EPA's Integrated Risk Information System (IRIS) Program

Progress Report and Report to Congress

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

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The mission of the U.S. Environmental Protection Agency (EPA) is to protect human health and the environment and to ensure that all Americans are protected from significant risks to their health. EPA's Integrated Risk Information System (IRIS) Program plays an important role in helping EPA accomplish this mission through the development of human health assessments that evaluate potential health effects that may result from exposure to environmental contaminants, such as chemicals in drinking water, pollutants in air, and contaminants in soil. IRIS assessments are not regulations, but they provide a critical part of the scientific foundation for decision-making to protect public health across EPA under an array of environmental laws (e.g., Clean Air Act; Safe Drinking Water Act; Comprehensive Environmental Response, Compensation, and Liability Act). They are also an important resource for state environmental and public health agencies, and are widely used by the scientific community throughout the U.S. and the world. IRIS assessments provide high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. IRIS is the top tier source of toxicity information used by EPA to make decisions and set cleanup levels – decisions that protect against cancer and other diseases. In providing the scientific and technical basis for many activities within EPA, the IRIS Program is essential for protecting public health.

In recent years, IRIS assessments have taken longer to complete than in the past. Over time, the length and complexity of IRIS assessments have increased mirroring the increased volume and complexity of scientific information. Because of the critical importance of IRIS assessments to EPA, public health officials, industry, NGOs, and others, a strong assessment development process that produces scientifically sound products is key to providing needed health risk information in a timely and transparent manner. The Agency took steps to strengthen and streamline its IRIS Program, in response to the April 2011 recommendations by the National Academies' National Research Council (NRC) on the draft IRIS assessment of formaldehyde.[1]

In May 2014, the NRC released their review of the IRIS assessment development process,[2] which was done as a follow-up to their 2011 report. The NRC report commended EPA's efforts to improve IRIS, noting that "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." Recognizing that EPA is still implementing changes they noted that substantial progress has been made in a short time, and that "overall the committee expects that EPA will complete its planned revisions in a timely way and that the revisions will transform the IRIS Program."

Previously, EPA, as requested by Congress, has provided progress reports describing the implementation of the 2011 NRC report recommendations. In the explanatory statement accompanying the Consolidated and Further Continuing Appropriations Act, 2015, Congress directed EPA to provide a report detailing the Agency's implementation of recommendations from the 2014 NRC report (requested in House Report 113-551[3]). The language in HR 113-551 stated:

> In May 2014, the National Academy of Sciences (NAS) provided a list of high priority recommendations that can be carried out within EPA's current revisions of the program. Specifically, an emphasis on

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[1] *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. Available from - http://www.nap.edu/catalog/13142/review-of-the-environmental-protection-agencys-draft-iris-assessment-of-formaldehyde.

[2] *Review of EPA's Integrated Risk Information System (IRIS) Process.* Available from - http://www.nap.edu/catalog/18764/review-of-epas-integrated-risk-information-system-iris-process.

[3] *House Report 113-551 – Department of the Interior, Environment, and Related Agencies Appropriations Bill, 2015.* Available from - https://www.congress.gov/congressional-report/113th-congress/house-report/551/1.

> transparency; reliance on high quality studies; improved methodologies for systematic review of the literature, for evaluating evidence, and for integrating evidence across different types of scientific information; improvements in peer review; and improved program management in order to keep pace with scientific advances that need to be implemented. Therefore, the Committee directs the Agency to provide to the Committee by March 1, 2015, a report detailing how EPA will apply all of the NAS high priority reforms to pipeline projects with particular emphasis on evidence integration.

Accordingly, the purpose of this report is to update Congress, stakeholders, and the public on the status of the IRIS Program's implementation of the most recent NRC recommendations.

