REVIEW OF EPA'S INTEGRATED RISK INFORMATION SYSTEM (IRIS) PROCESS

Statement of

David C. Dorman, DVM, PhD, DABT, DABVT

Professor of Toxicology
North Carolina State University

and

Member, Committee to Review the IRIS Process
Board on Environmental Studies and Toxicology
Division on Earth and Life Studies
National Research Council
The National Academies

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Committee on Science, Space, and Technology
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Good morning, Chairmen Broun and Schweikert and members of the subcommittees. My name is David Dorman. I am a professor of toxicology at North Carolina State University. I served as a member of the National Research Council (NRC) Committee to Review the IRIS Process and the NRC Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. The NRC is the operating arm of the National Academy of Sciences, National Academy of Engineering, and the Institute of Medicine of the National Academies, chartered by Congress in 1863 to advise the government on matters of science and technology.

I am pleased to appear before you today to discuss aspects of the report, *Review of EPA's Integrated Risk Information System (IRIS) Process*, which was released on May 6, 2014. Our review of the IRIS process was written by a 15-member committee with a wide array of scientific expertise, appropriate to the task. The committee was asked to assess the scientific, technical, and process changes being implemented or planned by EPA and recommend modifications or additional changes as appropriate to improve the scientific and technical performance of the IRIS program. It was also asked to review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments. We have provided a copy of the report for the subcommittees, and the summary is attached.

The IRIS program is responsible for developing toxicologic assessments of environmental contaminants. Over the last decade, the NRC has reviewed some of the more complex and challenging IRIS assessments, including those of formaldehyde, dioxin, and tetrachloroethylene. In 2011, an NRC committee released its review of the IRIS formaldehyde assessment. Like other NRC committees that had reviewed IRIS assessments, the formaldehyde committee identified deficiencies in the specific assessment and more broadly in some of EPA's general approaches and specific methods. Although that committee focused on evaluating the IRIS formaldehyde assessment, it provided general suggestions for improving the IRIS process and a roadmap for its revision (in Chapter 7 of that report) in case EPA

decided to move forward with changes to the process. After release of the NRC formaldehyde report, Congress instructed EPA to incorporate as appropriate the NRC recommendations. The report of the IRIS committee reviews the resulting changes that have been made to the IRIS assessment process.

Overall, the IRIS committee found that the changes that EPA has proposed and implemented to various degrees constitute substantial improvements in the IRIS process. If current trajectories are maintained, inconsistencies identified in the committee's report are addressed, and planned revisions still to be implemented are successfully completed, the IRIS process will become much more effective and efficient in achieving the program's basic goal of developing assessments that provide an evidence-based foundation for ensuring that chemical hazards are optimally assessed through a transparent and replicable approach.

Specifically, the IRIS committee found that EPA has implemented a new document structure that streamlines the assessments, drafted a preamble and a handbook that provide descriptions of the IRIS process, formed chemical assessment support teams to oversee the assessment-development process and ensure consistency among assessments, and implemented several initiatives to increase stakeholder input into the IRIS process. Those changes should substantially strengthen the IRIS process. The committee noted, however, that EPA still needs to indicate how the general principles described in the preamble are applied in a given assessment, it might also require outside experts to fill gaps in expertise in specific areas, and it might consider ways to provide technical assistance to under-resourced stakeholders to help them develop and provide input into the IRIS process.

The IRIS committee reviewed each step of the IRIS process and the changes that EPA has made or is planning to make, evaluated progress, and offered recommendations. For evidence identification, EPA has substantially improved its approach and is well on its way to adopting a more rigorous approach that when fully implemented should meet the recent Institute of Medicine standards for systematic review.

For evidence evaluation, EPA correctly identifies important study attributes but does not describe how it will assess risk of bias in the identified studies. Risk of bias is related to internal validity of a study and reflects study-design characteristics that can introduce a systematic error that might affect the magnitude and even the direction of the apparent effect. The IRIS committee recommended that EPA conduct risk-of-bias assessments on studies that are used as primary data sources, and that the results of the evaluations be fully described and reported in IRIS assessments. For evidence integration, EPA is moving toward a more structured approach. The IRIS committee described several qualitative and quantitative options in its report and suggested that EPA adopt the approach that best fits its plan for the IRIS program. However, the committee emphasized that quantitative approaches to integrating evidence will be increasingly needed and useful to EPA, and the agency should seriously consider expanding its ability to perform quantitative modeling for evidence integration. Regardless of the approach, EPA should develop templates for informative narrative justifications of the evidence-integration process and the conclusions reached. Finally, for dose-response assessment and calculation of toxicity values, the IRIS committee was encouraged by the improvements, particularly the shift away from choosing one study as the "best" one for deriving a toxicity value and toward deriving and graphically presenting multiple candidate toxicity values. However, the IRIS committee recommended that EPA develop formal methods for combining the results of multiple studies and selecting the final IRIS toxicity values and that EPA develop guidelines for uncertainty analysis and communication in the context of IRIS.

