma to any site whether the contamination was serious or negligible. Generally the risk has been overplayed, and it has become difficult from my position to educate the public about the difference between a brownfield site and a Superfund site.

This was the case even after the EPA Administrator Browner released over 30,000 sites that were on the CERCLIS list, and these were not contaminated enough to warrant any further EPA action.

I have a Superfund site in the City of Elizabeth. It is severely contaminated and way too costly to ever clean up. I also have brownfield sites. I am proud to report we developed many of those, IKEA Super Center, Jersey Gardens on a 166-acre former landfill.

Has four hotels as well as 2 million square feet of retail space. They are thriving, and they have created hundreds of jobs, promoted redevelopment, and has been an enormous success for our community.

I have submitted to the committee a report prepared by the Conference of Mayors that shows brownfield redevelopment in cities across the Nation have had the same positive impact because of local government's decisions.

EPA's dioxin reassessment will converge with the IRIS System, and this combination will impact a wide range of policy decisions. The Conference of Mayors believes this tool as applied to brownfield sites could bring back the stigma of a Superfund site. And as a tool the IRIS System relies on toxicity values that are established with a very wide margin of error that is intended to allow for uncertainty.

So when the IRIS System is used to inform risk management decisions, it must be noted that the compound effect of overly-conservative toxicity values with overly-conservative exposure scenarios can yield a very distorted characterization of risk.

For example, when EPA proposed to lower the dioxin soil concentration for a contaminated site remediation, they proposed to lower the existing guideline from one point—one part per billion to 76 parts per trillion or even 3.7 parts per trillion.

So not only is the exposure scenario unrealistic, but at 3.7 parts per trillion of dioxin, the soil in every urban center in this country would pose an unacceptable risk because background levels are normally two to four times higher than that.

So here is what troubles the mayors. People get 95 percent of dioxin from the foods they eat, not from a contaminated brownfield site. EPA continues to rely on a worst-case exposure scenario. So I have doubts about how this IRIS tool can be applied with any certainty.

So I would like to make some following suggestions. The EPA can continue to improve the IRIS and the information based on toxicity and exposure assessment. The exposure assessment is something that should be evaluated by the National Academies of Science to determine if more realistic assumptions are appropriate.

For example, it would be helpful to have actual measurements of a most-likely-case scenario in addition to a worst-case scenario.

IRIS should be a tool to advise decisions, not mandate them. Mayors need the best tools available to help us make sound decisions. Our goals for our cities are to protect the public health and the environment while encouraging economic vitality.

I want to thank you, Mr. Chairman, for this time, and thank Members of the committee as well.

[The prepared statement of Mr. Bollwage follows:]

PREPARED STATEMENT OF THE HONORABLE J. CHRISTIAN BOLLWAGE, MAYOR, CITY OF ELIZABETH, NEW JERSEY

My name is J. Christian Bollwage, and I am Mayor of the City of Elizabeth, New Jersey and Chair of the Conference of Mayors Brownfields Task Force for the past 15 years. I appreciate this opportunity to provide comments to the House Science Committee and I thank the Chairman for extending the invitation to participate in this panel.

I am here representing The United States Conference of Mayors which is the non-partisan organization that represents cities with populations of 30,000 or more

through their chief elected official, the Mayor. There are over 1,200 cities throughout the United States.

I want to emphasize that I am a Mayor, not a scientist and therefore I am not accustomed to participating in scientific and technical discussions. However, I was asked to come before you today to provide comments on the real-world impacts of applying scientific assessment tools at the community level, and this I have done since becoming a locally-elected official.

I am certainly not an expert on the IRIS system, but for want of a better tool, my staff are users of the IRIS system approach to hazard and human exposure assessment.

Mayors, with their City Councils and Department Managers, have to make decisions on the ground every day to run a city. While many of these decisions require the careful application of common sense, some are more complicated, and these types of decisions require the use of more sophisticated decision-making tools.

Risk management is one of those areas where local elected officials must make decisions, and we like to have the best tools available to assist us with our efforts.

The IRIS system is not some sort of "sacred tool" that should never be questioned or evaluated. It does seem, however, that it is shrouded in a mix of scientific measurement, expert guesswork, and deals with a high level of uncertainty.

I have been told that the IRIS method is one that combines measurement precision and a lot of guesswork about what might happen in humans if they are exposed to chemical substances. But, in the end, it is just a tool used by decision-makers.

I have learned through the experience of governing a city for nearly 2 decades that when you use a tool to guide decision-making, you want the right tool, applied to the right problem. And you want to use that tool the right way.

So, even though the IRIS method has some valid scientific components, it still has to yield a result that makes sense, even to the laypeople in the community.

That is what I want to comment on here today.

I worked closely with the Conference of Mayors starting 15 years ago to convince the EPA and Congress that not all contaminated sites in communities are the same.

There are grossly contaminated sites that are Superfund sites with New Jersey having more than its fair share. But there are hundreds of thousands of less contaminated sites, known as brownfields that could be a potential public health threat but could also be cleaned up and turned into property that contributes to the well-being of that community. As a Mayor, the public health in my community is a paramount consideration. I am seriously concerned about the health of our children, our pregnant women, our average citizens and our city employees. However, I also don't want to unnecessarily cordon off pieces of property that should be properly evaluated, cleaned up, and reclaimed.

That is why I worked so hard with the Conference of Mayors to get Congress and the Administration to establish Brownfield redevelopment policies.

Brownfield legislation has helped us remove the public health threat, and we have put these lands back into productive use creating jobs, urban redevelopment and new sources of revenues that are used to support public safety, public health and maintain our physical infrastructure.

One of the greatest impediments to this type of progress was the way EPA and the popular press characterized contaminated land in the 1980s. EPA was, in our opinion, 'less than careful' about how they originally characterized the risk to the public. In public hearings in many communities across the nation there was an unpardonable stigma attached to any site with contamination whether the contamination was serious or negligible. The popular press played an important role in fanning the flames of fear among the public. This made it virtually impossible to redevelop these properties. Developers wouldn't touch them, banks wouldn't lend money, and instead we had the abandonment of previously developed sites in favor of greenfields which contributed to urban sprawl.

Generally, the risk was so over-played that it became a burdensome task to educate Congress and the public about the difference between a brownfield site and a Superfund site. This was the case even after EPA Administrator Carol Browner released over 30,000 sites that were on the CERCLIS list and said that these were not contaminated enough to warrant any further EPA action.

I have a Superfund site in Elizabeth New Jersey. It is severely contaminated, and would pose a public health problem if it were not cordoned off properly- which it is. This site will likely plague the city for the next century because it was determined that it will cost too much money to clean it up.

I also have quite a few brownfield sites in Elizabeth. I am proud to report that we have redeveloped many of them including the IKEA Super Center and the Jersey Gardens, an economically thriving shopping center that has created hundreds of jobs, promoted redevelopment and has been an enormous help to the city's economy.

I am submitting to the Committee a report prepared by the Conference of Mayors that shows that brownfield redevelopment in cities across the nation have had the same positive impact because local government made the decision to clean these sites up, remove the potential public health threat and returned the land to productive use.

But once again I am in Washington on the topic of not stigmatizing the redevelopment of brownfields unnecessarily. EPA's dioxin reassessment will converge with the IRIS system, and this combination will impact a wide range of policy decisions, including Preliminary Remediation Goals (PRGs) for dioxin levels in soil. The Conference of Mayors' believes this could have a severe impact on brownfields and other urban and suburban development.

The U.S. Conference of Mayors is concerned that EPA's toxicity and exposure assumptions would drive dioxin PRG values down to levels that are below average concentrations in U.S. cities, and perhaps below current background levels in urban and suburban soils.

As a tool, the IRIS system relies on toxicity values that established with a very wide margin of error built in that is intended to allow for uncertainty. The system also relies on exposure assessment calculations that rely on substantial exaggeration on risk.

When the IRIS system is used to inform risk management decisions it must be noted that the compound effect of overly conservative toxicity values with overly conservative exposure scenarios yield a very distorted characterization of risk.

This type of calibration of the different parts of the tool leaves local decision-makers with a risk analysis that is not realistic.

For example, when EPA proposed to lower the dioxin soil concentrations for contaminated site remediation they intended to lower the existing guideline from 1 part per billion to 76 parts per trillion or even 3.7 parts per trillion. These lower standards were based on EPA's overly conservative approach to estimating dioxin toxicity in combination with assumptions about exposed children wallowing in the contaminated site soils.

Not only is the exposure scenario unrealistic, but at 3.7 parts per trillion of dioxin, the soil in every urban and suburban area would pose an unacceptable risk because background levels are normally two to four times higher than 3.7 parts per trillion.

Even lowering the dioxin standard in soil to 76 parts per trillion is lowering the so-called danger point to where the public will question their safety.

What is troubling about those proposals for a Mayor is two important facts:

1. All of our citizens are getting 95 percent of their dioxin from the foods they eat, not from a contaminated brownfield site, and,
2. Rather than rely on worst-case exposure scenarios, the University of Michigan published a study that looks at actual dioxin levels in people reports:
  - People who live on contaminated soil and have contaminated household dust do not have higher levels of dioxins in their blood. A study involving direct human measurement included 21 people who lived on soil contaminated at 1,000 to 11,200 ppt TEQ of dioxins.
  - The study authors stated that they believe their results apply to populations whose soil is contaminated in this range.

EPA exposure assumptions are predominantly determined by policy judgments that are so overwhelmingly reliant on worst-case scenarios that they do not at all reflect the realities of potential human exposure.

So, I have doubts about how this IRIS tool can be applied with any certainty. And I am very concerned that it is the wrong tool for making local decisions.

Our August 2010 Policy Paper highlights that these dioxin standards "at or below background levels and if implemented will have an immediate chilling effect on the successes achieved over the last two decades to clean-up [brownfields] sites and return these properties to productive use."

So using this tool with its distortion of risk does not pass the reasonable-sense test at the local level.

On the other hand, I understand the need for the EPA to develop assessment tools to help local decision-makers, so I would like to make the following suggestions.

1. The EPA should continue to improve IRIS and the information base on toxicity and exposure assessment
2. The exposure assessment assumptions should be evaluated by the National Academies of Science

- I think we are too smart in today's world to rely on one-size-fits-all assumptions in risk management when the stakes are so high
  - Instead of EPA focusing on "worst case scenarios", they should also look at the "most likely case". This would be more useful to decision-makers to better understand the true risk of their decisions.
3. The EPA should not force local officials to rely on the IRIS system to make local decisions until the Agency improves the toxicity and exposure assessment methods to better reflect reality
- In particular, EPA should not force state regulators to base brownfield site clean-up decisions on the IRIS system

Mayors need the best tools available to help us make sound decisions. Our goals for our cities are to protect the public health and the environment while encouraging the economic vitality. We need tools that are based in reality and common sense.

I want to thank the Chairman and this Committee for the opportunity to give a Mayor's perspective on this important issue.

Chairman BROWN. Thank you, Mr. Mayor. I thank you all for your testimony today.

Reminding Members that committee rules limit questioning to five minutes. The chair will at this point open the round of questions.

The chair recognizes himself for five minutes.

Dr. Charnley, to your knowledge does the IRIS Program reflect the framework outlined in the report, "Risk Assessment and Risk Management in Regulatory Decision Making," developed by the Presidential Congressional Commission on risk assessment and risk management?

Can you briefly outline the key aspects of the framework that should be reflected in IRIS risk assessments, and what does it mean to understand the context of a risk problem as discussed in the framework?

Dr. CHARNLEY. Well, what the risk commission framework does is emphasizes the importance of figuring out what the problem is you are trying to address before you address it, to clarify what your risk management goals are, and use those as a guide to risk assessment. As Dr. Anastas pointed out, however, the IRIS Program does not perform risk assessments. It generates safety values. It generates toxicity values that then a risk assessment would take, would use and compare to exposure values to come up with some understanding of what a human health risk might actually be.

So what the IRIS Program does is provide some of the information that could be used in risk management but doesn't, it doesn't have the same context.

Chairman BROWN. Okay. Congressman Dooley, 2 days ago Dr. Anastas participated in a press conference and offered some insight on a new and improved IRIS process that will allegedly incorporate the Academy's recommendations from April, while building upon the 2009 revisions proffered by Administrator Jackson.

Can you comment on the Agency's announcement?

Mr. DOOLEY. Yes.

Chairman BROWN. Congressman, press the button so we can hear you, please, sir.

Mr. DOOLEY. Yeah. We commend the EPA and Dr. Anastas on some of their recent actions. I think that whatever stakeholder you might be here, whether you are a member of Congress, a mayor,

whether you are representing consumer interest groups or environmental groups or if you are part of the industry, we want to have an IRIS Process that meets a gold standard. We heard Dr. Samet say today that he would barely give it a passing grade on the formaldehyde IRIS assessment. I don't think any of us think that that is adequate.

And so what we have been suggesting is that we are looking forward to the reforms that EPA is administering or enacting now to improve their program. I think we would all have a greater confidence that they were getting it right if for the next period of time that the next IRIS assessments that are coming out under these new reforms, that we would submit them to NAS just to make sure that we would have a double check on it to understand: did they enact the best processes, to ensure that we are using the best scientific process, that standards that ensure that the weight of evidence on the scientific research was adequate, that we had a peer review process that provided appropriate levels of transparency and independence.

That is what we are suggesting when the industry, as we were characterized, is asking for NAS to play a major role in reviewing the IRIS assessments that could be issued in the next few months under the new and improved guidelines. We would all benefit and have greater confidence if we had NAS, you know, taking a review, making sure they got it right.

Chairman BROUN. Thank you, Congressman.

Mayor Bollwage, I have got 1 minute left, so please answer quickly. Can you give us an idea of what sort of actions that you would need to consider as mayor if EPA proceeds with its proposed dioxin PRG, which as you note is at or below background levels, and what would it mean to your city, your constituents, your economy, your jobs, et cetera? What would be the positive outcomes of such a low dioxin PRG? That is, how would it affect safety?

Mr. BOLLWAGE. Thank you. Mr. Chairman, I can only explain it real quickly with we had an outdated plastics facility, and we wanted to convert it to Little League fields. We scraped away 3 inches of dirt and we mediated that and converted it into two healthy Little League fields.

If the levels are lowered, we are going to wind up scraping away, what, 8 inches, 10 inches, 12 inches, a lot more of the dirt in order to make that area safe for Little League.

You make the cost of a municipality increase substantially, and I don't know of any kids who are rolling around in the brownfields who have caught dioxin.

Chairman BROUN. My time has expired.

Now I recognize Ms. Edwards for five minutes.

Ms. EDWARDS. Thank you, Mr. Chairman, and thank you to our witnesses today.

I just want to start out by noting that I do share Mr. Rohrabacher's view that it is important for us to know who is before us and who is influencing a process but merely working in an industry or working at an organization that advocates for a certain position is not a reason to exclude either that testimony or information.

Nonetheless, I think it is also important that we have the same kind of transparency and accountability that we are demanding of the EPA and other agencies and their process is the same kind of transparency and accountability that we want in those who seek to influence or advocate in the process because it could otherwise operate to the detriment of the public health.

Dr. Charnley, I have looked at your resume. It is very impressive, and I note that you are currently serving on the National Academy of Sciences Board of Environmental Science and Toxicology. Your appointment began in 2009. Is that correct?

Dr. CHARNLEY. Yes.

Ms. EDWARDS. Thank you, and when you joined the—I also note in your testimony you indicated that you participated on numerous peer review panels convened by the EPA. You say that in your participation you acted independently. Isn't that correct?

Dr. CHARNLEY. Correct.

Ms. EDWARDS. Thank you, and when you joined the National Academy of Science Board on Environmental Science and Toxicology, we have been told that you would occasionally maybe once or some number of times recuse yourself from board discussions of formaldehyde. Is that right?

Dr. CHARNLEY. That is correct.

Ms. EDWARDS. And why did you feel a need to or were you required to recuse yourself, and in addition, who was paying you at the time, and what were you being paid to do that required your recusal?

Dr. CHARNLEY. Nobody was paying me at the time but before I joined the board I had given some advice to the Formaldehyde Council on how the National Academy of Sciences process works, and so when I served on the board, although the Academy does not believe that previous employment counts as a conflict, I felt that from an optics point of view, from a perception point of view that it would make sense to recuse myself from any discussions on formaldehyde just so that—

Ms. EDWARDS. Thank you.

Dr. CHARNLEY. Yeah.

Ms. EDWARDS. Well, let us not talk about optics. Let me just ask were you specifically in your—previous to your—prior to your appointment, were you paid to advise the Formaldehyde Council about ways in which they could use the NAS process to, you know, to thwart the assessment process through IRIS?

Dr. CHARNLEY. Of course not.

Ms. EDWARDS. And so I am just curious, were you paid by them to advise you on how to get an Academy study on the EPA's IRIS draft assessment for formaldehyde?

Dr. CHARNLEY. I was not.

Ms. EDWARDS. Okay. So what we will do is perhaps ask you some questions, specific questions on the record and also the Academy about the recusal process and about your work for the Formaldehyde Council and whether that had any impact on its work.

Mr. Dooley, when we go to the Formaldehyde Council's webpage right now, and I have it, we are directed to a page that has the ACC logo on it. And then both organizations are shown to reside

at the same address in Arlington, Virginia. What do you say about that?

Mr. DOOLEY. The Formaldehyde Council, just earlier this year, I guess about 6 months ago, moved from being an independent agency to become one of among 50 different specific product panels that we have under ACC. So they are a self-funded group that is operated under the umbrella of the American Chemistry Council.

Ms. EDWARDS. So I am—maybe I am confused, but—so what we have here today is we have an organization that has taken on the work of the Formaldehyde Council, an expert who advised the Formaldehyde Council, in my view, I think, to just use its power to get the NAS study started. And then we are also aware, I know I am, that Dr. Anastas's appointment was held up in the Senate by Senator Vitter until EPA would agree to fund the NAS formaldehyde review. And then we have one of the people who was advising the Formaldehyde Council on how to get a report requested of the Academy, I believe, and that report is now being misused to excuse or cripple EPA's assessment process.

And so, as far as I am aware, none of that is—and—or those relationships have been disclosed to the committee, but it certainly puts your testimony in an informative light. Thank you very much, and I yield.

Chairman BROWN. Thank you, Ms. Edwards. The Chairman now recognizes Dr. Benishek for five minutes.

Dr. BENISHEK. Thank you, Mr. Chairman. I find this all kind of scary because we have limited resources to deal with these risks, and when you hear conflicting testimony as to the accuracy and broadness of the investigation concerning a chemical risk, you want to spend your resources toward the chemical that has the most risk. And to not have that risk be politicized so you are wasting your resources on something that is not where you should be spending your resources.

Dr. CHARNLEY, do you have these same concerns that I do about this process? I am concerned about the Scientific Advisory Board for the EPA being open and not being biased. I find in different areas of the EPA the Scientific Advisory Boards don't have the experts on the panel that they should have, that have enough knowledge of the thing that they are actually judging the scientific validity of the people there, and not the experts in the field. Do you have any information about that that you can relate to us here?

Dr. CHARNLEY. Well, I think that is probably correct. I think that the difference with the Academy process is that a committee is convened of scientists to specifically address the substance or subject under consideration so that their expertise does directly inform whatever the subject matter is. And I do agree with you that putting resources towards substances that do not pose big public health impacts directs us away from issues and substances that do, and I don't think that is appropriate.

Dr. BENISHEK. I so much agree with you. Mr. Dooley, let me ask you a question. Do you think that the people in the formaldehyde business want trouble with formaldehyde?

Mr. DOOLEY. No, absolutely not. I mean—but this, again, comes to the essence of what this hearing is all about, how do we establish an IRIS assessment process that has the confidence of the



NGO community or industry, that we are ensuring that it is using the best science and the best scientific process? When the NAS reviewed the IRIS review of formaldehyde, they found it was significantly flawed. That doesn't serve anyone's purpose.

Formaldehyde is a building block chemical. But, even this IRIS assessment, it has consequences. The EPA was proposing there was an assessment level for formaldehyde, in terms of where it could be a concern for cancer, that they set a reference dose level that was .008 parts per billion. That was the level that they said consumers should be concerned about a risk of exposure. The World Health Organization had also done an assessment and concluded that the average person's breath contains up to 8 parts per billion. So, you back up and you say, is this IRIS risk assessment providing information that is really informing public health concerns, when by their own action level—or reference is 1,000 times greater than the formaldehyde in the air that we exhale.

And that is where we think that we have got to step back and understand is how are we going to establish an IRIS process that is assessing—or considering hazard and exposure to some degree that actually can provide information that allows them there to make the responsible decision, that allows State regulators also to impose actions, and informs other Federal regulatory actions that emanate from this IRIS risk assessment. It needs to be done right. And what we are suggesting is until we have the confidence that it is right, we ought to allow NAS to review the IRIS assessment. And hopefully the reforms that Dr. Anastas spoke about this week will give us that positive outcome.

Dr. BENISHEK. Appreciate it. I yield back my time. Thank you.

Acting Chairman BUSHON. I recognize the gentleman from North Carolina, Mr. Miller.

Mr. MILLER. Thank you, Mr. Chairman. My questions are similar to Ms. Edwards. Dr. Charnley, you testified that you were not testifying on behalf of anyone. Your disclosure statement says simply that you are not testifying on behalf of anyone. I assume that means nobody is paying you for sitting here today. I haven't asked you a question yet. But our research that our staff did shows that you have, in the past, worked for the Tobacco Institute, Phillip-Morris, Covenant and Burling, a law firm that presumably—representing industry, Chlorine Chemical Council, which is part of the American Chemistry Council, American Chemistry Council, Crop Life America, which is a pesticide manufacturer, Food Industry Dioxin Working Group, coal companies, and then a long list of groups that are funded by those industry groups. You have written papers or testified about perchlorate, dioxin, mercury. You have produced papers and editorial correspondence to learned journals, challenging the idea that children should get any extra measure of protection in regulatory science.

You spoke of optics. Do you think the optics here would not have required that you tell the—this committee some of your—the work that you have done for industry?

Dr. CHARNLEY. Well, I think I stated clearly that I am a toxicology consultant. In my written testimony I state that work for—I consult to private entities, and it is, you know, you found who I work for, so, I mean, I—it is not like—that I am not disclosing that.

I would be happy to—I have a list here of a lot of the organizations that I have worked for, and I will——

Mr. MILLER. Could you provide that to the——

Dr. CHARNLEY. Absolutely.

Mr. MILLER. —and could you also provide the issues that you have worked for on them?

Dr. CHARNLEY. Sure.

Mr. MILLER. Worked on them for them.

Dr. CHARNLEY. I would be happy to.

Mr. MILLER. Okay. That would——

Dr. CHARNLEY. Most of the work I do is pro bono, by the way.

Mr. MILLER. Pro bono?

Dr. CHARNLEY. Yes.

Mr. MILLER. Okay. Well, we—actually, our able committee staff also found an invoice that you had done a couple years ago that showed your billing rate was \$325 an hour. So you do—also do some work for pay?

Dr. CHARNLEY. I do. I do——

Mr. MILLER. Okay.

Dr. CHARNLEY. —both.

Mr. MILLER. Okay. You spoke earlier of recusing yourself from a peer review panel when formaldehyde came up, which is admirable. I applaud that. If you have got an apparent conflict, then you should recuse yourself. But was that before or after you wrote a letter to—what is the name of the—the Health—Environmental Health Perspectives, that did not disclose that your—the research that you referred to in the letter was funded by the chlorine industry?

Dr. CHARNLEY. I have never failed to disclose the source of my funding in anything I have published.

Mr. MILLER. Okay. Did you write a letter to the Environmental Health Perspectives?

Dr. CHARNLEY. Yes.

Mr. MILLER. Did it have to do with chlorine?

Dr. CHARNLEY. I don't remember which one you are referring to, I am sorry——

Mr. MILLER. Okay. Do you——

Dr. CHARNLEY. —at the moment.

Mr. MILLER. You don't——

Dr. CHARNLEY. But I——

Mr. MILLER. You don't recall a controversy in which—Environmental Health Perspectives I assume is a learned journal? A peer reviewed learned journal?

Dr. CHARNLEY. It is a peer reviewed journal, yes.

Mr. MILLER. Okay. You don't recall that they changed their disclosure requirements as a result of a controversy about a letter that you wrote?

Dr. CHARNLEY. No. I recall that I said to the editor that I did not believe that I had a conflict because I no longer worked for the organization that had funded this similar work earlier. And according to the National Academy of Science's definition of conflict, which would apply to current employment, I did not have a conflict. However, I voluntarily disclosed that I had worked for such an entity in the past.

Mr. MILLER. Okay. It sounds like this whole issue is coming back to you now.

Dr. CHARNLEY. No—well, go ahead.

Mr. MILLER. Sorry. No, that is all right, I—Mr. Chairman, I have no further questions, but this remains a frustration in witnesses before this committee, who simply fill out this—and I had a discussion in the committee when our rules were adopted that substantially limited the disclosure statement—disclosure requirements, in which I was assured that if a witness had substantial economic interests, those would be disclosed. And we have seen repeatedly witnesses appear before this committee and appear and testify simply as public-spirited, disinterested citizens, and it appears their entire livelihood has come from the industry whose interests are at stake in the committee hearing. I would certainly hope that we could do better in the future.

Acting Chairman BUSHON. Thank you. I will take that up with the full committee Chairman. Thanks for your comments. I will now recognize myself for some questions, and assure the panel that I won't spend my entire time trying to defame all of your character.

First I want to make a few brief comments about the—what I am hearing today. As a new member of Congress, I think the American people, if they were hearing this hearing today about EPA, and about the assessment they are making on chemicals, the American people would feel they are not getting a good bang for their buck. Just remind everyone that the budget of the EPA in 2008 was \$7.6 billion. The budget was 10.3 billion in 2010. And, believe it or not, the EPA received \$7.2 billion in stimulus money, and yet we are at a hearing today discussing the fact that we have the inability to properly assess chemicals at the EPA, and that is not my opinion. Let me read from—the GAO testified before the Subcommittee that—in 2009 that EPA has not been able to complete timely credible chemical assessments or decrease its backlog of 70, as of 2008, ongoing assessments, even though they received 7—well, I think 7—around 7.2 billion in stimulus money.

And it says further, because the EPA staff time was dedicated to completing assessments in the backlog, EPA's ability to both keep the more than 540 existing assessments up to date and initiate new assessments was limited. So I think, from my perspective, this calls into question a lot of the rules that the EPA is currently putting out across the economic spectrum that is hurting our economy. And it is becoming pretty clear to me we don't have solid scientific evidence to back that up. So what I want to do is direct my questions, first to Congressman Dooley, about a couple of areas. Do you see that the assessment ability of IRIS, as being adequate? And I think you have stated before that you don't think it is. And based on that, do you see that there are longstanding economic impacts of their decision-making process, based on this information, that is hurting our job creation in our country?

Mr. DOOLEY. First off is that the American Chemistry Council is very supportive of the suggestions that the NAS made to EPA for reforms. You know, we are encouraged that the EPA has indicated that they are going to try to enact some of those reforms. It is not mutually exclusive to have an IRIS risk assessment that is being operated in a manner that is consistent with what NAS has rec-

commended and be a more efficient, and result in quicker IRIS assessments being done. And there shouldn't be any disagreement among any of us on that issue.

When I was in Congress, I represented a district in the central valley of California. It was the fifth lowest per capita GDP district in the nation, out of 435. And the actions that IRIS could take to establish reference doses that are below those that pose any public health safety impact at expected levels of exposure, whether it is formaldehyde or dioxin, or whether it is arsenic, and that goes below what are background levels existing naturally, is that that has not only public health impacts, but it has public welfare impacts.

If you require a lot of the low income communities in my district to comply with what is now a new arsenic standard that goes below what is naturally occurring, is that they have to allocate resources to water treatment systems that then aren't available for public health or education or, other public benefits, just as I said with dioxin. It also has an impact on private sector investments. If we have to divert revenues to achieve a higher level of remediation, or change processes that go to achieve an IRIS assessment that is below background levels, you are taking capital that could otherwise be invested in a new manufacturing capacity, creating jobs, that is going for a use that has very little benefit, and very little public health benefit.

Acting Chairman BUSHON. I think the answer is yes, it is having a significant impact, and at this time I will yield the rest of my time. And recognize the gentleman from Michigan, Mr. Clarke.

Mr. CLARKE. Thank you, Mr. Chair. In addition to IRIS, which is located in the EPA, there are other programs that conduct assessments of chemical risks that are located in other agencies and departments. And this question's to anyone here. To what degree have these assessments provided conflicting guidance or conclusions, and to what degree have these different programs provided—really been duplicating work? And if you found any conflicts or duplication, what proposals do you have to better coordinate and reduce the likelihood of conflicts and reduce the cause of duplication?

Ms. STEINZOR. If I could respond to that? IRIS is the premiere international source of reference dose information, which is the level below which exposure is acceptable and above which exposure is not acceptable. So it really measures whether—if we fed you dioxin on a spoon, what the level would be that would cause problems. As has been said repeatedly here, it is not a risk assessment process. It doesn't make a determination. IRIS itself is a scientific database that doesn't make a determination about what to do about the risk. It simply talks about what the reference dose is. It receives 2,000 visits a day on the Internet from all over the world. That is a pretty high number for a database that is this technical. And, if anything, it needs to be bigger, better and stronger, not abolished, not paralyzed, because without it people would really not know what a toxicological profile—what the reference dose was for chemicals. So it really is unique, and it provides a tremendous service, I would say.

Mr. DOOLEY. Maybe, as Ms. Steinzor mentioned, the IRIS reference dose is a standard which is not acceptable. And so I go back,

and I will use the formaldehyde example, where you had the World Health Organization said the breath that you exhale has eight parts per billion. IRIS said a reference dose of .0008 parts per billion. You can also use the example of arsenic, where you have a little bit of a difference in standards internally, where you had an IRIS a risk assessment level of 1.4 parts per billion. But then you also have, in the safe drinking water standard, 10 parts per billion for drinking water. So there is some inconsistencies among various organizations there.

So I think that is where we made a suggestion from ACC that there ought to be a role for OMB to play in this whole re-evaluation of the risk assessment. And what we are driving at here is because you have got multiple agencies—you have got FDA that is involved with some chemicals, whether it is food contact notification or assisting it, you have the Agency For Toxic Substance And Disease Registry, you have the National Toxicology Program, that does the report on carcinogens, you have EPA and IRIS—is that there needs to be a quarterback. That someone should not make determinations and evaluate necessarily the risk assessment, but that there is a common scientific process being utilized that is ensuring that we are incorporating the best laboratory practices, and that we are using the best weight of evidence practices, to reach conclusions. And that ought to be consistent across all these multiple agencies. And that is where we suggest that there is an appropriate role for OMB to play, to ensure that you have that consistency so that you don't have disparity and conclusions in action levels across various organizations that are maybe addressing the same chemical.

Ms. STEINZOR. Can I just add one point? My son, who is 20, is sitting behind me, and one of the most distressing things I have heard today is that he had formaldehyde in his body and exhales it at levels that are much higher than the reference dose set by the EPA database. That didn't happen because he is walking through a natural paradise on the Chesapeake Bay, although I wish that were true. It is because the air is polluted. We live in a non-attainment area that is awash in toxics and all sorts of other problems, and that is why that has happened. I also want to just say for the record there are two scientists, two, who work at OIRA. So making them the quarterback of anything would be a strange football game indeed.

Acting Chairman BUSHON. The gentleman's time has—

Mr. CLARKE. If I can just respond to the formaldehyde?

Acting Chairman BUSHON. The gentleman's time has expired. We will get—we will try to get back to you.

Mr. CLARKE. Thanks.

Acting Chairman BUSHON. I would like to recognize the gentleman from Maryland, Mr. Sarbanes.

Mr. SARBANES. Thank you, Mr. Chairman. Thank the panel. Congressman Dooley, I wanted to—you said a lot of nice things about the National Academy of Sciences, and I guess that is the basis for your proposal that they come in and review the risk assessments that IRIS is performing for some period of time. And you have also responded positively to changes that the EPA has said they are going to make in response to the National Academy of Science rec-

ommendations and so forth. On that basis, I assume you have pretty good feelings about this silver book, because that is a product of the National Academy of Science on the very topic that we are discussing here today, so I wanted to get your reactions to whether this is a constructive resource.

Mr. DOOLEY. We think it is a very constructive resource. It is not that we agree with every element in it, but we think that it really does set a road map that has a lot that we can all learn from and incorporate into our government processes of assessing safety of chemicals.

Mr. SARBANES. I haven't read it from front to back. Actually, I have just read the back, as you may have seen. But from what I understand, I am assuming it is proposing recommendations that would allow the EPA and IRIS to operate in a way that would not require a kind of constant follow up assessment by NAS with respect to each specific chemical or toxic substance that was being assessed. And I am nervous about your recommendation on that, because I am worried that you are proposing adding more steps into a process, with the potential to kind of just drag the whole thing down and further contribute to the delay that is so frustrating for so many people, particularly when it comes to the issue of the worst of the worst.

I mean, I keep hearing this phrase, I heard it in the other committee I served on in the last term, when we were looking at the Toxic Substances Control Act. I think, actually, you testified—some of those hearings. The worst, the worst. We can't seem to get even the worst of the worst—the place where we don't have to fear those substances anymore. And a lot of it has to do with this kind of, well, we need another study. We need to get the OMB in here as a quarterback, you know, OIRA and so forth and so on. We need to get moving on this stuff. And I think what this is attempting to do is propose how you can get the process and the framework that EPA uses to a place where it is working pretty well, and I am worried about that sort of getting off track.

And then, Dr. Charnley, in the time I had, you had talked about your own view, that the changes proposed this week are promising ones, and I think has—have also said that you regard the National Academy of Science recommendations as helpful and constructive. I don't see how that jives with your suggestion that we should “start over” with the process that we currently have. I think that would be a mistake. Maybe you can clarify how you reconcile those two perspectives.

Dr. CHARNLEY. Sure. I did not mean stop IRIS. I did not mean disband IRIS. I meant that past efforts to modify the process have not produced meaningful improvements, apparently, because the Academy keeps coming back and making the same recommendations they have made for years. And for that reason I think that, in order to implement the changes recommended in Chapter 7 of the formaldehyde report, that implementation would itself benefit from guidance from the National Academy of Sciences, from a group of unbiased experts who can—who have been thinking about this problem for a long time and can provide helpful guidance.

Mr. SARBANES. Well, I think—thank you. I think that guidance is there. I think it is constructive, and I think the EPA is ready

to move forward and keep this process of improving on a, you know, on a positive track. Let us not get off that track. Let us keep this process moving. With that, I yield back, Mr. Chairman.

Acting Chairman BUSHON. Thank you. At this point I would like to ask unanimous consent to add a number of documents to the record that have already been shared with the minority, and I understand they wish to add the records as well. Hearing no objection, so ordered.

[The information appears in Appendix II:]

Acting Chairman BUSHON. I would like to thank the witnesses for their valuable testimony and the Members for their questions. The Members of the Subcommittee may have additional questions for the witnesses, and we will ask you to respond to those in writing. The record will remain open for two weeks for additional comments from Members. The witnesses are excused, and the hearing is now adjourned.

[Whereupon, at 12:24 p.m., the Subcommittee was adjourned.]





## Appendix I:

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### ANSWERS TO POST-HEARING QUESTIONS

ANSWERS TO POST-HEARING QUESTIONS

*Responses by The Honorable Paul Anastas, Assistant Administrator,  
Office of Research and Development, U.S. Environmental Protection Agency*

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT  
HOUSE COMMITTEE ON SCIENCE, SPACE AND TECHNOLOGY

**Questions for the Record**  
**“EPA’s IRIS Program: Evaluating the Science and Process  
Behind Chemical Risk Assessment”**

Thursday, July 14, 2011  
10:00 a.m. – 12:00 p.m.  
2318 Rayburn House Office Building

**Questions for Dr. Paul Anastas,  
Assistant Administrator, Office of Research and Development,  
U.S. Environmental Protection Agency**

**Questions Submitted by Dr. Paul Broun, Chairman**

- 1. The Center for Progressive Reform has suggested cutting back or curtailing peer review by limiting the use of external peer reviews.**
  - a. Do you believe EPA’s current peer review processes are sufficient, too burdensome, or ineffective?**

EPA strongly believes that its current peer review processes are sufficient and effective. Independent, open-to-the public, scientific peer review is a cornerstone of the IRIS process and is the foundation upon which IRIS is built. IRIS peer review standards are among the most rigorous in the federal government and the broader scientific community. Every draft IRIS assessment is subject to independent, external scientific peer review. For most assessments, the peer review is organized independently by a contractor with many years of experience in assembling expert technical review panels. For a smaller group of assessments, EPA’s Science Advisory Board conducts the peer review. On rare occasions, EPA may choose to send a draft IRIS assessment to the NAS for review. Each of these peer review mechanisms is effective in providing an abundance of constructive expert feedback on how to improve draft assessments.

- 2. IRIS was developed to coordinate assessment values throughout EPA Line Offices.**
  - a. Is this still the case, or do Line Offices ever use assessment values different from IRIS?**

IRIS was developed to coordinate assessment values for use throughout EPA, and this is still the case. IRIS coordinates assessment values that may be used throughout EPA. The IRIS program develops health assessments and toxicity values in concert with scientists from across EPA’s programs and regions. This robust development process includes two

periods for internal Agency review, step 2 and step 6a ([http://www.epa.gov/iris/pdfs/IRIS\\_PROCESS\\_FLOW\\_CHART.PDF](http://www.epa.gov/iris/pdfs/IRIS_PROCESS_FLOW_CHART.PDF)). The IRIS Program is responsible for developing the health assessments and adding the toxicity values to the IRIS database. However, some EPA program offices may not be required to use IRIS values and may, in some cases, use other assessment values. Some program offices have published information on how they choose toxicity values for use in decision-making. For example, EPA's Office of Solid Waste and Emergency Response issued a directive outlining a hierarchy of toxicity values to be used in making decisions at Superfund sites (<http://www.epa.gov/oswer/riskassessment/pdf/hhmemo.pdf>). This directive states that IRIS is the preferred choice for toxicity values, and the directive points to other sources of toxicity values in the event an IRIS value is not available for a given chemical of concern. In some cases, such as when making decisions at CERCLA sites, EPA may be required to use a state legally enforceable standard if one exists and it is more stringent than a National level. In these cases, EPA must use an Applicable or Relevant and Appropriate Requirements (ARAR) level in making site decisions, and it is possible these ARARs may have been developed using a toxicity value other than IRIS. Additionally, the IRIS Program is aware that EPA's Office of Chemical Safety and Pollution Prevention performs health assessment work. EPA's Office of Pesticide Programs (OPP) is the lead for evaluating and developing pesticide risk assessments as part of their registration/registration review processes. However, IRIS evaluates some cancelled pesticides when they are of significant interest to EPA programs as pollutants (e.g., when present in hazardous waste sites). In addition, OPP sometimes uses IRIS information in its evaluation of certain pesticides, e.g., pesticide inert ingredients, certain antimicrobial pesticides.

**b. Do Line Offices have to concur with IRIS determinations?**

No, individual Program Offices are not required to concur with IRIS determinations. IRIS hazard assessments are developed with input from scientists from across EPA's programs and regions, and some IRIS assessments are developed collaboratively with a certain program office or region. The IRIS process provides for two periods of internal Agency review. During these steps, scientists from EPA's programs and regions may review and provide comments on the draft IRIS assessment to help identify scientific issues and determine the scope of peer review needed, as well as the required scientific disciplines of the peer review committee. When program offices and regions provide comments, the IRIS programs carefully considers them and works with the commenters to discuss the issues they raised.

**c. If Line Offices are using toxicity levels that differ from IRIS levels, please provide a list of those chemicals, the Line Offices that they are using, as well as the level listed in the IRIS database**

The IRIS Program is responsible for developing IRIS health assessments and providing the associated toxicity values in the IRIS database. EPA's program and regional offices determine which toxicity values to use in their work. While we know that IRIS values are widely used, the IRIS Program does not track what toxicity values the Program Offices use in every aspect of their work.

3. **With respect to scientific peer review, currently, it appears it is the IRIS office that a) writes the draft IRIS assessment; b) evaluates the public comments, peer review findings and recommendations; c) decides what to include, what to exclude, what changes to make and what changes not to make; and d) decides whether or not such changes are accurate and adequate.**
- a. **If this is indeed the current process, how does the EPA ensure unbiased objectivity in the assessment process? What office or official in the EPA checks to be sure that a revised IRIS assessment has accurately and adequately addressed public comments and peer review findings and recommendations? In sum, who is the "honest broker" in this process?**

As discussed in response to question one, EPA uses an open, public process coupled with rigorous independent scientific peer review to ensure the scientific quality and transparency of its IRIS assessments.

EPA develops IRIS assessments using an open and scientifically rigorous process that provides multiple opportunities for federal agency scientists and members of the public (including industry, academia and NGOs) to participate. This participation can take multiple forms including: a) presenting scientific data and/or other materials at public listening sessions and peer review meetings; b) providing written comments and other documents to EPA; c) participating in scientific workshops related to specific IRIS assessments, (recent examples includes dioxin and phthalates); and, d) commenting on initial drafts of assessments both before and following external peer review. Reviewers also offer specific peer review questions. The assessments are reviewed, discussed and approved within EPA at multiple levels including senior managers. Because EPA engages the scientific community, as it always does, at all stages of the process, the scientific community is the "honest broker".

One way that EPA ensures objectivity of our peer reviews is to have the program reviewed by external experts. For example, over the past several years, the IRIS program has been extensively reviewed by EPA's Board of Scientific Counselors (BOSC). BOSC stated that IRIS assessments are among the most heavily peer reviewed documents produced by scientists anywhere, and the comprehensiveness, transparency and consistency of the IRIS approach have made it the internationally recognized standard in hazard characterization (<http://www.epa.gov/osp/bosc/pdf/hhra0804rpt.pdf> and <http://www.epa.gov/osp/bosc/pdf/hhramc1008rpt.pdf>).

4. **In the recent Academies' review of the IRIS formaldehyde assessment, NAS expressed concerns about the methods and criteria EPA used for selecting and critically evaluating epidemiological studies.**

**a. Does EPA adhere to a clear set of criteria in determining which studies should be relied upon in assessing potential risk?**

EPA risk assessment guidelines provide criteria for evaluating studies, and the IRIS program follows these criteria in developing health assessments. To more clearly communicate these criteria, and in response to the NAS comments, the IRIS Program is developing a preamble that will be included in each future assessment that clearly articulates the criteria outlined in EPA's guidance documents that should be used in determining which studies should be relied upon. Many of these guidance documents are focused on specific endpoints. They can be found at <http://www.epa.gov/iris/backgrd.html>. The NRC, in its review report in Appendix B, provides descriptions of some of the existing EPA guidance documents on weighing evidence. Additionally, EPA scientists have academic training and work experience in how to evaluate study quality and statistical issues in determining if individual studies are well conducted.

The NRC review of EPA's draft formaldehyde assessment suggested that EPA needed to ensure standardization of review and evaluation approaches and also establish standard protocols for evidence identification. In response, EPA is streamlining IRIS assessment documents and more fully documenting the approach for assembling and evaluating the range of scientific data. EPA is also implementing a more uniform approach to the evaluation of the strengths and weaknesses of critical studies to increase the clarity of the rationale for selecting the studies used to calculate toxicity values. Lastly, EPA is increasing the use of evidence tables that summarize the factual details of pertinent studies for each health hazard and developing standardized language to describe study strengths and limitations. This is an evolving area and one in which EPA will continue to improve.

**b. Are these criteria consistent across all studies?**

As indicated in question 4a, EPA risk assessment guidelines provide some criteria for evaluating studies, and the IRIS program follows these criteria in developing health assessments. Many EPA guidance documents exist for different endpoints and, therefore, criteria are variable in different EPA guidance documents. As studies of different types of health endpoints have distinct attributes and standard practices, some of the different health endpoints have their own specific guidelines for evaluation. EPA has developed guidelines for cancer effects as well as distinct guidelines for specific types of noncancer effects.

To more clearly communicate these criteria, and in response to the NAS comments, the IRIS Program is developing a preamble that will be used in each future assessment that will clearly articulate how the criteria are applied within the IRIS Program. For example, the EPA guidelines for neurotoxicity, reproductive toxicity, and developmental toxicity risk assessment discuss which types of outcomes are considered adverse and provide guidance on when the available evidence may be considered "sufficient" in defining the minimum evidence necessary to characterize the hazard and conduct a dose-response

analysis (EPA, 1998; EPA 1996; EPA 1991). Similarly, the EPA RfC methods document includes an appendix which presents criteria to define adverse respiratory health effects observed in epidemiologic studies (EPA 1994).

**c. Are the criteria clearly articulated in the IRIS assessment?**

The NAS expressed specific comments regarding the criteria for evaluating the noncancer health effects. All of the EPA guidelines described above informed how EPA scientists characterized the overall Weight of Evidence (WOE) for noncancer health effects in Section 4.4 of the assessment. Because EPA has articulated recommendations for many of these steps in general guidance documents or reviews, EPA's draft formaldehyde assessment did not include a section articulating the criteria for all of the above steps.

As EPA moves forward to revise the IRIS formaldehyde assessment, it will ensure that the criteria to which EPA adheres are clearly articulated and consistently applied with specific differences as appropriate for different types of health endpoints.

- 5. In the NAS Review of formaldehyde, NAS notes that EPA did not provide documentation on the methods and criteria for assessing the weight of evidence, i.e., methods EPA would use to weigh multiple studies or even different types of evidence in reaching a conclusion.**
  - a. Since weight of evidence is such a critical element of an IRIS assessment, should the IRIS Program first, adopt such guidance, and then, apply this consistently to all pending IRIS assessments in order to ensure the best available scientific methods are being used?**

The NAS panel addressed this issue with specific reference to the formaldehyde assessment, when it wrote, "Although the committee suggests addressing some of the fundamental aspects of the approach to generating the draft assessment later in this chapter, it is not recommending that the assessment for formaldehyde await the possible development of a revised approach." [p. 151-152 final publication hard copy, p. 112 in the prepublication pdf version]. NAS further states: "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." [p. 152 final publication hard copy, p. 113 in the prepublication pdf version]. Therefore, EPA will continue ongoing work on assessments as it develops and refines new guidance on how to more clearly document its methods and criteria for assessing the weight of the evidence. In addition in response to the NAS, EPA will improve the clarity regarding the criteria used to exclude, include and advance studies for derivation of RfCs, RfDs, and cancer risk estimates. EPA has already committed to more fully document its approach for evaluating the range of scientific data and more clearly describe why studies and

endpoints were chosen for inclusion or ruled out. EPA will make appropriate improvements based on the NRC recommendations and develop better ways to describe how these judgments are made.

**b. Please describe EPA's current weight of evidence approach in evaluating evidence in the IRIS process.**

As noted earlier in question 4b, EPA has an extensive set of peer-reviewed guidelines that address multiple aspects of hazard and dose-response assessment including guidance on specific kinds of health endpoints. These provide EPA with some guidance on how to weigh a complex set of studies and data for particular endpoints. EPA's current weight of the evidence approach in evaluating evidence in the IRIS process includes searching for relevant peer-reviewed studies, evaluating the quality of the studies for the purpose of hazard assessment, examining all credible studies whether they find associations or effects or not, and evaluating what conclusions are consistent with those studies.