Transparency

IRIS assessments are developed using a robust, transparent, and public process. However, the 2011 NRC report discussed the need for additional transparency in the form of changes to the structure of IRIS assessments and also noted broadly that "consideration needs to be given to how each step of the process could be improved and gains made in transparency and efficiency." In response to the 2011 report, EPA initiated a number of activities to further increase transparency in the IRIS Program and its documents. Highlights include:

- Releasing additional preliminary materials during draft development, including the literature search and tables showing the design and results of pertinent studies;
- Establishing Bimonthly Public Science Meetings, which provide opportunities for public comment at three points prior to the release of a draft assessment for peer review;
- Expanding access at public meetings through the use of webinars that allow individuals in remote locations to fully participate in scientific discussions. Thus far, up to 160 participants have attended each meeting, with half generally participating by webinar; and
- Reorganizing the structure of IRIS assessments to have distinct *Hazard Identification* and *Dose Response* sections, a preamble that summarizes existing EPA guidance, an executive summary that summarizes the conclusions of the assessment, and increased use of evidence tables and graphical representations of the data. The volume of text also has been reduced to improve clarity.

The 2014 NRC report applauded the changes that the IRIS Program made in response to their 2011 report. For example, the NRC committee stated that the new document structure "leads to better organized and streamlined assessments and reduces redundancies," and that the "use of evidence tables and graphic displays also has reduced text volume and increased clarity and transparency." In addition to the NRC feedback, peer review reports[4] by the Science Advisory Board's (SAB) Chemical Assessment Advisory Committee (CAAC) on assessments currently under development also note improvement in the format of IRIS assessments and commend the progress made by the IRIS Program.

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[4] *Science Advisory Board Review of the IRIS Draft Toxicological Review of Trimethylbenzenes,* available at - http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f648525742400690127/ee1e280e77586de985257b65005d37e7!OpenDocument&TableRow=2.3#2.
Science Advisory Board Review of the IRIS Draft Toxicological Review of Ammonia, available at - http://yosemite.epa.gov/sab/SABPRODUCT.NSF/b5d8a1ce9b0729348525737500701 2b7/2fe334e0bec7a3cf85257b65005c500b!OpenDocument&TableRow=2.3#2.

The 2014 NRC report also encouraged EPA to "continue its efforts to develop clear and transparent processes that allow external stakeholder input early in the IRIS Process." In response to these recommendations, the IRIS Program is incorporating additional initiatives to increase transparency and continuing early involvement of stakeholders in assessment development. These activities include:

- Adding experts, identified by the NRC, to IRIS public science meetings. In October 2014, the IRIS Program announced a contract with the NRC to arrange for independent, expert input on the science underlying the development of IRIS assessments. This substantive effort to ensure a broader range of viewpoints reflects EPA's continued commitment to scientific rigor and integrity;
- Continually evaluating the format and content of materials that are discussed at public science meetings. The meeting format and accompanying materials are continuing to evolve based on stakeholder input and the IRIS Program's goal to facilitate more scientific discussion (e.g., the addition of problem formulation information to meeting materials and more focused scientific questions to guide discussion, augmenting discussant panels with independent experts identified by the NRC). The IRIS Program will continue to improve these meetings based on public feedback, as well as our own observations regarding the quality of the scientific discussion and their utility to assessment development; and
- Advancing the state-of-the-science of human health risk assessment through publicly-held workshops. The IRIS Program will hold 3-4 workshops over the next year that will cover topics that are cross-cutting, may affect multiple chemical assessments, or may concern forward-thinking topics that are expected to impact future assessments. Four topics that will be the subject of upcoming workshops include: advances in the application of systematic review in the IRIS Program; epigenetics and cumulative risk assessment; characterizing critical exposure windows in human health risk assessment; and furthering the analysis and communication of uncertainty in IRIS assessments.

In the 2014 NRC report, the committee noted the importance of transparency throughout the IRIS process. The IRIS Program anticipates the format of IRIS assessments and bimonthly meeting materials, as well as stakeholder engagement strategies, will continue to evolve based on public involvement and peer review recommendations.