To ensure that the IRIS program provides the best assessments possible, the IRIS committee identified three broad areas on which EPA should focus attention. First, the assessment methods will need to be updated in a continuing, strategic fashion, and EPA should develop a plan for doing so. Second, the sources of inefficiencies in the IRIS process need to be identified and addressed systematically. Third, EPA management needs to evaluate the human and technologic resources that are needed to conduct IRIS assessments and support methodologic research and the implementation of new approaches. The IRIS

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

As noted, the IRIS committee found that substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report. The NRC formaldehyde committee recognized that its suggested changes would take several years and an extensive effort by EPA staff to implement. Substantial progress, however, has been made in a short time, and the IRIS committee's recommendations should be seen as building on the progress that EPA has already made. The IRIS committee recommended further peer review as the EPA completes the revisions.

Thank you for the opportunity to testify. I would be happy to answer any questions the subcommittees might have.

Summary

The Integrated Risk Information System (IRIS) is a program within the US Environmental Protection Agency (EPA) that is responsible for developing toxicologic assessments of environmental contaminants. IRIS assessments contain hazard identifications and dose-response assessments of various chemicals that cover cancer and noncancer outcomes. Although the program was created to increase consistency among toxicologic assessments within the agency, other federal agencies, various state and international agencies, and other organizations have come to rely on IRIS assessments for setting regulatory standards, establishing exposure guidelines, and estimating risks to exposed populations. Over the last decade, the National Research Council (NRC) has been asked to review some of the more complex and challenging IRIS assessments, including those of formaldehyde, dioxin, and tetrachloroethylene. In 2011, an NRC committee released its review of the IRIS formaldehyde assessment. Like other NRC committees that had reviewed IRIS assessments, the formaldehyde committee identified deficiencies in the specific assessment and more broadly in some of EPA's general approaches and specific methods. Although the committee focused on evaluating the IRIS formaldehyde assessment, it provided general suggestions for improving the IRIS process and a roadmap for its revision in case EPA decided to move forward with changes to the process.

After release of the formaldehyde report, Congress held several hearings to examine the IRIS program. The House Report (112-151) that accompanied the Consolidated Appropriations Act of 2012 (Public Law 112-74) stated that "EPA shall incorporate, as appropriate, based on chemical-specific datasets and biological effects, the recommendations...of the National Research Council's Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde into the IRIS process." To ensure that EPA adequately considers the recommendations, Congress requested that NRC assess the scientific, technical, and process changes being implemented or planned by EPA and recommend modifications or additional changes as appropriate to improve the scientific and technical performance of the IRIS program. This committee, the Committee to Review the IRIS Process, was convened by NRC as a result of that request. In addition to reviewing the changes in the IRIS program, the committee was asked to review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments. The present report provides the committee's review and recommendations, which are organized around the general depiction of the IRIS assessment process shown in Figure S-1.

SYSTEMATIC REVIEW

In 2011, the same year that the NRC formaldehyde report was released, the Institute of Medicine (IOM) released a report that recommended standards for systematic review.[1] As defined by IOM, systematic review "is a scientific investigation that focuses on a specific question

[1]IOM (Institute of Medicine). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press.

Overall, the changes that EPA has proposed and implemented to various degrees constitute substantial improvements in the IRIS process. If current trajectories are maintained, inconsistencies identified in the present report are addressed, and objectives still to be implemented are successfully completed, the IRIS process will become much more effective and efficient in achieving the program's basic goal of developing assessments that provide an evidence-based foundation for ensuring that chemical hazards are assessed and managed optimally.