- 6. Considerable research by academic investigators and others over the last 20 years—much of it sponsored by EPA and other federal agencies – has been conducted and published on how chemicals cause toxicity at the molecular and cellular level and the relevance of these mechanisms to human health risks.**
- a. Should IRIS assessments make use of the chemical-specific datasets and biological effects- in other words, knowledge and data on mode of action and human relevance – in IRIS assessments?**

Yes. When developing IRIS assessments, EPA conducts a full literature review and makes use of any relevant data that is available in the peer-reviewed scientific literature. Additionally EPA asks the public to contribute data and information on specific chemicals. Data on mode of action and human relevance for cancer and noncancer effects, as well as any other pertinent data on a chemical, are part of the information that is considered in characterizing the hazard and dose-response assessment.

- 7. Can chemicals cause cancer by different mechanisms? Should non-genotoxic chemicals be assessed using a threshold approach?**

Yes, chemicals can cause cancer by different mechanisms. As stated on p.1-10 of EPA's Guidelines for Carcinogen Risk Assessment (2005), "there are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression." The Guidelines state in Section 3-3 that "Threshold, or non-linear, extrapolation is used when there is sufficient data to establish a mode of action and conclude that it is not linear at



low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses. Non-threshold, or linear, extrapolation should be used when there is mode of action data to indicate that the dose-response curve is expected to have a linear component close to the point of departure (e.g., mutagenic activity or key precursor events in the carcinogenic process expected at background or human exposure doses). Linear extrapolation should also be used in the absence of information to establish a mode of action. Both linear and non-linear extrapolation may be used when multiple modes of action are operative."

As further stated on p. 1-10 of the Guidelines, "Elucidation of a mode of action for a particular cancer response in animal or humans is a data-rich determination. Significant information should be developed to ensure that a scientifically justifiable mode of action underlies the process leading to cancer at a given site. In the absence of sufficiently, scientifically justifiable mode of action information, EPA generally takes public health-protective, default positions regarding the interpretation of toxicologic and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity." The Guidelines also state on page 1-8 that "When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency may decide to give greater weight to one set of procedures than another in a specific assessment or management decision."

EPA interprets "significant biological support" as having enough scientific evidence about the mode of action to identify key events and to have reasonable confidence in the sequence of events and how they relate to the development of tumors. Therefore, it would not be appropriate to make an assumption that non-genotoxic chemicals should be assessed using a threshold approach without knowledge of the mode of action at low dose.

**a. How many carcinogens has EPA assessed in the IRIS program over the last 10 years?**

Since 2000, the IRIS program has evaluated 46 chemicals that had human or animal data indicating a positive cancer response. Not all these assessments are finalized. The majority of these chemicals have little or no data available for informing the mode of action and the dose-response at low doses.

**b. Of these, how many has the IRIS program concluded- in either draft or final assessments- that the data supports a threshold, non-linear approach for estimating human risks?**

Three final IRIS health assessments (perchlorate, chloroform and EGBE) conclude that the data support a threshold, non-linear approach for evaluating carcinogenicity.

For perchlorate, a determination was *not likely to be carcinogenic to humans*. In particular, EPA stated that it is not likely to pose a risk of thyroid cancer in humans, at least at doses below those necessary to alter thyroid hormone homeostasis, based on the hormonally-mediated mode of action in rodent studies and species differences in thyroid function (U.S. EPA, 2005; <http://www.epa.gov/iris/subst/1007.htm#carc>).

For chloroform, the available data indicate that it is *likely to be carcinogenic to humans* under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues, and that it is *not likely to be carcinogenic to humans* under exposure conditions that do not cause cytotoxicity and cell regeneration (U.S. EPA, 2001; <http://www.epa.gov/iris/subst/0025.htm#carc>).

For EGBE (ethylene glycol butyl ether), the available data indicate that carcinogenic effects are not likely to occur in humans in the absence of critical noncancer effects, including hepatic hemosiderin staining and irritant effects at the portal of entry, and that EGBE is *not likely to be carcinogenic to humans* exposed at levels at or below the RfC and RfD values established in the assessment (U.S. EPA, 2010; <http://www.epa.gov/iris/subst/0500.htm>).

- c. **And for how many has the IRIS program concluded that the highly conservative, default linear NO THRESHOLD approach should be used in assessing potential health risks?**

As stated on page 1-10 of the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), “In the absence of sufficiently, scientifically justifiable mode of action information, EPA generally takes public health-protective, default positions regarding the interpretation of toxicologic and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity.”

A default low-dose linear approach has been utilized (in some cases in draft assessments) to estimate the cancer potency of 34 of the 46 chemicals discussed above, for which little or no mode of action information is available.

A low-dose linear extrapolation approach has been used for estimating the cancer potency for nine of the 46 chemicals due to a determination of a mutagenic mode of action.

8. **To what extent will the IRIS assessment on formaldehyde be influenced by HHS’ 12<sup>th</sup> Report on Carcinogens?**

- a. **How do you respond to the following quote from a June 24, 2011, Inside EPA.com story: “I think that the NTP report pretty much sealed the deal on formaldehyde and makes the IRIS classification a sideshow,” a source told EOA last week. “After**

**all, once NTP speaks, it is pretty hard to unring the bells,” which likely “emboldens” the agency on its formaldehyde assessment.”<sup>1</sup>**

EPA’s IRIS Program and NTP’s Report on Carcinogens Program are separate and distinct programs that serve two different purposes. NTP’s Report on Carcinogens (RoC) is a congressionally mandated, science-based, public health report that identifies agents, substances, mixtures, or exposures in our environment that may potentially put people in the United States at increased risk for cancer. The National Toxicology Program (NTP) prepares the NTP RoC on behalf of the Secretary, Department of Health and Human Services. For each listed substance, using criteria specific to the NTP, the NTP RoC contains a substance profile which provides information on: (1) cancer studies that support the listing—including those in humans, animals and on possible mechanisms of action; (2) potential sources of exposure to humans; and (3) current Federal regulations to limit exposures.

In an addendum to their 12<sup>th</sup> Report on Carcinogens (RoC), the NTP discusses the draft IRIS assessment for formaldehyde and the review of that draft assessment by the National Academy of Sciences (NAS). The NTP states that “the RoC evaluation involved a multistep comprehensive assessment of the literature, and resulted in a narrative justification for the NTP’s conclusions that was developed independently from the EPA IRIS assessment.”

The IRIS Program provides science-based health assessments for a variety of chemicals. EPA will look closely at the National Research Council’s report reviewing the draft IRIS formaldehyde assessment, all the public comments on its external peer review draft assessment of formaldehyde and the advice it gets during the review process as it revises the assessment. EPA will consider all the input it receives during this process and will reach its best judgment based on the available scientific data and understanding.

**9. To what extent is there overlap of the substances assessed in the IRIS Program with those evaluated in the ATSDR (Agency for Toxic Substances & Disease Registry) Toxicology Profile Program.**

- a. In most cases, it appears the guidance provided on chemicals in both the IRIS database and ATSDR differ. If this is true, why do they differ?**
- b. When there are differences, how should a user of this information interpret the different information?**

EPA’s IRIS Program and ATSDR’s Toxicological Profiles Program are separate and distinct programs with two different purposes. However, EPA works closely with

<sup>1</sup> The Inside Story, “Talking up Formaldehyde Listing,” InsideEPA.com, June 24, 2011, available at: <http://insideepa.com/201106242368190/EPA-Blog/The-Inside-Story/talking-up-formaldehyde-listing/menu-id-97.html>

ATSDR on some assessments to ensure our work in developing human health assessments is complementary and not duplicative and to share data and information on specific assessments. Through a Memorandum of Understanding, EPA works with ATSDR to share data and discuss specific chemical assessments.

ATSDR and the IRIS program are similar in that they both develop health assessments for noncancer health effects. However, they are different in that ATSDR does not develop cancer assessments, whereas IRIS does. Additionally, ATSDR derives subchronic and acute toxicity values, whereas IRIS typically does not.

ATSDR is congressionally mandated to provide toxicological profiles for hazardous substances commonly found at National Priorities List (NPL) sites. In contrast, the IRIS program provides health assessments for a variety of chemicals, some of which are found at NPL sites, but some of which are not. ATSDR is also charged with assessing the presence and nature of health hazards to communities living near Superfund sites, and they are authorized to conduct public health assessments at these sites upon request. ATSDR's Toxicological Profiles derive Minimal Risk Levels (MRLs) for noncancer health effects. These are developed using science based practices similar to that of EPA's Reference Dose and Reference Concentration for noncancer endpoints. Per ATSDR's website, "these substance specific estimates, which are intended to serve as screening levels only, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. **It is important to note that MRLs are not intended to define clean up or action levels for ATSDR or other Agencies.**" The levels are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites<sup>2</sup> Per EPA's Office of Solid Waste and Emergency Response directive outlining a hierarchy of toxicity values to be used in making decisions at Superfund sites (<http://www.epa.gov/oswer/riskassessment/pdf/hhmemo.pdf>), IRIS is the preferred choice for toxicity values, but other values that meet certain criteria (including ATSDR MRLs) may be used in the absence of an IRIS value.

EPA's IRIS is a human health assessment program that evaluates quantitative and qualitative risk information on effects that may result from exposure to specific chemical substances found in the environment. Through the IRIS Program, EPA provides the science-based human health assessments to support the Agency's regulatory activities as well as other stakeholders and users. IRIS health assessments provide toxicity values for both cancer and noncancer health effects where data are available as well as qualitative estimates of human carcinogenic potential. This is in contrast to ATSDR where only noncancer values are derived (for chronic, subchronic, and acute health effects). The IRIS database, like the ATSDR database, contains information that can be used to support the first two steps (hazard identification and dose-response evaluation) of the risk assessment process. Combined with specific exposure information, government and private entities use IRIS and/or ATSDR values to help characterize public health risks of chemical

<sup>2</sup> <http://www.atsdr.cdc.gov/mrls/index.asp>

substances in a site-specific situation and thereby support risk management decisions designed to protect public health.

Within EPA, the Office of Solid Waste and Emergency Response has outlined a hierarchy of toxicity values to be used in making decisions at Superfund sites (<http://www.epa.gov/oswer/riskassessment/pdf/hhmemo.pdf>). This directive indicates that IRIS is the preferred choice of toxicity values for use in Superfund risk assessment activities, and it points to other sources of toxicity values, including those developed by ATSDR, that one can use in the event an IRIS value is not available for a given chemical of concern.

If users of IRIS have questions about specific IRIS assessments, they should contact the IRIS hotline at [http://www.epa.gov/iris/contact\\_hotline.htm](http://www.epa.gov/iris/contact_hotline.htm).

**10. Some questions have been raised about the experience of scientists employed by the EPA to work on IRIS.**

- a. Could you tell us roughly how many scientists work on the IRIS assessments and of those, how many are board-certified Toxicologists, how many are board-certified Epidemiologists, and how many are statisticians?**

There are 60 scientists currently assigned to work on IRIS health assessments. Within this group there are 17 statisticians and 17 board-certified toxicologists (DABT, or Diplomate of the American Board of Toxicology). There are currently 12 epidemiologists working on IRIS assessments, however, there is currently no board certification for epidemiologists. Additionally, there is 14 staff with various other essential scientific training necessary to complete IRIS health assessments (e.g., biologists, environmental health scientists, engineers, etc.)

Among the group of toxicologists working on IRIS, there is a well-balanced mix of sub-specialties which allows us to address specific types of issues as needed (e.g., neurotoxicity, developmental toxicity, etc.). IRIS scientists have demonstrated leadership within the scientific community through publications and leadership in professional societies. Over the past several years, the IRIS program has been extensively reviewed by EPA's Board of Scientific Counselors (BOSC). In their reviews, the BOSC has emphasized that the Human Health Risk Assessment Research Program (HHRA, of which IRIS is a core part) is "internationally recognized as a leader in risk assessment methods development and implementation" and that HHRA scientists "have broad-based expertise including environmental engineering, environmental health science, risk assessment, epidemiology, geology, microbiology, physiology, statistics, toxicology, and management." The BOSC, in 2008, noted that "HHRA scientists have a strong record of scientific service on journal editorial boards, in professional societies, and as adjunct faculty at universities, and have won numerous awards from EPA and external

organizations.” The BOSC also recognized that “the HHRA program has been viewed as a major source of core expertise for EPA.” Additionally, they noted that “Taken as a whole, the evidence speaks to a community of highly trained and productive scientists, many of whom are leaders in their field, who are providing leadership to the United States and international governments as well as scientific communities and are engaged in risk assessment science and in solving important risk assessment problems.”<sup>3</sup>

**b. Are these numbers sufficient?**

Over the last several years, the current staffing of IRIS has allowed us to complete approximately 10 final assessments per year. Since many of the major assessments, such as trichloroethylene, that have been in development over the last years are coming to completion, and new assessments are under development using the streamlined May 2009 IRIS process, it is anticipated that the staff will be sufficient.

**c. Are the proportions appropriate?**

The current mix of toxicologists, epidemiologists, statisticians and other scientists represents an appropriate balance for completing IRIS health assessments. As noted above, the BOSC has stated that “the HHRA Program is internationally recognized as a leader in risk assessment methods development and implementation.” They have additionally noted that “IRIS assessments are considered to be of the highest quality and reliability” and that HHRA scientists “have broad-based expertise including environmental engineering, environmental health science, risk assessment, epidemiology, geology, microbiology, physiology, statistics, toxicology, and management.” The BOSC noted that “HHRA scientists have a strong record of scientific service on journal editorial boards, in professional societies, and as adjunct faculty at universities, and have won numerous awards from EPA and external organizations.” The BOSC also recognized that “the HHRA program has been viewed as a major source of core expertise for EPA.”<sup>4</sup>

**11. On July 12, you were involved in a press conferencing espousing plans to improve IRIS in response to recommendations received on April 8, 2011, from the National Academies of Science.**

- a. Will the new plans apply to any of the assessments scheduled to come out this year?**
- b. If not, why?**

<sup>3</sup> Board of Scientific Counselors. 2008. Human Health Risk Assessment Subcommittee Program Review Report. <http://www.epa.gov/osp/bosc/pdf/hhra0804rpt.pdf>

<sup>4</sup> Board of Scientific Counselors. 2008. Human Health Risk Assessment Subcommittee Program Review Report. <http://www.epa.gov/osp/bosc/pdf/hhra0804rpt.pdf>

**c. When *can* we expect IRIS assessments that incorporate these new and improved actions?**

EPA is making changes to all of its IRIS assessments following the NAS's recommendations. Documents at the later stages of assessment are being considerably streamlined and reviewed for clarity. Documents not yet begun will incorporate all of the NAS recommendations. For example, EPA recently posted on its IRIS website the final Toxicological Review for Urea (<http://www.epa.gov/iris/toxreviews/1022tr.pdf>). Before completing and posting the assessment, EPA rigorously edited the document to improve the clarity and readability of the document and to reduce the text volume and address redundancies and inconsistencies.

**12. You also mentioned in the July 12 conference call that the message EPA received from the Academies' April report is a need for more "accessibility and transparency". In that spirit, will you pledge to make available the internal EPA review comments from the line offices that currently are unavailable to the public?**

Until EPA has worked through its internal deliberations, there is not an official draft that can be released. Therefore, at this time, the draft – as well as Agency comments on the draft – is considered internal and deliberative. Disclosure of such pre-decisional and deliberative information could cause public confusion about the bases and statements in the draft that is released for public comment and may inhibit staff to be less candid if they believed their comments would be prematurely released.

**13. EPA's July 12 IRIS Progress report states that "for draft assessments that are in later stages of development, EPA will implement the recommendations as feasible without taking the assessments backwards to earlier steps of the process."**

- a. Does this statement mean that despite your commitment to implementing each and every recommendation of the NAS, EPA intends to complete certain ongoing IRIS assessments addressing those recommendations?**
- b. If so, won't this just perpetuate issuance of flawed IRIS assessments that fall short of meeting the standards for the data analyses and casual determinations laid out by the NAS?**

EPA is making changes to all of its IRIS assessments following the NAS's recommendations. Documents at the later stages of assessment are being considerably streamlined and reviewed for clarity. Documents not yet begun will incorporate all of the NAS recommendations. For example, EPA recently posted on its IRIS website the final Toxicological Review for Urea (<http://www.epa.gov/iris/toxreviews/1022tr.pdf>). Before completing and posting the assessment, EPA rigorously edited the document to improve the clarity and readability of the document and to reduce the text volume and address redundancies and inconsistencies.

- 14. Please identify each chemical substance now in some stage of IRIS assessment process that EPA does not intend to subject to full set of IRIS reforms called for by the NAS.**
- a. For each, what steps will EPA take to ensure that the methodological flaws identified by NAS do not undermine the IRIS assessment?**
  - b. Please identify the precise criteria you will employ to determine which IRIS assessments will in fact receive the full benefit of these IRIS reforms and which will not.**

EPA's overriding goal is to continually improve IRIS assessments. We consider the recommendations from the NAS to be helpful, and we will fully implement them. Regarding the recommendations from the NAS related to the development of draft IRIS assessments, The NAS committee recognized "that the changes suggested would involve a multiyear process and extensive effort." To that end, EPA is categorizing assessments into three groups:

- a) Assessments that have already been peer reviewed or released for peer review:  
EPA is revising these assessments to address peer review comments, with particular attention to those that call for increased transparency and clarity of study selection and evidence evaluation. In addition, EPA is editing the text of these assessments to reduce volume where possible, either by removing redundant text or by moving study descriptions into appendices to enhance readability. Major assessments that have been through multiple peer reviews, e.g., trichloroethylene (TCE) and tetrachloroethylene (perc) are not being substantially shortened at this late stage in the IRIS process.
- b) Assessments currently under development but not yet released for peer review:  
For each of the chemicals in this group, draft health assessments have already been completed and some assessments are nearing the external peer review stage in the IRIS process. EPA is re-examining and revising these assessments to ensure that the rationale for study selection and evidence evaluation is clear; these assessments will also be streamlined and edited to reduce redundancy.
- c) For all other assessments EPA will comprehensively implement the NAS recommendations. We expect continual improvement in how we conduct assessments, with ongoing refinements as we gain further experience.

- 15. In its IRIS Progress Report and elsewhere, EPA has emphasized the importance of public input into IRIS assessments. That input is equally important for the purposes of the IRIS reforms EPA is pursuing. For example, EPA is consulting with the SAB regarding creation of a standing SAB committee to peer review all draft assessments. Members of the public no doubt have useful input to provide as to an appropriate composition of any such committee. Please describe any formal process you intend to provide to seek public comment on the Agency's proposed IRIS reforms.**



In a July 12, 2011, press conference and news release, EPA reaffirmed its continual interest in seeking ways to involve the public. For instance, EPA is working closely with the agency's Science Advisory Board on how to bring to bear its expertise on an ongoing basis to focus on the quality, transparency and scientific rigor of IRIS assessments and guide EPA's response to the NAS recommendations

- 16. If an EPA program office requests an assessment of a compound and you discover there is an insufficient data for establishment of values, how do you respond? Do you tell the program office that the IRIS assessment will need to be deferred until sufficient data are available? If not, why not?**

In most cases, if EPA learns that insufficient data are available to develop an assessment or derive any values, EPA will notify the program office.

- 17. For peer review, some have suggested that all of the IRIS draft assessments in the interim should be handled by NAS. The EPA Acute Exposure Guideline Level (AEGL) program relies on a standing NAS Subcommittee to independently peer review and assess the scientific validity of the preliminary AEGL values that are developed for specific chemicals.**

- a. Have you considered this as a model for IRIS?**

As we move forward, we are looking at all examples in the federal government.

- b. If not, why not?**

Rigorous, open scientific peer review is the cornerstone of the IRIS process, and EPA will continue to adhere to its rigorous peer review process. As we move forward, we are looking at all examples for peer review.

At the July 14, 2011, hearing on IRIS in the House Committee on Science, Space and Technology: Subcommittee on Investigations and Oversight, Jonathan Samet, the chair of the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, stated that "there are many ways to have successful peer review. The Science Advisory Board of the EPA, which I serve on, being one. The Academy being another. I will say that now speaking individually, the effort involved in completing this review [formaldehyde] was substantial as I have mentioned. A 15-member committee of volunteers working in four meetings in 8 months and producing a, you know, a report over 100 pages. So substantial effort would be involved, and I think if the full load of peer review were somehow placed before the Academy, I am certain that would stress the community of scientists who carry out such reviews."

- 18. The NAS committee notes that the draft IRIS assessment for formaldehyde contains contradictory statements regarding systemic delivery of formaldehyde- "some parts of the draft assume that the high reactivity and extensive nasal absorption of formaldehyde restrict systemic delivery of inhaled formaldehyde so that formaldehyde does not go beyond the upper respiratory tract, and other parts of the draft assume that systemic delivery accounts in part for the systemic effects attributed to formaldehyde**

**exposure.” The NAS committee concludes that direct evidence of systemic delivery of formaldehyde is generally lacking. How do you respond?**

EPA is committed to eliminating any inconsistencies or contradictory statements in the formaldehyde document regarding the potential for systemic delivery of formaldehyde to non-respiratory sites. Examples of contradictory language identified by the Panel will be resolved. Additionally, Panel suggestions regarding the interpretation of specific study data in EPA’s consideration of this topic, the inclusion of recently-published references, and differentiation between systemic delivery of formaldehyde and systemic effects (see NAS report pages 35 and 36) will be addressed. The NAS Panel noted that “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, especially irritation, inflammation, and stress.”

- 19. The NAS report on formaldehyde recommended strongly that EPA use biologically based dose-response (BBDR) model for the derivation of unit risk estimates for formaldehyde, noting that the formaldehyde BBDR model is one of the “best-developed...to date” and that the positive attributes of the BBDR model generally – and the limitations of the human data- led NAS to recommend that the EPA use the BBDR model and compare the results with the model used in its draft IRIS assessment for formaldehyde.**

**What are EPA’s plans regarding of the BBDR model, particularly in light of the NAS recommendation?**

The question characterizes the NAS report as strongly recommending that the BBDR model results be the basis for EPA’s inhalation unit risk. However, the NAS committee actually said the following (section 3, page 50): “EPA, on the basis of extreme alternative model scenarios, chose not to use the BBDR models developed by Conolly et al. (2003, 2004); however, the committee questions the validity of some of these scenarios and recommends that the BBDR models developed by Conolly and co-workers be used (with the flaw in one numeric approach identified by EPA corrected), that the results be compared with those of the approach currently presented in the draft IRIS assessment, and that the strengths and weaknesses of each approach be discussed.” Additionally, the report states (on p. 135) that: “The committee agrees that EPA’s choice of NPC, Hodgkin lymphoma, and leukemia to estimate the unit risk is appropriate given that the use of Hodgkin lymphoma and leukemia primarily supports the assessment of uncertainty and the magnitude of cancer risk where there is a lack of evidence to support the biologic plausibility of a relationship between formaldehyde exposure and the two cancers.”

The formaldehyde BBDR model was developed for the purpose of extrapolating human respiratory cancer risk from animal toxicology data. EPA will follow the NAS Report recommendations and will present results obtained by implementing the BBDR model for formaldehyde. EPA will compare these estimates with those currently presented in the External Review draft of the assessment and will discuss their strengths and weaknesses. As

recommended by the NAS committee, appropriate sensitivity and uncertainty analyses will be an integral component of implementing the BBDR model.

- 20. EPA's proposed change in the cancer slope factor for inorganic arsenic represents a 17-fold increase from the current IRIS value. This means that exposure to most background levels of arsenic in U.S. soils and drinking water supplies would result in unacceptable cancer risks using the Agency's default exposure assumptions.**

- a. Are you aware of any studies showing the background levels of inorganic arsenic in these environmental media are associated with adverse health effects of any kind?**

EPA is aware of studies that report an association between exposure to inorganic arsenic at concentrations similar to background levels and health effects (see Table 1). Background levels of inorganic arsenic in drinking water are variable but are frequently in the low part per billion range (*ATSDR, 2007*). Public water systems must comply with EPA's maximum contaminant level for arsenic of 10.0 parts per billion. Several studies in humans have identified health effects at arsenic exposure levels in drinking water at environmentally relevant concentrations (ranging from 5 -300 ppb; see Table 1), including hyperkeratosis, hyperpigmentation, increased blood pressure, cardiac abnormalities, fetal loss and mortality, decreased nerve function and respiratory symptoms (Ahsan et al., 2006; Kwok et al., 2007; Li et al., 2006; Mazumder et al., 2000, 1998; Mumford et al., 2007; Rahman et al., 2007; Xia et al., 2009).

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**Table 1**

Study	Endpoint	Methodology	Effect Level (ppb) *
Ahsan et al. (2006a)	Dermal (hyperpigmentation, keratosis)	Cross-sectional study of skin lesion prevalence in 11,746 Bangladeshi adults (men and women); individual exposure (well concentration) data	8.1–40 (prevalence odds ratio = 1.88; 95% confidence interval = 1.20 – 2.94)
Xia et al. (2009)	Dermal effects (hyperkeratosis, hyperpigmentation, depigmentation)	Cross-sectional study of 12,334 residents of Ba Men region of Inner Mongolia; self-reported dermal lesions (hyperkeratosis, hyperpigmentation, depigmentation) verified by nurse or physician, individual well concentration data	5.1–10 (odds ratio = 2.52; 95% confidence interval = 1.47 – 4.30)
Mazumder et al. (1998)	Dermal effects (keratosis, hyperpigmentation)	Cross-sectional study of 7,683 residents of West Bengal, India; household tube well concentrations measured	No NOAEL or LOAEL identified in the study; statistically significant exposure-response trends for hyperpigmentation, keratosis, possibly extending through 50–99 stratum
Kwok et al. (2007)	Elevated blood pressure (hypertension)	Cross-sectional study of 8,790 women in Ba Men region of Inner Mongolia; 3,260 provided age, BMI data; exposure assessed by "subvillage" well concentrations	LOAEL = 21–50
Mumford et al. (2007)	Cardiac repolarization abnormalities (QT interval)	Measured QTc prolongation (> 0.44 sec) in 313 men in Ba Men, Inner Mongolia	LOAEL = 100–300, relative to group exposed to 0–21 (odds ratio = 3.829; 95% confidence interval = 1.128 – 12.993)

Rahman et al. (2007)	Reproductive (fetal loss and neonatal mortality)	Retrospective study of 29,134 pregnancy outcomes in Matlab, Bangladesh from 1991–2000; exposure data from individual household wells	LOAEL = 164–275 (relative risk of infant death = 1.24; 95% confidence interval = 1.04 – 1.47)
Li et al. (2006)	Peripheral nerve function (pinprick sensitivity)	Cross-sectional study of peripheral nerve function and symptoms in 321 residents of Ba Men, Inner Mongolia	50% Decrease in pinprick sensation at 71–159
Mazumder et al. (2000)	Respiratory symptoms	Cross-sectional study of 6,864 residents of West Bengal, symptoms = cough, weakness, chest sounds, shortness of breath	LOAEL = 500–3400, statistically significant exposure-response trend for cough and chest sounds.

\*All effect levels were determined by the study authors.

**21. The California Office of Environmental Health Hazard Assessment (CA OEHHA) proposed a public health goal for total Trihalomethanes in drinking water, including chloroform, in September, 2010, which rejects the principle that chloroform acts as a threshold carcinogen (see p.2 of the September, 2010 draft “Public health Goal for Trihalomethanes in Drinking Water”).**

**a. Is the current EPA plan for an IRIS review of chloroform a product of this proposal and the memorandum of understanding between EPA and CA OEHHA?**

No. The ongoing development of the IRIS assessment of chloroform is independent of the Cal/EPA proposal and the Memorandum of Understanding between EPA and Cal/EPA’s Office of Environmental Health Hazard Assessment. The MOU serves as a mechanism for increased communication and cooperation in the development of risk assessment methods and toxicological assessments; however, EPA’s IRIS assessments are independent from Cal/EPA’s public health goals.

**b. What new scientific evidence has been published to refute the research that shows chloroform produces cancer only following sustained toxicity at high doses in target tissues in lab animal studies?**

EPA’s IRIS health assessment for chloroform is currently under development. The Agency is evaluating all of the new published literature as a part of this process.

**22. Are you concerned about comments in the public docket by EPA professional staff in headquarters and regional offices that characterize the Agency’s proposed cancer slope factor for inorganic arsenic as “unexpected and bewildering”<sup>5</sup> and saying it is in need of a “reality check,”<sup>6</sup> with one Region refusing to concur with the draft assessment?**

<sup>5</sup> Memo from Susan Griffin, EPA – Region 8, to Abdel Kadry, Director, IRIS program, April 17, 2009

<sup>6</sup> Ibid

**a. If not, why not?**

EPA listens to and considers all comments received in developing IRIS assessments. This input is essential to the development and refinement of draft IRIS assessments. The comments referred to in this question were made in response to a request for Agency review of an earlier 2009 draft internal EPA document. Robust and open scientific debate are part of the IRIS process, and divergent views are welcomed and considered. Scientists from multiple EPA programs and regions also commented in response to this request for review, with most supportive of the qualitative and quantitative conclusions presented in that draft of the IRIS cancer assessment for inorganic arsenic. The draft document was subsequently revised and improved based upon the comments from Agency reviewers prior to the February 2010 release of the document for public comment and review by the Science Advisory Board. EPA considers internal and external reviews to be an important and essential aspect of the development and refinement of draft IRIS assessments.

**Questions Submitted by Rep. Sandy Adams**

1. **The purpose of the hearing was to identify some improvements that will make the IRIS process more effective and transparent, particularly as it relates to identifying emerging contaminants that are threats to human health.**

A primary objective of the risk assessment process in general and the IRIS program in particular is to identify the exposure level of contaminants that are associated with an adverse effect in humans. Recently, EPA noticed its intention to promulgate a Maximum Contaminant Level "MCL" for perchlorate. EPA's decision comes in spite of the fact that the National Academy of Sciences "NAS" Committee stated unequivocally that adverse health effects have not been clearly demonstrated in any human population exposed to perchlorate (NAS 2005 p. 177 & OIG 2010 Response to Comments p. E-6).

Given that the decision to regulate perchlorate appears to be based on an observed effect rather than an adverse effect, do you think that applying this standard protecting against all human exposure vs. limiting adverse effects) for all future unregulated contaminants will improve or weaken our confidence in the IRIS process to protect human health.

We do not believe this decision impacts confidence in the IRIS process.

2. **EPA's own OIG indicated that a further lowering of the perchlorate levels in drinking water is not an effective approach to addressing this public health issue. They attribute this to the fact that perchlorate is but one of four stressors on the thyroid (lack of iodine, nitrate & thiocyanate being, the others). Perchlorate's impact on the thyroid is but a small fraction of the other three. Given that the OIG identified perchlorate as the weakest of the four thyroid inhibitors, what does it**

**mean for the future of the risk assessment process and IRIS when it produces a costly regulation that apparently does not significantly improve public health?**

IRIS health assessments are not full risk assessments, nor are they regulations. IRIS health assessments are scientific documents that provide information on the hazard identification and dose-response. Neither the IRIS process nor EPA's risk assessment process produce regulations; rather they provide scientific assessments of the health effects of exposure to contaminants that inform risk management decisions, such as the determination to regulate perchlorate under the Safe Drinking Water Act. EPA's determination to regulate perchlorate is a middle step in a process that leads to a final drinking water regulation. EPA has begun the development of a proposed drinking water regulation for perchlorate. EPA will continue to evaluate the science as we develop the proposed regulation. EPA will also consult with the National Drinking Water Advisory Council, the Science Advisory Board, and the Secretary of Health and Human Services. The Agency will then publish a proposed regulation and request comment. EPA will consider public comments on the proposal prior to promulgating the final regulation.

**3. EPA's recent decision to regulate perchlorate, a chemical with solid science indicating no need to further regulate, is a clear example of the breakdown of the entire EPA drinking water contaminants review process. What are your recommendations to prevent such a lapse in the future?**

EPA does not believe the decision to regulate perchlorate is a breakdown of the drinking water contaminant review process.

**4. Has EPA done any economic analysis on the impact these regulations on perchlorate may have to the communities most affected by them?**

Not yet. However as part of the process of proposing a NPDWR for perchlorate EPA will conduct a cost and benefit analysis (referred to as a health risk reduction cost analysis under the Safe Drinking Water Act), that will include an evaluation of quantifiable and non quantifiable benefits and costs of alternative maximum contaminant levels (MCL). EPA will also analyze the availability of feasible treatment technologies and small system compliance technologies. These analyses will inform the Agency's decision making on the proposed drinking water regulation and will be available for the public when the Agency publishes the proposed regulation.

*Responses by Mr. David Trimble, Director, Natural Resources and Environment,  
U.S. Government Accountability Office*

Response to Questions Submitted by Dr. Paul Broun, Chairman:

**(1) In GAO's prior work, it has questioned the credibility of EPA's IRIS assessment process. Could you provide us with some examples of the issues GAO identified that led you to believe that the process was not credible?**

In our March 2008 report we found that the lack of transparency with regard to the Office of Management and Budget's (OMB)/interagency review process reduced the credibility of EPA's IRIS assessments. At that time, the IRIS assessment process included two OMB/interagency reviews of draft IRIS assessments.<sup>1</sup> According to OMB, the purpose of these reviews was to obtain input from OMB and other federal agencies to help ensure and increase the quality of IRIS assessments as they were being developed. However, because OMB/interagency comments on IRIS assessments were considered deliberative internal executive branch documents, they were not made public. It was this lack of transparency that limited the credibility of the IRIS assessments. Given the importance of IRIS assessments, we believe it is essential that input from all parties, including other federal agencies, be part of the public record. Transparency is especially important because agencies providing input through OMB include those that may be affected by the assessments should they lead to regulatory or other actions.

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<sup>1</sup>GAO, *Chemical Assessments: Low Productivity and New Interagency Review Process Limit the Usefulness and Credibility of EPA's Integrated Risk Information System*, GAO-08-440 (Washington D.C.: Mar. 7, 2008).



**(2) Under the current revised IRIS process, it is estimated that an assessment would be completed in 23 months. Is this realistic?**

We are currently reviewing EPA's revised IRIS process, including its estimates for completing IRIS assessments under the new process. We expect to issue a report on the revised process later this year.

**(3) A 2006 GAO report and a 2000 EPA Science Advisory Board report expressed the importance of considering outside stakeholder input early in the process. Can you elaborate further on the pros and cons of such input at the early stages?**

We reported in 2006 that, because of the large number of internal and external stakeholders interested in the results of an IRIS assessment, it is important to ensure that the assessment addresses the needs of all stakeholders.<sup>2</sup> One way to do this is to identify stakeholders' concerns from the outset and incorporate them into the analysis and characterization of potential health risks of long-term chemical exposures. By involving stakeholders early, risk assessors can ensure that they ask the right questions, make appropriate assumptions, determine the best way to summarize information, and identify key issues and studies that need to be considered in the analysis—thereby potentially making the resulting assessment more credible to these parties. However, stakeholder involvement may also affect the timeliness and credibility of the IRIS assessment process—depending on the manner in which various stakeholders are involved. For example, as we reported in March 2008, OMB and other federal agencies were involved in EPA's IRIS assessment process in a manner that limited the credibility and transparency of, and hindered EPA's ability to manage, IRIS assessments.<sup>3</sup> Specifically, OMB's control of the process led to unacceptably long delays because it prevented EPA from advancing or finalizing IRIS assessments until OMB determined that EPA has satisfactorily addressed all OMB/interagency comments. In an attempt to address OMB and other federal agencies concerns regarding scientific uncertainty, some key IRIS assessments were delayed for years to await new research—instead of relying on the best available science at the time. In our March 2008 report we recommended that EPA provide at least 2 years' notice of its intent to assess specific chemicals, which would allow agencies and other interested parties the opportunity to conduct the research needed to fill any data gaps.

<sup>2</sup>GAO, *Human Health Risk Assessment: EPA Has Taken Steps to Strengthen Its Process, but Improvements Needed in Planning, Data Development, and Training*, GAO-06-595 (Washington, D.C.: May 31, 2006).

<sup>3</sup>GAO-08-440.

**(4) On July 12, Dr. Anastas participated in a press conference on EPA'S efforts to incorporate the Academies' recommendations from April. Please comment on EPA's new proposal.**

The National Academies report offered suggestions for improving the preparation and presentation of draft health risk assessments in general. Our work to date has not focused on these aspects of IRIS assessments. Instead, our body of work on the IRIS program has more broadly evaluated the overall IRIS assessment process and the challenges the program has faced in implementing it. We are, however, currently undertaking a review of EPA's proposal to incorporate the National Academies' recommendations and expect to issue a report later this year.

Response to Questions Submitted by Representative Sandy Adams:

**Q1) The purpose of the hearing was to identify some improvements that will make the IRIS process more effective and transparent, particularly as it relates to identifying emerging contaminants that are threats to human health.**

A primary objective of the risk assessment process in general and the IRIS program in particular is to identify the exposure level of contaminants that are associated with an adverse effect in humans. Recently, EPA noticed its intention to promulgate a Maximum Contaminant Level "MCL" for perchlorate. EPA's decision comes in spite of the fact that the National Academy of Sciences "NAS" Committee stated unequivocally that adverse health effects have not been clearly demonstrated in any human population exposed to perchlorate (NAS 2005 p. 177 & OIG 2010 Response to Comments p. E-6).

**Given that the decision to regulate perchlorate appears to be based on an observed effect rather than an adverse effect, do you think that applying this standard (protecting against all human exposure vs. limiting adverse effects) for all future unregulated contaminants will improve or weaken our confidence in the IRIS process to protect human health?**

EPA's 2011 decision to regulate perchlorate was based primarily on its reassessment of the degree to which populations served by public drinking water systems, in particular sensitive subpopulations, are exposed to perchlorate. The toxicity of perchlorate, as described in the IRIS assessment, was not at issue in EPA's recent decision. The issues raised by the National

Academy of Sciences and EPA's Office of Inspector General were outside the scope of our work.

**Q2) EPA's own OIG indicated that a further lowering of the perchlorate levels in drinking water is not an effective approach to addressing this public health issue. They attribute this to the fact that perchlorate is but one of four stressors on the thyroid (lack of iodine, nitrate & thiocyanate being the others). Perchlorate's impact on the thyroid is but a small fraction of the other three. Given that the OIG identified perchlorate as the weakest of the four thyroid inhibitors, what does it mean for the future of the risk assessment process and IRIS when it produces a costly regulation that apparently does not significantly improve public health?**

According to the April 2010 OIG report, EPA used a single chemical risk assessment for perchlorate when a cumulative risk assessment would have better described the nature and sources of risk.<sup>4</sup> The scientific dispute between EPA and the OIG was outside the scope of our work, and we did not review findings from the OIG study or whether the issues were addressed in the recent decision to regulate perchlorate.

**Q3) EPA's recent decision to regulate perchlorate, a chemical with solid science indicating no need to further regulate, is a clear example of the breakdown of the entire EPA drinking water contaminants review process. What are your recommendations to prevent such a lapse in the future?**

We have not assessed EPA's recent decision to regulate perchlorate in drinking water. In our May 2011 report on the Safe Drinking Water Act,<sup>5</sup> however, we did assess EPA's 2008 preliminary regulatory determination to not regulate perchlorate and found that the agency used a process and scientific analyses that were atypical, lacked transparency, and limited the agency's independence in developing and communicating scientific findings. In our May 2011 report we made 17 recommendations, including that the EPA Administrator require (1) the development of criteria to identify contaminants that pose the greatest health risk, (2) improvements in its unregulated contaminants testing program, and (3) the development of

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<sup>4</sup>Report No. 10-P-0101

<sup>5</sup>GAO, *Safe Drinking Water Act: EPA Should Improve Implementation of Requirements on Whether to Regulate Additional Contaminants*, GAO-11-254 (May 27, 2011).

policies or guidance to interpret the broad statutory criteria. EPA agreed with 2 recommendations but took the position that developing guidance and taking the other recommended actions are not needed. GAO believes EPA needs to adopt all of the recommendations to better assure the public of safe drinking water.

**Q4) Has EPA done any economic analysis on the impact these regulations on perchlorate may have to the communities most affected by them?**

EPA's decision to regulate perchlorate marks the beginning of the regulatory process. Under the Safe Drinking Water Act, following the decision to regulate a particular chemical, EPA is required to conduct a cost-benefit analysis as part of the standard-setting process.

*Responses by Dr. Jonathan M. Samet, MD, MS, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine, University of Southern California; and Chair, Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, National Research Council, The National Academies*

**Questions Submitted by Dr. Paul Broun, Chairman**

1. *The Academy noted in its formaldehyde report that many of the concepts and approaches they recommended are elementary and already exist in EPA's guidelines. You went on to state "the current state of the formaldehyde draft IRIS assessment suggests that there might be a problem with the practical implementation of the guidelines in completing the IRIS assessments."*

- *Can you explain what guidelines they are currently not following?*

The EPA draft IRIS formaldehyde assessment refers to multiple guidelines related to the various health outcomes considered, e.g., the EPA cancer guidelines. The problem highlighted in the report refers to the actual utilization of these guidelines for the evaluation of evidence. The National Research Council (NRC) report notes the number of guidelines referred to in the IRIS assessment and the heterogeneity of these guidelines, which are intended, in part, to provide guidance on evidence interpretation. The NRC committee could not identify clear linkages between the various guidelines and the evidence evaluation in the draft assessment; that is, there was not a transparent connection between the language of the guidelines and the approach used by EPA to assess weight-of-evidence.

2. *The Center for Progressive Reform has suggested cutting back or curtailing peer review by limiting the use of external peer reviews. It seems to me peer review should be strengthened, not diminished – can you comment on the CPR suggestion?*

I am in agreement that peer review should generally be strengthened and not diminished. It is central to assuring the veracity and credibility of scientific documents, and represents the normative approach of the scientific community.

3. *Scientific peer review and its consequences for draft IRIS assessments.*

- *What suggestions do you have for EPA to strengthen its peer review?*

EPA currently has a number of mechanisms available for peer review, beginning with the interactions among the scientists who prepare the drafts. It should be acknowledged that the drafting groups should have some level of exchange that contributes to the quality of the documents. However, such internal interactions are not transparent, nor do they constitute an independent peer review. The EPA has mechanisms available for independent peer review, including utilizing the Scientific Advisory Board (SAB) or turning to the National Academies. Both mechanisms have been used. As with the draft formaldehyde assessment, there are instances in which the National Academies have provided peer review for particularly challenging IRIS draft assessments. The circumstances leading to review by the National Academies have varied.

Regardless of the reviewing group, the EPA peer review process could be strengthened by following the widely used approach of formally responding to peer review comments, and leaving a transparent trail as to how reviewer concerns were addressed. Thus, for example, reports of the National Academies are typically reviewed by panels that may include ten to fifteen reviewers. The committee and staff prepare a response to each peer review comment, documenting how changes have been made or explaining why no action was taken. Thus, there is a clear record of how comments have been addressed. The current IRIS process does not provide for this type of documentation. I note that the EPA has begun to provide a relatively detailed response to the Clean Air Scientific Advisory Committee (CASAC) following its peer reviews of documents related to the NAAQS. CASAC requested that the staff provide such documentation to assure transparency and to provide direction to CASAC as to how to focus its reviews of revised documents.

- *Do you see an appropriate role for the Academies in this area :*

The National Academies have a lengthy record of providing useful peer review for IRIS assessments. I am doubtful, however, as to whether the Academies could provide review of a large number of assessments, given the substantial effort required. The National Academies could assemble review panels for more challenging documents or for those requiring special expertise, not well represented on the EPA SAB. Perhaps, tiered strategies could also be considered, with the National Academies serving as reviewers in a second-stage, as needed.

4. *Do you think that EPA's IRIS program, in its current state, represents the gold standard for toxicological information?*

- Typically, the term "gold standard" refers to the approach that is considered the most accurate. This phrasing may not be the best way to characterize the IRIS program, as

similar risk estimates are not uniformly generated by other programs. That said, given the concerns raised about the current IRIS assessment approach, the term “gold standard” may not be appropriate.

Nonetheless, because a similar resource on risks of chemicals is not available, EPA’s IRIS program has provided valuable assessments of hazard and developed risk estimates for application. For example, we heard from Mayor Bollwage at the hearing with regard to the utilization of IRIS assessments and the implications of risk assessments based in IRIS at the local level. The IRIS program offers a unique data base on risk for the many organizations that could not carry out hazard identifications and develop risk estimates on their own.

5. *Are there weight-of-evidence approaches currently available for study evaluations that EPA could use to help improve its current process?*

Weight-of-evidence approaches are widely used. Most have their origins in methods developed for evaluating evidence on causation, initially for assessing the evidence on smoking and disease causation. Over time, the general approach has evolved and been widely applied, not only in EPA guidelines but by many other bodies, such as the World Health Organization’s International Agency for Research on Cancer (IARC). Similar approaches are used for evaluating evidence for assessing the state of evidence on clinical problems and elaborating guidelines.

6. *Does the current IRIS process offer a transparent approach to reviewing studies for inclusion in its assessments?*

The NRC committee that reviewed EPA’s formaldehyde draft IRIS assessment identified concerns about transparency. For example, the general approach used in the assessment was not well described; EPA’s methods are described in a two-page introduction to a 1,000-page document. Various guidance documents are cited in EPA’s assessment, but their specific roles in preparation of the draft are not clear. Furthermore, the links between relevant evidence and calculation of the reference concentrations and unit risk values are not always clear. Finally, the committee did not find sufficient documentation of methods and criteria for identifying the epidemiologic and experimental evidence to be reviewed, for evaluating individual studies, for assessing weight of evidence, for selecting individual studies for derivation of toxicity and risk estimates, or for characterizing uncertainty and variability. The committee’s findings with regard to transparency are similar to those of other NRC committees that have conducted reviews of IRIS assessments of other chemicals, such as dioxin and tetrachlorethylene.

*Are comments from EPA Line Offices made public?*

I am not familiar with the agency’s practices on this matter.

7. *Is Ms. Steinzor's observation scientifically correct? Do humans exhale formaldehyde because "the air is polluted?" Please elaborate.*

Yes, Ms. Steinzor did express concern with regard to hearing that formaldehyde is present in exhaled breath. Unfortunately, she was not informed as to the natural origin of this formaldehyde, which comes from the one-carbon metabolism that is fundamental to our cells. In fact, one complexity in interpreting the evidence on inhaled formaldehyde is addressing how additional risk could come from the inhalation of formaldehyde, when cells already have naturally-produced formaldehyde throughout. This topic is addressed at length in the report.

**Question Submitted by Ms. Donna F. Edwards, Ranking Member**

1. *The Subcommittee received testimony relating to Dr Charnley's service on the Board for Environmental Science and Toxicology (BEST). You are the immediate-past Chair of BEST. The Subcommittee was particularly interested in conflict of interest issues that may color testimony we received on the IRIS program, and the COI situation for Dr. Charnley on BEST was a matter that received some attention at the hearing. Please provide to the Subcommittee answers to the following questions as well as any supporting documentation that you believe appropriate to clarify the NAS/NRC policy.*

*On what date did Dr. Charnley's appointment to BEST take effect?*

9/1/2009

*Dr. Charnley's husband, Mr. E. Donald Elliott, had previously served on the BEST from approximately 2004 to 2009. Can you please provide the exact dates of his service?*

9/1/2003 to 8/31/2009

*Please provide for the record the NAS/NRC financial disclosure and conflict of interest policies regarding disclosures and recusals. Please also clarify expectations regarding disclosure and recusal for the work of a spouse.*

The NAS/NRC policies on committee composition and balance and conflicts of interest (including expectations related to a spouse) are described on the institution's web site at [http://www8.nationalacademies.org/cp/information.aspx?key=Conflict of Interest](http://www8.nationalacademies.org/cp/information.aspx?key=Conflict_of_Interest)



*Please provide any records regarding recusal agreements for either Mr. Elliott or Dr. Charnley during their terms of service on BEST. Please identify the matter that they were recused from, the reason for recusal, and the time period these recusals were in effect.*

BEST does not enter into advance written "recusal agreements" such as those used in government agencies. However, pursuant to the conflict of interest policies referenced above, board members routinely disqualify themselves from participating in matters in which they, their immediate family members, their employers, or their clients have a conflict of interest, and they also disclose any biases that do not rise to the level of a conflict of interest. Consequently, during Professor Elliott's term of service on BEST, he recused himself from all matters on which he or his spouse were working, or on which his employer or clients had an interest. Professor Elliott's term of service on BEST ended before the board held any discussions about formaldehyde.