Systematic Review and Study Quality Evaluation

The 2011 NRC report provided a framework for communicating the evaluation of study quality in a more systematic and transparent manner than the general practices that were being employed in the IRIS Program at that time. In response to the 2011 NRC report, the IRIS Program:

- Established procedures to develop, implement, and document comprehensive literature search strategies for all assessments;
- Held two meetings in 2013 on the implementation of systematic review (one for federal agencies and one for the general public and scientific community); and
- Began to utilize multiple approaches to evaluate study quality for epidemiological, experimental, animal, and mechanistic studies.

These developments are consistent with the recommendations in the 2014 NRC report. However, the 2014 NRC report further recommended the development of a formalized protocol to describe the

systematic review methods used in IRIS to evaluate study quality and methods for evidence integration and the description of hazard potential for noncancer endpoints. The IRIS Program agrees with these recommendations and has undertaken the following additional measures:

- Development of the 2015 draft IRIS Handbook of Operating Procedures (a revision of the draft handbook reviewed by the NRC in the 2014 report), incorporating new information regarding procedures for conducting a comprehensive literature search and evaluating epidemiology and experimental animal studies. The draft Handbook also will include a comprehensive discussion of the identification, evaluation, and use of pharmacokinetic models and of other mechanistic studies. It will provide specific information regarding components to be included in a systematic review protocol for conducting the literature search, screening for relevant studies, abstraction of results, study quality evaluation; standard procedures to be used for evidence integration will also be described (discussed in more detail below).
- Development of draft methods for evaluating study quality relating to types of bias and to the appropriateness of study design and conduct. For example, specifically for epidemiology, the domains include exposure measures, outcome measures, population selection, potential confounding, statistical analysis, selection of reported results, and sensitivity of the design (i.e., the ability to detect a difference if a difference exists). For experimental animal studies, the domains include test animal selection, experimental design, exposure, endpoint evaluation procedures, and outcome data presentation.
- Development of case studies and comparative analyses of approaches used to evaluate epidemiology and experimental animal studies. The case studies under development use several different sets of studies covering different types of effects (e.g., neurodevelopmental, male reproduction, allergy and asthma, thyroid) and draw upon expert consultants to assist in the development and testing of specific criteria and the rating process. The outcome of this exercise will inform the selection and application of approaches in future IRIS assessments.
- Developing tools to improve the efficiency of systematic review, such as tools for reference screening, extraction and display of study methods information, evaluation of study attributes that could influence results, tabular and graphical display of study results, and calculation of statistical significance testing and trend tests within and across studies.
- Plans for annual workshops on systematic review, highlighting advances in methods and harmonization across approaches. IRIS is working with representatives from the National Toxicology Program (Office of Health Assessment and Translation and Report on Carcinogens), Navigation Guide, and international groups to exchange developments in the application of systematic review to environmental health.

Moving forward, the IRIS Program is committed to building on the efforts outlined above and to demonstrate leadership in the field of systematic review and to ensure that the methods and principles that are being adopted are refined and validated.

Evidence Integration

The IRIS Program uses EPA's five-tier system for classifying cancer hazards (*carcinogenic to humans, likely to be carcinogenic,* etc). EPA has not formally developed a similar system for evaluating other health outcomes and past assessments have not necessarily been consistent in describing the strength of the evidence for effects other than cancer.

In 2011, the NRC recommended that the IRIS Program develop uniform language to describe strength of evidence on noncancer effects. In response, the IRIS Program now provides an explicit hazard statement for each noncancer effect. Recent assessments have begun to standardize the terms used to describe strength of evidence. For example, the draft assessment for benzo[a]pyrene uses the terms *human hazard, potential human hazard,* or *does not support a potential human hazard* to describe the conclusions for each noncancer health outcome.