Specifically, the present committee finds that the new document structure improves the organization of and streamlines the assessments and reduces redundancies. EPA's use of evidence tables and graphic displays has also reduced text volume and enhanced clarity and transparency. The new approaches bring IRIS assessments much more into line with the state of practice for systematic reviews. The preamble is a useful statement, which will presumably be updated as methods and procedures are modified and updated, but it does not substitute for an overview that indicates how the general principles in the preamble have been applied in any given assessment. The handbook is critical for providing consistency among the assessment teams and contributors, and the final version should be peer-reviewed to ensure that the document is on target and provides the needed guidance.

The committee is encouraged by the efforts to strengthen the overall scientific expertise in the assessment process through the addition of the CASTs and recommends that IRIS assessments clearly identify the members of all teams involved in the development of any given assessment. To strengthen the process further, experts from outside EPA and the government might be needed to fill gaps in expertise in specific areas. Experts should be engaged when needed to augment teams and to conduct peer review of the draft and final assessments.

Finally, the committee applauds EPA initiatives to involve stakeholders in the IRIS process earlier and more fully. Those initiatives are likely to improve assessment quality and to strengthen the program's credibility. However, not all stakeholders who have an interest in the IRIS process have the same scientific or financial resources to provide timely comments, and expanded opportunities for stakeholder involvement might lead to a further imbalance of public input. Therefore, similar to other EPA technical-assistance programs, EPA should consider ways to provide technical assistance to under-resourced stakeholders to help them to develop and provide input into the IRIS process.

PROBLEM FORMULATION AND PROTOCOL DEVELOPMENT

As noted, EPA is incorporating principles of systematic review as it revises the IRIS process. Critical elements of conducting a systematic review include formulating the specific question that will be addressed (problem formulation) and developing the protocol that specifies the methods that will be used to address the question (protocol development). Although the NRC formaldehyde report did not provide any specific recommendations regarding those elements, the present committee found that some discussion of them is warranted.

A major challenge for EPA in the problem-formulation step is to determine what adverse outcomes should be evaluated in a specific IRIS assessment. The committee suggests a three-step process for conducting problem formulation. First, with the support of an information specialist who is trained in conducting systematic reviews, EPA should perform a broad literature search designed to identify possible health outcomes associated with the chemical under investigation. The broad search should not be confused with the comprehensive literature search that is conducted for evidence identification in a systematic review (see Figure S-1); some EPA materials do not sufficiently distinguish between the two. Second, a table should be constructed to guide the formulation of specific questions that would be the subjects of specific systematic reviews. The table could be organized by the lines of evidence typically available to EPA (human, animal, and mechanistic studies) and the various health outcomes to investigate. Third, the table should be examined to determine which outcomes warrant a systematic review and how to define the systematic-review question, such as, Does exposure to chemical X result in neurotoxic effects?

describe how it will assess risk of bias in the identified studies. The committee notes that assessing the quality of the study is not equivalent to assessing the risk of bias in the study. An assessment of study quality evaluates the extent to which the researchers conducted their research to the highest possible standards and how a study is reported. Risk of bias is related to the internal validity of a study and reflects study-design characteristics that can introduce a systematic error (or deviation from the true effect) that might affect the magnitude and even the direction of the apparent effect. An assessment of risk of bias is a key element in systematic-review standards; potential biases must be assessed to determine how confidently conclusions can be drawn from the data.

The committee emphasizes the importance of assessing risk of bias for all study types. Although several approaches are described in the present report, the committee is not recommending the adoption of any specific approach. For a scientifically defensible method, however, EPA should select assessment tools for which empirical evidence links an assessment item with an associated risk of bias. Standardized methods might need to be developed, and EPA might need to conduct or support research on the development and evaluation of empirically based instruments for assessing bias in human, animal, and mechanistic studies relevant to chemical-hazard identification. It might want to consider pooling data across IRIS assessments to determine whether, among various contexts, candidate risk-of-bias items are associated with overestimates or underestimates of effect.

Incorporating risk-of-bias assessments into the IRIS assessment process might take some time, and approaches will depend on the complexity and extent of data on a chemical and the resources available to EPA. An important limitation of all existing tools for assessing study methods is that research reports might not include sufficient details to enable assessment. Consequently, EPA might be hampered by differences in reporting standards for some scientific literature, although the committee expects reporting of toxicology research to improve as risk-of-bias assessments are incorporated into the IRIS process. However, a coordinated effort by government agencies, researchers, publishers, and professional societies will be required to improve the completeness and accuracy of reporting toxicology studies in the near future. Regardless, a risk-of-bias assessment should be conducted on studies that are used by EPA as primary data sources for the hazard identification and dose-response assessment. Whatever approach is adopted, the assessment approach and the results should be fully described and reported in the IRIS assessment.