Dr. Charnley had no involvement with the National Research Council's review of EPA's draft IRIS assessment of formaldehyde. She was not a member of that committee, nor did she attend any of its meetings. She recused herself from all board discussions concerning formaldehyde, which took place on 10/8/2009, 7/19/2010, and 12/2/2010, and she left the room during those discussions. She stated that she was not currently consulting for industry on formaldehyde at the time of those discussions but had done so prior to her term of service on BEST. Although NAS/NRC conflict-of-interest policy does not consider past relationships to constitute a conflict of interest, Dr. Charnley decided to recuse herself from those discussions to eliminate the possible appearance of a conflict.

*Responses by The Honorable Calvin Dooley, President and Chief Executive Officer,  
American Chemistry Council*

**Questions Submitted by Dr. Paul Broun, Chairman**

**Question1**

***In your testimony, you indicated IRIS peer reviews, at least for the interim, should be conducted by the NAS. What is the basis for this?***

- ***Are you worried that this could bring the process to a halt?***

First and foremost, it is clear that the current policies and practices of the IRIS program do not foster the use of best available scientific data and methods and, because of this, IRIS assessments have consistently fallen well short of meeting the highest of standards of scientific inquiry, objectivity and transparency. Citing problems with the IRIS assessments that have persisted for over a decade, the NAS committee that conducted the independent peer review of the IRIS draft formaldehyde assessment devoted an entire chapter of the report to point out the scientific inadequacies in policies, procedures and practices of the IRIS program, and to recommend fundamental and permanent changes to the manner in which the IRIS program obtains scientific data, analyzes studies, integrates data using weight of evidence, conducts causal determinations and assesses uncertainty. This NAS report clearly documents the types of changes needed to elevate the IRIS program to a level where it can meet the benchmarks of objectivity, scientific accuracy and transparency necessary to ensuring high quality, reliable assessments.

In oral testimony before Congress on July 14, 2011, Dr. Anastas fully concurred with the NAS recommendations that changes are needed in the IRIS program, stating “we seek out this type of peer review in order to continuously improve...that’s why we accept those recommendations and that’s why we’ll build them into our revision.” As EPA moves forward to implement the needed changes in IRIS, it is critical that IRIS assessments undergo a thorough and completely independent peer review. The NAS panel’s findings of deficiencies in IRIS and its recommendations for changes in the procedures for data evaluation, data integration using weight of evidence and causal determination provide a specific “roadmap” that lays out the course EPA needs to follow for all future IRIS assessments. Half measures or procedural cosmetic changes in IRIS will not achieve the necessary improvements. Therefore, to verify that these improvements in scientific evaluation procedures and methods have indeed been made, ACC has recommended that, in the short-term, IRIS assessments should be subjected to peer review by NAS. There is no other organization in the U.S., arguably in the entire

***Responses to questions from the Subcommittee on Investigations and Oversight, House Committee on Science, Space, and Technology. Submitted by Cal Dooley, president and CEO of the American Chemistry Council, August 16, 2011.***

world, which has the scientific stature, integrity and track record of the NAS in conducting such scientific peer reviews. Given the importance IRIS scientific evaluations have for EPA program offices, other federal agencies, state governments, and private and public sector impacts, peer review by the NAS is an important verification step that will serve to assure EPA, Congress, and all stakeholders that EPA has in fact fully implemented the changes needed to restore confidence in the scientific foundation of IRIS assessments.

Presently, the IRIS program office is the lead entity, and in many cases the sole EPA unit, engaged in the design of the IRIS evaluation, the analysis of the data, the determination of conclusions, the development of the charge questions for peer review, and the revision of the assessment following peer review and public comment. In addition, in EPA-run peer reviews, in contrast to NAS peer review, peer reviewers are at times overly deferential to EPA and reluctant to be seen as criticizing EPA staff. Also, EPA staff is given unfettered ability to comment throughout the peer review meetings, and their constant presence may have a chilling effect on frank and open discussion among the peer reviewers. Furthermore, currently in the IRIS program, there is no “honest broker” to oversee and ensure that IRIS adequately incorporates changes in response to peer review and public comment. Therefore, in the interim, as EPA moves forward in implementing the needed changes in IRIS, ACC recommends that assessments revised after peer review are then submitted to the peer review panel as a quality assurance check to evaluate whether the peer review findings were completely and adequately addressed. This step is necessary, at least in the interim, because EPA has often selectively discounted or ignored peer review findings and recommendations.

There is no reason to believe that implementing NAS peer review in the short term would “bring the process to a halt.” As for the time and level of effort required for peer review, if EPA fully implements the changes needed to improve the scientific evaluation procedures in IRIS, the peer review should be more efficient and faster than previously.

#### **Question 2**

***In her testimony, Ms. Steinzor claims your organization is interested in increasing OIRA oversight on the IRIS program, and including the NAS in all IRIS assessment reviews, to ostensibly slow down the IRIS process.***

- ***Is it your goal to see the IRIS program terminated?***

***Responses to questions from the Subcommittee on Investigations and Oversight, House Committee on Science, Space, and Technology. Submitted by Cal Dooley, president and CEO of the American Chemistry Council, August 16, 2011.***

ACC's expectations are clear. Like all stakeholders, we expect that the science relied on by IRIS will be firmly based on up-to-date scientific knowledge, meet the highest of standards of scientific inquiry, and be evaluated in accordance with acceptable scientific approaches. Unfortunately, IRIS assessment practices continue to suffer from a range of features that have been identified years ago as problematic. These features systematically exaggerate actual risks and thereby seriously compromise the value of risk assessments as inputs to regulations and regulatory impact analyses. Having confidence in the IRIS Program and assessments, therefore, is critical. Yet, despite the continued evolution of the EPA IRIS process, it has become increasingly clear that fundamental improvements in the policies and practices of the IRIS program are necessary to ensure that the IRIS assessments developed by EPA are firmly based on up-to-date scientific knowledge, meet the highest of standards of scientific inquiry and integrity, and are evaluated in accordance with acceptable scientific approaches. It's for these reasons that, consistent with the findings of the NAS formaldehyde peer review panel, ACC has recommended improvements in the IRIS Program.

ACC has called upon the Office of Management and Budget (OMB) to play a greater role in the coordination and review of chemical safety assessments by federal agencies, including EPA. Stronger leadership from OMB will help ensure scientific integrity and eliminate duplicative, often conflicting, evaluations by agencies that cause confusion for consumers, chemical manufacturers, and their customers.

There appears to be considerable overlap across EPA's IRIS program, the Dept. of Health and Human Services' Report on Carcinogens (RoC), and the Agency for Toxic Substances Disease Registry (ATSDR) Toxicological Profile program. Each of these routinely develop assessments of chemicals hazards and risk. Of the IRIS chemicals, approximately one-third are also evaluated in the ATSDR Toxicological Profile program. And, both programs promulgate health protective exposure guidance values: the IRIS Reference Doses (RfDs) and the ATSDR Minimum Risk Levels (MRLs). The RfDs and MRLs are defined very similarly:

*Reference Dose (RfD): An estimate of a daily oral exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a BMDL, a NOAEL, a LOAEL, or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. [Durations include acute, short-*

**Responses to questions from the Subcommittee on Investigations and Oversight, House Committee on Science, Space, and Technology. Submitted by Cal Dooley, president and CEO of the American Chemistry Council, August 16, 2011.**

*term, subchronic, and chronic and are defined individually in this glossary].*

*[http://www.epa.gov/iris/gloss8\\_arch.htm#r](http://www.epa.gov/iris/gloss8_arch.htm#r)*

*An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. <http://www.atsdr.cdc.gov/mrls/index.asp>*

At times the RfD and MRL values are close to one another, and may even be identical. But in many cases they differ, in some instances markedly so, by an order of magnitude or more. These differing exposure guidance values create uncertainty in the regulated community and raise questions about the inconsistent evaluation of scientific evidence.

The recent concurrent evaluations of formaldehyde in EPA's IRIS program and in HHS's 12th Report on Carcinogens (12th RoC) are an example of the disconnect between the Administration's stated commitment to scientific integrity and the actions taken by some federal agencies. Just a few weeks after NAS concluded that EPA's IRIS program had failed to scientifically justify its conclusion that formaldehyde causes specific types of leukemia, the 12th RoC concluded exactly the opposite, asserting that studies in humans have shown that formaldehyde causes myeloid leukemia (Report: <http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Formaldehyde.pdf>). By failing to sufficiently reflect the conclusions of NAS and producing a contradictory report, the 12th RoC has created the potential for public confusion, alarm, and economic harm to the 600,000 Americans employed in industries reliant on the production and use of formaldehyde.

OMB should address this apparent duplication of agency efforts to ensure the chemical assessment processes followed are consistent, reflect up-to-date scientific knowledge, meet the highest standards of scientific inquiry, and employ best practices for stakeholder involvement and scientific peer review, including processes for acting on comments and peer review recommendations.

### **Question 3**

***Some people have criticized industry studies, calling them biased and unreliable. How do you respond to that?***

ACC has a long and unwavering track record in supporting the use of the best available science in hazard characterization and risk assessment, irrespective of research funding

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results, and does not include examination of laboratory study records or raw data. The purpose for journal peer review is to judge whether the study has been conducted and reported according to internationally recognized, general scientific standards and whether the study meets the interest level for dissemination to the scientific community. It is not designed to provide assurance of accuracy or to recalculate raw data, and it does not provide an opportunity for independent audit of the study.

Evaluating the safety of any substance should include review of all relevant studies utilizing a systematic weight-of-evidence framework. Although not all studies that are useful for hazard characterization and risk assessment may be amenable to GLP

(e.g., epidemiology and mechanistic studies, studies conducted before the acceptance of current GLP), this does not obviate their consideration. Each study, GLP and non-GLP, should be evaluated and weighed in accordance with fundamental scientific principles. Factors to evaluate include: a) verification of measurement methods and data; b) control of experimental variables that could affect measurements; c) corroboration among studies; d) power (both statistical and biological); e) universality of the effects in validated test systems using relevant animal strains and appropriate routes of exposure; f) biological plausibility of results; and g) uniformity among substances with similar attributes and effects.

In conducting chemical hazard and risk assessments, it is imperative that objective criteria for determining data quality and study reliability be used in conjunction with a structured evaluative framework to provide a systematic approach for assessing the overall weight of the evidence for observed effects and the postulated mode of action. In this manner, data from laboratory experiments, epidemiological investigations, and cutting-edge mechanistic research from all relevant studies—GLP and non-GLP—and from all investigators, regardless of affiliation or funding source, can be comprehensively reviewed, given appropriate weight, and integrated in a manner that provides a robust, biologically plausible understanding of the potential hazards and risks that exposures to a substance could pose. These basic principles of causal inference are widely endorsed and practiced (e.g., NAS formaldehyde peer review report, Chapter 7, 2011), and such analysis will reveal the strengths and flaws of a study, independent of study authorship or funding.

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source or affiliations of investigators. Industry funded or conducted studies are of consistently high quality, and regulatory agencies have increased confidence in both the relevance and quality of industry sponsored or conducted scientific studies for safety decisions.

To meet regulatory requirements, most of the chemical hazard scientific studies undertaken by industry employ agency-required test procedures, use standardized and validated test methods, and comply with Good Laboratory Practices (GLP) regulations. Compliance with GLP requires investigations to be conducted by trained experts, test devices and instruments to be appropriately calibrated, and their accuracy assured, and, most importantly, all of the data, including raw laboratory records, to be collected, subjected to quality assurance review and retained for independent review by a regulatory agency. Relevant internationally agreed test methods are used by industry to generate toxicity data for safety determinations by regulatory agencies. Incorporation of GLP in these laboratory tests assures that written protocols and standard operating procedures for each study component are developed and carefully and completely followed. GLP also requires meticulous adherence to dosing techniques; the use of adequate group sizes to allow meaningful statistical analysis; characterization (identity, purity, concentration) of test and control substances, including dosing solutions; detailed recording of study measurements and data; and, collection of all raw laboratory data in a manner that can be retained and made available for regulatory agencies to audit and reach independent conclusions. Quality control procedures, quality assurance reviews, and facility inspections are also used to monitor and enforce GLP compliance. The relevance, reliability, sensitivity, and specificity of most test methods required of industry by regulatory agencies are well understood because they have been subjected to extensive, round-robin validation programs conducted in numerous laboratories throughout the world.

Whereas all study records and data from GLP investigations are available to agencies, rarely, if ever, are such details made available as part of the peer-review process for publishing a manuscript in a scientific journal. This can limit the ability of an agency to independently evaluate conclusions or to conduct alternative analyses of the data. The challenges faced by the peer-review procedures of journals have been recently highlighted (Nature 2006), and it has been pointed out that "...scientists understand that peer review per se provides only a minimal assurance of quality, and that the public conception of peer review as a stamp of authentication is far from the truth" (Jennings 2006). Journal peer review relies on summarization of experimental procedures and

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As discussed by Conrad and Becker,<sup>1</sup> it is a given that scientific research and testing has always been paid for by some entity – be it a foundation, industry, or government. And any funding can have an inherent potential to influence results, whether the funding is from industry, environmental groups, or government. Conflicts and bias are not unique to industry. Academics can also be subject to powerful biases arising from career advancement interests (publish or perish), personal advancement objectives, desire to increase one's status in a professional field, interest in obtaining positive results, etc. It's for these reasons consensus is coalescing around approaches designed to (i) increase confidence that the experimenter did not shape or skew the results, or (ii) enable others to assess independently whether such influence occurred.

Furthermore, since its inception in 1999, the chemical industry's visionary Long-Range Research Initiative (LRI) has been focused on improving science-based chemical testing and risk assessment practices and policies impacting new product development and government regulatory evaluations. The following principles govern the LRI.

- Scientific Excellence. Research will pursue scientific excellence by using the best scientists and by seeking advances in scientific understanding.
- Transparency and Action. The research process will be transparent, results will be made public, and industry will act on the results in a timely fashion.
- Fair and Unbiased Conduct. The research process will prevent conflicts of interest and guard against bias in decision-making.
- Chemical Industry Relevance. Research needs and priorities will be set with consideration of the relevance of the research to the chemical industry and to meet the overall goal of funding research that increases scientific understanding about the potential health and environmental impacts of chemicals.

Having confidence in scientific procedures and data is the foundation for determining the safety of chemicals and chemical products. For decisions of safety, there must be rigorous and thorough application of fundamental scientific practices, irrespective of the purpose of the study and where it is conducted. As detailed above, arguing that one scientific study deserves more or less credence based simply on who conducted or funded it is antithetical to the scientific method. Instead, consistent, objective, and transparent procedures should be applied to evaluating study validity and data quality so that data from all relevant studies can be comprehensively and systematically

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<sup>1</sup> Conrad JW Jr., Becker RA, 2010 Enhancing Credibility of Chemical Safety Studies: Emerging Consensus on Key Assessment Criteria. *Environ Health Perspect* 119(6): doi:10.1289/ehp.1002737



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reviewed, given appropriate weight, and integrated using a weight of evidence procedure.

#### **Question 4**

*In his written testimony, Dr. Anastas said that "Assessments that have already been peer-reviewed or released for peer review: We are revising these assessments to address peer review comments, especially those that call for increased transparency of study selection and evidence evaluation." He also said, "Assessments currently under development but not yet released for peer review: We are re-examining these assessments to ensure that the rationale for study selection and evidence evaluation is clear. These assessments will also be edited to reduce redundancy." Notably, Dr. Anastas made no mention of additional analysis or re-analysis to address, as applicable, the recommendations in Chapter 7 of the NAS Formaldehyde peer review.*

- *Do you think these actions proposed by Dr. Anastas will address the fundamental shortcomings of faulty data evaluation procedures or inconsistent and lack of transparent weight of evidence evaluations in these IRIS assessments?*
- *If not, what specific actions do you recommend be considered for these assessments?*

As I testified, we welcome the changes reflected in Dr. Anastas' testimony and the July 12, 2011, EPA announcement (<http://www.epa.gov/IRIS/pdfs/irisprogressreport2011.pdf>). Unfortunately, these improvements in IRIS procedures and practices may not address key deficiencies in IRIS assessments that are currently in development.

EPA has announced that for all new assessments, the Agency will fully implement the NAS recommendations. We agree this is the proper course of action for new assessments.

Yet for IRIS assessments that have already been peer-reviewed or released for peer review, EPA intends to revise "these assessments to address peer-review comments, especially those that call for increased transparency of study selection and evidence evaluation." And for assessments currently under development but not yet released for

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peer review, EPA will initiate actions “re-examining these assessments to ensure that the rationale for study selection and evidence evaluation is clear; these assessments will also be edited to reduce redundancy.” Taking only these actions for ongoing assessments is problematic, since it has been clearly documented that considerably more attention needs to be given to improving the scientific evaluation procedures used in IRIS.

If EPA honestly intends to improve the IRIS program by implementing the recommendations of the NAS, then fundamental changes are needed in data evaluation and interpretation policies and practices for all ongoing assessments, not just the new assessments. EPA should review all ongoing assessments, even ones that have been peer reviewed but not yet finalized, and determine whether these assessments meet the data evaluation and integration standards described in the NAS recommendations. In cases where the NAS recommendations are not met, required additional analyses must be conducted to meet current practice standards of data evaluation, weight of evidence, and causal inference. Anything less than this will likely lead to scientifically unsound assessments, unsupportive of potential regulatory action. Therefore, EPA’s proposal to move forward with only minimal review of, and few changes to, ongoing IRIS assessments will be an inefficient use of time and resources.

With respect to the findings and recommendations of the NAS formaldehyde peer review panel, Dr. Anastas emphatically stated at the July 14, 2011 House hearing, that EPA would adopt every NAS recommendation. Given the extent and number of NAS recommendations - which in toto necessitate an entire redrafting of the formaldehyde IRIS assessment - ACC strongly urges EPA to seek additional peer review of the revised assessment. Indeed, during his remarks at the House hearing, Dr. Samet noted that the revised IRIS assessment should undergo further review. In this regard, ACC believes that the revised formaldehyde IRIS assessment should be reviewed again by the NAS, to evaluate whether the peer review findings were completely and adequately addressed by EPA.

ACC believes it is critical that IRIS assessments reflect best available science, and that they be timely. A timely assessment that falls short of meeting the scientific standards of practice is of little to no use to any one – to the agency or stakeholders. As stated above, ACC recommends EPA review all ongoing IRIS assessments, even ones that have been peer reviewed but not yet finalized, and determine whether these assessments

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meet the data evaluation and integration standards described in the NAS Chapter 7 recommendations. In cases where they do not, the required additional analyses to meet current practice standards of data evaluation, weight of evidence, and causal inference must be conducted.

ACC also recommends that peer review activities be enhanced. Presently, the IRIS office is the sole entity engaged in the design of the assessment, the conduct of the evaluation, the development of the charge questions for peer review, and the revision of the assessment following peer review and public comment. There is no "honest broker" to oversee and ensure that IRIS adequately incorporates changes in response to peer review and public comment.

Therefore, ACC makes the following recommendations:

**A. Problem formulation and data acquisition.** Engaging stakeholders in a dialogue on the problem formulation can help ensure risk assessments are based on the best available information and are appropriately scaled and oriented to the relevant questions. Stakeholder engagement is needed to inform EPA of ongoing studies, to supply studies that EPA may not be aware of, and to discuss with EPA data needs that can be addressed through additional research and testing. This would allow the Agency to identify and then collect scientific information on possible modes of action at the right time in the process (at the literature search/request for data stage), so that these can be explored, evaluated, and if appropriate, used in the quantitative stage of the assessment. At an early stage, the IRIS Office should undertake an initial review of the available data on a chemical to be reviewed to identify the perceived issues/concerns anticipated in preparing the assessment. The initial review should be based on a preliminary review of the available data and should seek to identify: 1) key science issues that could benefit from supplemental information/data generation; 2) issues likely to be considered controversial among stakeholders; and 3) analyses that could be performed within the short-term that might provide greater clarity on science issues that will need to be addressed.

**B. Stakeholder dialogue with EPA on the peer review charge questions** can help clarify the scope and depth of the peer review and the expertise needed among peer reviewers. ACC recommends that EPA initiate the development of charge questions at the problem formulation stage of a risk assessment, and then solicit public input on the draft charge questions concurrent with public input on the draft risk assessment. The charge questions should be written to facilitate objective consideration of alternative

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plausible scientific views rather than only reviewing the scientific sufficiency of the risk assessment. As recommended in *Improving the Use of Science in Regulatory Policy*, EPA should explicitly differentiate between questions that involve scientific judgments and questions that involve judgments about economics, ethics, and other matters of policy.

C. EPA-run peer reviews should be restructured to encourage open scientific dialogue and thoughtful scientific deliberation between both peer reviewers and the public. Presently, the public commenters have at most five minutes to rush through their presentations while the peer review members passively listen. Greater effort should be made to structure the meetings so public input is provided and deliberated at appropriate times. In addition, the peer review report should explicitly reference or otherwise discuss scientific input from public commenters. EPA should always respond in writing to comments when issuing an assessment that has been revised following peer review and in a case where the Agency elects not to address a peer review finding or recommendation, EPA should issue a written justification.

D. In the interim, as EPA moves forward in implementing recommendations for improving IRIS, assessments revised after peer review should be submitted to the peer review panel as a quality assurance check to evaluate whether peer review findings were completely and adequately addressed.

E. As a long-term solution, ACC recommends that the Assistant Administrator of EPA's Office of Research and Development -- independent from the IRIS Office -- issue a certification at the time an IRIS assessment is disseminated as a final agency action, that the assessment reflects best available science and the Agency has adequately addressed both public comments and independent peer review findings and recommendations.

ACC is also concerned that the July 12, 2011, announced improvements in IRIS fail to address two critical aspects. First, EPA has not signaled agreement that they will implement the full set of weight of evidence evaluation recommendations made by the NAS in Chapter 7. The NAS directs EPA to:

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

- *"Review use of existing weight-of-evidence guidelines."*
- *"Standardize approach to using weight-of-evidence guidelines."*
- *"Conduct agency workshops on approaches to implementing weight-of-evidence guidelines."*

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- *“Develop uniform language to describe strength of evidence on noncancer effects.”*
- *“Expand and harmonize the approach for characterizing uncertainty and variability.”*
- *“To the extent possible, unify consideration of outcomes around common modes of action rather than considering multiple outcomes separately.”*

Yet in EPA’s July 12, 2011 proposed IRIS revisions, EPA makes no mention of reviewing existing weight-of-evidence guidelines or standardizing the approach to using weight-of-evidence guidelines, or conducting agency workshops on approaches to implementing weight-of-evidence guidelines. In many IRIS assessments, scientific reviewers, including EPA’s own peer reviewers, have remarked that EPA’s use of default linear extrapolation is not justified, and instead, EPA should base the IRIS assessment on extensive research which demonstrates that non-linear modes of action are applicable. Failure by EPA to fully and adequately address the NAS panel’s recommendations for improving weight of evidence evaluations in IRIS assessments will perpetuate IRIS assessments that fail to reflect best available scientific knowledge and scientific inquiry practice standards.

Consistent with the NAS recommendations, IRIS should consistently use objective criteria for determining data quality and study reliability<sup>2</sup> coupled with an existing weight of evidence framework<sup>3</sup> to provide a systematic approach for assessing the overall weight of the evidence for observed effects and the postulated mode of action. In this manner, data from laboratory experiments, epidemiological investigations, and mechanistic research from all relevant studies—GLP and non-GLP—and from all investigators, regardless of affiliation or funding source, can be comprehensively reviewed, given appropriate weight, and integrated in a manner that provides a robust,

<sup>2</sup> For example: Schneider K, Schwarz M, Burkholder I, Kopp-Schneider A, Edle L, Kinsner-Ovaskainen et al. 2009. “ToxRTTool,” a new tool to assess the reliability of toxicological data. *Toxicol Lett* 189:138–144.

<sup>3</sup> For example: Boobis AR, Cohen SM, Dellarco V, McGregor, D, Meek, ME, Vickers C, et al. 2006. IPCS Framework for analyzing the relevance of a cancer mode of action for humans. *Crit Rev Toxicol* 36:781–792; Boobis AR, Doe JE, Heinrich-Hirsch B, Meek ME, Munn S, Ruchirawat M, et al. 2008. IPCS framework for analyzing the relevance of a noncancer mode of action for humans. *Crit Rev Toxicol* 38:87–96; Rhomberg, LR; Bailey, LA; Goodman, JE. 2010. “Hypothesis-based weight of evidence: A tool for evaluating and communicating uncertainties and inconsistencies in the large body of evidence in proposing a carcinogenic mode of action - naphthalene as an example.” *Crit. Rev. Toxicol.* 40 : 671-696; Rhomberg, LR; Bailey, LA; Goodman, JE; Hamade, A; Mayfield, D. 2011 “Is Exposure to Formaldehyde in Air Causally Associated with Leukemia? – A Hypothesis-Based Weight-of-Evidence Analysis.” *Crit Rev Toxicol.* 2011 Aug;41(7):555-621. Epub 2011 Jun 2.

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biologically plausible understanding of the potential hazards and risks that substance exposures could pose.

#### **Question 5**

***In responding to a question from the Committee, one of the witnesses, Ms. Rena Steinzor, lamented that one of the most distressing things she had heard during the hearing is that her 20-year old son – used as a metaphor for the population in general – had formaldehyde in his body and that he was exhaling it as levels “that are much higher than the reference dose set by the EPA database.” The reason for this, she added, is “because the air is polluted. We live in a non-attainment area that is awash in toxics and all sorts of other problems, and that is why that has happened.”***

- ***Is Ms. Steinzor’s observation scientifically correct? Do humans exhale formaldehyde because “the air is polluted?” Please elaborate in your reply.***

Ms. Steinzor’s comments show a lack of understanding of human biology. Formaldehyde is a basic molecule of life, produced naturally by our bodies, (WHO 2010, at p. 122) and present in low concentrations in the cells of all living organisms, including as a normal component of human blood. Formaldehyde is a simple chemical compound made of hydrogen, oxygen and carbon, with the formula  $H_2CO$ . Formaldehyde is naturally made (an endogenous chemical) in the body and serves as a building block for the biosynthesis of more complicated molecules. (Neuberger 2005).

Formaldehyde (gas) is highly water soluble and when inhaled reacts rapidly at the site of first contact in the nose and nasal cavity to form methanediol, which is also called formaldehyde acetal or FAcetal, which reacts rapidly with other molecules, preferentially with glutathione (GSH) to form thioacetal (also called S-hydroxymethylglutathione). Importantly, all of these chemicals are natural constituents of every cell in the bodies of humans, and other animals.

Formaldehyde occurs naturally in the environment and does not accumulate in either the environment or in people, plants or animals. Virtually every living creature, including trees, fish, and humans, respire out small amounts of formaldehyde. It is a matter of biology. Thus, humans join other living creatures in respiring (exhaling) naturally formed formaldehyde in small levels.

The World Health Organization (WHO) reports that “Human exhaled air contains formaldehyde in concentrations in the order of 0.001-0.01  $mg/m^3$ , with an average of about 0.005  $mg/m^3$ .” (WHO 2010, at p. 111). For the sake of comparison, these values

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are 0.81 to 8 parts per billion (ppb), with an average of 4 ppb.<sup>4</sup> The National Research Council's Committee reviewing EPA's Draft IRIS Assessment of Formaldehyde writes, "The committee concludes, however, that regardless of the methodologic issue related to breath analysis, formaldehyde is normally present at a few parts per billion in exhaled breath after the measurement error associated with a trace contaminant in the reagent gas used in previous mass-spectrometric methods is taken into account." (NRC 2011, at p. 23). Although there are analytical challenges in accurately determining formaldehyde concentrations in human breath (Moser et al., 2005; Kushch et al., 2008), the levels detected using a chemical-specific methodology fall into the low-ppb range (i.e., <0.5–1.7 ppb) (Riess et al., 2010). (Golden 2011).

Formation of formaldehyde and these other chemicals are independent of any external source of formaldehyde. Andersen et al., have studied the basic biology in experimental animals and humans and developed a biologically-based pharmacokinetic (PBPK) model to describe inhalation, natural formation and movement of formaldehyde through the body. In a recent publication by Andersen et al., they included Figure 1, shown below, which describes the rates that formaldehyde can enter the body via inhalation and natural production ( $k_o$ ). Thus, unexposed people will naturally produce and exhale formaldehyde (shown as the dotted line from the hydrated form of formaldehyde ( $\text{CH}_2(\text{OH})_2$ ). (Andersen et al., 2010a).

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<sup>4</sup> To convert  $\text{mg}/\text{m}^3$  to ppb, use the calculation:  
 $(X \text{ ppb}) = [(\text{mg}/\text{m}^3)(24.45) / (\text{molecular weight})] (1000)$

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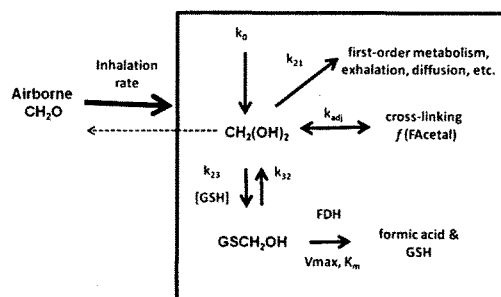


FIG. 1. The tissue biochemistry PK model for FA. Inhaled FA is rapidly hydrated to FAcetal—CH<sub>2</sub>(OH)<sub>2</sub>. The acetal is lost by first-order processes, i.e., diffusion back to the air phase, diffusion onto deeper tissues, first-order metabolism, etc., and by reaction with GSH to form the thioacetal. The thioacetal (GSCH<sub>2</sub>OH) can dissociate to FAcetal or be converted by FDH to formic acid with release of GSH. The rate constants here are used in the tissue PK model to estimate the relationship between tissue FAcetal and inhaled FA. K<sub>adj</sub> estimates DNA binding from the calculated FAcetal.

Source: Anderson, M.E. et al., 2010. Formaldehyde: Integrating dosimetry, cytotoxicity, and genomics to understand dose-dependent transitions for an endogenous compound. *Toxicol. Sci.* 118(2):716-731.

The WHO reports that 90-95% of inhaled formaldehyde is immediately absorbed (Garcia et al, 2009) in the nasal tissue where the moisture in these tissues rapidly convert formaldehyde gas into the hydrated (water soluble) form of formaldehyde; the remaining amount, about 5%, travels into the lower respiratory tract, where it is absorbed and converted. (WHO 2010).

Additionally, in aqueous systems, including moist tissues, formaldehyde exists primarily (>99.9%) in its hydrated form of methanediol, with only a small amount (<0.1%) as free formaldehyde. Because free formaldehyde can diffuse from tissues in the upper respiratory tract into exhaled air, small, but measurable, amounts can be detected in the breath. (Golden 2011).

Scientists have studied and characterized these well-known metabolic changes and concluded that the metabolized components from inhaled formaldehyde remain in the tissues of initial contact (upper respiratory tissues) and are unlikely to move into the blood or distant tissues. (Lu et al, 2010; Swenberg et al, 2010; Moeller et al., 2011; NRC 2011). Research has shown that inhalation of formaldehyde at levels that most people are normally exposed does not alter the formaldehyde levels naturally present in the body. (Kimbell et al., 2001; Andersen et al., 1999, and 2010b). In his March 18, 2010 testimony, before the House Committee on Energy and Commerce, Dr. Andersen stated, "Our current studies, in an area called pharmacokinetic modeling, show that formaldehyde inhaled at concentrations of 100 ppb or below would not increase cellular



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formaldehyde in cells in the nose significantly over physiological concentrations.” (Andersen 2010c).

Recent studies have used radiolabeled ( $C^{14}$ ) formaldehyde to investigate the movement of inhaled formaldehyde in the body. These radiolabeled studies distinguish between inhaled (exogenous) formaldehyde, which can be radiolabeled, and naturally-formed (endogenous) formaldehyde, which are not. Older studies did not make this differentiation, thus, as scientists interpret the findings from these older studies, they are required to question whether it is biologically plausible that inhaled formaldehyde in the presence of high levels of naturally produced formaldehyde can be attributed to the health effect reported. Clearly then, the source of formaldehyde becomes an important factor in evaluating the health effect and assessing the potential risk attributed to inhaled formaldehyde.

EPA is proposing a cancer risk value for *inhaled* formaldehyde that is lower than the natural formaldehyde levels we humans exhale. Thus, when EPA proposes a risk value of 0.0008 ppb, it is proposing to set the  $10^{-6}$  cancer risk projection level below that which is naturally present in all cells of living organisms and below that which humans and most living creatures exhale.

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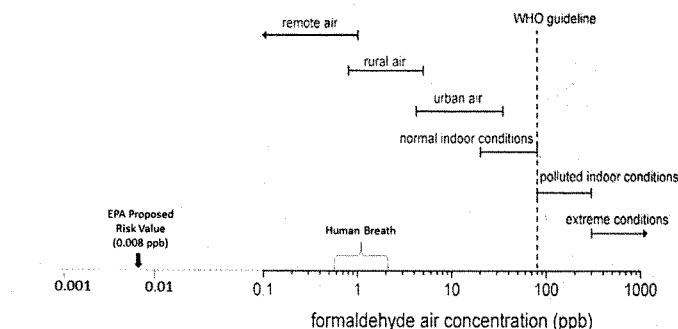


FIGURE 1-2 Formaldehyde concentration in various environments. Abbreviation: WHO, World Health Organization. Source: Salthammer et al. 2010. Reprinted with permission; copyright 2010, American Chemical Society.

Graphic adapted from NRC. 2011. Review of the EPA Draft IRIS Assessment of Formaldehyde. At p.13.

ACC adapted NRC Figure 1-2 (above) to include EPA's proposed risk value for formaldehyde and the most recent levels of formaldehyde reported from human breath (corrected for methodologic issues). Of note is the dotted line showing the WHO's indoor air guideline. WHO's indoor air guideline for formaldehyde is based on a review of the scientific literature, the relevance to risk assessment, and the application of exposures. WHO provides a health protective value for formaldehyde at  $0.1 \text{ mg/m}^3$  (80 ppb) and reports that this guideline is protective for any short-term exposure (30-minute period) and for long-term health effects. (WHO 2010, at pg. xxv and 141).

The proposed IRIS cancer risk projections suggest the range of formaldehyde in normal exhaled human breath would pose a cancer risk greater than EPA's acceptable level of  $10^{-4}$ . Projections of risk in the Draft IRIS Assessment attributable to formaldehyde at levels typically seen in indoor air or our own breath do not accord with reasonable upper estimates of potential human cancer risk. Several of the comments from other federal agencies that reviewed the draft IRIS assessment suggested there should be a "reality check" on some of the conclusions reached. For example, the Department of Defense stated:

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“A reality check of formaldehyde in the diet and in healthy individuals compared with lifetime risks of leukemia should be presented. Although an estimated 1 to 10 mg per day ingestion is cited (EPA 2010, page 2-11), it is not in proximity to, nor compared with, neither the existing data on risk of leukemia from all sources nor with the unit cancer risk of  $8.1 \times 10^{-2}$  per ppm ( $6.6 \times 10^{-5}$  per  $\mu\text{g}/\text{m}^3$ ).

Similarly, in its comments, OMB called on EPA to reconcile the Draft IRIS Assessment with real-life observations and experience. (OMB 2010).

There are numerous sources of formaldehyde, which are well described in the NRC’s Review of EPA’s Draft IRIS Assessment of Formaldehyde:

“Formaldehyde is a common environmental chemical that is found in ambient and indoor air. It is also present naturally in some foods and is a metabolic intermediate in the human body. For ambient air, major emission sources include power plants, incinerators, refineries, manufacturing facilities, and automobiles (ATSDR 1999; IARC 2006). Formaldehyde is also produced by vegetative decay, animal wastes, forest fires, and photochemical oxidation of hydrocarbons in the lower atmosphere (ATSDR 1999; IARC 2006). The most recent EPA data on ambient-air concentrations indicate that the annual means at monitoring sites range from 0.56 to 36.31 ppb, and the overall mean is 2.77 ppb (EPA 2010). If the data are categorized by land use, agricultural locations have the lowest mean, 1.68 ppb, and locations affected primarily by mobile sources have the highest mean, 5.52 ppb.

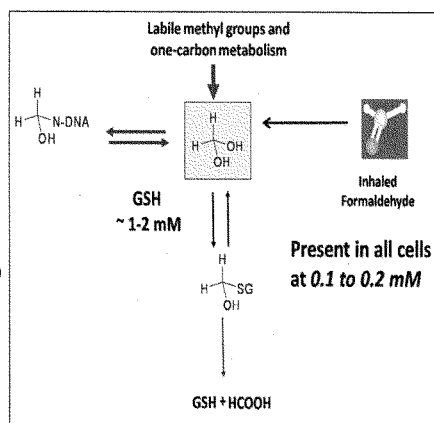
Indoor air typically has higher formaldehyde concentrations than ambient air (ATSDR 1999; IARC 2006; EPA 2010). Major indoor emission sources include building materials, consumer products, gas and wood stoves, kerosene heaters, and cigarettes. Indoor-air concentrations depend on the age and type of construction. Older conventional homes have lower formaldehyde concentrations than newer constructions, and conventional homes have lower formaldehyde concentrations than mobile homes. Formaldehyde concentrations in indoor air have been decreasing since the 1980s, when restrictions on formaldehyde emissions from building materials were tightened (ATSDR 1999; EPA 2010; Salthammer et al. 2010). However, on the basis of a review of international studies, Salthammer et al. (2010) estimated the average formaldehyde exposure of the general population to be 16-32 ppb in air. Figure 1-2 provides ranges of formaldehyde air concentrations in various environments.” (NRC 2011, at p. 13).

In written comments to the National Toxicology Program (NTP), Dr. M. Andersen outlined the chemistry of formaldehyde to respond to NTP’s mischaracterization of

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formaldehyde in its draft Report on Carcinogens. Specifically, Dr. Andersen was responding to the need to correct the following sentence: "It is also well recognized that formaldehyde exists in equilibrium with methanediol and with S-hydroxymethylglutathione, both of which offer possible mechanism for formaldehyde to enter the blood and be transported to other tissues." (NTP 2009). "The sentence shows a lack of understanding of the chemistry and biochemistry of formaldehyde in tissues and should be corrected." (Andersen 2010c). Below is Dr. Andersen's description to justify correcting this NTP statement.

**"Chemistry:** As shown in the figure to the right from my presentation, formaldehyde, as a non-hydrated aldehyde, predominates only in the air phase. Whether in the extracellular spaces or within cells, free formaldehyde will be present at extremely low concentrations. It first reacts reversibly with water to form an acetal (i.e., formaldehyde acetal shown in the blue box). The equilibrium constant for acetal versus free formaldehyde is somewhere between 5,000 and 10,000. The acetal reacts with a variety of other tissue nucleophiles, preferentially interacting with glutathione (GSH) to form what a chemist would call thioacetal. The text refers to the acetal as methanediol and the thioacetal as S-hydroxymethylglutathione.



Both of these are natural constituents of every cell in the body – in the nose, in the blood, in the bone marrow, everywhere. Importantly, each tissue has an endogenous rate of formaldehyde production due to various pathways involved in single carbon metabolism. The combined steady-state concentration of thioacetal and acetal in cells is large, about 0.1 to 0.2 mM, a very significant concentration that exists without causing toxicity or pathology. With a dissociation constant of 1.5 mM for the GSH-thioacetal, approximately 60% of formaldehyde in any tissue is expected to be in the S-hydroxymethylglutathione pool.

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Mammalian cells have robust processes to insure that the endogenous formaldehyde acetal is tightly controlled. The thioacetal formed with glutathione is the substrate for formaldehyde dehydrogenase that converts the thioacetal to formic acid with release of free GSH. When we speak of formaldehyde in tissues, we actually mean a mixture of acetal, thioacetal, other reversible interaction products and extremely small amounts of free formaldehyde ( $\text{CH}_2\text{O}$ ) at any time. Of these forms, the thioacetal is the major cellular form of formaldehyde under normal conditions.

In the nose, most inhaled formaldehyde is absorbed into the first epithelial surfaces encountered by the gas during inspiration. In these areas concentrations of the acetal increase leading to higher tissue reactivity and toxicity due to complexing of all available GSH and partial saturation of FDH. Some acetal will diffuse to adjacent tissues where it becomes diluted and enters into the pool of acetal and especially thioacetal. At all times and in all tissues, there is a high concentration of the acetal and thioacetal. Small amounts of these forms of formaldehyde, i.e., the methanediol and S-hydroxymethylglutathione, moving from the contact site to distant tissue will have no appreciable influence on total levels of formaldehyde in these distant tissues. Neither will they serve as a delivery for unreacted formaldehyde to these tissues.

With formaldehyde, low dose linear extrapolations are unwarranted since these methodologies completely ignore the basic biology of this important endogenous compound. At the highest tolerable inhaled concentrations of formaldehyde, there will be responses at the site of contact and not in distant tissues. At concentrations only slightly below those causing toxicity, the risks of any response even in the nose falls rapidly as the increment of tissue formaldehyde – acetal, thioacetal, etc. - from inhalation becomes small with respect to normal background production in tissues.

In summary, the concluding sentences of the toxicokinetics section in the report are incorrect and misleading. Neither the acetal nor the thioacetal represent ways in which significant amounts of formaldehyde could enter the circulation and reach distant tissues. The panel needs to justify this statement since it is contrary to our extensive understanding of formaldehyde chemistry and biochemistry. In addition, the comment in the last sentence says that high endogenous levels represent a challenge for extrapolation. They certainly do. The challenge for the panel should have been to provide any reasonable argument that inhaled formaldehyde can in any way cause biologically appreciable increases in tissue concentration at sites remote from the epithelial cells lining the respiratory tract. There was no attempt at justification because none is possible." (Andersen 2010d).

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**Questions Submitted by Ms. Donna F. Edwards, Ranking Member**

**Question 1**

*In your testimony you said The Formaldehyde Council had become one of about “50 different specific product panels that we have under ACC. So they are,” you said, “a self-funded group that is operated under the umbrella of the American Chemistry Council.” Please provide us with a list of all of these or other organizations “operated under the umbrella of the American Chemistry Council.” This list should include:*

- *The full name of the organization or group, including not-for-profit corporations or other affiliated entities;*
- *The year the organization began its association with the ACC.*

The ACC Chemical Products and Technology Division provides technical and management services, issue management activities, specialized advocacy, research, education, communication and evaluation services to a core group of more than 50 self-funded sector and product groups (or “Panels”). The following is a list of the current Chemical Products and Technology Division Panels and the charter date for each Panel:

Panel	Charter Date
Acetone Panel	1990
Aliphatic Diisocyanates Panel	2001
Aliphatic Esters Panel	1999
Alkanolamines Panel	2003
Amines Panel	1999
Biocides Panel	1986
Calcium Chloride Panel	2004
Center for Advancing Risk Assessment Science and Policy	2008
Chelants Panel	2003
Chemical Information Technology Center	2005
Chemical Industry Quality Management Group	1990
Cresols Panel	1984
Crystalline Silica Panel	1989
Cumene Panel	1985
Diisocyanates Panel	2000
Ethylbenzene Panel	1994
Ethylene Oxide/Ethylene Glycols Panel	1982 (EO), 1986 (EG) combined in 2002



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Panel	Charter Date
Fatty Nitrogen Derivatives Panel	2003
FluoroCouncil	2011
Formaldehyde Panel	2010
Gamma Butyrolactone and 1,4 Butanediol Panel	2000
Glycol Ethers (Ethylene & Propylene) Panel	2002
Hexavalent Chromium Panel	2009
High Molecular Weight Phthalate Esters Panel	2011
Higher Olefins Panel	1991
Hydrocarbon Solvents Panel	1995
Hydrogen Fluoride Panel	1988
Hydrogen Peroxide Panel	2001
Industrial Gases Panel	2011
Isophorone EDSP Consortium	2010
Isopropanol Panel	1987
Ketones Panel	1980
Lubricant Additives Alkyl Phenol Panel	2006
Nanotechnology Panel	2004
North American Flame Retardant Alliance	2010
Olefins Panel	1994
Oxo Process Panel	1986
Petroleum Additives Panel	1990
Petroleum Additives Fuel Additives Task Group	1990
Petroleum Additives Health, Environmental and Regulatory Task Group	1990
Petroleum Additives Product Approval Protocol Task Group	1990
Phenol Panel	2003
Phosgene Panel	1972
Phthalate Esters Panel	1973
Pine Chemicals Panel	2011
Propylene Oxide/Propylene Glycol Panel	1993
Pyridine Panel	2000
Sodium Chlorite-Chlorine Dioxide Panel	2000
Solvents Industry Group	1995
Specialty Acrylates/Methacrylates Panel	1987
Specialty Plasticizers Panel	2008
Toluene & Xylene Panel	2002
Vinyl Chloride Health Committee	1974

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The Chlorine Chemistry Division, which represents major producers and users of chlorine in the U.S. and promotes and protects the sustainability of chlorine chemistry processes, products and applications, engaging in regulatory activities for chlor-alkali and chlorine products, is a self-funded division of ACC. The Chlorine Chemistry Division (formerly known as the Chlorine Chemistry Council) was formed in 1993.

The Research Foundation for Health and Environmental Effects (RFHEE) is a 501(c)(3) tax-exempt organization established by the Chlorine Chemistry Division. RFHEE was incorporated in 1995.

The Plastics Division, which advocates for and promotes the economic, environmental and societal benefits of plastic products, is a self-funded division of ACC. The Plastics Division was formed in 2002 as a result of a merger between ACC and the American Plastics Council. The Plastics Division contains the following self-funded product groups:

Product Group	Charter Date
Progressive Bag Affiliates	2008
Center for the Polyurethanes Industry	2002
Plastics Foodservice Packaging Group	2002
Spray Foam Coalition (self-funded group of CPI)	2010
Polycarbonate/BPA Global Group	2002
Rigid Plastic Packaging Group	2002

**Question 2**

***Please provide a more specific explanation of the relationship between the ACC and The Formaldehyde Counsel [sic] as it has evolved since 2007. In your testimony, you indicated that the Formaldehyde Counsel [sic] has come under ACC's umbrella in the last six months. Please explain the nature of the relationship between the ACC and FC. For example, have you shared offices? Staff, officers or board members? Has there been any kind of financial arrangement and who has provided support to whom? How did the FC come to be absorbed by ACC and what is the legal status of the FC at this point of time?***

The Formaldehyde Council dissolved in January 2011 and no longer exists as an organization. Companies with an interest in formaldehyde formed a new self-funded panel under the ACC umbrella in 2010. Prior to the formation of the new formaldehyde panel at ACC in 2010, ACC had limited, if any, involvement in formaldehyde-related issues.

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ACC has never shared offices, staff, officers or board members with The Formaldehyde Council. ACC did enter into a sublease agreement with The Formaldehyde Council on January 1, 2007, whereby ACC subleased space to The Formaldehyde Council at its former headquarters at 1300 Wilson Boulevard in Arlington, Virginia. The Formaldehyde Council vacated this space in September 2009.

There has never been any kind of a financial relationship between ACC and The Formaldehyde Council, as both organizations operated independently of each other and relied on their own separate funding.