In May 2014, the NRC recognized these improvements and offered options for moving forward, suggesting that the EPA consider which approach best fits the IRIS Program. The IRIS Program promptly convened a public science workshop on the NRC recommendations in October 2014, with systematic integration of evidence streams as a major topic. The IRIS Program asked workshop participants to compare the relative merits of alternative approaches and to discuss lessons learned from experience at other health agencies. A major point of discussion during this workshop was the use of a guided-expert-judgment process compared to a structured process (e.g., GRADE) as a framework for evidence integration. Many of the speakers rejected a dichotomy between the two frameworks, referring to a "structured judgment" approach that may best suit IRIS. The IRIS Program is examining existing methodologies and how they might be used in the development of assessments. It is likely that the IRIS Program will ultimately utilize a process that combines elements of expert judgment with a more structured approach.

Building on the NRC's recommendations and on the workshop, the IRIS Program is considering development of a hazard classification system that describes the strength of each evidence stream using uniform terms and then integrates the human, animal, and mechanistic evidence into an overall evaluation for each health outcome. This is intended to promote transparency, clarity, and consistency across assessments.

Peer Review

Rigorous, independent peer review is a cornerstone of the IRIS Program. In the past, peer reviews were accomplished through the SAB, a contractor-organized, independent review, or in rare cases, a review by the NRC. All peer reviews, regardless of reviewing body, included public comment periods, and the revised assessments included an appendix that documented how peer review and public comments were addressed.

In 2013, EPA announced improvements to its conflict of interest review process for contractor-organized peer reviews. The same year, EPA's SAB announced the formation of the CAAC, to review IRIS assessments. As a standing committee of the SAB, the CAAC offers consensus advice for Agency consideration as well as overlapping membership for greater consistency across assessments. EPA expects that the vast majority of IRIS assessments will be reviewed by the CAAC.

The establishment of the CAAC is consistent with the NRC committee's observation in its 2014 report that there needs to be "continuing and consistent expert oversight of individual assessments and the overall IRIS program," but they also noted that the CAAC also might be utilized for input on issues earlier in assessment development. The CAAC is currently reviewing four draft assessments (ammonia, 1,2,3-, 1,2,4- and 1,3,5-trimethylbenzene, ethylene oxide, and benzo[a]pyrene). Additionally, in direct response to the NRC's advice to consider how the CAAC's input might be expanded beyond formal review of draft assessments, the IRIS Program is evaluating how best to engage the CAAC to provide

advice on the 2015 draft IRIS Handbook and on cross-cutting scientific issues associated with assessments.

Program Management

The 2014 NRC report encouraged EPA to consider developing a strategic plan for the IRIS Program that allows it sufficient versatility to keep pace with cutting-edge scientific advances (e.g., next generation risk assessment methodologies) that may need to be incorporated in the program. As EPA addresses the recommendations in the 2011 and 2014 reports, it also is considering how best to incorporate advances in science. Below are planned and ongoing initiatives to help the IRIS Program be more responsive to emerging science.

- The IRIS Program is committed to holding public science workshops to provide enhanced input from the scientific community. These workshops, as discussed above, may focus on the state-of-the science for a given chemical, or on a cross-cutting scientific issue. In both cases, they provide the latest information from scientific experts that will directly inform the development of assessments.
- The IRIS Program is working with EPA program offices and regions to archive a number of IRIS entries for pesticides that have been assessed more recently by EPA's Pesticides Program. The IRIS Program announced in 2004[5] that chemicals that are solely used as pesticides would not be re-assessed. Web links to the more recent assessments will be provided.
- The IRIS Program is developing a process to update and maintain finalized IRIS assessments that do not require a full reassessment but may warrant reevaluation due to the availability of significant new research or methods after the existing assessment was completed.
- The 2014 NRC report observed that increased capacity, in the form of staff and financial resources, is needed for the IRIS Program to further improve how it develops its assessments and implements new approaches. EPA is planning to increase the capacity of the IRIS Program through a focused hiring effort aimed at recruiting highly-qualified scientific staff and managers to join the IRIS Program.
- The major challenge in environmental health risk assessment is that we do not have the tools to assess toxicity in a manner that is efficient, with respect to time and cost. Current approaches take two to five years to conduct and analyze, and cost two to six million dollars per chemical. Furthermore, available animal models used in traditional toxicity testing methods provide little or no information on possible mechanisms of action, and they are not sensitive in the low dose range characteristic of ambient environmental exposures. Also, the relevance of the result to human risk assessment can be uncertain. Given the large number of chemicals in commercial use in the United States, new test methods are needed that are faster, cheaper, and are more relevant for human risk assessment with respect to mechanisms of action and exposure levels. To address this need in environmental health risk assessment, EPA developed, with strong endorsement by the National Academy of Sciences, the National Center for Computational Toxicology in 2005. The Center has been very effective in integrating chemistry, computer technology, and molecular biology to develop automated, high-throughput approaches to assess the toxicity of chemicals using human cell lines and low dose exposures. The health assessors in NCEA are collaborating with researchers in the Computational Toxicology Center to see how the tools and approaches can be used to increase the productivity of the IRIS Program. The present