EVIDENCE INTEGRATION FOR HAZARD IDENTIFICATION

The NRC formaldehyde committee provided several recommendations regarding evidence integration, including reviewing the use of weight-of-evidence guidelines, standardizing an approach to using them, developing uniform language to describe the strength of evidence on noncancer effects, and providing more integrative and transparent discussions of weight of evidence. As in other recommendations, there is an emphasis on transparency and standardization of approach. In response, EPA has provided guidelines in the preamble for what considerations ought to inform the experts who are charged with integrating human, animal, and mechanistic evidence, and it gives extensive guidance on the qualitative categorization that the experts should use, but it articulates no systematic process by which the experts are to come to a conclusion. In the handbook, EPA provides extensive guidelines for synthesizing evidence within each category but no guidelines for integrating evidence among categories. The guidelines and the classification schemes offered for epidemiologic and other studies are reasonable, and similar ones have been used by other organizations with similar aims.

The committee appreciates that EPA's improvements for evidence integration are still being developed but offers some options for moving forward. Several qualitative and quantitative options are available for overall evidence integration. Qualitative options include guided expert judgment, such as the approach used by the International Agency for Research on Cancer

dose-response modeling, developing candidate toxicity values, and characterizing confidence and uncertainty in toxicity values has yet to be developed for the draft handbook.

The committee is encouraged by the improvements that EPA has made in the IRIS process for deriving toxicity values, particularly the shift away from choosing one study as the "best" study for deriving a toxicity value and toward deriving and graphically presenting multiple candidate toxicity values. As the program evolves, EPA will need to make the best use of the totality of evidence with increased attention to distinguishing the quality and relevance of studies for assessing human dose-response relationships. That will require EPA to develop clear criteria for judging the relative merits of individual mechanistic, animal, and epidemiologic studies for estimating human dose-response relationships. Although subjective judgment remains an inherent feature of deriving toxicity values, EPA should develop formal methods for combining the results of multiple studies and selecting the final IRIS values with an emphasis on achieving a transparent and replicable process. EPA could also improve documentation of dose-response information by clearly presenting two dose-response values: a central estimate (such as a maximum likelihood estimate or a posterior mean) and a lower-bound estimate for a point of departure from which a final toxicity value is derived.[2] Reporting both values provides information on statistical uncertainty, such as sampling variation, and makes available to the risk assessor the full range of information. Finally, EPA should develop guidelines for uncertainty analysis and communication in the context of IRIS to support the consistent and transparent treatment of uncertainties.

FUTURE DIRECTIONS

The committee commends EPA for the improvements that it has made in the IRIS assessment-development process and expects the revisions when completed to result in a transformation of the IRIS program. To ensure that the IRIS program provides the best assessments possible, the committee identified three broad areas on which EPA should focus attention. First, the assessment methodology will need to be updated in a continuing, strategic fashion, and EPA should develop a plan for doing so. Specifically, the agency will need to consider how methods relevant to all elements of the process will evolve and how such progress can be tracked and incorporated into the IRIS assessment-development approach. Second, EPA staff, the CASTs, and the Chemical Assessment Advisory Committee should be encouraged to identify inefficiencies in the IRIS process, which should then be addressed systematically by the IRIS program leadership. EPA should continue to pursue development of firm stopping rules for key points throughout the process to guard against delay and should consider working with other agencies to avoid duplication of effort. Third, EPA management needs to evaluate the human and technologic resources that are needed to conduct IRIS assessments and support methodologic research and the implementation of new approaches. If sufficient financial and staff resources are not available to EPA, it will not be able to continue to improve the IRIS program and keep pace with scientific advancements.

Overall, the committee finds that substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report. The NRC formaldehyde committee recognized that its suggested changes would take several years and an extensive effort by EPA staff to implement. Substantial progress, however, has been made in a short time, and the present committee's recommendations should be seen as building on the progress that EPA has already made.

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[2]The lower bound becomes an upper bound for a cancer slope factor but remains a lower bound for a reference value.