**Question 3**

***The American Chemistry Council has several subsidiary bodies, such as the Chlorine Chemistry Council, and subsidiary foundations. Please provide a full report of how much the ACC and its subsidiary entities spends each year on research and public communications designed for use in influencing risk assessment or risk management discussions? Please provide an accounting for 2008 to the present with a break out by year, funding organization, funding recipient, purpose, deliverable, and amount.***

ACC, its divisions and self-funded product groups have spent a total of \$45,515,356.85 on research since 2008. The breakdown of these expenditures is as follows:

Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Aliphatic Diisocyanates Panel	2008	\$11,218.32	Belcan Services Group Ltd. Partnership	HDI Study.
Aliphatic Diisocyanates Panel	2008	\$60,000.00	The Hamner Institutes for Health Sciences	Evaluation and Mapping of HDI-induced Lung Lesions for Dosimetry Modeling Efforts.
Aliphatic Diisocyanates Panel	2008	\$30,000.00	The Hamner Institutes for Health Sciences	Measurement of Uptake of Hexamethylene Diisocyanate (HDI) in the Upper Respiratory Tract of F344 Rats and Calibration of Interspecies Respiratory Tract Dosimetry Models Study
American Solvents Council	2008	\$10,000.00	NPCA	Environmental study.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Amines Panel	2008	\$75,214.80	BASF Aktiengesellschaft	Study of Diamylamine (Dipentylamine).
Amines Panel	2008	\$72,209.50	BASF Aktiengesellschaft	Study of Dibutylamine Hydrochloride.
Amines Panel	2008	\$72,209.50	BASF Aktiengesellschaft	Study of Dimethylamine Hydrochloride.
Amines Panel	2008	\$34,043.93	BASF Aktiengesellschaft	Study of In vitro Chromosomenanalyse (V79-Zellen) and Diamylamine (Dipentylamine).
Amines Panel	2008	\$27,235.13	BASF Aktiengesellschaft	Study of In vitro Chromosomenanalyse (V79-Zellen) and Methylaminoethanol.
Amines Panel	2008	\$18,803.70	BASF Aktiengesellschaft	Study of Methylaminoethanol.
Amines Panel	2008	\$72,209.50	BASF Aktiengesellschaft	Study of Morpholine Hydrochloride.
Biocides Panel	2008	\$89.00	ISSA	447 Cleaning Times Calculator Kit (for AEATF II Study).
Brominated Flame Retardant	2008	\$312.97	EPL Archives Inc	Annual Storage Charges.
Brominated Flame Retardant	2008	\$571.65	WIL Research Laboratories LLC	Archival Storage.
Center for the Polyurethane Industry (CPI)	2008	\$11,000.00	Air Quality Sciences, Inc	Comprehensive research project to determine the types and levels of chemicals emitted from spray polyurethane foam insulation.
Center for the Polyurethane Industry (CPI)	2008	\$9,500.00	Polyisocyanurate Insulation Manufacturers Association	Unavailable.
Center for the Polyurethane Industry (CPI)	2008	\$10,000.00	Spray Polyurethane Foam Alliance	SPFA CpvC 2008 testing research study.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Crystalline Silica Panel	2008	\$14,131.79	University of Vermont	Protocol For A Study Of The Relationship Between Mortality And Silica Exposure In Vermont Granite Workers.
Diisocyanates Panel	2008	\$86,950.00	Bayer Material Science LLC	ACC/NIOSH TDI Epidemiology Study - Industrial Hygiene Sample Analysis Summary Report.
Diisocyanates Panel	2008	\$29,150.00	Bayer Material Science LLC	Study of 2,4- and 2,6-Toluene Diisocyanate for the DII-NIOSH Research Collaboration Project.
Ethylbenzene Panel	2008	\$48,500.00	Dow Chemical Company	For initiation, lab work, synthesized radiotracers and microsomes
Ethylbenzene Panel	2008	\$587.00	Huntingdon Life Sciences Inc.	Storage Fees.
Ethylbenzene Panel	2008	\$1,000.00	Research Foundation For Health & Environmental Effects	Retrieval of NHANES data.
Ethylene Glycol Panel	2008	\$67,998.19	Battelle Memorial Institute	Develop a Physiologically Based Pharmacokinetic Model.
Ethylene Glycol Panel	2008	\$54,340.00	Dow Chemical Company	In Vitro Percutaneous Absorp.
Ethylene Glycol Panel	2008	\$98,000.00	Dow Chemical Company	In Vivo & In Vitro. Execution of the Oral Gavage work.
Ethylene Glycol Panel	2008	\$28,500.00	Dow Chemical Company	Unavailable.
Ethylene Glycol Panel	2008	\$48,108.64	Louisiana State University	Cell culture studies on metabolism of Ethylene Glycol in Kidney cells.
Ethylene Glycol Panel	2008	\$35,546.42	LSU Health Sciences Foundation	Studies on the pharmacodynamics of DEG
Global Affairs	2008	\$159,692.00	Cefic	Study on chemical industry GHG emissions

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Glycol Ethers Panel	2008	\$78,683.44	Battelle Memorial Institute	Study of BEAA pharmacokinetics in rats.
Glycol Ethers Panel	2008	\$585.00	Charles River Laboratories	Archiving Services.
Glycol Ethers Panel	2008	\$45,150.00	Dow Chemical Company	In-Life Study.
Health, Products, & Science Policy	2008	\$30,000.00	Summit Toxicology LLP	Biomarker - Internal dose relationship manuscript.
Health, Products, & Science Policy	2008	\$35,000.00	Summit Toxicology LLP	Development of a Manuscript to Improve Derivation of Biomonitoring Equivalents.
Health, Products, & Science Policy	2008	\$65,000.00	Summit Toxicology LLP	Enhancing the Use of Biomonitoring Equivalents.
Health, Products, & Science Policy	2008	\$40,000.00	Summit Toxicology LLP	Outreach to Inform and Educate on Biomonitoring Equivalents in Important Venues.
Health, Products, & Science Policy	2008	\$108.89	WIL Research Laboratories LLC	Archiving fees.
Ketones Panel	2008	\$2,700.00	Integrated Laboratory Systems, Inc	Manuscript Methyl Isobutyl Ketone Induced $\alpha$ 2u-Globulin Nephropathy in Male and Female F344 Rats
Long Range Research	2008	\$7,500.00	American Association For Aerosol Research	Sponsorship of the 2010 International Specialty Conference "Air Pollution and Health: Bridging the Gap from Sources to Health Outcomes" held March 22-26, 2010 in San Diego, CA.
Long Range Research	2008	\$24,928.06	Battelle - Northwest	Chlorpyrifos Human Health Risk Assessment.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Long Range Research	2008	\$4,040.23	Bette Meek	Travel Expenses for Attendance at the ICCA-LRI Workshop: Twenty-First Century Approaches to Toxicity Testing, Biomonitoring and Risk Assessment, Amsterdam
Long Range Research	2008	\$12,000,000	CIIT Centers For Health Research	Research activities in various fields including the study of the long-term environmental and human health effects of chemicals.
Long Range Research	2008	\$25,071.94	Dow Chemical Company	Unavailable.
Long Range Research	2008	\$25,000.00	Environ International Corporation	Unavailable.
Long Range Research	2008	\$16,613.00	Environ International Corporation	Unavailable.
Long Range Research	2008	\$214,942.60	ICF Incorporated	Project on "Olfactory Toxicity of Hydrogen Sulfide."
Long Range Research	2008	\$38,249.24	ICF Incorporated	Project on "Reverse Dosimetry."
Long Range Research	2008	\$22,159.82	ICF Incorporated	Project on "Using Genomic Technologies to More Efficiently Screen for Carcinogens." Summary for the ISEA air toxics symposium.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Long Range Research	2008	\$9,140.32	ICF Incorporated	Projects on "Olfactory Toxicity of Hydrogen Sulfide," "Innovative Experimental Techniques to Help Understand Exposure to Volatile Organic Air Toxics," implications of endocrine disruptors contamination in surface waters, and "Evaluating fence lizards for a reptile model for endocrine mediated toxicity studies."
Long Range Research	2008	\$11,123.38	ICF Incorporated	Projects on "Olfactory Toxicity of Hydrogen Sulfide" and "Reverse Dosimetry."
Long Range Research	2008	\$2,621.00	ICF Incorporated	Projects on "Reverse Dosimetry," and "Innovative experimental techniques to help understand exposure to volatile organic air toxics."
Long Range Research	2008	\$15,929.29	ICF Incorporated	Projects on "Reverse Dosimetry" and "Effects of a Sensitive Estrogen on Aquatic Populations: A Whole Ecosystem Study."
Long Range Research	2008	\$9,878.12	ICF Incorporated	Projects on "Reverse Dosimetry" and "Effects of a Sensitive Estrogen on Aquatic Populations: A Whole Ecosystem Study." Attended the International Society of Environmental Epidemiology/ International Society of Exposure Analysis.
Long Range Research	2008	\$16,537.41	ICF Incorporated	Projects on "Reverse Dosimetry" and "Innovative experimental techniques to help understand exposure to volatile organic air toxics."



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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Long Range Research	2008	\$39,025.00	ICF Incorporated	Projects on "Using Genomic Technologies to More Efficiently Screen for Carcinogens," "Making Sense of Genomic Data: a Dose-Response Analysis Approach," and "Effects of a Sensitive Estrogen on Aquatic Populations: A Whole Ecosystem Study."
Long Range Research	2008	\$34,481.35	ICF Incorporated	Projects on "Using Genomic Technologies to More Efficiently Screen for Carcinogens," "Making Sense of Genomic Data: a Dose-Response Analysis Approach," "Effects of a Sensitive Estrogen on Aquatic Populations: A Whole Ecosystem Study," "Olfactory Toxicity of Hydrogen Sulfide," and "Evaluating fence lizards for a reptile model for endocrine mediated toxicity studies."
Long Range Research	2008	\$29,361.42	ICF Incorporated	Research operations, management, and communications support.
Long Range Research	2008	\$100,000.00	Integrated Laboratory Systems, Inc	Validation studies of the intact adult male rat screening assay
Long Range Research	2008	\$800,000.00	National Institute of Child Health & Human Dev.	Research initiative entitled "New Study Design and Methods to Evaluate Gene and Environmental Chemical Interaction Data."
Long Range Research	2008	\$100,000.00	Research Triangle Institute	Validation studies of the intact adult male rat screening assay for four chemicals.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Long Range Research	2008	\$1,500,000	The Hamner Institutes for Health Sciences	Extension of ToxCast/Hamner Collaboration.
Long Range Research	2008	\$685.20	The Hamner Institutes for Health Sciences	OECD/IPCS Adv. Group-Toxicogenomics.
Long Range Research	2008	\$1,000,000	The Hamner Institutes for Health Sciences	Research involving Cytochrome C, F-actin, Tublin and c-Jun.
Lubricant Additives Alkyl Phenol Panel	2008	\$4,155.00	Locus Technologies	LAAPP Risk Assessment.
Lubricant Additives Alkyl Phenol Panel	2008	\$1,290.00	Locus Technologies	Wastewater and sediment collection study for analyzing Tetrapropenylphenol (TPP) from SI Group's Four Ashes Plant in the UK.
Lubricant Additives Alkyl Phenol Panel	2008	\$58,520.00	WIL Research Laboratories LLC	90-Day Dietary Dose Range-Finding Toxicity Study of Tetrapropenyl Phenol in Rats.
Methyl Bromide Industry Panel	2008	\$798.50	EPL Archives Inc	Annual Storage Charges.
Methyl Bromide Industry Panel	2008	\$3,001.13	TNO Voeding	Unavailable.
Methyl Bromide Industry Panel	2008	\$1,415.51	WIL Research Laboratories LLC	Storage fees.
Olefins Panel	2008	\$48,017.55	Cefic	Preparation of modified defined sequence of Oligonucleotides that contain site-specific Alkylated 2'-Deoxynucleosides (Mainly N7-Alkylated 2'-Deoxyguanosine residues). Studies on the biological consequences of adducts formed in DNA by epoxides.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Olefins Panel	2008	\$35,000.00	Centre National De La Recherche Scientifique Dr12	Investigation of DNA adducts.
Olefins Panel	2008	\$92,000.00	Dow Chemical Company	Unavailable.
Olefins Panel	2008	\$1,000.00	EPL Archives Inc	Annual Storage Charges.
Olefins Panel	2008	\$1,726.85	EPL Archives Inc	Setup and Storage Charges.
Olefins Panel	2008	\$3,114.62	EPL Archives Inc	Storage required under Good Laboratory Practice Standards (GLPs).
Olefins Panel	2008	\$60,000.00	GSF-Institut Fur Toxikologie	Research on in vitro metabolism of ethylene in rat, mouse and human tissue.
Olefins Panel	2008	\$40,000.00	Institute of Toxicology	Animal studies to support the development of a PBPK model for Butadiene.
Olefins Panel	2008	\$78,000.00	International Institute of Synthetic Rubber Products	Follow-up analysis on the female epidemiology study.
Olefins Panel	2008	\$50,000.00	Johannes G. Filser	Research on metabolism and kinetics of ethylene in the mouse
Olefins Panel	2008	\$25,000.00	Johannes G. Filser	Support the following publications: Results of Butadiene Metabolism in Perfused Livers. Data from In Vivo exposures of rats and mice to Butadiene.
Olefins Panel	2008	\$34,350.00	Michigan State University	Investigations on the histochemical and morphometric analyses of nasal tissues from a 90-day Inhalation toxicology study of ethylene.
Olefins Panel	2008	\$50,000.00	Minnesota Medical Foundation	Research on DNA adducts of Butadiene.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Olefins Panel	2008	\$10,000.00	Robert P. Fuchs	Investigation on DNA adducts.
Olefins Panel	2008	\$70,000.00	University Of North Carolina	Research on Hemoglobin Adducts in Butadiene exposed animals and workers.
Oxo Process Panel	2008	\$100,137.52	Battelle Memorial Institute	Diethylhexyl Terephthalate Diet Study.
Oxo Process Panel	2008	\$81,371.88	Battelle Memorial Institute	Study of Propanol Inhalation Kinetics.
Oxo Process Panel	2008	\$18,000.00	Dow Chemical Company	Analytical work for a two-generation inhalation reproductive toxicity study of butyl acetate in rats.
Oxo Process Panel	2008	\$80,000.00	WIL Research Laboratories LLC	Inhalation Two-Generation Reproduction Toxicity Study of n-Butyl Acetate in Rats.
Phenol Panel	2008	\$1,152.00	Huntingdon Life Sciences Inc.	Shipment Fees.
Phenol Panel	2008	\$479.00	Huntingdon Life Sciences Inc.	Storage Fees.
Phthalate Esters Panel	2008	\$6,500.00	Simon Fraser University	Preparation of a research paper on Bioaccumulation of Phthalate Esters in Staghorn Sculpin.
Plastics Division	2008	\$60,000.00	Mississippi State University	Research on a "Model for Predicting the Strain Rate and Temperature Sensitive Impact Performance of Plastic Components - Phase I."
Plastics Division	2008	\$73,764.00	University of Dayton	Optimization of specimens used for high rate testing of long-fiber filled-polymers
Plastics Division	2008	\$17,600.00	Vehicle Recycling Partnership	Steam Stripping Study for Reduction of PCB/s in Plastic from Shredder Residue.
Plastics Division	2008	\$18,000.00	Vehicle Recycling Partnership	Support "Recycling End-of-Life Vehicles of the Future."

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<b>Funding Cost Center</b>	<b>Year</b>	<b>Amount</b>	<b>Funding Recipient</b>	<b>Purpose</b>
Plastics Division	2008	\$12,000.00	Vehicle Recycling Partnership	Vacuum Devolitzation Project.
Polycarbonate/BPA Global Group	2008	\$208.14	Battelle Memorial Institute	Research on Bisphenol A.
Pyridine & Pyridine Derivative Panel	2008	\$9,375.00	Charles River Laboratories	Reproduction/developmental toxicity screening test in rats.
Toluene & Xylene Panel	2008	\$8,000.00	Research Foundation For Health & Environmental Effects	Retrieval of NHANES data.
Vinyl Chloride Health Committee	2008	\$36,875.00	Environ International Corporation	Study of "Exposure reconstruction for men employed in the vinyl chloride industry from 1942-1972."
Vinyl Chloride Health Committee	2008	\$2,495.00	Huntingdon Life Sciences Inc.	Storage Fees.
Vinyl Chloride Health Committee	2008	\$4,000.00	Research Foundation For Health & Environmental Effects	Retrieval of NHANES data.
<b>2008 Subtotal</b>		<b>\$18,728,983.45</b>		
Aliphatic Diisocyanates Panel	2009	\$85,500.00	The Hamner Institutes for Health Sciences	Measurement of Uptake of Hexamethylene Diisocyanate (HDI) in the Upper Respiratory Tract of F344 Rats and Calibration of Interspecies Respiratory Tract Dosimetry Models.
Aliphatic Diisocyanates Panel	2009	\$45,000.00	The Hamner Institutes for Health Sciences	Unavailable.

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Aliphatic Esters Panel	2009	\$15,340.00	Harlan Laboratories Ltd	Conducting the following tests: (1) Maleic acid, bis (1,3-dimethylbutyl)ester. (2) Adipic acid, dodecyl ester. (3) Azelaic acid, diisodecyl ester.
Aliphatic Esters Panel	2009	\$6,740.40	Harlan Laboratories Ltd	Test Materials - Adipic Acid, bis[2-(2-butoxyethoxy)ethyl] ester.
Aliphatic Esters Panel	2009	\$11,088.00	Harlan Laboratories Ltd	Test Materials - Glycol Esters.
Aliphatic Esters Panel	2009	\$3,349.65	Harlan Laboratories Ltd	Testing to determine the physico-chemical properties of test material.
Alkanolamines Panel	2009	\$256,691.33	BASF Aktiengesellschaft	ALK MEA HCL study.
Alkanolamines Panel	2009	\$12,500.00	Dow Chemical Company	ALK-Hepatic Choline Analysis.
Amines Panel	2009	\$56,411.10	BASF Aktiengesellschaft	Diamylamine (dipentylamine) in Wistar rats.
Amines Panel	2009	\$18,803.70	BASF Aktiengesellschaft	Diamylamine test study in Wistar rats.
Amines Panel	2009	\$43,325.70	BASF Aktiengesellschaft	Dimethylamine Hydrochloride in rats.
Amines Panel	2009	\$75,214.80	BASF Aktiengesellschaft	Methylaminoethanol in Wistar rats.
Amines Panel	2009	\$72,209.50	BASF Aktiengesellschaft	Morpholine Hydrochloride.
Amines Panel	2009	\$59,983.80	BASF Aktiengesellschaft	OECD 422 study via gavage of Diamylamine (mixed) CAS No. 2050-92-2
Amines Panel	2009	\$7,078.00	Fraunhofer Institute of Toxicology And Environment	Histopathology of the reproductive organs from the study "90 Tage Inhalationstoxizitätsprüfung mit Dibutylamin."
Biocides Panel	2009	\$4,435.00	Eurofins Product Safety Labs Inc	Studies conducted on BARDAC 2280.

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Biocides Panel	2009	\$22,386.80	Golden Pacific Laboratories	Freezer storage stability of C14 Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Dressing Sponges, Hand Washes, Inner Dosimeters, Outer Dosimeters, Air Sampling Tubes and Fiberglass Filters
Biocides Panel	2009	\$825,800.50	Golden Pacific Laboratories	Study for measurement of potential dermal and inhalation exposure during application of a liquid antimicrobial pesticide product using bucket and mop equipment for cleaning indoor surfaces
Brominated Flame Retardant	2009	\$312.97	EPL Archives Inc	Storage of Br. Dibenzofuran and 2,3,7,8-Tetrabromodibenzofuran.
Center for the Polyurethane Industry (CPI)	2009	\$59,940.00	Air Quality Sciences, Inc	Research to determine the types and levels of chemicals emitted from spray polyurethane foam insulation
Center for the Polyurethane Industry (CPI)	2009	\$9,750.00	Spray Polyurethane Foam Alliance	SPF Industry Model Life Cycle Assessment.
Center for the Polyurethane Industry (CPI)	2009	\$12,000.00	Spray Polyurethane Foam Alliance	SPT Attic & Crawl Space Fire Testing Protocol.
Chlorine Chemistry Division	2009	\$19,400.00	Research Foundation For Health & Environmental Effects	Support for 2009 Dioxin Science General (TECH-TOX).
Chlorine Chemistry Division	2009	\$145,950.00	Toxstrategies Inc	Literature Search/USEPA A Dose-Response Workshop on Dioxin

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Diisocyanates Panel	2009	\$97,850.00	Bayer Material Science LLC	To prepare the filter media for exposure sampling and subsequent analysis of the filters for 2,4 - and 2,6 - Toluene Diisocyanate for the DIINIOSH Research Collaboration Project
Ethylbenzene Panel	2009	\$5,000.00	Dow Chemical Company	Study of In Vitro Metabolism with Rat, Mouse and Human Liver and Lung Microsomes- Phase II Study
Ethylbenzene Panel	2009	\$22,500.00	Dow Chemical Company	Unavailable.
Ethylbenzene Panel	2009	\$708.00	Huntingdon Life Sciences Inc.	Ethylbenzene in Rat/Mouse/Rabbit for 4 Day Inhalation Toxicity Study.
Ethylene Glycol Panel	2009	\$7,602.18	Battelle Memorial Institute	Develop a Physiologically Based Pharmacokinetic Model.
Ethylene Glycol Panel	2009	\$25,300.00	Dow Chemical Company	Assistance in general research plans
Ethylene Glycol Panel	2009	\$91,100.00	Dow Chemical Company	Toxicokinetics Analysis
Ethylene Glycol Panel	2009	\$42,755.46	Louisiana State University	Cell Culture Studies on Metabolism of Ethylene Glycol in Kidney cells.
Ethylene Glycol Panel	2009	\$21,121.71	LSU Health Sciences Foundation	Studies on the pharmacodynamics of DEG
Fatty Nitrogen Derivatives Panel	2009	\$4,900.00	RCC Ltd	Dodecanamide.
Fatty Nitrogen Derivatives Panel	2009	\$3,947.00	RCC Ltd	Imidazole.
Fatty Nitrogen Derivatives Panel	2009	\$2,610.00	RCC Ltd	Imidazolium.
Glycol Ethers Panel	2009	\$1,085.07	Battelle Memorial Institute	BEAA Pharmacokinetics in Rats.



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Glycol Ethers Panel	2009	\$83.57	Battelle Memorial Institute	Research entitled "In Vivo Verification of Butoxy Acetic Rat RBC Hemolysis NOEL."
Health, Products, & Science Policy	2009	\$10,000.00	Environmental Health Research Foundation	Support of EHRF's online clearinghouse of comprehensive and authoritative information on the nature, uses, potential and limitations of biomonitoring technology.
Health, Products, & Science Policy	2009	\$18,000.00	The Keystone Center	Assessment of the perspectives of different stakeholders on issues related to conflict of interest and bias of scientific studies
Hexavalent Chromium Panel	2009	\$519,114.99	Toxstrategies Inc	Mode of Action Research
Hydrocarbon Solvents Panel	2009	\$3,050.00	ExxonMobil Biomedical Sciences Inc.	Cyclopentane-B.
Ketones Panel	2009	\$10,000.00	Dow Chemical Company	Unavailable.
Ketones Panel	2009	\$19,390.00	Dow Chemical Company	Unavailable.
Ketones Panel	2009	\$20,000.00	Dow Chemical Company	Unavailable.
Long Range Research	2009	\$7,500.00	American Association For Aerosol Research	Sponsorship of the 2010 International Specialty Conference "Air Pollution and Health: Bridging the Gap from Sources to Health Outcomes."
Long Range Research	2009	\$116,792.15	Battelle - Northwest	Chlorpyrifos Human Risk Assessment.
Long Range Research	2009	\$3,283.14	Dow Chemical Company	Unavailable.
Long Range Research	2009	\$4,924.71	Dow Chemical Company	Unavailable.

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Long Range Research	2009	\$25,000.00	Environ International Corporation	Unavailable.
Long Range Research	2009	\$5,000.00	Harvard School of Public Health	Support for the Harvard School of Public Health and the X2209, Sixth International Conference on Innovations Exposure Assessment.
Long Range Research	2009	\$73,155.20	ICF Incorporated	Dosimetry Perspective.
Long Range Research	2009	\$119,744.31	ICF Incorporated	Ecotoxicological and extrapolation work; work on Air Toxics.
Long Range Research	2009	\$33,905.19	ICF Incorporated	Ecotoxicological extrapolation.
Long Range Research	2009	\$33,679.77	ICF Incorporated	Perspective on improving assessment of exposure to mixtures of volatile organic air toxics; Reverse Dosimetry Perspective.
Long Range Research	2009	\$276,089.97	ICF Incorporated	Research operations, management, and communication support.
Long Range Research	2009	\$63,124.59	ICF Incorporated	Reverse Dosimetry Perspective.
Long Range Research	2009	\$87.00	ICF Incorporated	Unavailable.
Long Range Research	2009	\$5,000.00	Indoor Air Institute	Phthalates, Bisphenol-A, Pyrethroids, Flame retardants, Organophosphates and Siloxanes.
Long Range Research	2009	\$25,000.00	Integrated Laboratory Systems, Inc	DE-71, a polybrominated diphenyl ether mixture (0,3,30.60 mg/kg in corn oil) or allyl alcohol (AA) (0,10, 30, 40 mg/kg in 0.25% methylcellulose.

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Long Range Research	2009	\$75,000.00	Integrated Laboratory Systems, Inc	Validation studies of the intact adult male rat screening assay
Long Range Research	2009	\$25,000.00	International Society of Exposure Analysis	Assist with the 2010 Annual Joint Conference for the International Society of Exposure Science (ISES) and International Society of Environmental Epidemiology (ISEE) held in Seoul, Korea
Long Range Research	2009	\$10,000.00	National Academy of Sciences	BES and Toxicology.
Long Range Research	2009	\$10,000.00	National Academy of Sciences	Institute of Medicine Roundtable on Environmental Health Sciences, Research and Medicine.
Long Range Research	2009	\$1,000,000	National Institute of Child Health & Human Dev.	New study designs and methods to evaluate gene and environmental chemical interaction data
Long Range Research	2009	\$25,000.00	Research Triangle Institute	Validation studies of the intact adult male rat screening assay for four chemicals
Long Range Research	2009	\$200,000.00	Research Triangle Institute	Validation studies of the intact adult male rat screening assay for four chemicals
Long Range Research	2009	\$72,000.00	Summit Toxicology LLP	Incorporating Dosimetry and Exposure Considerations in Interpretation of ToxCast Data
Long Range Research	2009	\$1,000,000	The Hamner Institutes for Health Sciences	Assessing the Exposure-Dose-Toxicity Relationship within the EPA's ToxCast Program
Long Range Research	2009	\$2,000,000	The Hamner Institutes for Health Sciences	Program on Chemical Safety Sciences.

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Long Range Research	2009	\$3,100,000	The Hamner Institutes for Health Sciences	Unavailable.
Lubricant Additives Alkyl Phenol Panel	2009	\$4,866.50	Locus Technologies	Tetrapropenylphenol (TPP) Emission Measurements At Sites in the United Kingdom
Lubricant Additives Alkyl Phenol Panel	2009	\$455,840.00	WIL Research Laboratories LLC	Dietary two general reproductive toxicity study of tetrapropenyl phenol in rats
Olefins Panel	2009	\$15,923.89	Cefic	Organization of the workshop "Biological Significance of DNA Adducts Part II."
Olefins Panel	2009	\$6,500.00	Dow Chemical Company	Benchmark dose analysis on the morphometric data from the nasal tissues from the 90-day ethylene exposure study.
Olefins Panel	2009	\$39,946.00	Dow Chemical Company	Unavailable.
Olefins Panel	2009	\$1,500.00	Fletcher Allen Health Care	Review of the protocol titled: Biomarkers Responses in 1,3 Butadiene Exposed Workers in the Czech Republic II: Female-Male
Olefins Panel	2009	\$32,100.00	Institute of Toxicology	Animal studies to support the development of a PBPK model for Butadiene.
Olefins Panel	2009	\$185,000.00	Institute of Toxicology	Research on metabolism and toxicokinetics of Ethylene in the mouse.
Olefins Panel	2009	\$140,000.00	Michigan State University	Histopathologic, Morphometric and Quantitative RT-PCR analysis of nasal airway tissues from laboratory rats.
Olefins Panel	2009	\$50,000.00	Minnesota Medical Foundation	Research on DNA Adducts of Butadiene.

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Olefins Panel	2009	\$16,000.00	MSU/Department of Pathobiology and Diagnostic Investigation	90-day ethylene inhalation reproducibility study.
Olefins Panel	2009	\$24,000.00	MSU/Department of Pathobiology and Diagnostic Investigation	Investigations on the histochemical and morphometric analyses or nasal tissues from a 90-day Inhalation toxicology study of ethylene.
Olefins Panel	2009	\$60,825.00	Nu Horizon Environment And Health LLC	Characterization of Individual and Population Exposures to 1,3-Butadiene.
Olefins Panel	2009	\$165,000.00	The Hamner Institutes for Health Sciences	Inhalation Toxicology of Ethylene in Male Fischer 344 and Wistar Rats.
Olefins Panel	2009	\$70,000.00	University of North Carolina	Research on Butadiene Biomarkers.
Olefins Panel	2009	\$60,000.00	University of North Carolina	Research on Hemoglobin Adducts in Butadiene exposed animals and workers.
Oxo Process Panel	2009	\$8,445.00	Dow Chemical Company	Analytical work for a two-generation inhalation reproductive toxicity study of butyl acetate in rats sponsored by the Oxo Process Panel.
Petroleum Additives Panel	2009	\$13,300.00	Astrazeneca UK Limited	Biodegradability of poorly water soluble compounds.
Petroleum Additives Panel	2009	\$13,500.00	Wildlife International Ltd.	Test Substance: Alfol 1618 Alcohol.
Phthalate Esters Panel	2009	\$9,250.00	BASF Corporation	Analytical Testing.
Phthalate Esters Panel	2009	\$2,775.00	BASF Corporation	ERTG Analytical Testing.
Phthalate Esters Panel	2009	\$19,000.00	BEC Technologies, Inc.	Phthalate Ester Concentration.

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Phthalate Esters Panel	2009	\$119,250.00	Brown University	Development of inter-species bioassay to test phthalate susceptibility
Phthalate Esters Panel	2009	\$25,000.00	Michigan State University	Unavailable.
Plastics Division	2009	\$39,900.00	Energy Anew, Inc	Engineered Fuel Project.
Plastics Division	2009	\$40,000.00	Mississippi State University	Research on "Model for Predicting the Strain Rate and Temperature Sensitive Impact Performance of Plastic Components - Phase II" involving Polycarbonates and Polypropylene.
Plastics Division	2009	\$85,139.00	University of Dayton	Optimization of specimens used for high rate testing of long-fibre filled-polymers
Public Health Forum	2009	\$20,000.00	CropLife America	Study of Endocrine Disruption.
Public Health Forum	2009	\$25,000.00	Summit Toxicology LLP	Develop and refine procedures for derivation and use of Biomonitoring Equivalents to enable human biomonitoring results to be interpreted in a health risk context
Specialty Acrylates/Methacrylates Panel	2009	\$4,111.84	Centre International Toxicology	Conducting environmental and mammalian testing
Specialty Acrylates/Methacrylates Panel	2009	\$6,612.25	U Noack Laboratorien	Daphnia Acute Immobilization Test on isobornyl methacrylate (IBOMA, CAS No. 7534-94-3)
Specialty Acrylates/Methacrylates Panel	2009	\$458.46	U Noack Laboratorien	Unavailable.

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Specialty Acrylates/ Methacrylates Panel	2009	\$1,950.98	U Noack Laboratorien	Unavailable.
Specialty Acrylates/ Methacrylates Panel	2009	\$2,461.60	U Noack Laboratorien	Unavailable.
Specialty Acrylates/ Methacrylates Panel	2009	\$3,377.06	U Noack Laboratorien	Water solubility study on isobornyl methacrylate (CAS No. 7534-94-3) according to OECD Guideline No. 105
Vinyl Chloride Health Committee	2009	\$36,785.00	Environ	Unavailable.
Vinyl Chloride Health Committee	2009	\$36,965.00	Environ	Unavailable.
<b>2009 Subtotal</b>		<b>\$12,945,397.84</b>		
Aliphatic Diisocyanates Panel	2010	\$75,000.00	Yale University	Investigations on the "Transferability of aliphatic isocyanates from recently applied paints to the skin of auto body shop workers."
Aliphatic Esters Panel	2010	\$12,807.00	Harlan Laboratories Ltd	Expand testing to include phase II, Acute Algae, Biodegradability, and Mutagenicity (Ames)
Aliphatic Esters Panel	2010	\$4,060.00	Harlan Laboratories Ltd	Test Materials - Glycol Esters Task Group.
Aliphatic Esters Panel	2010	\$12,540.00	Harlan Laboratories Ltd	Test Materials - Sorbitan Esters Task Group.
Aliphatic Esters Panel	2010	\$12,540.00	Harlan Laboratories Ltd	Test Materials: Sorbitan monoesterate, Sorbitan monooleate, Fatty acids, tall-oil, monoesters with sorbitan, Sorbitan sesquioleate and Sorbitan trioleate.

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Aliphatic Esters Panel	2010	\$9,609.80	Harlan Laboratories Ltd	Test Materials: Adipic Acid, Bis[2-(2-butoxyethoxy_ethyl)]ester.
Aliphatic Esters Panel	2010	\$7,477.99	Harlan Laboratories Ltd	Unavailable.
Alkanolamines Panel	2010	\$124,000.00	BASF Aktiengesellschaft	Unavailable.
Amines Panel	2010	\$72,209.50	BASF Aktiengesellschaft	Dibutylamine hydrochloride.
Amines Panel	2010	\$28,883.80	BASF Aktiengesellschaft	Dimethylamine hydrochloride.
Amines Panel	2010	\$112,278.50	BASF Aktiengesellschaft	Methylaminoethonal.
Amines Panel	2010	\$7,098.00	Fraunhofer Institute of Toxicology and Environment	Histopathology of the reproductive organs from the study "90 Tage Inhalationstoxizitätsprüfung mit Dibutylamin."
Biocides Panel	2010	\$234,424.00	Golden Pacific Laboratories	Aerosol Study.
Biocides Panel	2010	\$16,790.10	Golden Pacific Laboratories	Freezer storage stability of C14 Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Dressing Sponges, Hand Washes, Inner Dosimeters, Outer Dosimeters, Air Sampling Tubes and Fiberglass Filters
Biocides Panel	2010	\$176,957.25	Golden Pacific Laboratories	Study for measurement of potential dermal and inhalation exposure during application of a liquid antimicrobial pesticide product using bucket and mop equipment for cleaning indoor surfaces



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Diisocyanates Panel	2010	\$76,650.00	Bayer Material Science LLC	To prepare the filter media for exposure sampling and subsequent analysis of the filters for 2,4 - and 2,6 - Toluene Diisocyanate for the DIINIOSH Research Collaboration Project
Ethylene Glycol Panel	2010	\$1,158.83	Battelle Memorial Institute	Develop a Physiologically Based Pharmacokinetic Model.
Ethylene Glycol Panel	2010	\$11,400.00	Dow Chemical Company	Toxicokinetics Analysis
Ethylene Glycol Panel	2010	\$12,618.26	Louisiana State University	Cell Culture Studies on Metabolism of Ethylene Glycol in Kidney cells.
Ethylene Glycol Panel	2010	\$8,003.21	LSU Health Sciences Foundation	Unavailable.
Ethylene Glycol Panel	2010	\$9,585.06	LSU Health Sciences Foundation	Unavailable.
Ethylene Glycol Panel	2010	\$10,198.76	LSU Health Sciences Foundation	Unavailable.
Ethylene Glycol Panel	2010	\$10,432.41	LSU Health Sciences Foundation	Unavailable.
Glycol Ethers Panel	2010	\$83.50	Battelle Memorial Institute	BEAA Pharmacokinetics in Rats.
Health, Products, & Science Policy	2010	\$407.04	Elsevier	Reprints-Tiered Testing doc.
Health, Products, & Science Policy	2010	\$135,000.00	Summit Toxicology LLO	Review paper on partitioning of compounds between maternal and cord blood
Hexavalent Chromium Panel	2010	\$1,423,624.30	Toxstrategies Inc	Mode of Action Research

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Ketones Panel	2010	\$69,450.00	Dow Chemical Company	Study for 2 years US EPA Endocrine Disruptor Screening Program (EDSP)
Long Range Research	2010	\$10,000.00	Board on Environmental Studies and Toxicology	Support of the Board on Environmental Studies and Toxicology (BEST).
Long Range Research	2010	\$25,000.00	Clarkson University	Support of the optimization and evaluation of the new multi-filter dichotomous sampler.
Long Range Research	2010	\$20,000.00	Environ International Corporation	Di(2-ethylhexyl)Phthalate.
Long Range Research	2010	\$10,000.00	Gordon Research Conferences	Environmental Endocrine Disruptors (EED)."
Long Range Research	2010	\$5,000.00	Gordon Research Conferences	Gordon Research Conferences.
Long Range Research	2010	\$500.00	Humane Society of the United States	ICCA-LRI Workshop 2010.
Long Range Research	2010	\$500.00	Humane Society of the United States	Professional Service for SST.
Long Range Research	2010	\$410,581.10	ICF Incorporated	Research operations, management, and communication support.
Long Range Research	2010	\$15,000.00	Indoor Air Institute	SVOC Workshop Support.
Long Range Research	2010	\$63,425.94	Integrated Laboratory Systems, Inc	Validation studies of the intact adult male rat screening assay
Long Range Research	2010	\$10,000.00	International Society of Exposure Science	ISES 2011 Annual Mtg.
Long Range Research	2010	\$1,730.00	International Society of Exposure Science	ISES-ISEE 2010 Conference.
Long Range Research	2010	\$20,000.00	International Society of Exposure Science	ISES-SETAC EU Symposium.

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Long Range Research	2010	\$800.11	Judith A Blake	Exposure Workshop expenses.
Long Range Research	2010	\$750.00	Judith A. Graham	Unavailable.
Long Range Research	2010	\$24.00	Michael A Callahan	Exposure Workshop expenses.
Long Range Research	2010	\$750.00	Michael Dong Sohn	Developing Exposures Indices for Rapid Prioritization of Chemicals in Consumer Products.
Long Range Research	2010	\$750.00	Miriam Diamond	Developing exposures indices for rapid prioritization of chemicals in consumer products.
Long Range Research	2010	\$100,000.00	Mount Desert Island Biological Laboratory	Facilitating the centralization and integration of exposure data through exposure ontology development and expanded accessibility to exposure studies
Long Range Research	2010	\$400,000.00	Regents of the University of California	Albumin Adducts as Measures of Total Human Exposure.
Long Range Research	2010	\$40,000.00	Regents of the University of California	An Exposure Ontology Curation Structured on the Exposome Concept.
Long Range Research	2010	\$71,376.00	Research Triangle Institute	Validation studies of the intact adult male rat screening assay for four chemicals
Long Range Research	2010	\$10,000.00	Roundtable on Environmental Health Sciences	Support of the Institute of Medicine Roundtable on Environmental Health Sciences, Research and Medicine.
Long Range Research	2010	\$750.00	Science Collaborative North Shore	Developing Exposures Indices for Rapid Prioritization of Chemicals in Consumer Products.

*Responses to questions from the Subcommittee on Investigations and Oversight, House Committee on Science, Space, and Technology. Submitted by Cal Dooley, president and CEO of the American Chemistry Council, August 16, 2011.*

Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Long Range Research	2010	\$750.00	Silent Spring Institute	Developing Exposures Indices for Rapid Prioritization of Chemicals in Consumer Products.
Long Range Research	2010	\$10,000.00	Society of Environmental Toxicology & Chemistry	Support of the SETAC Pellston Workshop "Influence of Global Climate Change (GCC) on the Scientific Foundations of Environmental Toxicology and Chemistry."
Long Range Research	2010	\$750.00	Stuart A Batterman	Developing Exposure Indices for Rapid Prioritization of Chemicals in Consumer Products.
Long Range Research	2010	\$55,500.00	Summit Toxicology LLP	Incorporating Dosimetry and Exposure Considerations in Interpretation of ToxCast Data
Long Range Research	2010	\$900,000.00	The Hamner Institutes for Health Sciences	Extension of Tox/Cast Hamner.
Long Range Research	2010	\$1,000,000	The Hamner Institutes for Health Sciences	Unavailable.
Long Range Research	2010	\$1,500,000	The Hamner Institutes for Health Sciences	Unavailable.
Lubricant Additives Alkyl Phenol Panel	2010	\$223,720.00	WIL Research Laboratories LLC	Dietary Two-Generation Reproductive Toxicity Study of Tetrapropenyl Phenol in Rats.
Methyl Bromide Industry Panel	2010	\$312.97	EPL Archives Inc	Storage services regarding Br.Dibenzofuran and 2,3,7,8-Tetrabromodibenzofuran.
Olefins Panel	2010	\$1,500.00	Dow Chemical Company	Dose analysis of the Morphometric Data from the Nasal Tissues from the 90-day Ethylene Exposure Study

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Olefins Panel	2010	\$106,221.00	Dow Chemical Company	Ethylene: 90 day whole body inhalation toxicity study in F344/DURCL rats
Olefins Panel	2010	\$95,688.00	Dow Chemical Company	Hemoglobin Adducts analytical method.
Olefins Panel	2010	\$10,000.00	Dow Chemical Company	Prepare Saghir manuscript
Olefins Panel	2010	\$105,835.90	Dow Chemical Company	Study design of Ethylene-Induced Nasal Effects in Rats
Olefins Panel	2010	\$10,000.00	Dr Johannes G. Filser	In vitro comparative (mouse, rat, human tissue) study on ethylene.
Olefins Panel	2010	\$100,000.00	Institute of Toxicology	Research of ethylene metabolism in perfused organs.
Olefins Panel	2010	\$40,069.00	Nu Horizon Environment And Health LLC	Characterization of Individual and Population Exposures to 1,3-Butadiene.
Olefins Panel	2010	\$65,000.00	University of North Carolina	Research on MMS & MNU - related adducts.
Olefins Panel	2010	\$10,000.00	University of Vermont	Unavailable.
Oxo Process Panel	2010	\$283.27	Battelle Memorial Institute	Diethylhexyl terephthalate diet study.
Oxo Process Panel	2010	\$20,468.75	Toxicology Excellence for Risk Assessment (TERA)	Project Propyl PBPK.
Oxo Process Panel	2010	\$106,415.51	WIL Research Laboratories LLC	Inhalation Two-Generation Reproduction Toxicity Study of n-Butyl Acetate in Rate.
Petroleum Additives Panel	2010	\$4,500.00	Wildlife International Ltd.	28-Day Non-GLP Carbon Dioxide Evolution Test.
Petroleum Additives Panel	2010	\$36,500.00	Wildlife International Ltd.	Ready Biodegradability by the Carbon Dioxide Evolution Test Method.
Phthalate Esters Panel	2010	\$3,580.36	BEC Technologies, Inc.	Developing phthalate ester exposure database
Phthalate Esters Panel	2010	\$23,875.00	BEC Technologies, Inc.	Phthalate Ester Concentration Database.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Phthalate Esters Panel	2010	\$3,105.00	BEC Technologies, Inc.	Unavailable.
Phthalate Esters Panel	2010	\$4,628.75	BEC Technologies, Inc.	Unavailable.
Phthalate Esters Panel	2010	\$174,250.00	Brown University	Development of inter-species bioassay to test phthalate susceptibility
Phthalate Esters Panel	2010	\$1,935.49	Cefic	Biomonitoring study.
Phthalate Esters Panel	2010	\$25,000.00	Toxicology Forum	Modeling Human Exposures to Phthalate Esters.
Plastics Division	2010	\$25,000.00	Association of Postconsumer Plastics Recyclers	2009 HDPE All bottle recycling rate report.
Plastics Division	2010	\$39,996.00	Michigan State University	Modeling Driven Dart Impact of Injection Molded Long Fibre Reinforced Thermoplastic Composites
Plastics Division	2010	\$140,032.00	Mississippi State University	Study on a "Model for Predicting the Strain Rate and Temperature Sensitive Impact Performance of Plastic Components – Phase II"
Plastics Division	2010	\$79,220.00	University of Dayton	Optimization of specimens used for high rate testing of long-fibre filled-polymers
Plastics Food Service Packaging Group (PFPG)	2010	\$8,000.00	Association of Postconsumer Plastics Recyclers	2010 Mixed Rigid Plastic Bale Audit and Non-bottle Rigid Plastic Analysis.
Specialty Acrylates/Methacrylates Panel	2010	\$2,587.45	U Noack Laboratorien	Daphnia Acute Immobilization Test on isobornyl methacrylate (IBOMA, CAS No. 7534-94-3)
Specialty Acrylates/Methacrylates Panel	2010	\$4,798.00	U Noack Laboratorien	Water solubility study on isobornyl methacrylate (CAS No. 7534-94-3) according to OECD Guideline No. 105

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Vinyl Chloride Health Committee	2010	\$37,752.15	Environ	Study of "Exposure reconstruction for men employed in the vinyl chloride industry from 1942-1972."
<b>2010 Subtotal</b>		<b>\$8,869,499.06</b>		
Aliphatic Esters Panel	2011	\$6,404.00	Harlan Laboratories Ltd	Expand testing to include phase II, Acute Algae, Biodegradability, and Mutagenicity (Ames)
Biocides Panel	2011	\$200,000.00	Golden Pacific Laboratories	Aerosol Study.
Biocides Panel	2011	\$10,890.00	Golden Pacific Laboratories	Freezer storage stability of C14 Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Dressing Sponges, Hand Washes, Inner Dosimeters, Outer Dosimeters, Air Sampling Tubes and Fiberglass Filters
Biocides Panel	2011	\$176,957.25	Golden Pacific Laboratories	Study for measurement of potential dermal and inhalation exposure during application of a liquid antimicrobial pesticide product using bucket and mop equipment for cleaning indoor surfaces
Center for the Polyurethane Industry (CPI)	2011	\$1,375.00	Hughes Associates, Inc.	Analysis of IRC Section MI306 on clearance
Diisocyanates Panel	2011	\$36,200.00	Bayer Material Science LLC	Prepare the filter media for exposure sampling and subsequent analysis of the filters for 2,4 - and 2,6 - Toluene Diisocyanate for the DIINIOSH Research Collaboration Project

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Environment	2011	\$2,000.00	Water Environment Research Foundation	Biosolids Trace Organics - Collaborative Research Effort.
Ethylene Glycol Panel	2011	\$4,681.39	Louisiana State University	Cell Culture Studies on Metabolism of Ethylene Glycol in Kidney cells.
Ethylene Glycol Panel	2011	\$13,614.31	LSU Health Sciences Foundation	Pharmacodynamics of DEG
Fatty Nitrogen Derivatives Panel	2011	\$11,459.40	RCC Ltd	Unavailable.
Health, Products, & Science Policy	2011	\$35,000.00	Summit Toxicology LLP	Expansion of the Biomonitoring Equivalents (BE) method to interpret human biomonitoring results in the context of potential health risk.
Health, Products, & Science Policy	2011	\$25,000.00	The Keystone Center	Support the Keystone's Research Integrity Roundtable.
Hexavalent Chromium Panel	2011	\$1,063,934.15	Toxstrategies Inc	Mode of Action Research
Ketones Panel	2011	\$200,950.00	Dow Chemical Company	Study for 2 years US EPA Endocrine Disruptor Screening Program (EDSP)
Long Range Research	2011	\$5,000.00	Gordon Research Conferences	Gordon Research Conferences.
Long Range Research	2011	\$2,000.00	Humane Society of the United States	LRI Health CAN Wrkshp-Humane.
Long Range Research	2011	\$1,510.00	Humane Society of the United States	Professional Service for SST.
Long Range Research	2011	\$1,470.00	ICF Incorporated	ISES Conf. Regis.
Long Range Research	2011	\$327,455.01	ICF Incorporated	Research operations, management, and communication support.