[5] Announced in the 2004 IRIS agenda – http://edocket.access.gpo.gov/2004/pdf/04-2711.pdf

thinking is that some of the approaches can be used to gain better insight into mechanisms of action and facilitate prioritization for further toxicity testing or screening. For example, EPA's Endocrine Disruptor Screening Program (EDSP) is examining the use of validated high-throughput assays and computational models to serve as alternatives for some of the currently approved assays in the EDSP Tier 1 battery.

- The IRIS Program is continuing to evolve its internal workflow structure to ensure consistency and quality are maintained during the assessment development process. The new structure has been implemented to increase productivity by ensuring that controversial scientific issues are addressed early in assessment development, the rationale for decisions have been adequately explained, and external peer review comments have been appropriately addressed. There are four inter-related groups that make up the new workforce structure: discipline-specific workgroups, the IRIS Management Council, the IRIS Science Council, and the IRIS Executive Review Committee. The mainstay of the internal workflow process is the use of scientific discipline-specific workgroups made up of staff scientists who ensure consistency, solve cross-cutting issues, and ensure the implementation of external peer review and NRC recommendations within their respective disciplines. The IRIS Management Council consists of NCEA managers whose staff work on IRIS assessments, and ensures the efficient operation of the program by making program-wide decisions about priorities and resource commitments, and shifting resources as needed across assessments and disciplinary workgroups. A newer addition to the internal workflow process is the IRIS Science Council. The Science Council consists of senior NCEA scientists, as well as the discipline-specific (e.g., epidemiology, neurotoxicology) workgroup co-chairs, and provides a venue for solving difficult, cross-cutting science or science-policy issues. The identification of research needs related to chemical-specific assessment development and the advancement of the state-of-the-science of risk assessment also are under the purview of the Science Council. The most recent addition to the workflow structure is the IRIS Executive Review Committee that is chaired by the Director of NCEA and consists of senior scientists and managers from across NCEA. This group provides a senior-level review of assessments. All assessments in the IRIS pipeline will be reviewed by the Executive Review Committee prior to public release.
- To help facilitate the coordination of scientific advances and research related to specific chemical assessments, the IRIS Program provides the public with an agenda that identifies assessments the IRIS Program will be undertaking in the next several years. With this information, the scientific community has the opportunity to initiate research that may inform the development of an IRIS assessment. In June 2014, EPA initiated an IRIS multi-year planning effort which prioritizes the chemicals on the 2012 Agenda to best meet the Agency's needs. Since that time, the IRIS Program has surveyed EPA's program and regional offices to determine their highest priority assessment needs, based on their evaluation of potential exposure and public health impact. It is anticipated that the results of this multi-year planning effort will be shared with the public as early as the first quarter of fiscal year 2016.

Assessments in the IRIS "Pipeline"

During 2014, in addition to final posting of the Libby amphibole asbestos IRIS assessment, the IRIS Program moved multiple assessments forward in the assessment development process (see table below). The number of assessments moving forward provides an indicator of productivity that will continue into 2015 and 2016.