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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Long Range Research	2011	\$625.00	Judith A. Graham	Unavailable.
Long Range Research	2011	\$44,056.00	Mount Desert Island Biological Laboratory	Facilitating the centralization and integration of exposure data through exposure ontology development and expanded accessibility to exposure studies
Long Range Research	2011	\$200,000.00	Regents of the University of California	Albumin Adducts as Measures of Total Human Exposure.
Long Range Research	2011	\$10,000.00	Regents of the University of California	Unavailable.
Long Range Research	2011	\$100,000.00	Regents of the University of California	Unavailable.
Long Range Research	2011	\$10,000.00	Regents of the University of California	Unavailable.
Long Range Research	2011	\$50,000.00	Regents of the University of California	Unavailable.
Long Range Research	2011	\$10,000.00	Society of Toxicology	2010 SOT Annual Conference.
Long Range Research	2011	\$2,000,000	The Hamner Institutes for Health Sciences	Albumin Adducts as Measures of Total Human Exposure
Long Range Research	2011	\$2,787.39	The Hamner Institutes for Health Sciences	LRI Health CAN Wrkshp.
Long Range Research	2011	\$160,000.00	The Regents of the University of Michigan	USEtox Prioritization Indices for Chemical Exposure from Consumer Products (USEtoxPI). Developing Exposure Indices for Rapid Prioritization of Chemicals in Consumer Products
Long Range Research	2011	\$3,000.00	Toxicology Forum	37th Annual Summer Mtg Support.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Long Range Research	2011	\$5,000.00	University of Michigan	UM 2011 Symposium.
Nanotechnology Panel	2011	\$20,000.00	ILSI Research Foundation	Research on Nanotechnology in 2010
Nanotechnology Panel	2011	\$20,000.00	ILSI Research Foundation	Research titled: NanoRelease-Consumer Products
Olefins Panel	2011	\$5,906.80	Cefic	Unavailable.
Olefins Panel	2011	\$10,000.00	Dr Johannes G. Filser	Publication of the data from the In Vitro comparative (mouse, rat, human tissue) study on Ethylene.
Olefins Panel	2011	\$25,000.00	Dr Johannes G. Filser	Publications regarding the following: Results of the Butadiene Metabolism in Perfused Livers. Data from the In Vivo exposures of rats and mice to Butadiene.
Olefins Panel	2011	\$7,500.00	Michigan State University	Histopathologic, Morphometric and Quantitative RT-PCR analyses of nasal airway tissues from laboratory rats.
Olefins Panel	2011	\$50,000.00	Michigan State University	Postdoctoral student work on the Ethylene Nasal finding.
Olefins Panel	2011	\$50,000.00	Minnesota Medical Foundation	Research on DNA adducts of Butadiene.
Olefins Panel	2011	\$21,576.00	Nu Horizon Environment and Health LLC	Supplement to Characterization of Individual and Population Exposures to 1,3-Butadiene.
Olefins Panel	2011	\$17,500.00	University of Vermont	Research on developing an In Vitro assay for detecting the mutation that is specific to chronic myelogenous leukemia.

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Funding Cost Center	Year	Amount	Funding Recipient	Purpose
Oxo Process Panel	2011	\$8,124.80	Battelle Memorial Institute	Intravenous and diet studies with di-2-ethylhexyl terephthalate in rats research study.
Phthalate Esters Panel	2011	\$14,500.00	Simon Fraser University	Analysis of phthalate ester concentrations in sludge samples from the National Sewage Sludge Survey.
<b>2011 Subtotal</b>		<b>\$4,971,476.50</b>		
<b>Total</b>		<b>\$45,515,356.85</b>		

The research supported by ACC makes a valuable contribution to the available scientific database that informs risk assessment and risk management decisions by EPA and other government agencies. ACC is an active participant in risk assessment and risk management discussions and takes full advantage of public comment periods provided by these agencies.

#### **Question 4**

*Please provide an accounting of all the work that Dr. Charnley has done for the ACC or its subsidiary organizations over the last five years (2006-2011). Please identify the funding organization, the amount of funding (if any), the duration of the work, the purpose of the work, and identify any deliverables associated with the funds. Please provide copies of deliverables to the Committee.*

Our records indicate that ACC has made no payments directly to Dr. Charnley during the 2006 to 2011 time period. However, ACC has paid a total of \$31,568.84 during this period for work performed by HealthRisk Strategies, where Dr. Charnley is a Principal. This amount is broken out as follows:

Payment Date	Amount	Funding Cost Center	Expense Description
5/30/2008	\$1,226.12	Chlorine Chemistry Division	Reimbursement for expenses associated with attending the annual meeting of the Society for Risk Analysis and chairing a symposium on dioxin and public health in San Antonio, TX, December 9-13, 2007
11/11/2008	\$5,721.16	Ethylene Glycol Ethers Panel	For services related to preparing and presenting comments on EPA's draft

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			EGBE IRIS review
7/11/2008	\$3,900.00	Ethylene Glycol Ethers Panel	For services related to drafting comments on EPA's draft IRIS risk assessment of EGBE
<b>ACC Subtotal</b>	<b>\$10,847.28</b>		
10/7/2010	\$14,400.00	RFHEE	For services related to written and oral comments to EPA's Science Advisory Board on EPA's <i>Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments</i>
12/14/2010	\$5,143.50	RFHEE	For services related to written and oral comments to EPA's Science Advisory Board on EPA's <i>Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments</i>
1/20/2011	\$1,178.06	RFHEE	For services related to written and oral comments to EPA's Science Advisory Board on EPA's <i>Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments</i>
<b>RFHEE Subtotal</b>	<b>\$20,721.56</b>		
<b>Total</b>	<b>\$31,568.84</b>		

Please find attached the deliverables associated with this work: (1) Comments of the Ethylene Glycol Ethers Panel of the American Chemistry Council on the April 2008 External Review Draft of the IRIS Toxicological Review for EGBE (June 24, 2008) and (2) Comments to the U.S. Environmental Protection Agency on the 2010 Draft Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (September 15, 2010).

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**Question 5**

*The Formaldehyde Council has been replaced by ACC's own working group on formaldehyde. However, The Formaldehyde Council appears to have been absorbed by the ACC itself and its address, as you acknowledged in the hearing, is identified as being the same as that of the ACC. Please provide all records related to Dr. Charnley's work for The Formaldehyde Council during the years 2006-2011.*

ACC has no records related to Dr. Charnley's work for The Formaldehyde Council during the years 2006-2011. The Formaldehyde Council was a separate and independent organization throughout that time period and maintained its own records.

*Responses to questions from the Subcommittee on Investigations and Oversight, House Committee on Science, Space, and Technology. Submitted by Cal Dooley, president and CEO of the American Chemistry Council, August 16, 2011.*

Questions Submitted by Rep. John Sarbanes

You made the point at the hearing that EPA's proposed 2010 reference concentration (Rfc) for chronic exposure to formaldehyde (via inhalation) is significantly lower than the levels of formaldehyde exhaled by people, as referenced in the World Health Organization report "Indoor Air Quality Selected Pollutants 2010"

[http://www.euro.who.int/data/assets/pdf\\_file/0009/128169/e94535.pdf](http://www.euro.who.int/data/assets/pdf_file/0009/128169/e94535.pdf)

Question 1

***Do you believe that the formaldehyde in exhaled breath is from biological sources (cellular metabolism), industrial/anthropogenic sources, or both?***

Formaldehyde is a basic building block chemical composed of carbon, hydrogen, and oxygen with the formula  $\text{CH}_2\text{O}$ . Formaldehyde is formed during any N-demethylation steps from components such as amino acids and other nutrients. Formaldehyde is naturally produced in the body at relatively high levels and it performs key metabolic functions in the body. No inhaled formaldehyde is involved with this natural (endogenous) formaldehyde formation.

In tissues, and other aqueous systems, formaldehyde exists primarily (>99.9%) in its hydrated form of methanediol, with only a small amount (<0.1%) as free formaldehyde. Because free formaldehyde can diffuse from tissues in the upper respiratory tract into exhaled air, small, but measurable, amounts can be detected in the breath. (Golden 2011).

The World Health Organization (WHO) reported that "Human exhaled air contains formaldehyde in concentrations in the order of 0.001-0.01  $\text{mg}/\text{m}^3$ , with an average of about 0.005  $\text{mg}/\text{m}^3$ ." (WHO 2010 at p.111). For the sake of comparison, these values are 0.81 to 8 parts per billion (ppb), with an average of 4 ppb.<sup>1</sup> The National Academy of Science's Committee reviewing EPA's Draft IRIS Assessment of Formaldehyde writes, "The committee concludes, however, that regardless of the methodologic issue related to breath analysis, formaldehyde is normally present at a few parts per billion in exhaled breath after the measurement error associated with a trace contaminant in the reagent gas used in previous mass-spectrometric methods is taken into account." (NRC 2011, at p. 23). Although there are analytical challenges in accurately determining formaldehyde

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<sup>1</sup> To convert  $\text{mg}/\text{m}^3$  to ppb, use the calculation:  
 $(\text{X ppb}) = [(\text{mg}/\text{m}^3)(24.45) / (\text{molecular weight})] (1000)$

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concentrations in human breath (Moser et al., 2005; Kushch et al., 2008), the levels detected using a chemical-specific methodology fall into the low-ppb range (i.e., <0.5–1.7 ppb) (Riess et al., 2010). (Golden 2011).

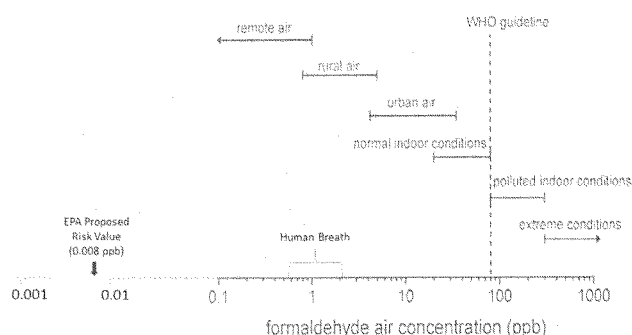


FIGURE 1-2 Formaldehyde concentration in various environments. Abbreviation: WHO, World Health Organization. Source: Salthammer et al. 2010. Reprinted with permission; copyright 2010, American Chemical Society.

Graphic adapted from NRC. 2011. Review of the EPA Draft IRIS Assessment of Formaldehyde. At p.13.

We adapted NAS Figure 1-2 (above) to include EPA's proposed risk value for formaldehyde and the most recent levels of formaldehyde reported from human breath (corrected for methodologic issues). Of note is the dotted line showing the WHO's indoor air guideline. WHO's indoor air guideline for formaldehyde is based on a review of the scientific literature, the relevance to risk assessment, and the application of exposures by a panel of international experts. (WHO 2010). WHO provides a health protective value for formaldehyde at  $0.1 \text{ mg/m}^3$  (80 ppb) and reports that this guideline is protective for any short-term exposure (30-minute period) and for long-term health effects of lung function as well as nasopharyngeal cancer and myeloid leukemia. (WHO 2010 at pp. xxv and 141).

Andersen et al., have studied the basic biology in experimental animals and humans and developed a biologically-based pharmacokinetic (PBPK) model to describe inhalation, natural formation and movement of formaldehyde through the body. In a recent publication, Andersen et al. (2010), included Figure 1, shown below, which describes the

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rates that formaldehyde can enter the body via inhalation and natural production ( $k_0$ ). Thus, unexposed people naturally produce and exhale (shown as the dotted line) formaldehyde. (Andersen et al., 2010).

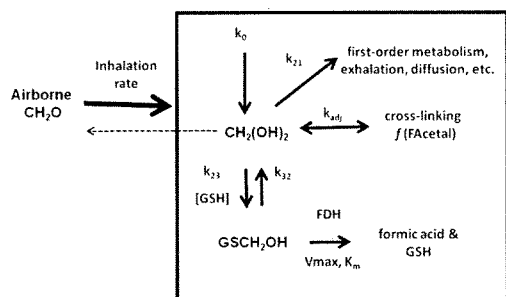


FIG. 1. The tissue biochemistry PK model for FA. Inhaled FA is rapidly hydrated to FAcetal—CH<sub>2</sub>(OH)<sub>2</sub>. The acetal is lost by first-order processes, i.e., diffusion back to the air phase, diffusion onto deeper tissues, first-order metabolism, etc., and by reaction with GSH to form the thioacetal. The thioacetal [GSCH<sub>2</sub>OH] can dissociate to FAcetal or be converted by FDH to formic acid with release of GSH. The rate constants here are used in the tissue PK model to estimate the relationship between tissue FAcetal and inhaled FA. Kad estimates DNA binding from the calculated FAcetal.

Source: Anderson, ME, et al., 2010. Formaldehyde: Integrating dosimetry, cytotoxicity, and genomics to understand dose-dependent transitions for an endogenous compound. *Toxicol. Sci.* 118(2):716-731.

## Question 2

***If it is ACC's view that the formaldehyde in exhaled breath is a mix of human and industrial/anthropogenic sources, what does ACC estimate the percentage from each source to be? Please provide scientific citations or other evidence to support your answer.***

While measurement challenges confounded past studies, scientists agree that a few parts per billion of formaldehyde is exhaled in human breath. (WHO 2010, NRC 2011, Golden 2011). Current data, however, are not sufficient to assess whether or to what extent inhaled formaldehyde is exhaled. To definitively answer the question about whether (and how much) inhaled formaldehyde is immediately exhaled will require a research study using radiolabeled formaldehyde to distinguish the inhaled (which can be radiolabeled) from the endogenous (which cannot be radiolabeled) formaldehyde in the breath.



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**Question 3**

***Your comment regarding EPA's reference dose/concentration compared to the exhalation level cited in the WHO report seemed to imply criticism of EPA, but wasn't clear exactly what your criticism was.***

- ***What is your specific point or concern regarding the EPA's proposed reference concentration versus the average level of formaldehyde exhalation cited by the WHO?***

As I stated in my testimony, "IRIS is one of the most important programs EPA uses to assess chemical safety. It serves as a leading source of health risk information for other federal, state, and international regulatory bodies. But over the years, the program has been repeatedly criticized for failing to consistently meet high standards of scientific inquiry, transparency and quality." The public is not well served if EPA's Draft IRIS Toxicological Review fails to provide the science quality needed to guide governmental standards.

EPA concluded that the typical (average) indoor formaldehyde level is between 16 to 32 ppb. (EPA 2010, Salthammer 2011). These indoor air levels are characterized similarly by the WHO.

In contrast, we note the difference between the proposed EPA cancer risk value of 0.008 ppb and the indoor air guidance value from WHO. WHO reviewed the substantially same scientific database and established an indoor air guideline for formaldehyde at 0.1 mg/m<sup>3</sup> (80 ppb) and reported that this guideline is protective for any short-term effects (30-minute period) and will also prevent long-term health effects of lung function as well as nasopharyngeal cancer and myeloid leukemia. (WHO 2010, at p. xxv and 141). WHO's indoor air guideline for formaldehyde is based on a review of the scientific literature, the relevance to risk assessment, and the application of exposures. (WHO 2010). Importantly, WHO states that, "Neither increased sensitivity nor sensitization is considered plausible at such indoor concentrations in adults and children."

Thus, using the WHO indoor air guidelines, human breath and typical indoor air exposures to formaldehyde would not pose a health risk to human health for either short-term (30 minutes) effects or long-term effects including cancer. In contrast, using the EPA's proposed cancer risk value of 0.008 ppb, both human breath and typical indoor air exposures to formaldehyde would be considered a human health risk.

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- ***Are you suggesting that EPA's proposed reference concentration is too conservative (too health protective) because it is somehow "regulating below background"?***

IRIS assessments of carcinogenic responses in high-dose animal studies typically take the most conservative default approach, rather than applying relevant mode of action and real world exposure information to more accurately characterize potential risk to humans. In the case of formaldehyde, EPA has failed to consider and account for the endogenous formaldehyde levels naturally produced in and exhaled from our bodies in determining its proposed cancer risk value.

In effect, IRIS has clung to approaches that assume there is no safe dose or threshold – even when the weight of biological evidence leads experts to conclude otherwise. Consequently, IRIS assessments fail to reflect the best available science upon which regulators must rely to make credible risk management and regulatory decisions.

- ***Is it ACC's view that the scientific credibility of EPA's proposed reference concentration is somehow compromised by the fact that it is the range of the exhalation levels cited in the WHO report?***

ACC is concerned that IRIS assessments often fail to fully consider biological systems and background levels (from both endogenous and natural exogenous sources), among other important factors. In assessing potential risks from exposure to naturally occurring chemicals in the body (endogenous chemicals), such as formaldehyde, fundamental questions should be addressed, including "What are the tissue concentrations of formaldehyde naturally formed in the body (endogenous) compared to concentrations from inhaled formaldehyde (exogenous sources)? If the endogenous concentrations represent the predominate form of formaldehyde in the body, then "Can the (purported) health effect(s) be from endogenous formaldehyde or from exogenous formaldehyde or neither?"

- ***Do you agree that the reference concentration under IRIS is intended to identify an acceptable level, or "safe level", of exposure expected to be without deleterious effects (within an order of magnitude) for the whole population, including children, over a lifetime of breathing formaldehyde-contaminated air?***

EPA states, "For noncancer effects, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk

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of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used.” (EPA 2010 at p. 5-1).

Current policies and practices of the IRIS program do not foster the use of best available scientific data and methods, and because of this, IRIS assessments have consistently fallen well short of meeting the highest standards of scientific inquiry, objectivity, and transparency. Citing problems with the IRIS assessments that have persisted for over a decade, the NAS committee that conducted the independent peer review of the IRIS draft formaldehyde assessment devoted an entire chapter of the report to point out the scientific inadequacies in policies, procedures and practices of the IRIS program. The Committee recommended fundamental and permanent changes to the manner in which the IRIS program obtains scientific data, analyzes studies, integrates data using weight of evidence, conducts causal determinations, and assesses uncertainty. This NAS report clearly documents the types of changes needed to IRIS to raise the program up to a level where it can meet the benchmarks of objectivity, scientific accuracy, and transparency necessary to ensuring high quality, reliable assessments.

For EPA to derive a reliable, science-based RfC for formaldehyde, or any other substance, EPA must initiate a comprehensive overhaul of the program to make IRIS effective and efficient in the future:

- Assessments must rely on proven scientific data instead of outdated assumptions;
- EPA must establish consistent data evaluation methods;
- EPA must adopt a consistent weight of evidence framework, based on transparent, rigorous evaluation methods, so all available data can be considered, with the best and most relevant science given the greatest weight;
- Assessments should be based on 21st century knowledge of how chemicals interact with the human body;
- EPA must adopt proven approaches for evaluating cause, effect, and uncertainty as part of IRIS assessments; and,
- EPA must enhance public comment and independent scientific peer review processes.

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**Question 4**

*The EPA's proposed reference concentration for inhalation of formaldehyde is intended to protect people from non-cancer "endpoints" such as asthma, allergies, eye irritation, etc. Those are all rather common ailments. Is ACC opposed to identifying a "safer level" or exposure below which such health effects might not occur?*

ACC firmly supports an objective review of the full weight of the scientific evidence as the basis for making chemical specific safety determinations. In the case of EPA's Draft IRIS Assessment of Formaldehyde, however, the NAS cited numerous scientific deficiencies in the manner in which EPA assessed non-cancer endpoints, including in particular asthma. Those deficiencies must be fully addressed, consistent with the NAS report, before deriving credible reference concentrations, below which health effects are unlikely to occur.

**Question 5**

*As you know, the reference doses and reference concentrations established under IRIS are not themselves regulations or risk assessments. Rather, they are health-based levels. Any actual regulatory standard setting (risk management) would follow under a different process, that generally will include consideration of costs, feasibility, etc. -- presumably with full opportunity for public notice and comment, judicial review, etc. EPA's formaldehyde assessment is clearly separating the scientific process of developing a health-based acceptable level of exposure from the later policy process of risk assessment and risk mitigation. Your criticism appears to conflate the two, criticizing EPA's science for not altering in the face of a future policy or regulation.*

- *Isn't that separation of the health determination and the regulation process something that the ACC supports?*
- *(b) If not, explain how a science assessment is supposed to be restrained by concerns for subsequent policy and regulatory discussions? Should harms be hidden in anticipation that their discovery might create a hard policy problem?*

For IRIS assessments to support regulatory actions, the assessment must be firmly based on up-to-date scientific knowledge, meet the highest of standards of scientific inquiry and be evaluated in accordance with acceptable scientific approaches. Unfortunately, the current policies and practices and resulting assessments of the IRIS program do not consistently meet these standards. The long-standing and persistent shortcomings of

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IRIS assessments were described by the NAS formaldehyde peer review panel in Chapter 7 of their report.

ACC indeed supports separate and distinct processes for assessing potential health risks and for evaluating potential risk-management regulatory actions. However, this is not to imply that risk assessment and risk management processes are not interrelated and integral to one another. In fact, as was clearly described by the Presidential/Congressional Commission on Risk Assessment and Risk Management in 1997, risk management is “the process of identifying, evaluating, selecting, and implementing actions to reduce risk to human health and to ecosystems. The goal of risk management is scientifically sound, cost-effective, integrated actions that reduce or prevent risks while taking into account social, cultural, ethical, political, and legal considerations” (<http://www.riskworld.com/Nreports/1997/risk-rpt/pdf/EPAJAN.PDF>).

So although the analysis of potential human health hazards and the likelihood of harm is a distinct process from selecting remedies to mitigate hazards and risks, it is not conducted in isolation. The scope of the risk analysis is guided by the overall context of the risk management program the assessment is to be used in. As the Presidential/Congressional Commission on Risk Assessment and Risk Management states, “The level of detail considered in a risk assessment and included in a risk characterization should be commensurate with the problem’s importance, expected health or environmental impact, expected economic or social impact, urgency, and level of controversy, as well as with the expected impact and cost of protective measures.”

EPA’s Guidance for Risk Characterization (<http://www.epa.gov/spc/pdfs/rcguide.pdf>) makes it clear that interactions between risk assessors and risk managers are expected and acceptable:

“The risk assessment process involves regular interaction between risk assessors and risk managers, with overlapping responsibilities at various stages in the overall process. Shared responsibilities include initial decisions regarding the planning and conduct of an assessment, discussions as the assessment develops, decisions regarding new data needed to complete an assessment and to address significant uncertainties. At critical junctures in the assessment, such consultations shape the nature of, and schedule for, the assessment.”

Having confidence in the scientific foundation of IRIS evaluations is critical to all stakeholders. Despite the continued evolution of the EPA IRIS process, it has become increasingly clear that fundamental improvements in the policies and practices of the

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IRIS program are necessary. To ensure transparency for stakeholders, peer reviewers, and risk managers, IRIS assessments should provide full disclosure of the following:

- data, methods, and models sufficient to allow independent reanalysis by qualified persons;
- rationale for choosing methods and models;
- a template or flow diagram illustrating requirements of applicable agency guidance, and explaining any instances in which guidance was not followed;
- assumptions and extrapolations and their impact on the assessment;
- impact on the assessment of models vs. measurements;
- plausible alternatives, the choices made among those alternatives, and impacts of one choice vs. another on the assessment;
- significant knowledge / data gaps, and other sources of uncertainty, and their implications for the assessment;
- scientific conclusions identified separately from default assumptions and policy calls;
- major conclusions and degree of confidence in them;
- relative strength of each component of the assessment and its impact on the strength of the overall assessment; and,
- where possible, as a “validity” or “plausibility” or “reality” check, comparison of resulting reference values and cancer unit risk values estimates with the actual health outcome statistics in relevant populations.

With respect to conducting a “reality” check, this is an important step often overlooked and not performed adequately in IRIS assessments. IRIS assessments rely on a number of models and assumptions, and typically generate upper bound estimates of risks. Depending upon the underlying data and the models used, such estimates can be far different from the “true” or most likely risks. Performing such a reality check can provide much needed perspective for risk managers and policy makers. For formaldehyde, and a number of other substances, IRIS assessments have not provided this “reality” check and thus ACC has criticized such assessments for not addressing a key information need of risk managers and policy makers. In fact, this “reality” check is an integral responsibility of the assessor generating the IRIS assessment. As stated in EPA’s Risk Characterization Guidance (emphasis added):

“Assessors are charged with (1) generating a credible, objective, realistic, and scientifically balanced analysis; (2) presenting information on hazard, dose-response, exposure and risk; and (3) explaining confidence in each assessment by clearly delineating strengths, uncertainties and assumptions, **along with the impacts of these**

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factors (e.g., confidence limits, use of conservative/non-conservative assumptions) on the overall assessment. They do not make decisions on the acceptability of any risk level for protecting public health or selecting procedures for reducing risks.”

Requiring the IRIS program to implement fundamental and permanent improvement to ensure generation of high quality, accurate, and reliable assessments that meet the established standards of objectivity, scientific accuracy, and transparency and which clearly portray the impacts of default assumptions and models and include a “reality” check in the context of background and endogenous levels is not undue influence of risk management on risk assessment. Nor should this be construed as “harms being hidden in anticipation that their discovery might create a hard policy problem.” Rather, it is simply an expectation that IRIS assessments be improved to overcome the “persistence of limitations of the IRIS assessment methods and reports” that have been well documented over the years and more recently explicitly noted by the NAS Formaldehyde peer review panel.

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**Comments of the Ethylene Glycol Ethers Panel of the American  
Chemistry Council on the  
April 2008 External Review Draft of the  
IRIS Toxicological Review for EGBE**

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**Comments on the April 2008 External Review Draft of the  
IRIS Toxicological Review of Ethylene Glycol Monobutyl Ether (EGBE)**

The Ethylene Glycol Ethers Panel of the American Chemistry Council<sup>\*</sup> appreciates this opportunity to comment on the April 2008 external review draft of the IRIS Toxicological Review for Ethylene Glycol Monobutyl Ether (EGBE) (USEPA, 2008a). The Panel has for many years sought to ensure that the potential toxicity of EGBE is thoroughly characterized, and sponsored or supported many of the critical studies published since the existing IRIS Review (USEPA, 1999) establishing modes of action for EGBE's effects in rodents and the relevance of these MOAs to humans. The Panel commends EPA for appropriately incorporating these studies into the cancer risk assessments in the draft IRIS Review, and encourages EPA to address the issues raised in these comments and finalize the Review as quickly as practicable.

These comments do not address all aspects of the draft and do not respond to all of the charge questions to the External Peer Review Panel (USEPA, 2008b). The Panel believes that in most respects the draft meets IRIS standards for accuracy, completeness, objectivity and transparency. However, with the assistance of the reviewers listed on the cover page of this submission, the Panel has identified six issues that should be reexamined or clarified before the IRIS Review is finalized. These issues, all of which pertain to the derivation of the non-cancer Reference Concentration (RfC) and Reference Dose (RfD), are the following:

1. The use of hemosiderin staining as the critical effect for deriving the RfC and RfD;
2. The use of male rat hemosiderin data as the POD for the RfC and RfD;
3. The choice of dose metric and the application of PBPK modeling in the derivation of candidate RfCs based on hematological data;
4. The use of inhalation data to derive the RfD;
5. The intrahuman and interspecies uncertainty factors applied in determining the RfC and RfD; and
6. The need for review and clarification of several aspects of the Benchmark Dose modeling.

**Executive Summary**

As discussed below, several key elements of the risk assessment approach adopted in the draft – especially the use of male rat liver hemosiderin staining as the point of departure – are at odds with the weight of the scientific data and should be reevaluated. The hemosiderin-based risk assessment adopted in the draft conflicts with the available biological and statistical data on EGBE's mode of action and dose-response characteristics in a number of important respects:

- Critical Effect: The critical effect selected in the draft, hemosiderin staining, has not been established as an adverse effect or a precursor of an adverse effect, and while it has been observed coincident to a number of secondary effects resulting from the hemolytic toxicity of EGBE, its biological significance has not been established.

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<sup>\*</sup> The members of the Panel are Arch Chemicals, the Dow Chemical Company, Eastman Chemical Company, and Equistar Chemicals LP.

- Dose Metric: The assertion in the draft that hemosiderin deposition is an appropriate critical effect because it increases in severity with duration of exposure is based entirely on interim study results at only the highest dose level tested (NTP, 2000); for this reason, the draft's choice of AUC as the dose metric is not adequately supported, particularly when the data convincingly show that  $C_{max}$  BAA is the appropriate metric for hemolysis, the primary effect of EGBE in sensitive species.
- POD: The draft uses male rat hemosiderin staining as the POD while repeatedly acknowledging that female rats are more sensitive to EGBE's hemolytic effects. Using the female rat data would be a more appropriate choice on the basis of biological plausibility, but the more important point is that the apparently greater sensitivity of male rats to hemosiderin deposition is another reason to question the validity of hemosiderin staining as the foundation for quantitatively assessing EGBE's hemolytic effects.

The upshot is that a risk assessment based on an appropriate hematological endpoint (instead of hemosiderin staining) would directly address regenerative hemolytic anemia, which is correctly recognized in the draft as the primary response to EGBE in sensitive species, and would use a step lying directly in the pathway of EGBE's mode of action. This is the approach taken in the existing IRIS assessment (USEPA, 1999). While the draft says that its proposed hemosiderin-based approach is founded on new mode of action data published since 1999, the new MOA data relate to effects that are secondary to EGBE's primary hemolytic effect. More importantly, neither the role of hemosiderin deposition in those secondary effects, nor its quantitative association with primary hemolytic effects, are understood.

The draft does contain candidate RfC and RfD determinations based on hematological endpoints. If these assessments are reconsidered in response to the public comments or external peer review of the draft, several important issues should be addressed.

First, as discussed in section 3 below, the estimates of  $C_{max}$  BAA and the human equivalent concentration (HEC) in the RfC section of the draft are markedly different from the corresponding values in the existing IRIS assessment (USEPA, 1999). There are indications that errors may have been made in the application of the Lee (1998) PBPK model in the draft. This should be examined as the Review is finalized and, if no corrections are made to the  $C_{max}$  BAA and HEC values, an explanation should be provided for the large differences from the 1999 IRIS assessment.

Second, as discussed in Section 4, the derivation of the RfD should be based on the NTP (1993) drinking water study in rats, as is the case in the existing IRIS assessment. The draft inappropriately uses hemosiderin data in male rats as the critical effect, an approach that necessitates a route-to-route extrapolation and adds uncertainty to the assessment. The existing IRIS Review finds the NTP (1993) study to be an adequate basis for deriving the RfD, and the draft cites no intervening data that call that finding into question.

Third, as developed in Section 5, the UFs for intrahuman and interspecies variability are greatly overprotective and should be reconsidered irrespective of the final determinations on the critical effect, dose metric and POD to be used in the derivation of the RfC and RfD. For example, the draft concludes (p. 87) that, "toxicodynamically, humans may be less sensitive than rats to the hematological effects of EGBE," but nevertheless assigns a UF of 1.0 for interspecies toxicodynamic variability. The Panel urges EPA to consider Health Canada's recent review of EGBE, which set the toxicodynamic interspecies UF at 0.1,

observing that “this would still be conservative” (Health Canada, 2002). As shown in Section 5, a similar case can be made that the proposed UF of 10 for intrahuman variability is also needlessly overprotective.

**1. The Use of Hemosiderin Staining as the Critical Effect for RfC and RfD Development Is not Biologically Appropriate and Is Inconsistent with the Available Dose-Response Data.**

The draft’s approach of assessing the noncancer risks of EGBE in humans on the basis of the observation of hemosiderin staining in male rats is not supported by the proposed mode of action or the majority of the scientific literature. This endpoint has not been established as an adverse effect or a precursor of an adverse effect. Hemolytic endpoints are used in the current IRIS assessment (USEPA, 1999), and remain the most appropriate basis for deriving the RfC and RfD. Based on the results of the NTP (2000) study, hematological changes should be used as the critical effect to develop the RfC. Such hematological changes are regarded as the most sensitive and early indicators of the primary toxicological effect of EGBE exposure in rodents, which is hemolysis. Hematological information is reported in these studies for either 14-week sub-chronic or 2-year chronic inhalation toxicity studies. Rats were observed to be more sensitive than mice to the hemolytic effects of EGBE in both the 14-week and longer duration studies. In addition, female rats were more sensitive than males.

There is no indication of an increased severity for the critical effect, hemolysis, following 14-weeks, 6 months or 1 year of exposure (Table 1). Unfortunately, the study design of the chronic inhalation studies did not allow for a hematological analysis of blood at the 31 ppm exposure level after 1 year of exposure. However, both the 14-week and 6-month data indicate a LOAEL in female rats of 31 ppm. Because the chronic studies provide longer-term exposure data confirming the results from studies of shorter duration, it is appropriate to use the results from these for setting an RfC value.

**Table 1**  
**Hematological Changes in Female Rats after 14-weeks, 6 Months or 1 Year of Exposure (Taken from NTP, 2000)**

	Chamber Control	31 ppm	62.5 ppm	125 ppm
		<u>RBC Count<sup>a</sup></u>		
14-Week	8.48 ± 0.05	8.08 ± 0.07**	7.70 ± 0.08**	6.91 ± 0.05**
6 Months	8.40 ± 0.07	7.50 ± 0.25**	7.54 ± 0.15**	6.89 ± 0.05**
1 Year	7.80 ± 0.05	NA	7.42 ± 0.06**	6.75 ± 0.05**
		<u>MCV<sup>b</sup></u>		
14-Weeks	55.1 ± 0.3	55.3 ± 0.2	56.4 ± 0.2**	58.7 ± 0.2**
6 Months	54.8 ± 0.3	54.8 ± 0.4	56.0 ± 0.3**	58.2 ± 0.2**
1 Year	56.8 ± 0.2	NA	58.8 ± 0.3**	60.3 ± 0.3**

<sup>a</sup> Red blood cells (erythrocytes) (10<sup>6</sup>/μL)

<sup>b</sup> Mean cell volume (fL)

\*\* Significantly different (P≤0.01) from the chamber control group by Dunn’s or Shirley’s test

The current (1999) IRIS assessment of EGBE is based on female rat hemolysis data from an NTP (1993) bioassay involving a 12-month exposure. Hemosiderin deposition was described as secondary to hemolysis and was not considered to represent the critical endpoint. The 2008 draft IRIS Review does not establish that the observation of hemosiderin staining in the liver of male rats should be considered either an adverse effect or a precursor to any adverse noncancer effect. The use of hemosiderin deposition in Kupffer cells of rats from chronic 2-year inhalation studies with EGBE is not an appropriate critical effect to use for setting either an RFC or an RfD value.

In Section 4.5 of the draft, the observation of hepatic hemosiderin deposition is described as a dose-related sequela of the hemolytic activity, not an endpoint anticipated to occur prior to the observation of hemolysis. Although coincident to a step in a proposed mode of action (MOA) for liver tumor formation in male mice, no definitive research directly links the presence of hemosiderin in Kupffer cells with the activation of those cells. Perhaps most importantly, the biological significance of minimal hemosiderin deposition to any of the effects reported for EGBE has not been established.

Any discussion of a “critical effect” must include a discussion of the biological significance of that effect. The draft designates hemosiderin deposition as the critical effect, rejecting other more accepted hematological parameters. Section 5.2.1 states that “...hematological effects signified by changes in RBC count, reticulocyte count, MCV, HCT, and Hb are considered precursor effects to the pathological findings of hemosiderin deposition...” This statement ignores the direct relevance of the hematological changes to the observed chronic and regenerative hemolytic anemia observed in both rats and mice, and turns the available scientific data on EGBE’s mode of action upside down.

The draft identifies intravascular hemolysis as “the primary response elicited in sensitive species following inhalation, oral or dermal administration of EGBE” (p. 46). Hemosiderin deposition, in contrast, is identified as coincident to a “number of secondary effects resulting from the hemolytic toxicity of EGBE” (p. 49). In certain pathological states, massive deposits of hemosiderin are found in the liver and other tissues (Harrison and Arosio, 1996). The pathological effects seen in the liver as a result of chronic hepatic iron overload are fibrosis and cirrhosis and hepatocellular carcinoma (Bonkovsky, 1991). In the rat and mouse chronic studies with EGBE, the minimal hemosiderin deposition noted was not accompanied by any other significant non-neoplastic pathological responses of the liver. These observations argue against any biological significance for the observed hemosiderin deposition in these studies.

Lacking a clear biological rationale, the draft seeks to justify designating hemosiderin deposition as the critical effect on the premise that its severity increases with duration of exposure. However, the NTP (2000) bioassay results do not support this premise. The 3-, 6-, and 12-month studies found (p. 58) that although the incidence of Kupffer cell pigmentation was significantly increased relative to the chamber controls, the severity of this lesion increased with exposure duration only at the highest dose. (See Table 2; severity is not reported with the 2-year results.) Thus, the draft IRIS Review makes its choice of critical effect solely on the basis of interim study results at only the highest dose level tested.

**Table 2**  
**Incidence and Severity of Kupffer Cell Pigmentation, Hemosiderin Deposition in Rats and Mice after 2-Year Chronic Inhalation Exposures (From NTP, 2000)**

	Incidence		Severity	
	Male	Female	Male	Female
<u>Rats - F344/N</u>				
Controls	23/50	15/50	1.3	1.4
31.2 ppm	30/50*	19/50	1.5	1.5
62.5 ppm	34/50*	36/50*	1.5	1.4
125 ppm	42/50*	47/50*	2.0	2.0
<u>Mice - B6C3F1</u>				
Controls	0/50**	0/50**	NA***	NA
62.5 ppm	0/50**	5/50*	NA	NA
125 ppm	8/50*	25/50*	NA	NA
250 ppm	30/50*	44/50*	NA	NA

\* Reported as significant

\*\* Not listed, assumed to be zero

\*\*\* Stated as minimal (NTP, 2000)

Based on these minimal findings, the authors of the NTP chronic studies suggested that the hemosiderin buildup was not related to the increased incidence of hemangiosarcomas seen in the chronic mouse studies (NTP, 2000, p. 84). This interpretation was further supported by the fact that hemosiderin deposition was only reported in 3 of the 4 high-dose male mice that developed this tumor. Female mice, although displaying a higher incidence of hemosiderin deposition than male mice (Table 2), did not develop this tumor.

In a more recent paper discussing this subject, Gift (2005) proposed that, although minimal, the large percentage of high-dose animals displaying the pigmentation could be the cause of the marginal (8% versus 2.5% historical background) increase in hemangiosarcomas in this study. Some support for this argument comes from the findings of Nyska et al. (2004), who reported a significant correlation between chemically induced hemosiderin deposition and hemangiosarcomas in the liver of mice in 130 NTP bioassays. Correlation, however, does not mean causation: Both effects are likely caused by the hemolytic effects produced by the chemicals which were associated with both hemosiderin deposition and hemangiosarcomas. What is not addressed by Gift is the large background (control) rate of hemosiderin deposition seen in both male and female rats, but not mice (Table 2). This high background rate of hemosiderin deposition in rats, coupled with the fact that rats (and female mice) do not develop hemangiosarcomas, argues against the direct involvement of hemosiderin deposition in the formation of this tumor. Nyska et al. (2004) suggest that the lack of an effect on hemangiosarcoma incidence in rats dosed with EGBE might be explained by the fact that rats have higher liver antioxidant levels that may protect the rat liver from oxidative damage caused by the induced hemolysis. But this hypothesis, even if accepted, does not support a direct role for hemosiderin in the mouse liver tumor MOA.

The male mouse has a higher background rate (spontaneous incidence) of liver hemangiosarcomas compared with the female mouse liver, while no spontaneous hepatic hemangiosarcomas have been reported in the rat. The higher spontaneous incidence of liver hemangiosarcomas in the male mice suggests that male mice have preexisting populations of initiated endothelial cells (compared to female mice and rats), that can then clonally

expand by exposure to chemicals that function at the promotion stage of the carcinogenesis process (such as EGBE). While hemosiderin deposition has not directly been shown to activate Kupffer cells (or other macrophages), it has been shown that hemolyzed RBCs induce DNA damage in endothelial cells, and can activate macrophages (Corthals et al., 2006). Activated macrophages were also shown to stimulate endothelial cell DNA synthesis when co-cultured with activated macrophages (Corthals et al., 2006). Therefore, if macrophages (Kupffer cells) are activated *in vivo* (by RBC hemolysis or other inputs), this event could be envisioned to result in the growth of preneoplastic endothelial cells selectively in the male mouse liver, due to the higher prevalence of initiated endothelial cell populations (evidenced by the higher background tumor response in male mice).

In the proposed MOA for male mouse liver tumor formation, a key step is the uptake of excess iron by Kupffer cells from the hemoglobin of damaged red blood cells (see USEPA, 2008a), followed by the generation of reactive oxygen species. Hemosiderin deposition does accompany the increased iron uptake, but the hemosiderin deposition seems more likely to be a coincidental finding rather than an integral step in the pathway for tumor development. The liver is the major organ of the body involved with iron storage (Anderson and Frazer, 2005). In conditions of iron overload or in certain pathological states, iron may be stored in the liver as ferritin and hemosiderin (Chasteen and Harrison, 1999; Anderson and Frazer, 2005). Hemosiderin itself is an insoluble pigment and is produced from ferritin within lysosomes, which inhibits release of potentially toxic iron (Harrison and Arosio, 1996). Hemosiderin consists of hydrated ferric oxide with associated proteins (Richter, 1978). It has been suggested that sequestration of iron as hemosiderin is a detoxification mechanism (Harrison and Arosio, 1996). In this regard, it has been reported that sequestration of iron by alveolar macrophages from smokers decreases extracellular hydroxyl radical formation, thus protecting surrounding cells from its cytotoxicity (Olakanmi *et al.*, 1993).

Published *in vitro* studies suggest that a more soluble form of iron than hemosiderin is responsible for the formation of reactive oxygen species in hepatocytes and Kupffer cells. Park *et al.* (2002) showed that neither EGBE nor BAA increased biomarkers of oxidative stress in rodent hepatocytes, while iron (ferrous sulfate) was capable of inducing such effects. This paper also demonstrated that oxidative stress biomarkers were enhanced when hepatocytes were co-exposed to iron (ferrous sulfate) and either EGBE or 2-butoxyacetic acid (BAA), the active metabolite of EGBE.

Although resistant to hemolysis by BAA, it is possible to observe slight, pre-hemolytic changes in human red blood cells at high *in vitro* concentrations of the acid (Udden, 2002). Thus, at a concentration of 150-fold or more of that causing similar effects in rat red blood cells, human red blood cells begin to display slightly decreased deformabilities and densities. The presence of these pre-hemolytic changes in human red blood cells is an argument for the appropriateness of the MOA for EGBE, but not necessarily for the direct involvement of hemosiderin deposition in that MOA.

The precursor to hemosiderin deposition, regenerative hemolytic anemia, cannot increase in severity over time. As the NTP (2000) bioassay report states (p. 82):

Apparently, there is a balance between the release of immature erythrocytes to the circulation and the aging process so that at any particular time, only a limited number of erythrocytes are susceptible to hemolysis; thus, the anemia is persistent without any dramatic changes in severity.

Choosing a hematological endpoint as the critical effect for assessing the risk of regenerative hemolytic anemia would reflect earlier EGBE-induced changes than does hemosiderin deposition, and would be grounded in a step lying directly in the pathway of the mode of action. In contrast, hemosiderin deposition has not been demonstrated to be an adverse effect or a precursor to an adverse effect; its biological significance in the secondary effects of EGBE-induced hemolysis is not understood; and its quantitative association with EGBE's primary hemolytic effects is not established. The IRIS Review should return to hematological endpoints to derive the RfC and RfD for EGBE.

**2. The Use of Male Rat Data as the POD Is Inappropriate Because the Available Data Convincingly Demonstrate that Female Rats Are More Sensitive to the Hemolytic Effects of EGBE.**

Regardless of the endpoint selected as the critical effect for the derivation of the RfC and RfD, the use of male rat data as the point of departure (POD) is not appropriate. Throughout the document the case is made repeatedly that female animals in general and female rats in particular are more sensitive to the effects of EGBE:

- "Female rats (NTP, 2000) appeared to be most sensitive among animals studied." (page 74)
- "...female rats, the most sensitive gender." (page 78)
- "With respect to gender sensitivity, it has been consistently noted (Ezov et al., 2002; NTP, 2000, 1993; Dodd et al., 1983; Carpenter et al., 1956) that female rats are more sensitive to EGBE-induced hemolysis than males. This gender difference is consistent with toxicokinetic data for male and female rats reported by the NTP (2000) 2-year study. Female rats eliminated BAA, the toxic metabolite of EGBE, more slowly from the blood, resulting in a larger AUC for the blood concentration of BAA versus time. This may be a result of the reduced renal excretion observed in female versus male rats." (page 48)

Then, presumably because benchmark dose modeling of the male rat data produced a lower BMD than that for female rats, the more "sensitive" male rat BMD was chosen as the point of departure. This choice is biologically implausible based on the evidence for female sensitivity described in the draft itself. Its tenuous nature is reflected by the fact that three different dose-response models all fit the data (see Table 5-7 of the draft). When three dose-response models that are basically curve-fitting procedures fit the data equally well, the choice of model should be based on biological plausibility, not goodness-of-fit. In this case, the biologically correct choice is the female rat data set.

**3. The Choice of Dose Metric, and the Application of PBPK Modeling in the Derivation of Candidate RfCs Based on Hematological Data, Should Be Reexamined.**

The selection of an internal dose metric to be used in the dose-response assessment using the incidence of hemosiderin staining is not adequately justified in the draft IRIS Review. Discussion is provided to establish that hemolytic effects would be closely related to the maximum concentration of BAA in the blood ( $C_{max}$  BAA). However, there is more evidence presented to establish hemosiderin staining as a result of hemolysis, rather than as an endpoint independent of the hemolytic effects. The AUC dose metric, rather than the



$C_{\max}$ , was selected as the appropriate dose metric because the endpoint selected as the critical effect (hemosiderin staining) was said to increase in severity with increased duration. However, as already shown, there is no indication of an increased severity for hemosiderin staining (see Table 2 above). Therefore, this endpoint does not appear to be the result of cumulative exposure and is most likely related to the relevant dose metrics associated with hemolytic effects. In these circumstances  $C_{\max}$  is the more appropriate dose metric.

The Lee et al. (1998) model has been incorrectly applied in the derivation of the  $C_{\max}$  BAA values reported for female rats in Table 5-4 of the draft IRIS Review (2008a). Lee et al. (1998) is cited as the source for the  $C_{\max}$  values used for the assessment of hematological endpoints in both the current assessment (USEPA 1999), as well as the draft (USEPA, 2008a, Table 5-4). However, the  $C_{\max}$  BAA values reported in each document are markedly different, with the values reported in the draft approximately a factor of 7 lower than those reported in the 1999 assessment. In comparing the values reported in Table 5-4 of the draft to the blood concentration data points and model simulations of BAA blood concentrations for male and female rats available in Lee et al. (1998; Figures 2, 5, and 10), the values presented in the draft are inconsistent with both the model simulation results and the observed data reported by Lee et al. (1998).

In the Lee et al. (1998) study, simulations of the blood concentration of BAA, as well as the observed data points provided by Dill et al. (1998), are provided for male and female rats following two weeks of exposure to EGBE (Figures 2 and 5)\*. The female rat values are consistent with the  $C_{\max}$  BAA values reported in the 1999 IRIS Review. In addition, the  $C_{\max}$  BAA values reported in the draft for the female rat are lower than the corresponding values reported for the male rat (Figure 2), which is inconsistent with the observation reported by Dill et al. (1998) that over the two year study, observed maximum blood concentrations ( $C_{\max}$ ) of BAA were higher in female rats than male rats at each concentration and duration of exposure. These comparisons indicate that the values reported in the 1999 Review for  $C_{\max}$  BAA in the female rat are correct and that the markedly lower  $C_{\max}$  BAA values reported in the draft represent an inappropriate application of the PBPK model reported in Lee et al. (1998). In any case, the large discrepancies between the  $C_{\max}$  BAA values reported in the 1999 IRIS review and the draft IRIS Review recently made available should be examined and either reconciled or explained.

Similar discrepancies are evident in the benchmark dose modeling based on hematological endpoints. For example, the draft determines the  $BMCL_{05}$  for BAA in blood to be 37.2  $\mu$ M, and uses the Corley (1997) PBPK model to back-calculate the HEC to be 81.4  $\text{mg}/\text{m}^3$  (USEPA 2008a, p. 81). The current (1999) IRIS Review estimates the  $BMCL_{05}$  for BAA in blood to be 225  $\mu$ M, and the HEC (based again on the Corley (1997) PBPK model) to be 380  $\text{mg}/\text{m}^3$  (USEPA 1999, p. 47) – i.e., higher than the draft Review by factors of about 5-6. It appears likely that a primary factor in these discrepancies is the inappropriate application of the Lee (1998) PBPK model, which the draft indicates was used in the BMD

\* The concentration units reported on Figure 5 for the simulated blood concentrations of BAA are  $\mu$ M; however, there must be an error on this table and the units should be mM. Dill et al. (1998) indicates that over the two year study, observed maximum blood concentrations ( $C_{\max}$ ) of 2BAA was higher in female rats than male rats at each concentration and duration of exposure. In comparing these simulations to similar simulations reported for the male rat (Figure 2), in order for the modeling to be consistent with the observed data (Dill et al. 1998), the blood concentrations of BAA would have to be mM.

modeling of the hematological endpoints (see pp. 80-81 and Table 5-4 of the draft). In any case, the large discrepancies between the BMCL<sub>05</sub> and HEC values generated from hematological endpoints reported in the 1999 Review and the draft should be examined and either reconciled or explained.

#### **4. The Use of Inhalation Data to Derive the RfD Is Inappropriate.**

The current IRIS Review of EGBE (USEPA, 1999) selects a 91-day drinking water study in rats as the principal study for the derivation of the RfD. No more appropriate longer-term oral studies have been performed with EGBE. Because information available from chronic inhalation studies with EGBE indicates that the primary effect, hematological changes, does not become more severe with prolonged exposures, the 91-day drinking water study in rats remains the appropriate POD for deriving the RfD. Use of this study would preclude the need for a route-to-route extrapolation from chronic inhalation data, with the substantial errors that can be associated with this type of analysis (Pauluhn, 2003).

In evaluating the results of the route-to-route extrapolation, a comparison to what is observed in the available oral studies is critical to determine whether the modeling results are realistic or whether, instead, the modeling results contribute additional uncertainty to the derived RfD. The route-to-route extrapolation in the draft IRIS Review is based on the observation of male rat liver hemosiderin staining from the NTP (2000) inhalation study. With that data set as the POD, PBPK modeling is used to derive the proposed new RfD of 0.14 mg/kg/day. In comparing this RfD to the results from the 13-week oral study in rats (NTP, 1993), a significant increase in hemosiderin staining was not observed in male rats until doses of 452 mg/kg/day were achieved or in female rats until a dose of 281 mg/kg/day was achieved (Table 4-1). In addition, significant changes in hematological endpoints were observed at lower doses (69 mg/kg/day). The doses associated with significant increases in hemosiderin staining are orders of magnitude above the POD of 1.4 mg/kg/day, suggesting that the use of the route-to-route endpoint is not appropriate. Additional analyses are needed to determine why a difference in response by route of exposure would be observed.

While route-to-route extrapolation is a valuable tool for chemicals for which no adequate study is available for a selected route of exposure, in the case of EGBE, an adequate oral study is available and should be used to derive the RfD.

#### **5. The Intrahuman and Interspecies Uncertainty Factors Applied in the Derivation of the RfC and RfD Are Greatly Overprotective and Should Be Reevaluated.**

##### **a. The Interspecies UF**

The incorporation of PBPK modeling into the dose-response process to replace the standard default uncertainty factor of  $10^{1/2}$  for possible interspecies differences in pharmacokinetics is a generally accepted practice. The availability of strong, well validated PBPK data from rodents and humans makes this approach appropriate in this case.

The draft IRIS Review repeatedly (e.g., pages 50, 59, and 109) mentions that humans are much less sensitive to the toxic effects of EGBE than are the rodents that provide the basis for derivation of the RfC and RfD. These differences in sensitivity are not simply due to pharmacokinetic differences (which are addressed in the PBPK modeling), but differences in inherent sensitivity – pharmacodynamics – as illustrated by the marked differences in sensitivity of human and rodent blood cells *in vitro* to EGBE and BAA. For example, the work of Udden (2002) demonstrates about a 150-fold greater sensitivity of rat blood cells

than human blood cells to the effects of BAA on red blood cell deformability, osmotic fragility, and hemolysis. Even potentially hypersensitive subgroups of the human population (the elderly, and patients with sickle cell disease or hereditary spherocytosis) show similar resistance to these effects of BAA (Udden 2002).

Given the consistent, substantial difference in sensitivity between human and rats and the data that is the basis for the RfD and RfC, there is no scientific justification for using a pharmacodynamic UF as large as 1.0. The weight of the evidence supports the use of a fractional value of perhaps 0.01, or even less. Specific statements in the draft IRIS Review supporting this conclusion include:

- "In conclusion, humans are significantly less sensitive to the hemolytic toxicity of EGBE than are typical laboratory species such as mice, rats, or rabbits, although human erythrocytes do appear capable of responding similarly to the causative EGBE metabolites, albeit at much higher exposures. This marked species difference in sensitivity has been demonstrated in several laboratory studies and through the use of in vitro studies using either whole blood or washed erythrocytes. Based on the results of in vitro testing, blood concentrations of the hemolytically active metabolite BAA must reach levels in human blood in excess of 7.5 mM for prehemolytic changes to occur. Comparable effects in rat blood occur at in vitro concentrations approximately 150-fold lower. In addition, blood from potentially sensitive individuals, including the elderly or those with congenital hemolytic disorders, does not show an increased hemolytic response when incubated with up to 2 mM BAA for 4 hours. Based on simulations from PBPK modeling, 6-hour whole-body exposure of humans to saturated atmospheres of EGBE will result in maximum blood concentrations of BAA below those needed to produce hemolysis (Corley et al., 2005a)." (page 50)
- "In an in vitro study of RBCs from hospitalized children and adults, concentrations of up to 150-fold higher than those used in rat studies, the highest tested in the study, did not produce hemolysis (Udden, 2002)." (page 59)
- "Observations regarding the potential relevance of EGBE toxicity to humans include the insensitivity of human RBCs to the hemolytic effects of EGBE and its metabolite, BAA . . . the relative insensitivity of human blood to the effects of EGBE [has] been demonstrated in numerous in vitro studies through the use of either whole blood or washed erythrocytes (e.g., Udden, 2002; Ghanayem and Sullivan, 1993)." (page 109)
- "Humans appear significantly less sensitive to the hemolytic toxicity of EGBE than are typical laboratory species, such as mice, rats, or rabbits . . . (Udden, 2002). These observations are inclusive of human RBCs from individuals with hereditary spherocytosis and sickle cell anemia, conditions characterized by RBC sensitivity to hemolysis. Available in vivo information with human exposure supports this species disparity in sensitivity to the hemolytic effects of EGBE." (page 109)

These findings lead the draft IRIS Review to conclude (p. 87) that, "toxicodynamically, humans may be less sensitive than rats to the hematological effects of EGBE."

Nevertheless, the draft assigns a UF of 1.0 for interspecies toxicodynamic variabilities, effectively assuming equivalent sensitivity while repeatedly finding that the scientific data support a much different conclusion. The contrast between the scientific data and the policy

determination leaves the impression that the decision is based on little more than blind and inflexible application of regulatory policy. While a policy reluctance to adopt interspecies UFs below 1 in most cases is certainly not surprising, the recent review of EGBE's toxicity by Health Canada shows that, at least in the case of this chemical, the weight of the evidence supports such a step. Specifically, Health Canada not only set the toxicodynamic interspecies UF for EGBE at 0.1, but also found that "this would still be conservative" (Health Canada, 2002). These findings underscore the need to reevaluate the interspecies UF of 1.0 assigned in the draft IRIS Review.

#### **b. The Intrahuman UF**

Furthermore, the default uncertainty factor of 10 for human variability is not needed. This factor is typically applied to account for variations in human sensitivity or to be protective of sensitive subpopulations. In this case, however, typical hypersensitive subgroups, such as the elderly, also show resistance to the hematological effects of BAA, as do individuals with disease conditions (patients with sickle cell disease or hereditary spherocytosis) that might be expected to make them more sensitive (Udden, 2002). While animal studies suggest that older animals are more sensitive than neonates, and females are more sensitive than males, these have been shown to be a reflection of differences in pharmacokinetics, not pharmacodynamics or sensitivity (Corley et al. 2005). Based on these findings, the proposed 10-fold intraspecies uncertainty factor is clearly excessive.

#### **6. There Are Several Problems with Benchmark Dose Modeling**

While benchmark modeling is the most scientifically appropriate approach for determining the point of departure (POD) using the available noncancer data for EGBE, there are several problems in the implementation of the procedure. The additional documentation of the modeling results provided in Appendix B of the draft has several deficiencies. The output provided in Appendix B for the hemosiderin modeling does not use the AUC doses so is not an example of the output used to derive the RFC. Specifically, the multistage model output labeled "BMD Method for RFC: Hemosiderin deposition in male rats versus AUC BAA, 2 year inhalation study (NTP 2000)" in Appendix B does not use the doses indicated in Table 5-6 as the AUC doses. The BMD and BMDL in this output are not the values reported in Table 5-7. The same is also true of the log-logistic output labeled "BMD Method for RFC: Hemosiderin deposition in female rats versus AUC BAA, 2 year inhalation study, (NTP, 2000)" in Appendix B. The BMD and BMDLs reported in these outputs are not given anywhere else in the document. In addition, in Table 5-7, the female rat multistage (1-stage) output has the BMDL in the BMD column and an incorrect number in the BMDL column (source unknown).

#### **Conclusions**

1. The use of hemosiderin staining as the critical effect in the derivation of the RfC and RfD is inappropriate. Hemosiderin deposition has not been shown to be an adverse effect or a precursor to an adverse effect; its biological significance in the secondary effects of EGBE-induced hemolysis is not understood; and its quantitative association with EGBE's primary hemolytic effects is not established. The IRIS Review should return to hematological endpoints to derive the RfC and RfD for EGBE.
2. Even if hemosiderin staining is used as the critical effect, it is not appropriate to use male rat data as the POD because, as the draft repeatedly acknowledges, female rats are more sensitive.

3. The dose metric used in the RfC derivation is not supported by the available scientific data. The data on hemosiderin staining does not show increased severity with increased duration and, therefore, this endpoint does not appear to be the result of cumulative exposure and is most likely related to the relevant dose metrics associated with hemolytic effects. In these circumstances  $C_{max}$  is the more appropriate dose metric.
4. In the case of the candidate RfCs derived in the draft based on hematological endpoints, there appear to be serious errors in the application of the PBPK model developed by Lee (1998) to determine  $C_{max}$  BAA values used in the derivation of the PODs based on both the LOAEL/PBPK and BMD methods. In any case, the large discrepancies between the  $C_{max}$  BAA, BMCL<sub>05</sub> and HEC values reported in the draft and the corresponding values reported in 1999 IRIS review should be examined and either reconciled or explained.
5. The derivation of the RfD should be based on the NTP (1993) drinking water study in rats, as is the case in the existing IRIS assessment. The approach adopted in the draft of using hemosiderin data in male rats necessitates a route-to-route extrapolation that adds uncertainty to the assessment.
6. The UFs for intrahuman and interspecies variability are greatly overprotective and should be reconsidered. Health Canada's recent review of EGBE illustrates that UFs below the default values for these variabilities – including UFs below 1.0 for interspecies sensitivity – can be applied for EGBE and “this would still be conservative.”

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*Responses by Dr. Gail Charnley, Principal, HealthRisk Strategies*

**Dr. Broun's questions**

- 1) There are those who have said that the IRIS program's assessment practices continue to suffer from a variety of issues that have been identified - in many cases, years ago - as problematic. And further, it has been alleged that many of these problems systematically exaggerate actual risks and thereby seriously compromise the value of assessments as inputs to regulations and regulatory impact analyses.
  - Can you comment on that?

According to National Academy of Sciences committees that have reviewed IRIS draft assessments, those assessments lack adequate description of the methods used to conduct them, are inconsistent with EPA risk assessment guidelines, lack clear links to an underlying conceptual framework, and do 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 toxicity values. In my view, the assessments give the impression that the most conservative (i.e., most stringent) toxicity values are chosen without following a consistent weight-of-evidence analysis that might lead the authors to different conclusions about risk if all the available evidence were considered objectively. Ideally, the reasoning process and bases for judgments about risk should be explicit and transparent so that, even if other observers differ with a particular set of conclusions, debate can focus on the soundness of the inferences and their connections to study results instead of descending into ad hominem debates about the political leanings of the observers (or how they earn a living).

- 2) Why is it important to use uniform and consistent procedures for evaluating toxicity data for IRIS assessments?
  - Should scientific studies be evaluated uniformly, irrespective of who conducted the study or what the funding source was?

According to EPA risk assessment guidance documents, it is EPA policy to evaluate toxicity information based on sound scientific practices and reach a position based on careful consideration of all such information (i.e., a process typically referred to as the "weight-of-evidence" approach).<sup>1</sup> The weight-of-evidence approach generally considers all relevant information in an integrative assessment that takes into account the kinds of evidence available, the quality and quantity of the evidence, the strengths and limitations associated of each type of evidence, and explains how the various types of evidence fit

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<sup>1</sup> EPA (Environmental Protection Agency). 2002. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency. EPA/260R-02-008. Office of Environmental Information, Washington, DC



together.<sup>2</sup> Risk assessment involves consideration of the weight of evidence provided by all available scientific data . . . Judgment on the weight of evidence involves consideration of the quality and adequacy of data and consistency of responses induced by the stressor.<sup>3</sup> Those policies do not distinguish among studies based on the identity of the scientists who conducted them or their source of funding.

- 3) In your testimony you say about the current IRIS process, “I think the solution is not to try once more to tweak or revamp the existing process but to get rid of it entirely and start over.”
- Starting over would effectively mean terminating IRIS while the program’s regenerated. Is the issue serious enough to warrant such a result, and what impact would this have on IRIS customers?
  - How would risk managers develop risk assessments?
  - How was this done before IRIS?

I believe that public health is not served by a broken, cumbersome, controversial process that lacks a rigorous scientific foundation and a transparent, replicable weight-of-evidence framework. Setting up a more effective process should follow the recommendations of a National Academy of Sciences committee convened for that purpose and should follow a weight-of-evidence procedure recommended by the Academy. Chapter 7 of the Academy’s formaldehyde report provides helpful guidance to that end, and notes that such changes can be made relatively quickly as was accomplished when EPA revamped its NAAQS review process. One possibility is that EPA program offices develop their own values, as they did before and as the air and pesticide offices continue to do.

- 4) Is it well-established in toxicology that chemicals act by different modes of action, and that some can cause cancer in high dose lab animal studies by non-genotoxic mechanisms?
- In these types of substances, is it appropriate to use a linear method for extrapolating risks to humans?
  - To the best of your knowledge, what has been the IRIS Program office’s approach?

According to EPA’s cancer risk assessment guidelines, when there is sufficient evidence to indicate that tumors are produced by a substance in laboratory animals only at high doses, a low-dose linear model should not be assumed. IRIS assessments have been reluctant to adhere to those guidelines, as evidenced by the IRIS dioxin assessment, for example, which continues to rely on the low-dose-linear assumption despite a National Academy of Sciences review in which the committee unanimously agreed that “the current weight of evidence on TCDD, other dioxins, and [dioxin-like compounds] carcinogenicity favors the use of nonlinear methods for extrapolation below the point of departure (POD) of mathematically modeled human or animal data.”<sup>4</sup> Reluctance to deviate from a low-dose-linear default even when the science supports doing so is a long-standing problem that has even been

<sup>2</sup> EPA (Environmental Protection Agency). 2003. A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information. EPA 100/B-03/001. Science Policy Council, Washington, DC

<sup>3</sup> EPA (Environmental Protection Agency). 2004. Risk Assessment Principles and Practices. EPA/100/B-04/001. Office of the Science Advisor, Washington, DC

<sup>4</sup> NAS/NRC (2006), Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment. National Academy Press, Washington, DC

recognized by the DC Circuit Court, which reversed EPA's decision to use a linear no-threshold model for chloroform despite accepting scientific evidence to contrary [*Chlorine Chemistry Council v. EPA*, 206 F.3d 1286 (D.C. Cir. 2000)].

- 5) What is the impact of EPA using a linear approach for determining human health cancer risks even when a mode of action evaluation indicates a threshold non-linear approach is supported by the best available science?
  - Would risks be overestimated? If so, how large would that overestimation be?
  - What kinds of impacts does this have on regulatory actions, such as on waste site cleanups? On drinking water treatments? On air permits?

Using a low-dose-linear model when a mode-of-action evaluation supports a threshold non-linear approach overestimates risk and leads to exposure limits that are more stringent than needed to protect public health. The extent of the overestimation would depend on the dose-response relationship for the substance in question and the exposure limit chosen. Overestimation leads to public and private spending on compliance measures that do not improve public health.

- 6) The CPR report included as part of Ms. Steinzor's testimony states: "The Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) is the most important toxicological database in the world. Not only is it the single most comprehensive database of human health information about toxic substances, it also serves as a gateway to regulation, as well as to a range of public and private sector efforts to protect against toxic substances." [p.1]
  - Since IRIS serves as a gateway to regulation, isn't it imperative that the programs have confidence in the values proposed?
  - How useful can it be to program offices when values are set below naturally occurring background levels or below current method detection limits?

As Ms. Steinzor notes, the reach of IRIS goes far beyond EPA as other federal agencies and state and local governments in the US and other countries lacking their own resources for generating chemical toxicity values have come to rely on those generated by IRIS. Because the influence of IRIS is so broad, the scientific quality and integrity of its reviews are critically important. Furthermore, IRIS assessments can become de facto components of regulatory decision-making without benefit of appropriate administrative process. Unfortunately, over time the IRIS process has become politicized and, as a result, it no longer has much scientific credibility outside the agency or, importantly, even within the agency.

Exposure to substances at naturally occurring background levels is generally safe. With rare exception, exposure limit values set below naturally occurring background levels defy common sense. Exposure limits set below method detection limits can be useful goals, not verifiable at present but potentially in the future as detection methods evolve.

- 7) The CPR report included as part of Ms. Steinzor's testimony states: "EPA should put faith in its own scientific expertise and rely on outside science review only in the most complex cases."  
[p.5]
- Many question whether the internal EPA peer review process is rigorous or independent. For instance, the program office writes the charge to the Science Advisory Board and there is seldom any pushback or discussion of the charge. The peer review panel is then developed based on the charge so they typically don't have the expertise to stray beyond the charge. Do you believe this is a truly independent process?

No, the SAB process is not truly independent. Politically appointed EPA officials select SAB members, formulate the charge questions, provide staff support for the review process, and observe SAB deliberations and report drafting. According to the SAB web site, "The Staff Office manages EPA requests for scientific and technical advice and peer review. The Staff Office also provides policy, technical and administrative assistance to advisory committees in conducting meetings and preparing reports. The SAB Staff Office oversees the formation of advisory committees and panels . . ." and so forth. In contrast, the National Academy of Sciences review process is truly independent. Truly independent peer review is the only way to give stakeholders confidence in the credibility of an outcome.

- 8) In responding to a question from the Committee, one of the witnesses, Ms. Rena Steinzor, lamented that one of the most distressing things she had heard during the hearing is that her 20-year old son - used as a metaphor for the population in general - had formaldehyde in his body and that he was exhaling it at levels "that are much higher than the reference dose set by the EPA database." The reason for this, she added, is "because the air is polluted. We live in a non-attainment area that is awash in toxics and all sorts of other problems, and that is why that has happened."
- Is Ms. Steinzor's observation scientifically correct? Do humans exhale formaldehyde because "the air is polluted?" Please elaborate in your reply.

No, Ms. Steinzor's observation is not scientifically correct. We learned in Biology 101 that formaldehyde is naturally occurring and present in every cell of the body, serving as the source of single carbon molecules used by every cell to build the chemicals it needs to conduct the business of life. (Presumably as a lawyer, Ms. Steinzor did not take Biology 101.) The amounts of formaldehyde detected in breath result from the naturally occurring formaldehyde present in all tissues as a part of normal metabolic processes. The presence of naturally occurring formaldehyde in every living cell challenges the IRIS program's presumption that there is no safe level of exposure to formaldehyde (the low-dose-linear assumption).

**Ms. Edwards' questions**

- 1) Your written testimony explicitly rejects using EPA's Science Advisory Board for independent external reviews of proposed IRIS assessments. You write that "the SAB review process is not independent." You then go on to note that "EPA officials select SAB members, formulate the charge questions, provide staff support for the review process, and observe SAB deliberations and report drafting." Since all SAB work is subject to similar dependence upon "EPA officials" is there any element of SAB work that you believe can be considered "independent?"

I believe that SAB members act honestly and independently. It is the system that is not independent of the goals EPA seeks to achieve.

- 2) My understanding is that National Research Council/National Academy of Sciences staff play a role very similar to the one you describe as being played by EPA staff. Please elaborate on the differences between the NAS process for review and the one you understand to be used at SAB?

Sponsors such as EPA are responsible for identifying subjects for NAS to address and for specifying charge questions. Having done so, EPA is no longer part of the process. NAS committee members are chosen independent of EPA guidance, based on the specific expertise required to address the charge, and conduct their reviews and deliberations independent of EPA interference. Most importantly, NAS is not invested in the outcome of a particular NAS committee's review and recommendations.

- 3) A review of the composition of the Board on Environmental Science and Toxicology (BEST) reveals a number of industry-affiliated figures as well as public advocacy representatives. Especially those whose living depends on selling their scientific services to industry, it would seem that disclosure of interests would be important, though problematic. Please provide copies of all conflict disclosure records you submitted to the National Academy of Sciences BEST prior to your appointment as a board member or since you became a member of the board.

BEST members' conflict disclosure forms are confidential and disclosing potential conflicts of interest is not problematic. In addition to filing written disclosure forms, members provide oral descriptions of potential conflicts and biases at BEST meetings in front of other BEST members, who can (and do) ask specific questions about any concerns. BEST members routinely disqualify themselves from participating in matters in which they (or their spouses) have a conflict of interest. The NAS conflict and bias policy is available at [http://www.nationalacademies.org/doi/bi-coi\\_form-0.pdf](http://www.nationalacademies.org/doi/bi-coi_form-0.pdf).

- 4) At the hearing you explained that the work you were paid to do on formaldehyde was all conducted prior to your appointment to the National Academy of Sciences Board on Environmental Science and Toxicology (BEST). According to records reviewed by our staff, you apparently spoke on behalf of The Formaldehyde Council on January 29, 2009 at an EPA meeting on proposed rulemaking regarding formaldehyde. Later that year in November 2009 you also gave a presentation on behalf of the "Troy Corporation" at a Formaldehyde Expert Panel Meeting on the "Report on Carcinogens (RoC)." The meeting was part of the National Toxicology Program and took place in Research Triangle Park, North Carolina.

The first meeting of BEST that I attended was held in October 2009. The conflict-of-interest form I submitted at that time described the work I did on formaldehyde and I described it orally at the meeting in front of other BEST members. I recused myself from all discussions of formaldehyde at that meeting and at all subsequent BEST meetings even after I no longer did any work on formaldehyde.

- 5) Please provide the exact date you began service on the BEST Panel. In addition, please provide a list of the exact dates or time-periods you have been employed by The Formaldehyde Council (FCI), the Troy Corporation or any other associations, entities or corporations for which you performed any work related to formaldehyde between 2006 and the present.

This list should include:

- The full name of the organization that employed you to work on formaldehyde issues;
- The dates of your work for each of these organizations;
- How much you were paid for your work; and
- The specific nature of your work for each of these groups, including the title, place and date of any articles you published or presentations you made as part of this work.

Please see response to question #4 above.

- 6) Your husband, Donald Elliott, served on the BEST panel from 2004 through 2009. During this time period you were engaged in consulting for industry on various chemicals, including formaldehyde. Was he required to submit any records to NAS/NRC regarding potential conflicts of interest due to the work you were engaged in? Did your husband ever recuse himself from any of his work on the BEST panel as a result of the work you were conducting or expected to conduct for corporate sponsors or business associations? If so, please indicate what issues you were working on, who you were working for that presented a potential conflict-of-interest and the dates of your work for that organization.

My husband noted my involvement in both formaldehyde and perchlorate on his BEST conflict-of-interest form. He advises me that he recused himself from all discussions of formaldehyde and perchlorate at all BEST meetings he attended.

**Mr. Miller's questions**

- 1) In answers to a question I asked you at the hearing, you said you would provide us with a list of the organizations that you have worked for in the past. You also indicated that you do a lot of "pro bono" work. Please provide a list of all organizations of any kind that you have worked for, and include the information listed below for all work from 2006 to the present:

- The full name of the organization, association or company;
- The specific nature of your work for each of these entities, including the title, place and date of any articles you published or presentations you made as part of this work.
- The time period of your employment for each of these organizations;
- Whether you engaged in this work on a "pro bono" basis or whether you were paid for this work;
- If you were paid for this work, please indicate how much you were paid.

I do have to work part-time for a living and the work for which my training is relevant (because I have a PhD in toxicology) focuses on understanding the relationships between chemical exposures, toxicity, and

the risk of human health effects. However, most of my work is *pro bono* for organizations such as the National Academy of Sciences, the Environmental Literacy Council, the National Toxicology Program, the Society for Risk Analysis, California's green chemistry science advisory board, and the Environmental Law Institute. When I get paid for work, my clients have been generally a mix of nonprofits, government, industry associations, companies, and law firms. I have also done some teaching (as a guest lecturer) at Yale, Harvard, Georgetown, and George Mason. An elaboration of the kinds of work I have conducted can be found on my website, [www.healthriskstrategies.com](http://www.healthriskstrategies.com).

- 2) In your testimony you said: "I have never failed to disclose the source of my funding in anything I have published." However, in carefully reviewing your employment history with various entities and your publication record staff have identified several examples where it appears that you neglected to reveal a financial relationship with interested parties when you either published or spoke on a matter. Please provide a written response to each of the specific questions listed below.
- In July 1998 your former boss, Myron Weinberg, President of the Weinberg Group sent a letter to the Chlorine Chemistry Council suggesting that he and you could each author a scientific report on "risk management" and have these articles placed in scientific journals. (I have attached a copy of this letter for your review.) In the letter, Mr. Weinberg specifically mentioned placing your articles in the journal *Risk Analysis* published by the Society for Risk Analysis. At the time, you were the president-elect of that organization. "We estimate that the costs for professional time for these efforts would be \$15,000 for the article by Dr. Charnley," wrote Mr. Weinberg. The letter further stated that Mr. Weinberg was "interested in proceeding forthwith" with these efforts so that this proposed article could be placed "in the early Fall 1998." In September 1998 you authored an article in the journal *Environmental Health Perspectives* titled: "A Public Health Context for Residual Risk Assessment and Risk Management Under the Clean Air Act." That article sounds quite similar to the one proposed by Mr. Weinberg.
    - o Please indicate whether the Chlorine Chemistry Council ever followed through with Mr. Weinberg's proposal to have you author an article on "risk management" for a fee of \$15,000 or any other fee.
    - o If you did author an article for the Chlorine Chemistry Council in return for a payment to the Weinberg Group (or to you personally) please provide the title and when and where it was published (if it was published).
    - o In addition, please indicate whether or not you or your employer received any funding from any entity for the article you published in *Environmental Health Perspectives* titled: "A Public Health Context for Residual Risk Assessment and Risk Management Under the Clean Air Act" in September 1998.

I am not responsible for what Mr. Weinberg may or may not have promised anyone and you would have to ask him what he had in mind. Because he was soliciting an article in July 1998 it is highly unlikely that he was referring to an article I had already submitted to *Environmental Health Perspectives* in January 1998, six months earlier. I wrote the article to which you refer with Dr. Bernard Goldstein based on the conclusions of the Presidential/Congressional Commission on Risk Assessment and Risk Management, mandated under the 1990 amendments to the Clean Air Act and with which we were both involved between 1994 and 1997. The Chlorine Chemistry Council did not sponsor it.



## Appendix A

### Comments to the U.S. Environmental Protection Agency on the 2010 Draft Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments

September 15, 2010

These comments are submitted to the US Environmental Protection Agency's Science Advisory Board pursuant to its review of EPA's 2010 Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (EPA/600/R-10/038A). The comments were prepared by Dr. Gail Charnley of HealthRisk Strategies in Washington, DC and Drs. Lorenz Rhomberg and Robyn Prueitt of Gradient, based in Cambridge, MA and Seattle, WA. HealthRisk Strategies provides independent policy analysis of issues relating to the assessment, management, and regulation of public health risks from chemical exposures. Gradient is an environmental and risk science consulting firm that specializes in employing sound science to resolve complex problems relating to chemicals in the environment, in the workplace, and in consumer products. These comments were prepared at the request of the Research Foundation for Health and Environmental Effects, a 501(c)(3) non-profit organization established by the American Chemistry Council's Chlorine Chemistry Division that supports joint research projects sponsored by industry, public agencies, academia, and other foundations.

Our comments address three areas: weight-of-evidence analysis, risk assessment of cancer effects, and risk assessment of noncancer effects. We are particularly concerned that EPA's 2010 dioxin reassessment fails to follow EPA's own risk assessment guidance as embodied in its 2000 Risk Characterization Handbook,<sup>1</sup> 2002 Information Quality Guidelines,<sup>2</sup> 2003 Assessment Factors handbook,<sup>3</sup> 2004 Risk Assessment Principles and Practices documentation,<sup>4</sup> and 2005 Guidelines for Carcinogen Risk Assessment,<sup>5</sup> and that it ignores the recommendations of the National Academy of Sciences committee that reviewed EPA's 2003 dioxin reassessment. The 2010 reassessment does not evaluate or portray the true weight of the scientific evidence and its assumptions about dioxin's carcinogenic mode of action are poorly supported. Its linear dose-response justification would set a

<sup>1</sup> EPA (2000) Risk Characterization Handbook. EPA 100-B-00-002. Science Policy Council, Washington, DC

<sup>2</sup> EPA (2002) Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency. EPA/260R-02-008. Office of Environmental Information, Washington, DC

<sup>3</sup> EPA (2003) A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information. EPA 100/B-03/001. Science Policy Council, Washington, DC

<sup>4</sup> EPA (2004) Risk Assessment Principles and Practices. EPA/100/B-04/001. Office of the Science Advisor, Washington, DC

<sup>5</sup> EPA (2005) Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Risk Assessment Forum, Washington, DC

precedent as a major science policy departure from accepted practice in the absence of the larger and fuller peer review that would be required for such a departure. The noncancer endpoints used for risk assessment are of questionable clinical relevance.

Thank you for the opportunity to submit these comments. We are happy to provide any additional information upon request.

#### WEIGHT-OF-EVIDENCE ANALYSIS

**(1) The primary shortcoming of EPA's 2010 dioxin reanalysis is that it fails to evaluate the potential human cancer and noncancer effects of dioxin using a weight-of-evidence analysis, despite the direction to do so provided by its own risk assessment guidance documents and by the National Academy of Sciences committee that reviewed EPA's 2003 dioxin reanalysis.**

A weight-of-evidence analysis for any potential health effects, including those for cancer or noncancer endpoints, should be more than a matter of describing a set of available studies with an array of results and then announcing one's overall professional judgment. It is important to be systematic and transparent about the information being drawn from the studies, the method used for evaluation and formulation of judgments, and the scientific reasoning behind any judgments offered. EPA's own Risk Characterization Handbook includes criteria for transparency in risk assessment so that any reader can understand all the steps, logic, key assumptions, limitations, and decisions made, and can easily comprehend the supporting rationale that lead to the outcome [p. 15]. Because judgments made about potential risk will usually not be definitive, it is important to present the strengths and weaknesses of alternative judgments that could be made, giving the reader a picture of how strongly one or another interpretation is supported vis-à-vis alternative possible explanations. This process is clearly mandated by EPA's guidance, as documented below. If, in the end, a position is espoused for which other reasonable conclusions could be drawn, and especially if the preferred position is chosen on the basis of a science policy or risk management consideration in the face of scientific uncertainty, it is important to forthrightly document this, rather than simply to present the chosen conclusion with a recitation of its supporting evidence, as EPA has done for both the cancer and noncancer findings in its 2010 dioxin reassessment.

Both the NAS review panel and EPA's own guidance recommend a weight-of-evidence process to evaluate the biological plausibility of potential human health effects. For example, EPA's 2002 Information Quality Guidelines recommend a weight-of-evidence approach in risk assessments.

- In the Agency's development of "influential" scientific risk assessments, we intend to use all relevant information; . . . evaluate that information based on sound scientific practices as described in our risk assessment guidelines and policies; and reach a position based on careful consideration of all such information (i.e., a process typically referred to as the "weight-of-evidence" approach). [p. 26]



Similarly, EPA's 2003 Assessment Factors Handbook addresses the need for weight-of-evidence analysis in risk assessment.

- The weight-of-evidence approach generally considers all relevant information in an integrative assessment that takes into account the kinds of evidence available, the quality and quantity of the evidence, the strengths and limitations associated of each type of evidence, and explains how the various types of evidence fit together. [p. 2]

EPA's 2004 Risk Assessment Principles and Practices document also advises the use of a weight-of-evidence evaluation.

- Risk assessment involves consideration of the weight of evidence provided by all available scientific data . . . Judgment on the weight of evidence involves consideration of the quality and adequacy of data and consistency of responses induced by the stressor. [p. 71]

In particular, a weight-of-evidence process should be used *prior* to the selection of studies for quantitative dose-response analysis, to integrate all relevant information on a particular response in a comprehensive and transparent manner.

The NAS committee that reviewed EPA's 2003 dioxin reassessment recognized the shortcomings of EPA's approach to evaluating potential human health effects and specifically recommended that the Agency perform a weight-of-evidence evaluation for relevant endpoints.

- . . . the committee notes that EPA does not use a rigorous approach for evaluating evidence from studies and the weight of their evidence in the Reassessment. [p. 47]
- The Reassessment provides an extensive catalog of studies but does not synthesize the significant insights or provide clear assessments of the key uncertainties in a way that allows the reader to determine the impact of various choices made. [p. 48]
- [T]he EPA Reassessment . . . relies largely on committee-based, consensus evaluation of the available data rather than on specifically commissioned, rigorous analyses constructed according to established criteria that both formally evaluate the strengths of the available evidence and integrate, by quantitative systematic review, the data across available studies. [pp. 163-164]
- The divergent data across the diverse studies assessing human noncancer end points have not been subjected to systematic review according to currently accepted approaches . . . nor has there been formal grading of the quality of the evidence according to accepted principles . . . [p. 173]
- For available human, clinical, noncancer end point data, EPA should establish formal principles of and a formal mechanism for evidence-based classification and systematic statistical review, including meta-analysis when possible. [p. 174]
- The quality of the available evidence should be reported, and the strength or weakness of a presumptive association should be classified according to currently accepted criteria for levels of evidence. [p. 196]

In the 2010 reanalysis, EPA did not follow the recommendations of the NAS committee, or those of their own guidance, to conduct a weight-of-evidence evaluation of potential effects of dioxin exposure.

Instead, EPA presented their study inclusion criteria and evaluation considerations for both cancer and non-cancer data. More specifically, EPA's study inclusion criteria preclude a weight-of-evidence analysis because they select solely for epidemiologic studies that demonstrate "an association between TCDD and an adverse health effect" [p. 2-7] or for which the "magnitude of animal responses is outside the range of normal variability exhibited by control animals" [p. 2-8]. EPA's inclusion criteria specifically exclude studies that demonstrate no effect, effectively preventing a balanced consideration of available evidence supporting or refuting the biological plausibility and likelihood of effects. Thus, the inclusion criteria relied upon in EPA's 2010 dioxin reassessment specifically violate the recommendations of its own 2002 Information Quality Guidelines, 2003 Assessment Factors Handbook, 2004 Risk Assessment Principles and Practices documentation, and the recommendations of the NAS committee that reviewed the 2003 dioxin reassessment. More generally, EPA's approach violates the criteria for transparency, consistency, and reasonableness found in its 2000 Risk Characterization Handbook.

A true weight-of-evidence analysis should explicitly present the criteria for inclusion and exclusion of studies so that *all* relevant information is included and so that biases toward inclusion of certain outcomes (e.g., only positive outcomes) are avoided. That is, negative or inconsistent results are important to address because their existence will have to be part of the overarching explanation of the array of results on hand. It is important to be explicit about what results are being drawn from each study and not focus just on positive outcomes. Methodologic strengths and weaknesses of each study should be noted without respect to study outcome in order to better assess similarities and differences in study outcomes. The goal is to be able to interpret possible reasons for disagreement, not to select the "best" study and rely on it even if it is contradicted by other study results.

Study results should be arrayed in such a way that does not unduly emphasize positives over negatives and, moreover, that attends to the reasoning and pitfalls involved with deciding what endpoints (and what measures of those endpoints) and what dose measures are to be considered comparable in comparisons across studies. In particular, creating a general category of response and then treating individual studies as corroborative even if the particular responses from study to study differ (though they may be in the same overarching category) can bias the analysis by failing to note the lack of corroboration of particulars. For instance, the assertion that dioxins lead to a broad increase in all human cancers, the particular studies that find increases only in particular cancers, or different studies that find increases in different kinds of cancer from one study to another, are in fact contradictory unless there is evidence of some basis for a general carcinogenic mechanism to act in different particular ways in different settings.

Performing a true weight-of-evidence analysis is consistent with requirements by all three branches of the federal government to use the best available scientific information in order to produce balanced, high quality decisions. For example, President Clinton's Executive Order 12866 (still in force) stipulates that agencies should base their regulatory decisions on the "best reasonably obtainable scientific, technical, economic, and other information."<sup>6</sup> Congress has consistently underscored a national policy requiring agencies to promulgate science-based regulations. For example, rules promulgated under the Safe Drinking Water Act must use the "best available, peer reviewed science" and present

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<sup>6</sup> Federal Register, Volume 58, No. 190 (October 4, 1993)

“comprehensive, informative, and understandable” risk information. Furthermore, the US Supreme Court’s Daubert decision established that expert opinion based on a scientific technique is inadmissible in lawsuits if the technique is not generally accepted as reliable in the relevant scientific community.<sup>7</sup> Thus, all branches of the federal government underscore the need to assess all available scientific information. Doing so requires a weight-of-evidence process that is consistent, comprehensive, balanced, and reproducible in risk assessment.

EPA itself addresses the use of best available scientific information in a variety of documents. For example, EPA’s 2002 Information Quality Guidelines define a weight-of-evidence approach and recommends that approach for risk assessment [p.26]. EPA clarified that recommendation in its 2003 Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information, which was intended to assure data transparency and to provide guidance for EPA’s weight-of-evidence analyses. According to that document, such analyses are meant to consider “all relevant information in an integrative assessment that takes into account the kinds of evidence available, the quality and quantity of the evidence, the strengths and limitations associated with each type of evidence and explains how the various types of evidence fit together [p. 2]. Similarly, EPA’s 2004 document Examination of Risk Assessment Principles and Practices makes a commitment to assess all available scientific information using a weight-of-evidence process that is consistent, comprehensive, balanced, and reproducible. Moreover, a weight-of-evidence approach is embraced as a key feature of EPA’s 2005 Guidelines for Carcinogenic Risk Assessment [p.1-11].

Finally, the need for a weight-of-evidence evaluation is at the heart of the recommendations made by the NAS committee that reviewed EPA’s 2003 Draft Dioxin Reassessment. Weight-of-evidence analysis is not a novel concept in EPA’s risk assessment paradigm and is addressed in numerous EPA guidance documents. Absence of a true weight-of-evidence approach from the 2010 Dioxin Reanalysis constitutes a glaring omission in light of these guidelines and policies.

## CANCER

- (2) EPA’s 2010 dioxin reanalysis states that there is insufficient evidence to support the use of a nonlinear cancer dose-response model, defaulting to a low-dose linear model instead. That conclusion is in conflict with the unanimous conclusions of the National Academy of Sciences review panel, with EPA’s own guidance and procedures, and with virtually every other scientific and regulatory government organization in the world that has reviewed dioxin.**

Instead of following the recommendations of the National Academy of Sciences and, in conflict with its own cancer risk guidelines, EPA’s 2010 dioxin reassessment continues to rely on a linear model for TCDD, adding some nonlinear calculations only as “illustrative examples”. There is no balanced weight-of-evidence analysis of the science supporting linearity versus nonlinearity and the reassessment reads like a lengthy justification for the predetermined policy choice of linearity.

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<sup>7</sup> Daubert v. Merrell Dow Pharmaceuticals Inc., 516 U.S. 869 (1993)

The 2010 reassessment's justification for choosing linearity is that TCDD's carcinogenic mode of action is unknown.

- The sequence of key events following binding of TCDD to the AhR and that ultimately leads to the development of cancer is unknown. [pp. 5-10 to 5-11]
- The mode of action of TCDD in producing liver cancer in rodents has not been elucidated. [p. 5-17]
- . . . a defined mechanism at the molecular level or a defined mode of action for TCDD-induced carcinogenicity is lacking . . . [p. 5-20]
- EPA believes that the mode of action is not known, so is using the default linear extrapolation approach specified by EPA's cancer guidelines. [p. 5-63]

In contrast, EPA's cancer guidelines actually state, "At least some information bearing on mode of action . . . is present for most agents undergoing assessment of carcinogenicity, even though certainty about exact molecular mechanisms may be rare" [pp. 2-36 to 2-37]. TCDD's exact *mechanism* of action may not be entirely clear, but its *mode* of action is. In fact, the reanalysis notes that the cancer guidelines define mode of action as "a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation" where a "key event" is an empirically observable precursor step that is itself a *necessary element* of the mode of action or is a biologically based marker for such an element [p. 5-10].

The reanalysis acknowledges that the necessary element associated with TCDD's carcinogenic mode of action is AhR receptor-mediated. Receptor-mediated modes of action are generally associated with nonlinear dose-response relationships.<sup>8</sup>

- Most evidence suggests that the majority of toxic effects of TCDD are mediated by interaction with the AhR. EPA considers interaction with the AhR to be a necessary, but not sufficient, event in TCDD carcinogenesis. [p. 5-10]

Furthermore, in its discussion of the plausibility of TCDD-induced human carcinogenesis, the reanalysis refers to the AhR-mediated mode of action in rodents.

- Several hypothesized modes of action have been presented for TCDD-induced tumors in rodents, all involving AhR activation. The available evidence does not preclude the relevance of these hypothesized modes of action to humans. [p. 5-9]
- TCDD is characterized as carcinogenic to humans [based on] general scientific consensus that the mode of TCDD's carcinogenic action in animals involves AhR-dependent key precursor events . . . [p. 5-20]

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<sup>8</sup> See, e.g.: NAS/NRC (2006), Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment; Ross and Kenalkin (2001), Pharmacokinetics: Mechanisms of drug action and the relationship between drug concentration and effect, pp. 31-43 in Goodman & Gilman's the Pharmacological Basis of Therapeutics, 10th Ed.; Kohn and Melnick (2002) J. Mol. Endocrinol. 29:113

Then, reiterating the assertion that TCDD's mode of action is unknown, the reanalysis chooses the low-dose-linear model as the appropriate default model for describing TCDD's dose-response. However, EPA's cancer guidelines explicitly state that both linear and nonlinear dose-response models can be considered "default" approaches.

- [D]efault approaches can be applied that are consistent with current understanding of mode(s) of action of the agent, including approaches that assume linearity or nonlinearity of the dose-response relationship, or both. [p. 1-14]

The cancer risk guidelines do *not* require full understanding of a nonlinear mode of action to support a nonlinear dose-response model, as long as there is significant scientific support for nonlinearity.

- Nonlinear extrapolation having a significant biological support may be presented in addition to a linear approach when the available data and a weight of evidence evaluation support a nonlinear approach, but the data are not strong enough to ascertain the mode of action applying the Agency's mode of action framework. [p.3-23]

If no scientific consensus exists regarding mode of action, the results of both linear and nonlinear approaches are shown.

- Where . . . no scientific consensus favors a single approach, an assessment may present results using alternative approaches. A nonlinear approach can be used to develop a reference dose or a reference concentration. [p. 1-15]

The decision about which approach is most appropriate then becomes a risk-management decision.

- When risk assessments are performed using only one set of procedures, it may be difficult for risk managers to determine how much health protectiveness is built into a particular hazard determination or risk characterization. When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency may decide to give greater weight to one set of procedures than another in a specific assessment or management decision. [p. 1-8]

The cancer guidelines also state that a decision about a substance's carcinogenic mode of action should reflect current scientific understanding, where "current understanding" [p. 1-14] of an agent's mode of action is to be determined based on a weight-of-evidence analysis.

- All pertinent studies are reviewed in analyzing a mode of action, and an overall weighing of evidence is performed, laying out the strengths, weaknesses, and uncertainties of the case as well as potential alternative positions and rationales. [p. 2-41]

However, what the reanalysis describes as its weight-of-evidence analysis [p. 5-3ff] is, in fact, a summary of the evidence EPA believes supports its classification of TCDD as carcinogenic to humans, not a weight-of-evidence analysis. Excluding studies that do not demonstrate a dose-response provides an

unbalanced context for those studies that do, and eliminates from consideration studies that provide useful information for understanding the range of uncertainty. Furthermore, omitting endpoints or studies that do not show a dose-response relationship in the direction EPA expects may discount valuable information, particularly information that could inform mode of action as well as dose-response.

According to the cancer guidelines, a decision about a substance's carcinogenic mode of action should also reflect current scientific understanding by determining the extent to which scientific consensus generally supports a particular mode of action.

- In reaching conclusions, the question of "general acceptance" of a mode of action should be tested as part of the independent peer review that EPA obtains for its assessment and conclusions. [p. 2-40]

The concept of "general acceptance" is also reflected by the reasonableness criteria specified in EPA's Risk Characterization Handbook.

- Reasonableness . . . demonstrates that the risk assessment process followed an acceptable, overt logic path and retained common sense in applying relevant guidance. [p. 18]
- Reasonableness is achieved when the risk characterization is determined to be sound by the scientific community . . . [and] . . . the assessment uses generally accepted scientific knowledge . . . [p. 18]

The question of "general acceptance" of TCDD's mode of action and choice of dose-response model is one that was put to the National Academy of Sciences committee that reviewed EPA's 2003 dioxin assessment. The committee was asked to evaluate "the validity of the nonthreshold linear dose-response model and the cancer slope factor calculated by EPA through the use of this model" [p. xvi]. The committee concluded unanimously that relying on a linear dose-response model for TCDD is not supported scientifically and that the weight of evidence supports nonlinearity.