Step in IRIS Process	Assessments
Problem formulation	
1: Draft development	Arsenic, inorganic Butyl benzyl phthalate Chromium VI Dibutyl phthalate Diethyl phthalate Di-isobutyl phthalate Di-isononyl phthalate Ethylbenzene Hexabromocyclododecane Naphthalene Polychlorinated biphenyls (PCBs; noncancer)
2: Agency Review	
3: Interagency Science Consultation	t-Butyl alcohol Ethyl tert-butyl ether (ETBE) Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)
Pre-4: Assessments released prior to the 2011 NRC report that will be re-released to step 4.	n-Butyl alcohol Formaldehyde Polycyclic aromatic hydrocarbons (PAH) relative potency factors
4: Public comment; Peer review	Ammonia (inhalation) Benzo[a]pyrene Ethylene oxide Trimethylbenzenes
5: Revise assessment	
6: Final Agency Review/Interagency Science Discussion	Vanadium pentoxide

Beginning in 2016, the IRIS Program will release scoping and problem formulation materials for new assessments identified as a high priority by Agency program and regional offices, consistent with the multi-year agenda discussed above, and will hold public meetings to seek input on those materials from the public and the scientific community. A new IRIS website, to be released in fall, 2015, will include diagrams of the existing IRIS process that will clearly indicate where the public can participate during assessment development for chemicals in the IRIS pipeline.

Consistent with the advice of the NRC, EPA has been implementing the recommendations in the 2011 NRC report using a phased approach, i.e., assessments that are in earlier stages of development will reflect more extensive changes than those further along in the process. This is necessary because it takes time for EPA to determine how best to implement various recommendations and, in some cases, to make substantive changes to existing methodologies or processes. For example, each assessment in step 4 and earlier implements principles of systematic review in response to the 2011 NRC recommendations. These assessments began with systematic and documented literature searches, evaluated pertinent studies in a uniform manner, and will base conclusions on an integration of human, animal, and mechanistic evidence. However, the degree of formality with which systematic review is implemented will differ across those assessments in the pipeline. The changes applied to a given assessment reflect the latest thinking and methods employed by the IRIS Program at that time.

Finally, while the overall goal of implementing the IRIS enhancements and NRC recommendations is to improve productivity and scientific quality in IRIS assessments, it is important that EPA also produces IRIS assessments in a timely and transparent manner. For this reason, the IRIS Program has been monitoring the time it takes for assessments to complete each step in the revised process as the July 2013 enhancements are fully implemented and several SAB CAAC peer reviews are nearing completion. An evaluation of the existing timelines will be conducted in the near future to improve the efficiency of the IRIS assessment development process. The IRIS Program is also examining its internal draft development process using the "Lean" process improvement methodology to increase program productivity, efficiency, and quality.

Conclusion

The evolving nature of science, input from the SAB CAAC, as well as frequent opportunities for stakeholder interaction provide the IRIS Program with regular feedback. In that context, it is important to acknowledge that revisions to the IRIS Program should and will continue, but that these revisions should not slow down assessments moving through the IRIS process. The NRC stated in both their 2011 and 2014 reports that some recommendations would take longer to implement than others – in some instances, an explicit recommendation was not made, but EPA was advised to evaluate approaches and identify what might work best for the IRIS Program.

In the next year, all newly started assessments will implement recommendations from the 2014 Report that address systematic review. The IRIS Program will address other recommendations over the next few years. During this timeframe, we also will continue to work with the scientific community on further improving assessment methodologies in areas such as Bayesian and other quantitative approaches to hazard identification, bringing new types of data into dose-response analysis, and communicating uncertainty and variability. As new assessments are developed, they will incorporate all the recommendations that have been fully implemented at the time the assessment is initiated.

Building on the efforts described in this report, EPA is improving scientific quality while increasing transparency and productivity in the IRIS Program. EPA values the opinions and recommendations provided by the NRC, SAB, stakeholders, and the public, and is committed to providing more high-quality assessments in a timely and transparent manner while maintaining scientific integrity. These actions will help ensure that decisions made by EPA to protect public health are based on a strong scientific foundation.