- The committee concludes that EPA's decision to rely solely on a default linear model lacked adequate scientific support. [p. 5]
- . . . the committee unanimously agreed that the current weight of scientific evidence on the carcinogenicity of dioxin is adequate to justify the use of nonlinear methods to extrapolate below the [point of departure]. [p. 16]
- The committee concludes that EPA did not support its decision adequately to rely solely on this default linear model . . . The committee determined that the available data support the use of a nonlinear model, which is consistent with receptor-mediated responses and a potential threshold . . . [p. 24]
- . . . the committee concludes that, although it is not possible to scientifically prove the absence of linearity at low doses, the scientific evidence, based largely on mode of action, is adequate to favor the use of a nonlinear model that would include a threshold response over the use of the default linear assumption. [p. 122]

- There is general consensus in the scientific community that nongenotoxic carcinogens that act as tumor promoters exhibit nonlinear dose-response relationships, and that thresholds (doses below which the expected response would be zero) are likely to be present. [p. 122]
- The committee unanimously agrees that the current weight of evidence on TCDD, other dioxins, and [dioxin-like compounds] carcinogenicity favors the use of nonlinear methods for extrapolation below the point of departure (POD) of mathematically modeled human or animal data. [p. 190]
- Quantitative evidence of nonlinearity below the point of departure (POD), the ED01 (effective dose), will never be available because the POD is chosen to be at the bottom end of the available dose-response data . . . EPA should give greater weight to knowledge about the mode of action and its impact on the shape of the dose-response relationship. The committee considers that the absence of evidence that argues against linearity is not sufficient justification for adopting linear extrapolation, even over a dose range of one to two orders of magnitude or to the assumption of linearity through zero, which would not normally be applied to receptor-mediated effects. [p. 178]

However, in concluding that a linear dose-response could not be completely ruled out, the committee recommended that, consistent with EPA's cancer guidelines, EPA's assessment of dioxin should present both linear and nonlinear models accompanied by a balanced description of the weight of evidence supporting each approach, all of which would communicate uncertainty better to the risk manager.

- The report recommends that EPA provide risk estimates using both nonlinear and linear methods to extrapolate below [points of departure]. [p. 5]
- The committee recommends adopting both linear and nonlinear methods of risk characterization to account for the uncertainty of dose-response curve shape below ED01. [p. 72]
- . . . the committee recognizes that it is not scientifically possible to exclude totally a linear response at doses below the POD, so it recommends that EPA provide risk estimates using both approaches and describing their scientific strengths and weaknesses to inform risk managers of the importance of choosing a linear vs. nonlinear method of extrapolation.

Thus, while believing that the science supports the choice of a nonlinear dose-response model over a linear model for TCDD, the National Academy of Sciences committee that reviewed EPA's 2003 dioxin assessment recommended that EPA provide results using both modeling approaches, accompanied by a discussion of the strengths and weaknesses of each, so that the extent of the uncertainty would be transparent. Although the committee did not believe that the science supported linearity, it recognized that completely ruling out low-dose linearity would never be possible scientifically and that "[t]o the extent that EPA favors using default assumptions for regulating dioxin as though it were a linear carcinogen, such a conclusion should be made as part of risk management" [p. 190].

The question of "general acceptance" of TCDD's mode of action and choice of dose-response model can also be addressed by comparing EPA's dioxin reassessment to the risk assessments performed internationally by other public health organizations. For example, the World Health Organization states

that “TCDD does not affect genetic material and there is a level of exposure below which cancer risk would be negligible” and that “[t]he experts concluded that a tolerable intake could be established for dioxins on the basis of the assumption that there is a threshold for all effects, including cancer.”<sup>9</sup> The WHO tolerable daily intake (or some version thereof) has been adopted by most other countries of the world. In addition, the International Agency for Research on Cancer recently noted that TCDD was the first substance to be classified as a known human carcinogen based primarily on sufficient data in animals on both carcinogenicity and mechanism of action, specifically, “sufficient evidence . . . for a mechanism via initial binding to the aryl hydrocarbon receptor (AhR), which leads to changes in gene expression, cell replication, and apoptosis.”<sup>10</sup> EPA’s own Risk Characterization Handbook specifies consistency criteria requiring EPA to include comparisons to assessments done by other agencies and organizations in order to put its own risk assessments in context. Thus in concluding that there are insufficient data with regard to TCDD’s carcinogenic mode of action to justify nonlinearity, EPA’s 2010 dioxin reassessment contradicts its own guidance as well as the generally accepted conclusions of esteemed international scientific organizations.

**(3) Invoking additivity-to-background and population heterogeneity arguments in support of low-dose linearity is a novel application of a new science-policy principle, and should not be done without thorough discussion and peer review.**

The arguments about population heterogeneity and the nature and existence of an additivity-to-background effect are complex and use of those arguments as the basis for determining appropriate dose-response analyses has not been widely accepted nor even widely discussed in the scientific community.<sup>11</sup> Its use would be a novel and inappropriate application of a new science-policy principle. This should not be done without thorough discussion and peer review. The few brief discussions in EPA’s 2010 reassessment of how the additivity-to-background argument is being invoked for dioxins are insufficient to provide a basis for such a major science policy departure from accepted practice. EPA’s argument for linearity should not be accepted without a larger and fuller review as an element of science policy.

The reassessment states that there is insufficient information to establish a threshold for dioxin-induced carcinogenesis because, although a particular receptor-mediated event in an individual may have a threshold, there will be a distribution of thresholds at the population level that may or may not bear a resemblance to an individual’s receptor kinetics.

- . . . in general, the population dose-response curve depends on (1) the distribution of individual thresholds in the neighborhood of zero, (2) the dose-response curve for each individual, and (3) the dose metric. Under EPA’s Cancer Guidelines, the zero-slope-at-zero criterion applies strictly to ingested dose, but the other two factors (distribution of individual thresholds and dose-

<sup>9</sup> <http://www.who.int/mediacentre/factsheets/fs225/en/index.html>

<sup>10</sup> Baan et al. (2009), [www.thelancet.com](http://www.thelancet.com) 10:1143

<sup>11</sup> Rhomberg (2009) *Environ. Health Perspect.* 117:141



response curve for each individual) need to be established before a zero slope at zero dose can be established. Otherwise the default linear extrapolation to zero approach applies. [p. 5-57]

- On the nature or the distribution of individual thresholds, often referred to as the population tolerance distribution, there is ongoing debate as to how receptor kinetics influence the shape of that distribution. Even within an individual, there is a lack of consensus as to whether receptor kinetics confer linear or sublinear attributes to downstream events, or whether receptor kinetics, themselves, are linear, sublinear, or supralinear. Whatever the nature of the form of receptor kinetics, it may have little or no influence on the ultimate population response. [p. 5-57]
- There is no *a priori* reason to believe that the shape of the dose-response curve in an individual has any relationship to the shape of the population response, particularly for quantal endpoints. [p. 5-57]

The reanalysis specifically invokes the additivity-to-background argument in support of low-dose linearity, justifying this argument by referring to a “state-of-the-science workshop” on issues in low-dose risk extrapolation held by EPA and Johns Hopkins Risk Science and Public Policy Institute in 2007<sup>12</sup> and to the 2009 National Academy of Sciences report *Science and Decisions: Advancing Risk Assessment*.

In invoking the additivity-to-background/nonthreshold argument, EPA suggests that endogenous AhR activity provides sufficient induction of gene expression and other down-stream effects – which are presumed to be the same as those induced by dioxins and responsible for high-dose tumorigenicity of dioxins – that even in unexposed populations, some tumors will result from the normal level of operation of such processes. (This is the “background” to which dioxins are being presumed to add.) Exposure to dioxins, in this view, can exacerbate the operation of these processes by providing additional binding to AhR, consequent increased levels of gene expression, consequent increases in down-stream consequences of those expression changes, and hence added risk of tumors by enhancing the magnitude of the process responsible for the background tumors. (This is the additivity effect to the inherent background that is being proposed.)

This schema is a rather specific mode-of-action assertion, requiring acceptance of a whole suite of presumptions about the nature of the tumorigenic process, its operation in the absence of dioxin exposure, and the dose-response relations among a series of intermediate stages. Elsewhere in its document, EPA has asserted that TCDD’s mode of action cannot be determined with sufficient certainty to form the basis for choosing a dose-response curve shape (see discussion of comment #2 above). Therefore, the speculation about TCDD’s mode of action entailed in invoking the additivity-to-background principle is illogical, inconsistent with those other assertions, and unacceptable.

In order for the proposed additivity to work, it must be the case that background tumors result from the same set of failures of control of cell division and differentiation that are induced by dioxins at higher exposures, but there is no basis to assert this.

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<sup>12</sup> White (2009) Environ. Health Perspect. 117:283

It must also be the case that individual thresholds exist, such that the discrete event of induction of a new tumor does not happen in all individuals with any level of endogenous AhR activity (because the whole population has such activity, and yet tumors are rare). Moreover, a small increase in an individual's level of AhR activity (as is presumed by the argument to be induced by a small dioxin exposure) must be sufficient to move that person from being a non-responder to having a tumor induced. It must be presumed that endogenous AhR ligands do not act as antagonists to, and therefore inhibitors of, dioxin binding or its efficacy, that displacement of endogenous ligands by dioxins does not simply lead to similar receptor occupancy by different ligands, and that the array of downstream effects of binding of exogenous dioxins and endogenous ligands are the same.<sup>13</sup> The existence of a dose-response relationship in the population must then be attributed to inter-individual variation in the individual thresholds, and the pattern of this must be such that some individuals have thresholds so low that they respond even without any dioxin exposure (and hence constitute the background), while many others hover on the verge of this level and require only a small dioxin exposure to push them over their individual thresholds. No basis for such a schema is presented and it is difficult to imagine one.

The schema presumes without evidence that any amount of change in the degree of AhR occupancy increases the magnitude of the downstream subsequent processes involved in tumorigenesis without a threshold. It is only in this way that small changes in AhR occupancy can lead to a tumor increase. Yet it is evident from AhR's role in such gene-expression effects as EROD activity that there is nonlinearity and indeed thresholds between the degree of receptor occupancy and the effects induced. This is also observed in most other receptor-mediated processes; the nonlinearity in response and the existence of thresholds comes not from the degree of receptor occupancy, but rather from the interactions of processes (including homeostasis perturbation, positive and negative feedbacks, etc.) downstream to the level of changes in gene expression. With all receptor-mediated processes, it is the complex interaction of such control networks, and not the linearity or nonlinearity of a single component, that dictates the dose-response relationship for the apical effect. The linearity of one component early in the sequence gives little information about this larger behavior of the system. Additivity to AhR occupancy, as invoked by the EPA, does not lead to linearity of these downstream processes. Assuming that all the downstream processes are individually linear and that the outcome of their interaction is linear – which is necessary in order to use linear effects of AhR-binding as evidence for linearity of cancer risk – constitutes assuming the truth of the proposition (dose-response linearity) that one is seeking to explain.

The additivity-to-background argument is an argument in principle, but it does not itself provide any basis for estimating the size of any low-dose linear component, for determining the range of doses over which additivity produces linearity, or whether the effect (even if it exists) substantially alters the dose-response relationship that would be estimated without reference to additivity-to-background.

In particular, even if an additivity-to-background effect occurs, it does not lead to linearity of the whole dose-response curve, but would only affect very small risks at very small doses, with the shape of most of the full dose-response curve (including that part we are able to observe in actual data)

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<sup>13</sup> Safe (1998) J. Animal Science 76:134

determined by mode of action. Simply invoking a linear extrapolation from some point higher in the dose-response relationship is not a way to incorporate additivity to background into the analysis. Forcing a linear curve fit or linearly extrapolating from some observable point on the curve results in a measure of low-dose linearity that has nothing to do with the reasons the linearity was invoked, and so such methods do not provide a basis for judging the actual magnitude of a low-dose linear component nor do they address for what limited range of low dose levels and low risk levels the presumed linear relationship should hold before it is overwhelmed by mode-of-action-driven influences on the dose-response shape at more substantial doses that may be of interest to risk assessors. Using such methods will produce misleading and unreliable estimates – most likely radical overestimates – of the actual effect even if the presumptions of the additivity-to-background effect are true.

In conclusion, EPA's decision to apply the new science policy principles of additivity to background and population heterogeneity runs counter to any semblance of a weight-of-evidence perspective and analysis as well as the spirit and intent of EPA's Risk Characterization Handbook. The Handbook's principles state that "[a] risk characterization should be prepared in a manner that is clear, transparent, reasonable, and consistent with other risk characterizations of similar scope prepared across programs in the Agency" [p. 14]. The policy goes on to state that the principles of transparency, clarity, consistency, and reasonableness need to be fully applied throughout every aspect of the risk assessment process.

## NONCANCER EFFECTS

### **(4) EPA's 2010 dioxin reanalysis ignores the recommendations of the NAS review panel and its own guidance by failing to evaluate the clinical relevance of the effects considered for RfD derivation.**

The NAS committee that reviewed EPA's 2003 dioxin risk assessment recommended that EPA evaluate the biological relevance of reported effects.

- Attention should also be directed to addressing the potential biological significance of very small statistically significant physiological or biochemical changes that remain well within the normal range of variation and adaptation. [p. 163]

In addition, EPA's 2004 Risk Assessment Principles and Practices document indicates the need to determine the biological relevance of an effect.

- As a general principle, our practice is not to base risk assessments on adaptive, non-adverse, or beneficial events. [p. 53]

In the 2010 reassessment, EPA considered the toxicological relevance of endpoints from animal studies, but did not do the same for human endpoints.

- In selecting POD candidates from the animal bioassays for derivation of the candidate RfDs, EPA had to consider the toxicological relevance of the identified endpoint(s) from any given study.

Some endpoints/effects may be sensitive, but lack general toxicological significance due to not being clearly adverse...being an adaptive response or not being clearly linked to downstream functional or pathological alterations. [p. 4-7]

For humans, EPA provided a brief justification for the use of the two endpoints (elevated TSH levels in neonates and decreased sperm concentration in adult males exposed during childhood) for dose-response modeling, choosing the endpoint with the lowest LOAEL (sperm concentration) for derivation of the RfD. The NAS committee had previously noted that the consideration of these endpoints as “adverse” is highly questionable, and recommended that EPA include a discussion of the magnitude of reported changes and whether they are within the normal range.

- [Regarding elevated TSH levels in the study by Pavuk et al. (2003),] [t]he discussion does not address the fact that the TSH differences, although statistically significant, are quantitatively extremely small and well within the normal range of circulating TSH levels. [p. 170]
- The draft Reassessment also highlights the higher TSH values reported in human infants by Pluim et al. (1993) and by Koopman-Esseboom et al. (1994)...but does not discuss the fact that the TSH changes were very small and possibly not of physiological or clinical significance. [p. 171]
- [Regarding studies of dioxin exposure and reproductive and developmental outcomes,] [t]he committee agrees that the results are subtle but disagrees that the reported effects are truly clinically adverse, especially when confidence in the observations is low and the reported changes could be non-significant at the biological level and clinical outcome. [p. 164]

Overall, the NAS committee concluded that the evidence for dioxin exposure as a cause of reproductive and hormonal abnormalities is not strong.

- Although the spectrum of reported human reproductive and hormonal abnormalities following dioxin exposure is generally similar to that found in animals, the strengths of the individual associations in studies thus far, are weak, and confidence in the causal nature of these associations while suggestive is not compelling. [p. 162]

In fact, the NAS committee stated that there is no convincing evidence of adverse, non-cancer effects as a result of dioxin exposure.

- In humans, the association of TCDD exposure with other reported, detrimental non-cancer effects has not been convincingly demonstrated. The available studies have not yet shown clear associations among TCDD exposures and the risks of individual, clinically significant, non-cancer end points. [p. 173]

Despite those conclusions of the NAS panel reviewing EPA’s 2003 dioxin reassessment, the 2010 dioxin reassessment nonetheless uses these endpoints as a basis for dose-response modeling and derivation of a non-cancer RfD.

For elevated neonatal TSH levels, as reported in the study by Baccarelli et al. (2008), EPA’s 2010 reassessment cites the World Health Organization (WHO) screening value for neonatal TSH concentration as justification for the use of this endpoint.

- The World Health Organization (WHO, 1994) established the 5  $\mu\text{U/mL}$  standard as an indicator of potential iodine deficiency and potential thyroid problems in neonates. Increased TSH levels are indicative of decreased thyroid hormone (T4 and/or T3) levels. The 5  $\mu\text{U/mL}$  “cutoff” for TSH measurements in neonates was recommended by WHO (1994) for use in population surveillance programs as an indicator of iodine deficiency disease (IDD). [p. 4-24]

EPA does not discuss whether a neonatal TSH concentration in excess of the WHO screening level of 5  $\mu\text{U/mL}$  is indicative of an adverse effect nor whether the “elevated” TSH levels of the subjects in the Baccarelli et al. (2008) study fall within the reported reference range for neonatal TSH levels. Neonatal TSH levels vary considerably during the first 24 hours of birth, with a surge of TSH common (and clinically irrelevant) during the first 12 hours of birth. EPA provides no discussion of whether the reported effect is clinically adverse or within the normal range of adaptive responses.

The justification given by EPA in the 2010 reassessment for using the endpoint of decreased sperm concentration, as reported by Moccarelli et al. (2008), also acknowledges reliance on a screening value intended to indicate that further investigation is appropriate, not that an adverse effect is occurring.

- Although a decrease in sperm concentration of 20% likely would not have clinical significance for an individual EPA's concern with the reported decreases in sperm concentration and total number of motile sperm (relative to the comparison group) is that such decreases associated with TCDD exposures could lead to shifts in the distributions of these measures in the general population. Such shifts could result in decreased fertility in men at the low end of these population distributions. While there is no clear cut-off indicating male fertility problems for either of these measured effects, a sperm concentration of 20 million/ml is typically used as a cut-off by clinicians to indicate follow-up for potential reproductive impact in affected individuals. [p. 4-26]

EPA acknowledged that the mean values for sperm concentration in the Moccarelli et al. (2008) study did not fall below the clinical level of concern (20 million/mL), but did not discuss whether there are any actual data to verify that men potentially at the low end of the distribution of sperm concentration values had higher dioxin exposures.

Both the Baccarelli et al. (2008) and Moccarelli et al. (2008) studies describe outcome measures that are useful clinical markers to guide further investigation but are not indicative of adverse effects in and of themselves. EPA does not accompany the use of the data from these studies for dose-response modeling and RfD derivation with a discussion of the clinical significance of the effects or the levels of change that represent an adverse effect for each of the endpoints.

The 2010 reassessment's focus on including data sets based on the simple ability to be subjected to dose-response analysis is a valid consideration, but it should come as the last of a series of considerations. The first consideration should be to establish that the endpoint in question is a valid potential human endpoint. Such a hazard characterization should include a weight-of-evidence analysis across available studies that examines whether the alleged effect is repeatable within settings and generalizable across settings (e.g., to other species), and evaluates what is known about the relevance to humans of the apparent mode of action. An approximate concordance across studies of apparent

effective dose levels, dose timing, and sensitive periods is an important part of establishing the existence of a commonality of causation that might apply to humans.

Once an endpoint is judged to be sufficiently robustly demonstrated and sufficiently plausibly applicable to human exposures, then the analysis should focus on identifying those studies among the set available that are deemed to best represent or exemplify this generally operating causal process. Only then, once this subset of data sets is identified, should the amenability to dose-response analysis enter the consideration, for only among such studies will the results of such an analysis be truly informative about potential human risk. It is important to attend to the measures of response and the arguments about how much change is being considered to be necessary for a relevantly adverse impact.

For example, a recent weight-of-evidence analysis for dioxin and non-cancer effects showed that there are no substantial, consistent effects of dioxins on thyroid endpoints in infants and children (Goodman et al., 2010). This evaluation looked for consistency and patterns within and across studies and examined whether associations were real and reproducible. The use of this type of rigorous analysis for all potential effects allows for the identification of endpoints with the strongest evidence for causality. Based on a weight-of-evidence review such as this, key studies for the endpoint(s) that will be considered in a subsequent quantitative dose-response analysis can be chosen with greater confidence in their relevance.

*Responses by The Honorable J. Christian Bollwage,  
Mayor, City of Elizabeth, New Jersey*

**Responses to Questions Submitted by Dr. Paul Broun, Chairman**

**1) How does the IRIS assessment approach present an impediment to brownfield redevelopment?**

I am a Mayor, not a scientist, but our City Council, Departmental Staff and I have to rely on scientific and technical information to make everyday decisions about land use and public health. That is the basis for my concern about the real-world impacts of applying scientific assessment tools at the community level. My experience in dealing with brownfield sites in our community over the last 20 years demonstrates that the greatest impediment to cleaning up these sites involves: public confusion concerning risk; and, unreasonable costs to remediate contaminated sites where the risks are over-exaggerated.

I worked closely with the Conference of Mayors starting 15 years ago to convince the EPA and Congress that not all contaminated sites in communities are the same. There are grossly contaminated sites that are Superfund sites, and there are hundreds of thousands of less contaminated sites, known as brownfields that could be a potential public health threat but could also be cleaned up at reasonable cost and turned into property that contributes to the well-being of that community. As a Mayor, the public health in my community is a paramount consideration. I am seriously concerned about the health of our children, our pregnant women, our average citizens and our city employees. However, I also don't want to unnecessarily cordon off pieces of property that should be properly evaluated, cleaned up, and reclaimed.

The conventional wisdom in the 1980s and early 1990s carried an unpardonable stigma attached to any site with contamination whether the contamination was serious or

negligible. The popular press played an important role in fanning the flames of fear among the public. This made it virtually impossible to redevelop these properties. Developers wouldn't touch them, banks wouldn't lend money, and instead we had the abandonment of previously developed sites in favor of greenfields which contributed to urban sprawl. Generally, the risk was so over-played that it became a burdensome task to educate the public about the difference between a brownfield site and a Superfund site. This was the case even after EPA Administrator Carol Browner released over 30,000 sites that were on the CERCLIS list and said that these were not contaminated enough to warrant any further EPA action. Cleaning up brownfield sites and redeveloping them was opposed at the local level because of the confusion over the level of risk and an indiscriminate stigma attached to 'contaminated' sites. Dioxin was promoted in the press as the most toxic substance known to mankind- a distinction that has since been corrected to some small degree.

Local elected officials seek local support for environmental improvements, but the stigma attached to brownfield sites because of dioxin and other chemical contaminants make it virtually impossible to convince the public to move forward on these projects.

There is a Superfund site in Elizabeth New Jersey that is severely contaminated, and would pose a public health problem if it were not cordoned off properly- which it is. This site will likely plague the city for the next century because it was determined that it will cost too much money to clean it up.

There are several brownfield sites in Elizabeth that have been redeveloped. In particular, the IKEA Super Center and the Jersey Gardens, include an economically thriving shopping center that has created hundreds of jobs, promoted redevelopment and has been an enormous help to the city's economy. This redevelopment was possible, in part, because the city undertook a major effort to convince the public that the public health risk would be reduced, if not eliminated, by remediating and redeveloping the site.

I submitted to the Committee a report prepared by the Conference of Mayors that shows that brownfield redevelopment in cities across the nation have had the same positive impact because local government made the decision to clean these sites up, remove the potential public health threat and returned the land to productive use.

But now the EPA runs the risk of reattaching the stigma to redevelopment of brownfields, unnecessarily. EPA's dioxin reassessment will converge with the IRIS system, and this combination will impact a wide range of policy decisions, including Preliminary Remediation Goals (PRGs) for dioxin levels in soil. The Conference of Mayors' believes this could have a severe impact on brownfields and other urban and suburban development.

The US Conference of Mayors is concerned that the combination of EPA's toxicity estimates for dioxin from the dioxin reassessment and its incorporation into the IRIS system, and the use of exposure assessment assumptions will drive dioxin PRG values down to levels that are below average concentrations in U.S. cities, and perhaps below current background levels in urban and suburban soils. Since both the toxicity level assessment and the exposure assessment assumptions are based on a wide margin of safety and high-end risk the resulting risk assessments portray worst case risk in an over-



exaggerated way. There is no 'most-likely' risk or 'most-probable' risk provided by the IRIS and exposure assessment process to portray a range of risk. It is widely accepted in the social sciences to consider ranges in estimates and predictions, but that is not available in the current public health risk models espoused by government regulatory bodies.

Stated another way, when the IRIS system is used to inform risk management decisions it must be noted that the compound effect of overly conservative toxicity values used in conjunction with overly conservative exposure scenarios the process yields a very distorted characterization of risk. This type of calibration of the different parts of the tool leaves local decision-makers with a risk analysis that is not realistic.

EPA has recently proposed to lower the dioxin soil concentrations guideline for contaminated site remediation from 1 part per billion to 76 parts per trillion or even 3.7 parts per trillion. These lower standards were based on EPA's overly conservative approach to estimating dioxin toxicity in combination with assumptions about exposed children wallowing in the contaminated site soils. Not only is the exposure scenario unrealistic, but at 3.7 parts per trillion of dioxin, the soil in almost every urban and suburban area would pose an unacceptable risk because background levels are normally two to four times higher than 3.7 parts per trillion. Even lowering the dioxin standard in soil to 76 parts per trillion is lowering the so-called danger point to where the public will question their safety.

Given the confusion over risk as described above, and, if guidelines for dioxin soil contamination levels is lowered to levels proposed by EPA, then it will be extremely difficult to allay public fear of risk and brownfield sites will be perceived by the public as Superfund sites again.

The practical implication for America's cities are that the very high cost of remediating Superfund sites are likely to drive remediation costs for brownfield sites. Thus we will experience a chilling effect on brownfield redevelopment, even though the true risk might be negligible.

## **2) What are the repercussions of disregarding an IRIS assessment safety level - not just for**

### **Dioxin, but any other chemical?**

Mayors do not disregard official government safety levels. That, however, does not imply that local government agrees with those levels or lacks the will to challenge them, especially when they seem to be overly conservative.

As a functional matter, in order to get the proper permits or 'sign-offs' for site remediation from a state regulating authority (and/or Regional EPA office, if required) a site evaluation is required. A risk assessment is normally conducted using the site evaluation information and the IRIS toxicity values. Additionally, an exposure assessment is part of the risk assessment process. Thus, it is neither probable nor advisable to forgo a risk assessment using the latest toxicity values available from the IRIS system.

The dilemma this poses for local government is that it is widely acknowledged that the resulting risk levels resulting from the process over-exaggerate risk to be well on the 'safe-side', (a precautionary approach to risk decisions). The risk assessment model offers no indication of real-risk. Real-risk may be as high as the results one yields from using the IRIS toxicity factors in combination with high-end risk exposure assumptions. Real-risk, however, may be much lower than that if the exposure assumptions are more realistic, and if one questions the margin of safety used to estimate the toxicity values in IRIS for chemical substances. This applies to dioxin and any other chemical substance in the IRIS system.

**3) Are there any other Mayors who share your concern for EPA's IRIS assessment for not**

**just Dioxin, but any other chemicals where the proposed IRIS value is at or below background levels?**

**What are they saying?**

- **Do you have an idea what those chemicals might be?**

My remarks apply primarily to dioxin and brownfield remediation efforts of local government. As Chair of the Conference of Mayors Brownfields Task Force I am speaking for The United States Conference of Mayors and its Member cities.

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. However, 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 calculation of the unit risk values is a complex process, involves many sources of uncertainty and variability, and is influenced by the low-dose extrapolation used (for example, linear vs threshold). The committee therefore 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; this is especially important given the use of a single study, the inconsistencies in the exposure measures, and the uncertainties associated with the selected cancers.

#### THE FORMALDEHYDE IRIS ASSESSMENT: THE PATH FORWARD

The committee recognizes that the completion of the formaldehyde IRIS assessment is awaited by diverse stakeholders, and it has tried to be judicious in its recommendations of specific changes noted in its report. However, the committee concludes that the following general recommendations are critical to address in the revision of the draft assessment. First, 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. Second, 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. Third, 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. Fourth, 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. Fifth, the rationales for selection of studies that are used to calculate RfCs and unit risks need to be articulated clearly. Sixth, 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.

The committee is concerned about the persistence of problems encountered with IRIS assessments over the years, especially given the multiple groups that have highlighted them, and encourages EPA to address the problems with development of the draft assessments that have been identified. The committee recognizes that revision of the 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, models for conducting IRIS assessments more effectively and efficiently are available, and the committee provides several examples in the present report. Thus, EPA might be able to make changes in its process relatively quickly by selecting and adapting existing approaches. As exemplified by the recent revision of the approach used for the National Ambient Air Quality Standards, this task is not insurmountable. If the methodologic issues are not addressed, future assessments may still have the same general and avoidable problems that are highlighted here.



THE UNITED STATES CONFERENCE OF MAYORS

**The United States Conference of Mayors  
Position Paper Regarding**

**EPA's Proposed Interim Guidance on Dioxin in  
Soils at CERCLA and RCRA Sites**

**Washington, DC  
August 31, 2010**



## THE UNITED STATES CONFERENCE OF MAYORS

2

### Executive Statement

#### EPA Action -

The EPA proposed new and stringent Preliminary Remediation Guidelines (PRGs) for dioxin concentrations in soils at brownfield sites. OMB review of the proposal is imminent, and EPA has not exercised its responsibility under the Federalism Executive Order 13132 to consult with state and local government before adopting rules, regulations and policies that have a substantial financial impact. The proposed PRGs for dioxin soil concentrations is at or below background levels and if implemented will have an immediate chilling effect on the successes achieved over the last two decades to clean-up these sites and return these properties to productive use.

#### Basis for Local Government Concern -

- Reversal of the EPA's and Administration's longstanding support of expedited brownfield site clean-up
- Local government momentum has achieved clean-up of over 2,667 brownfield sites that would otherwise remain abandoned, unused and present a threat of contamination migration
- The dioxin soil concentrations proposed for issuance and proposed for consideration are at or below background levels of dioxin in urban soils
  - EPA reported soil dioxin background levels in soil ranging from 2.26 to 13.6 ppt in the dioxin reassessment
    - A USCM report prepared by Rappe et al., 1999 indicates that urban soils exhibit mean dioxin background levels in urban soil at 19.6 ppt, and rural soils at 4.0 ppt
  - At these levels the PRGs will likely place a stigma on urban soils as well as brownfield sites, and
  - May impede arranging for remediation financing and insurance
- EPA is proposing these PRGs before responding to critical scientific questions concerning the dioxin reassessment raised by the National Academies of Science-National Research Council.
  - One of the critical questions raised by NRC is why EPA has not developed a safe-threshold dose of human exposure to dioxin like the other advanced-science nations in the world
  - EPA, through its dioxin reassessment process, is currently addressing key toxicity and exposure assumptions that may directly impact the scientific basis of



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the PRGs. EPA should ensure the PRG's are informed by its final dioxin reassessment, rather than issuing interim guidance at this time.

- What is at stake for the Nation's Principal Cities?
  - Additional costs on average of \$210/ton of soil removed and disposed of in a Subtitle C facility, with little or no improvement in public health
  - Stifle local job growth, including green jobs
  - Stifle local land based tax revenues
  - Likely to retard efforts to clean-up sites and protect human health and the environment from well recognized non-dioxin contaminants that have a demonstrated (not theoretical) impact on public health
  - Impede brownfield redevelopment and inadvertently promote Greenfield development
  - Hinder local government efforts to reduce carbon footprint

### Request –

EPA should defer finalizing the proposed dioxin soil concentration PRGs until the dioxin reassessment is completed and the consensus science can be used to consider any changes to current policy



### The U.S. Environmental Protection Agency Proposes New Standards on Dioxin in Soils at Brownfield Clean-up

The U.S. Environmental Protection Agency (EPA) proposed new interim guidance on acceptable levels of dioxin in soils at CERCLA and RCRA sites on December 29, 2009, (Fed. Reg. 1). The new guidance would replace existing guidance adopted in 1998. The guidance specifies the acceptable levels of dioxin in soils that are reclaimed as Preliminary Remediation Goals (or PRGs). PRGs are normally keyed to EPA's estimate of the low end of the risk range; meaning they are conservative, and usually represent the lowest level concentration thought to have an adverse effect on human health. According to EPA, "Until these draft recommended interim PRGs are finalized, EPA will continue to use the 1998 recommended interim PRGs (EPA 1998)".

The 1998 Office of Solid Waste and Emergency Response (OSWER) directive recommended that a soil concentration of 1 part per billion (ppb), which is equivalent to 1,000 parts per trillion (ppt) of dioxin (in Toxic Equivalency [TEQ] form) be generally used as a starting point for developing cleanup levels for residential CERCLA removal sites and as a PRG for CERCLA remedial sites (Table 1). For commercial/industrial exposure scenarios, a soil concentration within the range of 5 ppb (5,000 ppt) to 20 ppb (20,000 ppt) dioxin TEQ was recommended as a starting point for developing cleanup levels for CERCLA sites. A range in soil concentrations was recommended for commercial/industrial soils due to the greater variability in exposures associated with the commercial/industrial scenarios. The PRGs were also generally recommended as a starting point for actions taken at RCRA corrective action sites. These levels were recommended unless extenuating site-specific circumstances warranted a different level.

Also, EPA recommends evaluating non-cancer risk to a resident based on the soil intake rate of a child. For evaluation of cancer PRGs, residential exposure is assumed to begin at birth and extend for 30 years. This includes exposure for 6 years as a child and 24 years as an adult. Worker exposures are assumed to occur for 25 years, but only as an adult.

**Table 1: Current and Proposed PRGs for Dioxin in Soils at CERCLA and RCRA Sites**

Land Use	Receptor	Current Policy PRG (ppt TEQ)	Non-Cancer PRG (ppt TEQ)	Cancer PRG (ppt TEQ)
Residential	Resident	1,000	72	3.7
Commercial/Industrial	Indoor Worker	5,000 – 20,000 <sup>1</sup>	2,000	37
	Outdoor Worker		950	17

<sup>1</sup> Current policy does not distinguish between indoor and outdoor workers as receptors



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EPA is proposing to set the non-cancer PRGs (resident at 72 ppt TEQ; indoor worker at 2,000 ppt TEQ; outdoor worker at 950 ppt TEQ) as the new PRGs. EPA is also considering setting the PRGs based on cancer risk (3.7 ppt TEQ; 37 ppt TEQ and 17 ppt TEQ: resident, indoor worker, outdoor worker, respectively).

All of the proposed PRGs are dramatically more stringent than the current PRGs. Since the cancer risk-based soil concentration levels may be below background soil levels in urban environments (where many brownfield sites are located) local government is fearful that such standards may impede brownfield redevelopment. Similarly, the non-cancer risk-based PRGs for residential land use is less than an order of magnitude greater than background soil concentrations in urban environments, but many orders of magnitude lower than existing PRGs. Thus, local government is fearful that such a PRG will either stifle brownfield redevelopment or require additional costs that are not justified by the potential risk. In either case, the effects of the PRGs, if finalized and imposed on local government efforts to reclaim brownfield sites are likely to impede redevelopment, add substantial costs, jeopardize financing and insuring clean-ups, result in greater environmental threats from contamination lingering at unreclaimed sites, and promote Greenfield development and sprawl and expanded carbon footprint. Local government opposes this action by EPA because of the reasons mentioned above, but also because the basis for setting these soil concentration levels to protect public health is unproven and uses an incomplete science.

EPA's comprehensive human health and exposure assessment for dioxin, commonly called the *dioxin reassessment* is intended to form the scientific basis of EPA policy and regulatory actions. As noted on EPA's website, the latest draft dioxin reassessment (EPA 2003) is still undergoing revisions in light of a 2004 review by the National Academy of Sciences and an ongoing review by the Science Advisory Board. In developing its proposed interim PRGs, EPA relied on dioxin toxicity values, exposures assumptions and cancer risk levels that are subject to potential revision based on these reviews. Consistent with its commitment to using the "best available science," EPA should ensure the PRG's are informed by its final reassessment, rather than issuing interim guidance at this time.

### **Brownfield Redevelopment is a Critical Land Use Planning Element in America's Principal Cities**

#### **Brownfields redevelopment has a long history of support at the USCM**

Local government has long supported federal and state action to address land contamination to protect public health. Soon after the "Superfund" law was implemented with EPA regulations and the National Priority List (NPL) was established, it became clear that an enormous number of sites beyond the NPL were still of concern to the Agency because of a lack of information on whether or not they contaminated, and the extent of contamination. These non-NPL sites are referred to as brownfields or brownfield sites. The U. S. Government Accountability Office (GAO) estimated that there are between 400,000 and 600,000 brownfields throughout the nation. Brownfields, (as defined by the GAO and the USCM) are abandoned or underutilized properties where expansion or redevelopment is complicated by either real or perceived environmental





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contamination. Recognizing that there is a large universe of brownfield sites EPA identified 38,000 sites on their Superfund Tracking System List (called CERCLIS). A stigma was attached to these sites because they were either presumed contaminated or where entered onto the CERCLIS. These sites were subject to federal and state requirements, especially joint, several, and strict liability which was a primary reason why property owners would not sell or redevelop, and why banks and insurance companies would not finance reclamation activities. Many of these sites remained abandoned for decades, and the stigma was a disincentive to redevelop them.

Local governments had few choices under this regulatory regime. While cities supported clean-up of NPL sites, the thousands of brownfield sites proved to be much less contaminated, and indeed many of them were not contaminated at all. However, the stigma attached to these sites or being listed on CERCLIS resulted in thousands of urban center sites (and acres) with less onerous levels of contamination sat idly in cities while new site development opted for Greenfield development that encouraged sprawl.

The U. S. Conference of Mayors (USCM) began developing a national policy platform in 1993 calling for brownfields reform in Congress. A series of policy resolutions were adopted by the USCM that outlined a series of federal actions that were needed to modify CERCLA to address the marginally contaminated brownfield sites and recycle them to productive use.

In response to these policy recommendations and a dialogue between the USCM and EPA, then Administrator Carol Browner unveiled the EPA Brownfields Action Agenda at the Winter Meeting of the USCM in January 1995. Administrator Browner focused on three critical elements of the larger Action Agenda. First, EPA de-listed 25,000 of the 38,000 CERCLIS sites. The Administrator stated that the sites were either not contaminated or were being managed under state programs. Second, the Administrator announced the Agency would provide 50 grant awards to brownfield clean-up demonstration projects. Third, and of greatest importance to cities, the Administrator announced Agency plans to issue new rules, including policy and guidance to protect developers, banks and cities from third party liability related to the de-listed sites.

The goal of the EPA Brownfields Action Agenda initiative "...is to empower states, communities and other agents of economic development to work together in a timely manner to prevent, assess, safely clean up, and sustainably reuse brownfields". (EPA, February 1995) The Agency further stated that "The market value of older industrial sites can be depressed because the specter of environmental liability diminishes the attractiveness of investing in already-used industrial or commercial areas...Enactment of the Action Agenda will help to reverse the effects of declining property values and increased unemployment rates often found in inner-city industrial areas, while maintaining the deterrent to future contamination and EPA's focus on 'worst sites first'."

Mayors participating in the Winter Meeting applauded EPA's Brownfield Action Agenda. Task Force Co-Chair Freeman Bosley, then Mayor of the City of St. Louis discussed how the growth of brownfield sites in St. Louis shifted population in the Metro area. He stated "They (federal policy-makers) must be made to understand the overwhelming challenge we face and that we must be given relief and resources to meet this challenge." (McCarty 1995). He further stated "We mayors need the federal officials, who create the environment that we must operate in, to act as though they walked in our shoes every day." Louisville Mayor Jerry Abramson emphasized the need to recycle land and the "active, productive, job-creating opportunities" reuse of these properties creates for cities. (McCarty 1995)



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In 1997 EPA established the Brownfields National Partnership Action Agenda. President Clinton stated "We should restore contaminated urban land and buildings to productive use." (EPA, May 1977) This was a landmark effort to improve communities by establishing partnerships between public and private organizations and link environmental improvement to economic development. The goal of the Brownfields National Partnership is to "...protect public health and the environment, clean up contaminated properties, build economic viability, and create job opportunities." More than 25 organizations, including 15 federal agencies made commitments to partner for success.

The USCM was one organization in the partnership. The Conference of Mayors worked hard to bring the bankers and insurance industry to the table to work out details to instill confidence in private underwriting for clean-up projects.

Today the USCM continues to support and promote brownfield redevelopment. This activity continues to demonstrate growth in jobs, economic development, environmental restoration and protection of public health. Brownfields redevelopment was a critical local planning tool well before the Great Recession. A recent study released by the USCM, the National League of Cities and the National Association of Counties estimates that upwards of 500,000 state and local government jobs are likely to be lost over the next few years. (National Association of Counties, National League of Cities, US Conference of Mayors, July 27, 2010). It is important that brownfield redevelopment proceed unhindered. The proposed PRGs could hinder brownfield reclamation activities, and this is undesirable for local government because the PRGs under consideration rely too heavily on theoretical risk and fail to benefit from the dioxin reassessment that is not yet completed.

### **Brownfield Redevelopment has been Demonstrated to Create Jobs, Bring Idle Land to Productive Use and Create Local Tax Revenues**

The USCM has documented the success of brownfield redevelopment in a series of National City survey reports, (USCM, National Report on Brownfields Redevelopment, Vols. I – VIII). Several city surveys indicate a steady record of positive achievement (Table 2).

- **Creating Jobs:**

Actual jobs created in 2010, for example, included 19,761 jobs in remediation and redevelopment; and 55,085 jobs in post redevelopment/end use jobs. Job creation was down in 2010. In fact, actual job creation ranged from over 83,000 to over 186,000 in the survey years.

- **Reclaiming Land for Productive Use:**

In 2008, 150 cities reported that redevelopment of 1,578 sites for a total of 16,947 acres. In that same year 168 cities reported 1,235 sites were being redeveloped involving 15,357 acres. In 2010, 116 cities reported redeveloping 2,667 sites involving 11,096 acres of land. In that same year 122 cities reported 630 sites are being redeveloped comprising 7,492 acres.

- **Increasing Land Based Tax Revenues:**



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The 2008 City Survey reported that 56 cities realized \$408 million in local tax revenue generated from the redevelopment of brownfield sites. The 2010 City Survey reported that 45 cities realized \$108 million in local tax revenue generated from redeveloped brownfield sites.

Clearly, jobs created by clean-ups are significant; and the number of 'green' jobs related to the remediation phase is significant. An aggressive local government program of reclamation has resulted in recycling of 2,667 sites as of 2010; and another 630 sites are in process. Local government is realizing increased tax revenues as a result of brownfield redevelopment. While much has been accomplished, there is still much work to be done- unless the proposed PRGs for dioxin concentrations in soil at brownfield sites impede projects and progress.

### Environmental Improvement

In addition to generating jobs and land-based local tax revenues, brownfield redevelopment has provided environmental and public health benefits. For example, USCM case study reports, document remediation of contamination at brownfield sites. Site remediation is linked to protection of public health, (USCM, Brownfields Best Practices, Vols. I - IV). What is different, in regard to dioxin soil concentrations at brownfield sites, is that background levels in urban areas would likely trigger the stigma that was previously attached to Superfund sites that EPA and the Brownfields National Partnership organizations worked so hard to dispel.

There are additional environmental benefits associated with the redevelopment of brownfields and discouraging sprawl including reduction in greenhouse gas emissions, more efficient utilization of energy and resources, reduction in air pollution, protecting watersheds, and preserving farmland.

Brownfields are located where existing infrastructure – roads, water and sewer lines, utilities, etc. - already exists. According to former CEQ Chairman James Connaughton, "Urban centers are the most environmentally-efficient areas in the nation." (Sheahan, Coley, and Rosenberg, February 9, 2004).



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Table 2: USCM Brownfield Redevelopment City Survey Results

Survey Year	No. of Cities Responding	Estimated No. of Brownfield Sites	No. of Sites Cleaned-Up	Estimated Potential Revenues Range (in \$ bill) [No. of Respondents]	Estimated Jobs If all Brownfield Sites are Redeveloped	Actual Remediation/ Redevelopment Jobs [No. of Respondents]	Actual Post-Redevelopment/ End Use Jobs [No. of Respondents]
2003	244	24,000	900	0.79 – 1.9 [142]	570,000	NA	83,041 [74]
2005	216	20,000	1,187	0.4 – 1.1 [102]	213,146	25,621 [67]	91,443 [67]
2006	200	23,810	1,409	0.958 – 2.2 [105]	149,515	21,977 [72]	61,194 [72]
2008	209	24,896	1,578	1.3 – 1.6 [105]	191,238	71,288 [80]	115,624 [80]
2010	136	22,537	2,667	0.689 – 1.7 [81]	230,223	19,761 [76]	55,085 [76]

One of the best environmental practices is to efficiently utilize areas and buildings that are already in existence as opposed to building on pristine land where the infrastructure and the buildings have to be newly built. This development has negative environmental impacts through increased greenhouse gas emissions and air pollution through using additional energy and raw materials to create and maintain this new development and the infrastructure that goes with it. In addition, these new developments can potentially cause more air pollution through increased vehicle miles traveled as well as impacting the watershed by creating more impervious surfaces.

Another impact of not reutilizing brownfield sites and encouraging sprawl is the destruction of precious farmland. Chicago Mayor Richard M. Daley, past President of USCM said “Each year America destroys more farmland than any nation in the world.” The Conference of Mayors teamed up with American Farmland Trust to work on the issues of encouraging brownfields redevelopment and preserving farmland.

According to American Farmland Trust’s, *Farming on the Edge Report*:

- **America has been losing more than an acre of farmland per minute.**
  - Between 2002 and 2007, 4,080,300 acres of agricultural land were converted to developed uses—an area nearly the size of Massachusetts.
  - Between 1982 and 2007, 41,324,800 acres of rural land (i.e., crop, pasture, range, land formerly enrolled in CRP, forest and other rural land) were converted to developed uses. This represents an area about the size of Illinois and New Jersey combined.



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- **During the 25-year span, every state lost prime farmland.**  
States with the biggest losses included Texas (1.5 million), Ohio (796,000), North Carolina (766,000), California (616,000) and Georgia (566,000).
  - Between 2002 and 2007, 7,491,300 acres of rural land were converted to developed uses—an area nearly the size of Maryland. This amounts to an average annual conversion rate of 1,498,200 acres.
- **Our food is increasingly in the path of development.**  
An astounding 91% of our fruit and 78% of our vegetables are produced in urban-influenced areas.
- **Wasteful land use is the problem, not growth itself.**  
Wasteful land use is the problem, not development itself. From 1982 to 2007, the U.S. population grew by 30 percent. During the same time period, developed land increased 57 percent.

In USCM's Brownfields Study, *Recycling America's Land: A National Report on Brownfields Redevelopment* (USCM, National Report on Brownfields Redevelopment, Vol VIII), cities were asked if their city could support additional population capacity without burdening their existing infrastructure. 81 percent (121 cities) of the respondents stated that they could easily support additional people with 93 cities estimating that they could support more than 1.9 million people. Two years earlier, 82 cities estimated they could support more than 2.8 million people.

By making it more difficult to redevelop brownfield sites, as we believe this interim guidance does, we will see even greater negative environmental consequences as a result.

### Policy and Science Considerations

#### Timing of the Interim Guidance and Completion of the Dioxin Reassessment

What is especially troublesome is that EPA intends to issue the interim PRGs before completing the dioxin reassessment, or responding to serious questions raised in the National Academies of Science expert panel review concerning both potential cancer and non-cancer human health impacts from theoretical dioxin exposure. EPA acknowledges uncertainty regarding the PRGs, in their own discussion of the proposed PRGs (Interim Guidance, page 3), that they "do not take into account peer review comments on the new science that was reviewed by the National Academy of Sciences (NAS), and the new science that was released since the NAS review." Therefore, issuing the interim PRGs is premature. Further, there is no evidence of public imminent health impact that would justify imposing the proposed dioxin content standards, or the very stringent lower soil dioxin standards the Agency has asked the public to consider. They have no useful utility other than to cast a stigma on brownfield sites because background levels of dioxin in soil is so ubiquitous it will almost certainly be detected. Additionally, dioxin concentrations in soil at non-brownfield sites are almost certain to be detected, and that will likely cause confusion, concern and uncertainty in the general population that everyone is at elevated risk of cancer and non-cancer impacts.

Rather than create the conditions for widespread public fear, it makes more sense for EPA to finalize new soil standards for dioxin in clean-up sites after it completes its dioxin reassessment.



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This would provide EPA the opportunity to present new information to the public for consideration in developing appropriate dioxin soil standards that reflect the best available science.

### Public Health and Environmental Benefits of the Interim Guidance

Based on over a decade's worth of city experience in reclaiming brownfield sites utilizing conventional environmental assessments, conducting clean-up activities according to best work practices, subjecting all of this activity to regulatory oversight, it is safe to say that a reclaimed brownfield site has, in reality, significantly improved the local environment. On the other hand, EPA's proposed interim PRGs can only claim a potential and theoretical reduction of risk to human health. And, that potential and theoretical reduction in risk is related to only one class of contaminants. Has EPA considered that removing lead, cadmium and mercury from brownfield sites provides a much greater level of public health protection than the relatively minute levels of dioxins? This is an important question for local government because if the effect of imposing the interim PRGs impedes or stalls progress on clean-ups the public may be at greater risk than if the clean-ups continue unhindered.

Public health risk from dioxin exposure at brownfields sites is more remote than it is imminent. A scientific review of trends in human body burden of dioxin<sup>2</sup> indicates a dramatic rise and equally dramatic decline in dioxin body burden. Using modeling techniques and combining the various critical forms of dioxin (17 key congeners or chemical forms), "...a historical dose which began the century at low levels of approximately 0.5 pg TEQ/kg/day, rose during the middle decades of the 20th century to over 6 pg TEQ/kg/day, and declined to current levels of approximately 0.5 pg TEQ/kg/day." (Lorber 2002) The two conclusions one can draw from this information is that human body burdens of dioxin are significantly lower by about 90 percent; and that at 0.5 pg/kg/day Americans daily dioxin exposure is well below the goals set by the World Health Organization of 1 pg/kg/day.

There are several factors incorporated into EPA's proposal that do not provide adequate scientific reasoning to convince local government to support the proposed change in current policy.

- **Soil Levels of Dioxin and Human Body Burden**

Two studies indicate that direct contact with dioxin-contaminated soil does not result in dioxin uptake into the human body. An EPA study based in West Virginia showed no linkage between soil dioxin concentrations and blood dioxin levels of exposed residents. The same is true for a large exposure study completed in Michigan where residents living on contaminated soil showed no increase in their dioxin blood concentrations. (UMDES 2009) The well documented trend of declining blood dioxin levels and the lack of a demonstrated connection between soil levels of dioxin and blood levels does little to convince local government that they should halt brownfield redevelopment, or to agree to spend greater

<sup>2</sup> measured in Toxic Equivalency as TEQ in pico grams [ pg = one-millionth of a gram] per kilogram [kg = one-thousandth of a gram] of body weight per day – for example, 0.5 pg TEQ/kg/day .



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amounts of taxpayer dollars to clean-up a contaminant that does not add to impacts on public health.

- **PRG Guidance Relies on Non-Threshold Exposure for Cancer**

A National Academy of Science report identified critical questions challenging the scientific conclusions in EPA's draft dioxin reassessment. We understand that these questions are currently under SAB review, and are being addressed by EPA's Office of Research and Development (ORD). The critical scientific questions identified by NAS involve the very same information, assumptions and assertions EPA relies on to justify the proposed PRGs.

The most critical question involves EPA's reliance on the non-threshold exposure theory. EPA's risk characterization in the dioxin reassessment implies some level of risk at any exposure level. This linear model of exposure and resultant impact is supported by a theory of molecular biology observed in animal studies where doses of dioxin and dioxin-like compounds are purposely set at varying levels, but certain to include dose levels that will cause an effect. Translating animal studies at high doses of dioxin exposure to what might or might not happen at a brownfield clean-up site is, at best, a theoretical exercise and does not provide practical evidence of actual human risk.

As a policy matter, the EPA non-threshold exposure risk approach is one based on the precautionary approach to dioxin risk. Many advanced-science nations do not regulate dioxin based on a non-threshold basis. Indeed, it is widely accepted that a preponderance of evidence shows the risk is threshold in nature. Supported by the data, the threshold approach demonstrates that exposures below a certain level (the threshold) are without risk. This includes exposure below soil background levels.

- **Data used to develop PRGs is not relevant for evaluating potential risks from brownfields development**

Data on human health risks from dioxin generally come from studies of workers who manufactured dioxin-containing materials such as trichlorophenol, or acute, high level accidental dioxin exposures involving a combination of inhalation and direct contact to industrial contaminants, such as those experienced by Seveso, Italy residents in 1976. These types of exposures are site specific and atypical and do not reflect the type of soil exposures to weathered material where dioxins can be tightly adsorbed to carbon material in soil. Brownfields development will not generate comparable airborne exposure or direct contact with freshly deposited materials seen in these studies. To apply risk estimates derived from an exposure scenario that is not relevant leads to overly stringent PRG levels, poses an unnecessary remediation burden and stifles redevelopment.

### Impacts of the Interim Guidance on Dioxin Soil Concentration PRGs

The proposed PRGs and the more stringent PRGs under consideration by EPA are likely to have a chilling effect on urban brownfield redevelopment in America. The stigma attached to land that contains background soil concentrations of dioxin will return these sites back to the day



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when the mere mention of Superfund status and imposition of strict and several liability prevented tens of thousands of sites from proceeding to clean-up.

The impact on local government will be significant. Most importantly, a failure of the financial markets to service brownfield clean-ups will retard job growth, land based tax revenues, and stifle the return of idle land to productive use. The employment and economic redevelopment related tax revenues are worth hundreds of millions of dollars to local government.

Local government is legitimately concerned about how a chilling effect would retard, if not prevent, continuation of brownfield reclamation. As discussed previously, brownfield sites that are not cleaned-up may pose public health threats from the non-dioxin contaminants. Further, leaving hundreds of thousands of acres idle in urban centers will push development to Greenfield sites. This will only increase metropolitan carbon footprint and serve to increase both greenhouse gas emissions as well as particulates, nitrous oxides and sulfur emissions.

Remediation of sites will have dramatic cost implications for brownfields redevelopment. During site remediation, soil with levels exceeding PRGs would be expected to be excavated and transported off-site for disposal. EPA has not conducted an economic analysis of the PRGs. USCM believes that transportation and disposal costs alone would exceed \$210/ton, and could be significantly higher depending on the location of the disposal site. In addition, the absence of existing Subtitle C waste management capacity in the U.S. for dioxin waste may further hinder remediation efforts.

When compared to the potential and relatively marginal public health benefits from dioxin soil remediation at concentrations that are at or below background level there appears to be no strong public health argument to proceed with the proposed PRGs.

### **Request from the Nation's Mayors**

The U.S. Conference of Mayors, after careful consideration of the proposed PRGs and EPA's anticipated public health benefits, and after weighing the impacts the interim guidance would have on brownfield redevelopment efforts by local government, respectfully requests that EPA, OMB and the White House act quickly to defer approval of the proposal. The impacts on local government, jobs and land based tax revenues far outweigh the theoretical public health benefit of the proposed interim guidance. Furthermore, EPA should not go forward with proposed dioxin soil concentration PRGs until the dioxin reassessment is completed.





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## Appendix II

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ADDITIONAL MATERIALS SUBMITTED FOR THE RECORD

130 *Review of EPA's Draft IRIS Assessment of Formaldehyde*

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7

## A Roadmap for Revision

In reviewing the draft assessment *Toxicological Review of Formaldehyde-Induced Asthma: In Support of Summary Information on the Integrated Risk Information System (IRIS)*, the committee initially evaluated the methodology (Chapter 2) and then considered the desirability and toxicity of formaldehyde (Chapter 3) and the review of the evidence and selection of studies related to noncancer and cancer outcomes (Chapters 4 and 5). Finally, the committee addressed the calculation of the reference concentrations (RfCs) for noncancer effects and the unit risks for cancer and the treatment of uncertainty and variability (Chapter 6). In this chapter, the committee provides general recommendations for changes that are needed to bring the draft to closure. On the basis of "lessons learned" from the formaldehyde assessment, the committee offers some suggestions for improvements in the IRIS development process that might help the Environmental Protection Agency (EPA) if it decides to modify the process. As noted in Chapter 2, the committee distinguishes between the process used to generate the draft IRIS assessment (that is, the development process) and the overall process that includes the multiple layers of review. The committee is focused on the development of the draft IRIS assessment.

### CRITICAL REVISIONS OF THE CURRENT DRAFT IRIS ASSESSMENT OF FORMALDEHYDE

The formaldehyde draft IRIS assessment has been under development for more than a decade (see Chapter 1, Figure 1-3), and its completion is awaited by diverse stakeholders. Here, the committee offers general recommendations—in addition to its specific recommendations in Chapters 3-6—for the revisions that are most critical for bringing the document to closure. Although the committee suggests addressing some of the fundamental aspects of the approach to generating the draft assessment later in this chapter, it is not recommending that the assessment for formaldehyde await the possible development of a revised ap-

proach. The following recommendations are viewed as critical overall changes needed to complete the draft IRIS assessment:

- To enhance the clarity of the document, the draft IRIS assessment needs rigorous editing to reduce the volume of text substantially and address redundancy and inconsistency. Long descriptions of particular studies, for example, should be replaced with informative evidence tables. When study details are appropriate, they could be provided in appendices.

- 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 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 concise statements of criteria used to exclude, include, and advance studies for derivation of the RfCs and unit risk estimates.

- 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.

- 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. The present chapter provides general guidance on approaches to reviewing the critical types of evidence.

- 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.

- 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.

#### FUTURE ASSESSMENTS AND THE IRIS PROCESS

This committee's review of the draft IRIS assessment of formaldehyde identified both specific and general limitations of the document that need to be addressed through revision. The persistence of limitations of the IRIS assessment methods and reports is of concern, particularly in light of the continued evolution of risk-assessment methods and the growing societal and legislative pressure to evaluate many more chemicals in an expedient manner. Multiple

groups have recently voiced suggestions for improving the process. The seminal "Red Book," the National Research Council (NRC) report *Risk Assessment in the Federal Government: Managing the Process*, was published in 1983 (NRC 1983). That report provided the still-used four-element framework for risk assessment: hazard identification, dose-response assessment, exposure assessment, and risk characterization. Most recently, in the "Silver Book," *Science and Decisions: Advancing Risk Assessment*, an NRC committee extended the framework of the Red Book in an effort to make risk assessments more useful for decision-making (NRC 2009). Those and other reports have consistently highlighted the necessity for comprehensive assessment of evidence and characterization of uncertainty and variability, and the Silver Book emphasizes assessment of uncertainty and variability appropriate to the decision to be made.

*Science and Decisions: Advancing Risk Assessment* made several recommendations directly relevant to developing IRIS assessments, including the draft formaldehyde assessment. First, it called for the development of guidance related to the handling of uncertainty and variability, that is, clear definitions and methods. Second, it urged a unified dose-response assessment framework for chemicals that would link understanding of disease processes, modes of action, and human heterogeneity among cancer and noncancer outcomes. Thus, it suggested an expansion of cancer dose-response assessments to reflect variability and uncertainty more fully and for noncancer dose-response assessments to reflect analysis of the probability of adverse responses at particular exposures. Although that is an ambitious undertaking, steps toward a unifying framework would benefit future IRIS assessments. Third, the Silver Book recommended that EPA assess its capacity for risk assessment and take steps to ensure that it is able to carry out its challenging risk-assessment agenda. For some IRIS assessments, EPA appears to have difficulty in assembling the needed multidisciplinary teams.

The committee recognizes that EPA has initiated a plan to revise the overall IRIS process and issued a memorandum that provided a brief description of the steps (EPA 2009a). Figure 7-1 illustrates the steps outlined in that memorandum. The committee is concerned that little information is provided on what it sees as the most critical step, that is, completion of a draft IRIS assessment. In the flow diagram, six steps are devoted to the review process, and thus the focus of the revision appears to be on the steps after the assessment has been generated. Although EPA may be revising its approaches for completing the draft assessment (Step 1 in Figure 7-1), the committee could not locate any other information on the revision of the IRIS process. Therefore, the committee offers some suggestions on the development process.

In providing guidance on revisions of the IRIS development process (that is, Step 1 as illustrated in Figure 7-1), the committee begins with a discussion of the current state of science regarding reviews of evidence and cites several examples that provide potential models for IRIS assessments. The

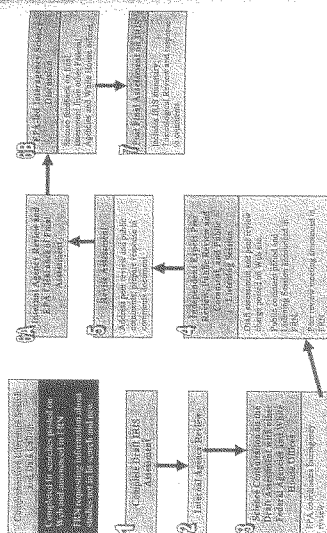


FIGURE 7-1 New IRIS assessment process. Abbreviations: FRN, Federal Register Notice; IRIS, Integrated Risk Information System; and EPA, Environmental Protection Agency. Source: EPA 2009a.

committee also describes the approach now followed in reviewing and synthesizing evidence related to the National Ambient Air Quality Standards (NAAQS), a process that has been modified over the last 2 years. It is provided as an informative example of how the agency was able to revise an entrenched process in a relatively short time, not as an example of a specific process that should be adopted for the IRIS process. Finally, the committee offers some suggestions for improving the IRIS development process, providing a "roadmap" of the specific items for consideration.

#### An Overview of the Development of the Draft IRIS Assessment

In Chapter 2, the committee provided its own diagram (Figure 2-1) describing the steps used to generate the draft IRIS assessment. For the purpose of offering committee comments on ways to improve those steps, that figure has been expanded to indicate the key outcomes at each step (Figure 7-2). For each of the steps, the figure identifies the key questions addressed in the process. At the broadest level, the steps include systematic review of evidence, hazard identification using a weight-of-evidence approach, and dose-response assessment.

The systematic review process is undertaken to identify all relevant literature on the agent of interest, to evaluate the identified studies, and possibly to

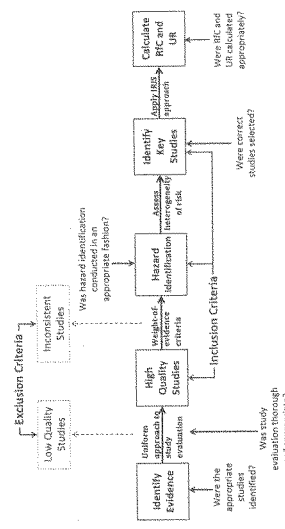


FIGURE 7-2 Elements of the key steps in the development of a draft IRIS assessment. Abbreviations: IRIS, Integrated Risk Information System; RfC, reference concentration; and UR, unit risk.

provide a qualitative or quantitative synthesis of the literature. Chapter 1 of the draft IRIS assessment of formaldehyde provides a brief general description of the process followed by EPA, including the approach to searching the literature. However, neither Chapter 1 nor other chapters of the draft provide a sufficiently detailed description of the approach taken in evaluating individual studies. In discussing particular epidemiologic studies, a systematic approach to study evaluation is not provided. Consequently, some of the key methodologic points are inconsistently mentioned, such as information bias and confounding.

For hazard identification, the general guidance is also found in Chapter 1 of the draft IRIS assessment. The approach to conducting hazard identification is critical for the integrity of the IRIS process. The various guidelines cited in Chapter 1 provide a general indication of the approach to be taken to hazard identification but do not offer a clear template for carrying it out. For the formaldehyde assessment, hazard identification is particularly challenging because the outcomes include cancer and multiple noncancer outcomes. The various EPA guidelines themselves have not been harmonized, and they provide only general guidance. Ultimately, the quality of the studies reviewed and the strength of evidence provided by the studies for deriving RfCs and unit risks need to be clearly presented. More formulaic approaches are followed for calculation of RfCs and unit risks. The key issue is whether the calculations were conducted appropriately and according to accepted assessment procedures.

### Brief Review of Established Best Practices

The following sections highlight some best practices of current approaches to evidence-based reviews, hazard identification, and dose-response assessment that could provide EPA guidance if it decides to address some of the fundamental issues identified by the committee. The discussion is meant not to be comprehensive or to provide all perspectives on the topics but simply to highlight some important aspects of the approaches. The committee recognizes that some of the concepts and approaches discussed below are elementary and are addressed in some of EPA's guidelines. However, the current state of the formaldehyde draft IRIS assessment suggests that there might be a problem with the practical implementation of the guidelines in completing the IRIS assessments. Therefore, the committee highlights aspects that it finds most critical.

### Current Approaches to Evidence-Based Reviews

Public-health decision-making has a long history of using comprehensive reviews as the foundation for evaluating evidence and selecting policy options. The landmark 1964 report of the U.S. surgeon general on tobacco and disease is exemplary (DHEW 1964). It used a transparent method that involved a critical survey of all relevant literature by a neutral panel of experts and an explicit framework for assessing the strength of evidence for causation that was equivalent to hazard identification (Table 7-1).

The tradition of comprehensive, evidence-based reviews has been continued in the surgeon general's reports. The 2004 surgeon general's report, which marked the 40th anniversary of the first report, highlighted the approach for causal inference used in previous reports and provided an updated and standardized four-level system for describing strength of evidence (DHHS 2004) (Table 7-2).

The same systematic approaches have become fundamental in many fields of clinical medicine and public health. The paradigm of "evidence-based medicine" involves the systematic review of evidence as the basis of guidelines. The international Cochrane Collaboration engages thousands of researchers and clinicians throughout the world to carry out reviews. In the United States, the Agency for Healthcare Research and Quality supports 14 evidence-based practice centers to conduct reviews related to healthcare.

There are also numerous reports from NRC committees and the Institute of Medicine (IOM) that exemplify the use of systematic reviews in evaluating evidence. Examples include reviews of the possible adverse responses associated with Agent Orange, vaccines, asbestos, arsenic in drinking water, and secondhand smoke. A 2008 IOM report, *Improving the Presumptive Disability Decision-Making Process for Veterans*, proposed a comprehensive new scheme for

TABLE 7-1 Criteria for Determining Causality

Criterion	Definition
Consistency	Persistent association among different studies in different populations
Strength of association	Magnitude of the association
Specificity	Linkage of specific exposure to specific outcome
Temporality	Exposure comes before effect
Coherence, plausibility, analogy	Coherence of the various lines of evidence with a causal relationship
Biologic gradient	Presence of increasing effect with increasing exposure (dose-response relationship)
Experiment	Observations from "natural experiments," such as cessation of exposure (for example, quitting smoking)

Source: DHHS 2004.

TABLE 7-2 Hierarchy for Classifying Strength of Causal Inferences on the Basis of Available Evidence

- Evidence is *sufficient* to infer a causal relationship.
- Evidence is *suggestive but not sufficient* to infer a causal relationship.
- Evidence is *inadequate* to infer the presence or absence of a causal relationship (evidence that is sparse, of poor quality, or conflicting).
- Evidence is *suggestive of no causal relationship*.

Source: DHHS 2004.

evaluating evidence that an exposure sustained in military service had contributed to disease (IOM 2008); the report offers relevant coverage of the practice of causal inference.

This brief and necessarily selective coverage of evidence reviews and evaluations shows that models are available that have proved successful in practice. They have several common elements: transparent and explicitly documented methods, consistent and critical evaluation of all relevant literature, application of a standardized approach for grading the strength of evidence, and clear and consistent summative language. Finally, highlighting features and limitations of the studies for use in quantitative assessments seems especially important for IRIS literature reviews.

The review approach for hazard identification embodies the elements described above and uses the criteria for evidence evaluation that have their origins in the 1964 report of the U.S. surgeon general (DHEW 1964) and the writings of Austin Bradford Hill, commonly known as the Hill criteria (see Table 7-1, Hill 1965). The criteria are not rigid and are not applied in a check-list manner, in fact, none is required for inferring a causal relationship, except for temporality inasmuch as exposure to the causal agent must precede the associated effect. The conclusion of causal inference is a clear statement on the strength of evidence of causation. For the purpose of hazard identification, such statements should follow a standardized classification to avoid ambiguity and to ensure comparability among different agents and outcomes.

Beyond the surgeon general's reports used here as an example, there are numerous examples of systematic approaches to hazard identification, including the monographs on carcinogenicity of the International Agency for Research on Cancer and the National Toxicology Program.<sup>1</sup> They have the same elements of systematic gathering and review of all lines of evidence and classification of the strength of evidence in a uniform and hierarchic structure.

#### Current Approaches to Dose-Response Assessment

The topic of dose-response assessment was covered in *Science and Decisions* (NRC 2009), which reviewed the current paradigm and called for a unified framework, bringing commonality to approaches for cancer and noncancer endpoints. That report also provides guidance on enhancing methods used to characterize uncertainty and variability. The present committee supports those recommendations but offers additional suggestions on the complementary coverage of the use of meta-analysis and pooled analysis in dose-response assessment.

IRIS assessments should address the following critical questions: Which studies should be included for derivation of reference values for noncancer outcomes and unit risks for cancer outcomes? Which dose-response models should be used for deriving those values? The latter question is related to model uncertainty in quantitative risk assessment and is not addressed here in this report. The former question is related to a fundamental issue of filtering the literature to identify the studies that provide the best dose-response information. A related question arises about how to combine information among studies because multiple studies may provide sufficient dose-response data. For this section, the committee assumes that the previously described evidence-based review has identified studies with adequate dose-response information to support some quantification of risk associated with exposure.

As suggested above, it would be unusual for a single study to trump all other studies providing information for setting reference values and unit risks. The combination of the analysis outcomes of different studies falls under the

<sup>1</sup>See <http://monographs.iarc.fr/index.php> and <http://ntp.niehs.nih.gov/>.

general description of meta-analysis (Normand 1999). The combination and synthesis of results of different studies appears central to an IRIS assessment, but such analyses require careful framing.

Stroup and colleagues (2000) provide a summary of recommendations for reporting meta-analyses of epidemiologic studies. Their proposal includes a table with a proposed check list that has broad categories for reporting, including background (such as problem definition and study population), search strategy (such as searchers, databases, and registries used), methods, results (such as graphic and tabular summaries, study description, and statistical uncertainty), discussion (such as bias and quality of included studies), and conclusion (such as generalization of conclusions and alternative explanations). Their recommendations on methods warrant specific consideration with reference to the development of an IRIS assessment, particularly those on evaluation and assessment of study relevance, rationale for selection and coding of studies, confounding, study quality, heterogeneity, and statistical methods. For the latter, key issues include the selection of models, the clarity with which findings are presented, and the availability of sufficient details to facilitate replication.

In combining study information, it is important that studies provide information on the same quantitative outcome, are conducted under similar conditions, and are of similar quality. If studies are of different quality, this might be addressed by weighting.

The simplest form of combining study information involves the aggregation of p values among a set of independent studies of the same null hypothesis. That simple approach might have appeal for establishing the relationship between some risk factor and an adverse outcome, but it is not useful for establishing exposure levels for a hazard. Thus, effect-size estimation among studies is usually of more interest for risk-estimation purposes and causality assessment. In this situation, a given effect is estimated for each study, and a combined estimate is obtained as a weighted average of study-specific effects in which the weights are inversely related to the precision associated with the estimation of each study-specific effect.

The question is whether EPA should routinely conduct meta-analysis for its IRIS assessments. Implicitly, the development of an IRIS assessment involves many of the steps associated with meta-analysis, including the collection and assessment of background literature. Assuming the availability of independent studies of the same end point and a comprehensive and unbiased inclusion of studies, questions addressed by a meta-analysis may be of great interest. Is there evidence of a homogeneous effect among studies? If not, can one understand the source of heterogeneity? If it is determined that a combined estimate is of interest (for example, an estimate of lifetime cancer risk based on combining study-specific estimates of this risk), a weighted estimate might be derived and reported.



### Case Study: Revision of the Approach to Evidence Review and Risk Assessment for National Ambient Air Quality Standards

Approaches to evidence review and risk assessment vary within EPA. The recently revised approach used for NAAQSs offers an example that is particularly relevant because it represents a major change in an approach taken by one group in the National Center for Environmental Assessment (EPA 2009b, 010a,b).

Under Section 109 of the Clean Air Act, EPA is required to consider revisions of the NAAQSs for specified criteria air pollutants—currently particulate matter (PM), ozone, nitrogen dioxide, sulfur dioxide, carbon monoxide, and lead—every 5 years. Through 2009, the process for revision involved the development of two related documents that were both reviewed by the Clean Air Scientific Advisory Committee (CASAC) and made available for public comment. The first, the criteria document, was an encyclopedic compilation, sometimes several thousand pages long, of most scientific publications on the criteria pollutant that had been published since the previous review. Multiple authors contributed to the document, and there was generally little synthesis of the evidence, which was not accomplished in a systematic manner.

The other document was referred to as the staff paper. It was written by a different team in the Office of Air Quality Policy and Standards, and it identified the key scientific advances in the criteria document that were relevant to revising the NAAQSs. In the context of those advances, it offered the array of policy options around retaining or revising the NAAQSs that could be justified by relevant research evidence. The linkages between the criteria document and the staff paper were general and not transparent.

The identified limitations of the process led to a proposal for its revision, and it took 2 years to complete the changes in the process. The new process replaces the criteria document with an integrated science assessment and a staff paper that includes a policy assessment. For the one pollutant, PM, that has already completed the full sequence, a risk and exposure analysis was also included.

The new documents address limitations of those used previously. The integrated science assessment is an evidence-based review that targets new studies as before. However, review methods are explicitly stated, and studies are reviewed in an informative and purposeful manner rather than in encyclopedic fashion. A main purpose of the integrated science assessment is to assess whether adverse health effects are causally linked to the pollutant under review. The integrated science assessment offers a five-category grading of strength of evidence on each outcome and follows the general weight-of-evidence approaches long used in public health. The intent is to base the risk and exposure analysis on effects for which causality is inferred or those at lower levels if they have particular public-health significance. The risk and exposure analysis brings

together the quantitative information on risk and exposure and provides estimates of the current burden of attributable morbidity and mortality and the estimates of avoidable and residual morbidity and mortality under various scenarios of changes in the NAAQS. Standard descriptors for uncertainty are now in place.

The policy assessment develops policy options on the basis of the findings of the integrated science assessment and the risk and exposure analysis. The policy assessment for the PM NAAQS is framed around a series of policy-relevant questions, such as, Does the available scientific evidence, as reflected in the integrated science assessment, support or call into question the adequacy of the protection afforded by the current 24-hr PM<sub>10</sub> standard against effects associated with exposures to thoracic coarse particles? Evidence-based answers to the questions are provided with a reasonably standardized terminology for uncertainty.

For the most recent reassessment of the PM NAAQS, EPA staff and CASAC found the process to be effective; it led to greater transparency in evidence review and development of policy options than the prior process (Samet 2010). As noted above, the present committee sees the revision of the NAAQS review process as a useful example of how the agency was able to revise an entrenched process in a relatively short time.

### Reframing the Development of the IRIS Assessment

The committee was given the broad charge of reviewing the formaldehyde draft IRIS assessment and also asked to consider some specific questions. In addressing those questions, the committee found, as documented in Chapter 2, that some problems with the draft arose because of the processes and methods used to develop the assessment. Other committees have noted some of the same problems. Accordingly, the committee suggests here steps that EPA could take to improve IRIS assessment through the implementation of methods that would better reflect current practices. The committee offers a roadmap for changes in the development process if EPA concludes that such changes are needed. The term *roadmap* is used because the topics that need to be addressed are set out, but detailed guidance is not provided because that is seen as beyond the committee's charge. The committee's discussion of a reframing of the IRIS development process is based on its generic representation provided in Figure 7-2. The committee recognizes that the changes suggested would involve a multiyear process and extensive effort by the staff of the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others. The recent revision of the NAAQS review process provides an example of an overhauling of an EPA evidence-review and risk-assessment process that took about 2 years.

In the judgment of the present and past committees, consideration needs to be given to how each step of the process could be improved and gains made in transparency and efficiency. Models for conducting IRIS reviews more effectively and efficiently are available. For each of the various components (Figure 1-2), methods have been developed, and there are exemplary approaches in assessments carried out elsewhere in EPA and by other organizations. In addition, there are relevant examples of evidence-based algorithms that EPA could draw on. Guidelines and protocols for the conduct of evidence-based reviews are available, as are guidelines for inference as to the strength of evidence of association and causation. Thus, EPA may be able to make changes in the assessment process relatively quickly by drawing on appropriate experts and selecting and adapting existing approaches.

One major, overarching issue is the use of weight of evidence in hazard identification. The committee recognizes that the terminology is embedded in various EPA guidelines (see Appendix B) and has proved useful. The determination of weight of evidence relies heavily on expert judgment. As called for by others, EPA might direct effort at better understanding how weight-of-evidence determinations are made with a goal of improving the process (White et al. 2009).

The committee highlights below what it considers critical for the development of a scientifically sound IRIS assessment. Although many elements are basic and have been addressed in the numerous EPA guidelines, implementation does not appear to be systematic or uniform in the development of the IRIS assessments.

#### 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; for example, include standard approaches for reviews of various types of studies to ensure uniformity.
- Assess disciplinary structure of teams needed to conduct the assessments.

#### 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, 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

- 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.

#### Weight-of-Evidence Evaluation: Synthesis of Evidence for Hazard Identification

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

#### Selection of Studies for Derivation of Reference Values 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.

#### Calculation of Reference Values and Unit Risks

- 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.
- 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.

- 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.
- 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 appendices, which might be made available only electronically, should be provided when appropriate.

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REVIEW OF THE ENVIRONMENTAL PROTECTION  
AGENCY'S DRAFT IRIS ASSESSMENT OF  
**FORMALDEHYDE**

## Summary

Formaldehyde is ubiquitous in indoor and outdoor air, and everyone is exposed to formaldehyde at some concentration daily. Formaldehyde is used to produce a wide array of products, particularly building materials; it is emitted from many sources, including power plants, cars, gas and wood stoves, and cigarettes; it is a natural product in some foods, and it is naturally present in the human body as a metabolic intermediate. Much research has been conducted on the health effects of exposure to formaldehyde, including effects on the upper airway, where formaldehyde is deposited when inhaled, and effects on tissues distant from the site of initial contact.

For more than a decade, the U.S. Environmental Protection Agency (EPA) has been in the process of re-evaluating the health effects of formaldehyde; in June 2010, it released its draft health assessment of formaldehyde for EPA's Integrated Risk Information System (IRIS). Given the complex nature of the assessment and recognition that the assessment will be used as a basis of risk calculations and regulatory decisions, EPA asked the National Research Council (NRC) to conduct an independent scientific review of the draft IRIS assessment and to answer questions related specifically to its derivation of reference concentrations (RfCs) for noncancer effects and unit risk estimates for cancer. In response to EPA's request, NRC convened the Committee to Review EPA's Draft IRIS Assessment of Formaldehyde, which prepared this report.

In addressing its charge,<sup>1</sup> the committee reviewed the draft IRIS assessment provided. It did not perform its own assessment, which would have been beyond its charge. Accordingly, the committee 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 literature.

<sup>1</sup>See Chapter 1 for the committee's verbal statement of task.

### THE DRAFT IRIS ASSESSMENT

Overall, the committee noted some recurring methodologic problems in the draft IRIS assessment of formaldehyde. Many of the problems are similar to those which have been reported over the last decade by other NRC committees tasked with reviewing EPA's IRIS assessments for other chemicals. Problems with clarity and transparency of the methods appear to be a repeating theme over the years, even though the documents appear to have grown considerably in length. In the roughly 1,000-page draft reviewed by the present committee, little beyond a brief introductory chapter could be found on the methods for conducting the assessment. Numerous EPA guidelines are cited, but their role in the preparation of the assessment is not clear. In general, the committee found that the draft was not prepared in a consistent fashion; it lacks clear links to an underlying conceptual framework, and 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. This summary highlights the committee's substantive comments and recommendations that should be considered in revision of the draft IRIS assessment; more detailed comments and recommendations can be found at the conclusions of individual chapters or following the discussions on individual health outcomes.

### Toxicokinetics

The committee reviewed the extensive discussion on toxicokinetics of formaldehyde in the draft IRIS assessment and focused on several key issues: the implications of endogenous formaldehyde, the fate of inhaled formaldehyde, the systemic availability of formaldehyde, the ability of formaldehyde to cause systemic genotoxic effects, and the usefulness of various models.

**Endogenous formaldehyde.** Humans and other animals produce formaldehyde through various biologic pathways as part of normal metabolism. Thus, formaldehyde is normally present at low concentrations in all tissues, cells, and bodily fluids. Although there is some debate regarding interpretation of the analytic measurements, formaldehyde has been measured in exhaled breath and is most likely present normally at a concentration of a few parts per billion. 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. Despite species differences in uptake due to differences in breathing patterns and nasal structures, formaldehyde is absorbed primarily at the site of first contact where it undergoes exten-

### Summary

sive local metabolism and reactions with macromolecules. Thus, 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. The draft IRIS assessment provides divergent statements regarding systemic delivery of formaldehyde that need to be resolved. Specifically, some parts of the draft assume that the high reactivity and extensive nasal absorption of formaldehyde restrict systemic delivery of inhaled formaldehyde so that formaldehyde does not go beyond the upper respiratory tract, and other parts of the draft assume that systemic delivery accounts in part for the systemic effects attributed to formaldehyde exposure.

The committee concludes that the weight of evidence suggests that formaldehyde is unlikely to appear in the blood as an intact molecule except perhaps at concentrations high enough to transiently overwhelm the metabolic capability of the tissue at the site of exposure. Thus, direct evidence of systemic delivery of formaldehyde is generally lacking. Furthermore, it is unlikely that formaldehyde reaches distal sites via its hydrated form, methanediol. Although equilibrium dynamics indicate that methanediol would constitute more than 99.9% of the total free and hydrated formaldehyde, experimental data provide compelling evidence that hydration of formaldehyde does not enhance delivery beyond the portal of entry to distal tissues. Pharmacokinetic modeling also supports that conclusion.

**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 is causing cytogenetic effects at distant sites. First, the observed effects have occurred in highly exposed people, and extrapolating to more typical environmental exposures is difficult given the uncertainty surrounding the form of the dose-response curve for cytogenetic changes. Second, a mechanism that would explain the occurrence of cytogenetic effects in circulating blood cells has not been established. That gap in mechanistic understanding is particularly problematic because the data strongly suggest that formaldehyde is not available systemically in any reactive form. Thus, the committee can only hypothesize that the observed effects result from an unproven mechanism in portal-of-entry tissues.

**Usefulness of various models.** Computational fluid dynamics (CFD) models have been developed to help to predict the dose to nasal tissues from inhaled formaldehyde. EPA fairly evaluated the 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 re-

its in the revised IRIS assessment, and explain clearly its use of CFD modeling approaches.

A biologically based dose-response (BBDR) model that has been developed for formaldehyde could be used in the derivation of the unit risk estimates. EPA explored the uncertainties associated with the model and sensitivities of various model components to changes in key parameters and assumptions and, on the basis of those extrapolations, decided not to use the BBDR model in its assessment. Although the committee agrees that EPA's evaluation of the model included some important findings on model sensitivity, some of the manipulations are extreme, may not be scientifically justified, and should not have been used as the basis of rejection of the use of the BBDR model in its assessment. Model manipulations that yield results that are implausible or inconsistent with available data should be rejected as a basis for judging the utility of the model.

The primary purposes of a BBDR model are to predict as accurately as possible a response to a given exposure, to provide a rational framework for extrapolations outside the range of experimental data (that is, across doses, species, and exposure routes), and to assess the effect of variability and uncertainty in model parameters. In developing a BBDR model, a model structure and parameter values should be chosen to constrain model predictions within biologic and physical limits; all relevant data should be reconciled with the model, and model predictions should be reconciled with credible outcomes. Thus, it provides a valuable method for predicting the range of plausible responses in a given exposure scenario. Given that the BBDR model for formaldehyde is one of the best-developed BBDR models to date, the positive attributes of BBDR models generally, and the limitations of the human data, the committee recommends that EPA use the BBDR model 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 for Formaldehyde Carcinogenesis

*Mode of action* is defined as a sequence of key events that describe the biologic pathway from exposure to adverse outcome. Understanding the mode of action is important because it can provide support for conclusions regarding causality, and it can affect how unit risk estimates are calculated. Potential modes of action for formaldehyde carcinogenesis have been debated. 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. Because multiple modes of action may be operational, the committee recommends that EPA provide additional calculations that factor in regenerative cellular proliferation as a mode of action, com-

#### Summary

pure the results with those presented in the draft assessment, and assess the strengths and weaknesses of each approach.

Little is known about a potential mode of action for hematopoietic cancers, such as leukemias, that have been attributed to formaldehyde exposure and that are assumed to arise from sites distant from the portal of entry. The draft IRIS assessment speculates that formaldehyde could reach the bone marrow and cause the mutagenic effects that lead to the cancers noted. However, despite the use of sensitive and selective analytic methods that are capable of differentiating endogenous exposures from exogenous ones, numerous studies have demonstrated that systemic delivery of formaldehyde is unlikely at concentrations that do not overwhelm metabolism. The draft assessment further speculates that circulating hematopoietic stem cells that percolate the nasal capillary bed or nasal-associated lymphoid tissues may be the target cells for the mutagenic effects that eventually lead to the cancers noted. However, experimental evidence supporting that mechanism is lacking.

#### Portal-of-Entry Health Effects

EPA evaluated a wide array of outcomes that the committee chose to characterize as portal-of-entry health effects or systemic health effects.<sup>2</sup> The portal-of-entry effects include 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. For a few outcomes, however, as noted below, 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, the committee would not have advanced a particular study or would have advanced other studies to calculate the candidate RfCs. Comments on the specific outcomes are provided below.

*Irritation.* Formaldehyde has been consistently shown to be an eye, nose, and throat irritant, and EPA used several studies of residential exposure to calculate candidate RfCs. However, the favorable attributes of one particular selected study (Richie and Lehnen 1987)<sup>3</sup> were outweighed by the potential for participant-selection bias, and EPA should not have used it to calculate an RfC. Fur-

<sup>2</sup>Portal-of-entry effects are defined here as effects that arise from direct interaction of inhaled formaldehyde with the airways or from the direct contact of airborne formaldehyde with the eyes or other tissue, and systemic effects are defined as effects that occur outside those systems.

<sup>3</sup>Richie, I. M., and R. G. Lehnen. 1987. Formaldehyde-related health complaints of residents living in mobile and conventional homes. *Am. J. Public Health* 77(3):323-328.

more, EPA set aside the chamber and occupational studies too soon in the process. Although the chamber studies are of acute duration, they are complementary with the residential studies and provide controlled measures of exposure and response. Therefore, the committee recommends that EPA present the concentration-response data from the occupational, chamber, and residential studies on the same graph and include the point estimate and measures of variability in the exposure concentrations and responses. The committee notes that EPA did not (but should) review research findings on transient-receptor-potential ion channels and evaluate the utility of this evidence for improving understanding of the mode of action for sensory irritation and respiratory effects attributed to formaldehyde exposure.

**Decreased pulmonary function.** The committee agrees with EPA that formaldehyde exposure may cause a decrease in pulmonary function, but EPA could provide a clear rationale to support that conclusion. Furthermore, although the committee supports the use of the study by Kryzanowski et al. (1990)<sup>6</sup> to calculate a candidate RfC, EPA should provide a clear description of how the study was used to estimate a point of departure and should also consider the studies conducted by Kriebel et al. (1993, 2001)<sup>7</sup> and the chamber studies for possible derivation of candidate RfCs.

**Respiratory tract pathology.** Animal studies in mice, rats, and nonhuman primates clearly show that inhaled formaldehyde at 2 ppm or greater causes cytotoxicity that increases epithelial-cell proliferation and that after prolonged inhalation can lead to nasal tumors. Although the committee agrees with EPA that human studies that assessed upper respiratory tract pathology were insufficient to derive a candidate RfC, it disagrees with EPA's decision not to use the animal data. The animal studies offer one of the most extensive datasets on an inhaled chemical, and EPA should use the data to derive a candidate RfC for this outcome.

**Asthma.** Asthma is a term applied to a broad phenotype of respiratory disease that comprises an array of symptoms resulting from underlying airway inflammation and associated airway hyper-reactivity. In infants and children, sneezing illnesses that are the result of lower respiratory tract infections are often labeled as asthma, and in adults, the symptoms can overlap with those of other chronic diseases, such as chronic obstructive pulmonary disease. Thus, a critical review of the literature is essential to ensure that what is being evaluated as asthma. The committee notes that this issue is not adequately addressed in the

## Summary

draft IRIS assessment and that EPA advanced a study (Runchev et al. 2002)<sup>8</sup> that most likely suffers from misclassification of infection-associated wheezing in young children as asthma. The draft IRIS assessment also provides little discussion of the current understanding of the mechanisms of asthma causation and exacerbation. Given the abundant research available, the committee recommends that EPA strengthen its discussion of asthma to reflect current understanding of this complex disease and its pathogenesis. Although the committee agrees that the study by Garrett et al. (1999)<sup>9</sup> should be used to calculate a candidate RfC, the approach taken to identifying the point of departure needs further justification.

**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. On the basis of EPA cancer guidelines, the committee agrees that there is sufficient evidence (that is, the combined weight of epidemiologic findings, results of animal studies, and mechanistic data) of a causal association between formaldehyde and cancers of the nose, nasal cavity, and nasopharynx. It disagrees 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)<sup>10</sup> is the most appropriate for deriving a unit risk value but notes that this study is being updated.

## Systemic Health Effects

The systemic effects evaluated by EPA include immunotoxicity, neurotoxicity, reproductive and developmental toxicity, and lymphohematopoietic (LHP) cancers. As noted above, 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

<sup>6</sup>Runchev, K.B., J.T. Spickett, M.K. Bulara, M.R. Phillips, and S.M. Stick. 2002. Domestic exposure to formaldehyde significantly increases the risk of asthma in young children. *Eur. Respir. J.* 20(2):403-408.

<sup>7</sup>Kriebel, D., S.R. Sanna, and B. Coconour. 1993. Reversible pulmonary responses to formaldehyde. A study of clinical anatomy students. *Am. Rev. Respir. Dis.* 148(6 Pt 1):1509-1515.

<sup>8</sup>Kryzanowski, M., J.J. Quackenbush, and M.D. Lebowitz. 1990. Chronic respiratory effects of indoor formaldehyde exposure. *Environ. Res.* 52(2):117-125.

<sup>9</sup>Garrett, M.H., A. Hooper, B.M. Hooper, P.R. Rayment, and M.J. Abramson. 1999. Mechanism of allergy in children due to formaldehyde exposure in homes. *Allergy* 54(6):330-337. [Erratum-*Allergy* 54(12):1527].

<sup>10</sup>Hauptmann, M., J.H. Lubin, P.A. Stewart, R.B. Hayes, and A. Blair. 2004. Mortality from solid tumors among workers in formaldehyde industries. *Am. J. Epidemiol.* 159(12):1117-1130.



ence it. The committee agrees with EPA that available data indicate that there are possible differences in susceptibility to formaldehyde at various life stages and in various disease states. The epidemiologic studies used to calculate the candidate RfCs for respiratory effects and sensory irritation included people in susceptible populations (children and people who have asthma). However, the modes of action for formaldehyde's effects are not sufficiently understood to ensure that all potential susceptible populations and factors contributing to susceptibility have been identified and adequately described. Thus, the committee supports the use of a UF<sub>H</sub> of 3 to calculate candidate RfCs for studies identified in the draft IRIS assessment on reduced pulmonary function, asthma, and sensory irritation, noting that the committee does not support the advancement of the studies by Ritchie and Lehnen (1987)<sup>10</sup> and Rumchev et al. (2002).<sup>11</sup>

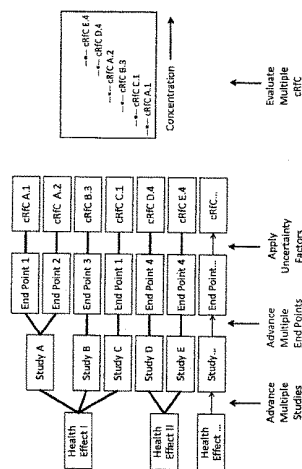
Determining the appropriate value of the UF<sub>D</sub> involves consideration of the breadth and depth of the data available on a specific chemical. The database on formaldehyde is extensive and includes the evaluation of a full array of health outcomes in the human population and laboratory animals. Although there are some gaps in the data on reproductive, developmental, immunologic, and neurotoxic effects, the likelihood that new effects will be observed at concentrations below those at which respiratory effects have been observed is low. Thus, the committee supports the use of a UF<sub>D</sub> of 1 with the caveat that research of the types noted should be pursued.

Overall, the committee is troubled by the presentation and derivation of the proposed RfC values and strongly recommends the approach illustrated and described in Figure S-1. A similar approach was recommended by the NRC Committee to Review EPA's Toxicological Assessment of Tetrachloroethylene and used in recent EPA assessments of tetrachloroethylene and trichloroethylene. Appropriate graphic aids that enable the visualization of the concentration ranges of the candidate RfCs may identify a central value, isolate especially low or high RfC values that might not be consistent with the body of literature, and ultimately improve the ability of the assessment to make a compelling case that the RfC proposed is appropriate for the most sensitive end point and protective with regard to other potential health effects.

#### Derivation of Unit Risk Estimates for Formaldehyde

Unit risk for formaldehyde can be defined as the estimate of extra risk caused by inhalation of one unit of formaldehyde, such as 1 ppm or 1 µg/m<sup>3</sup>, in

<sup>10</sup>Ritchie, L.M., and R.G. Lehnen. 1987. Formaldehyde-related health complaints of residents living in mobile and conventional homes. *Am. J. Public Health* 77(3):323-328.  
<sup>11</sup>Rumchev, K.B., J.T. Spickett, M.K. Baisara, M.R. Phillips, and S.M. Stick. 2002. Domestic exposure to formaldehyde significantly increases the risk of asthma in young children. *Eur. Respir. J.* 20(2):403-408.



**FIGURE S-1** Illustration of potential process for identifying an RfC. Health effects associated with exposure to the chemical are identified. For each health effect, studies that meet inclusion criteria are advanced. From each study, one or more health end points that meet specified criteria are advanced, and a point of departure is identified or derived. Uncertainty factors are selected and applied to the point of departure to yield a candidate RfC (eRfC). All eRfCs are evaluated together with the aid of graphic displays that incorporate selected information relevant to the database and to the decision to be made. A final RfC is selected from the distribution after consideration of all critical data that meet the inclusion criteria.

air. EPA used studies of the National Cancer Institute (NCI) cohort of U.S. workers exposed to formaldehyde through its production or its use (Hauptmann et al. 2004<sup>12</sup>; Beane-Freeman et al. 2009)<sup>13</sup> to estimate unit risk values for three cancers—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; however, the studies are not without their weaknesses, which should be clearly discussed and addressed in the revised IRIS assessment. Although there are uncertainties as discussed above regarding the causal relationship of

<sup>12</sup>Hauptmann, M., J.H. Lubin, P.A. Stewart, R.B. Hayes, and A. Blair. 2004. Mortality from solid cancers among workers in formaldehyde industries. *Am. J. Epidemiol.* 159(12):1117-1130.

<sup>13</sup>Beane-Freeman, L.E., A. Blair, J.H. Lubin, P.A. Stewart, R.B. Hayes, R.N. Hoover, and M. Hauptmann. 2009. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: The National Cancer Institute cohort. *J. Natl. Cancer Inst.* 101(10):751-761.