National Academy of Sciences (NAS)
Board on Environmental Studies and Toxicology
Committee to Review Advances Made to the IRIS Process
Public Workshop, 1-2 February, 2018

We welcome this opportunity to submit written comments to the National Academy of Sciences (NAS) for consideration by the Committee undertaking review of the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) program.[1] We are pleased that the Committee is reviewing the progress of the IRIS program and believe this is an important opportunity to discuss recent changes implemented by the Program, for the NAS to hear from stakeholders, and to provide beneficial feedback to IRIS.

We are a group of scientists at the University of California, San Francisco in the Program on Reproductive Health and the Environment. Our program's mission is to protect public health by creating a healthier environment for human reproduction and development. We work towards this mission by advancing scientific inquiry, clinical care, and health policies that prevent exposures to harmful chemicals in our environment-- particularly during critical time periods of life stages, such as pregnancy and child development, that can have acute and long-term adverse impacts on health. In particular, we have developed and disseminated the Navigation Guide systematic review methodology, a novel method for systematically and transparently establishing the strength of evidence of the toxicity of environmental chemicals. We have conducted substantive research and outreach about the methodology, including over 18 publications. The Navigation Guide informed the development of the method now used by the National Toxicology Program (NTP) for its decision-making about reproductive and developmental health hazards of environmental chemicals[2] and it has been cited by the NAS[3,4] as exemplary of the type of methodology EPA should use in its chemicals assessments. We declare collectively that we have no direct or indirect financial or fiduciary interest in the topics of discussion relevant to this report.

IRIS is a non-regulatory program created in 1985 to foster consistency in the evaluation of chemical toxicity across the Agency; it provides critical information and scientific expertise to identify, assess, and characterize potential health hazards of chemicals found in the environment.[5] IRIS chemical assessments support decision-making across the Agency's programs and regional offices, as well as in other federal agencies, states, localities, tribes, and international agencies. The IRIS program is considered the "gold standard" of hazard and dose-response assessment and is a vital resource to decision-makers. These independent chemical assessments have no direct regulatory impact until they are later integrated with exposure, risk characterization, or risk management (such as economic, social, legal, and technological factors)

[1] National Academy of Sciences. 2018. https://www8.nationalacademies.org/cp/meetingview.aspx?MeetingID=9674&MeetingNo=2
[2] Stephens ML, Betts K, Beck NB, Cogliano V, Dickersin K, Fitzpatrick S, Freeman J, Gray G, Hartung T, McPartland J, Rooney AA. 2016. The emergence of systematic review in toxicology. Toxicological Sciences. 152(1):10-6.
[3] National Research Council (NRC). 2014. Review of the Environmental Protection Agency's State-of-the-Science Evaluation of Nonmonotonic Dose–Response Relationships as They Apply to Endocrine Disruptors. Washington, DC: The National Academies Press. https://doi.org/10.17226/18608
[4] National Research Council (NRC). 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764
[5] US EPA. 2018. Basic Information about the Integrated Risk Information System. https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system

considerations to inform policy- and decision-making on hazardous chemicals, including the development of regulations and clean-up standards.

The IRIS program plays an important role in supporting EPA's mission of protecting public health. Critical to this mission is EPA's scientific independence, integrity and the continued support and success of the IRIS program in its current placement within the Agency.

There are several particularly noteworthy recent changes and achievements of IRIS that demonstrate the positive direction of the Program. We highlight these briefly here, and expand on these in detail further below.

1) **Current IRIS and NCEA leadership is well-positioned to ensure the success of the Program;**
2) **IRIS is seeking to utilizing collaborative approaches in adapting methodologies for use in chemical assessments;**
3) **IRIS is actively integrating transparent, objective, and state-of-the-art systematic review methods to summarize existing data on chemical toxicity from diverse evidence streams;**
4) **IRIS actively contributes to and supports specialized software programs at the forefront of leading machine learning approaches to increase the efficiency of systematic review processes that will be widely beneficial to the environmental health and systematic review community; and**
5) **IRIS is committed to including a broad set of potentially affected stakeholders.**

We strongly support the progress of the IRIS program to date and are optimistic that these advances will continue into the future, propelling the evolution of this Program to ensure the protection of human health. In support of this, we highlight several recommendations that we believe are critical to the Program's success briefly here, and expand on these in detail below.

We recommend:

1) **Fully funding the IRIS program and maintaining its current independent location within the Office of Research and Development (ORD);**
2) **IRIS' continued incorporation of scientific best practices in its process for chemical assessment, including but not limited to: the use of systematic review methodology, appropriate evaluation of study risk of bias (not numerical scoring of reporting quality), integrating primary toxicity information and health effects from animal and human studies, supported by mechanistic or other types of data, integrating recommendations to improve risk assessment, and using free and open source collaborative software to facilitate cross-Agency collaborations, communication, and public transparency;**
3) **Continued efforts to actively include a broad set of stakeholders that can inform assessments or are potentially affected by the chemicals that are being assessed, including but not limited to non-government organizations (NGOs), academics, members of the general public, tribal communities, and representatives from environmental justice communities. Stakeholders should be required to disclose financial conflicts of interest; and**

4) **EPA's selection of scientific advisors who represent support for the protection of human health and the environment, consistent with the mission of the Agency. This includes ensuring a transparent vetting process to identify financial conflicts of interest that could bias towards undervaluing the scientific evidence on health hazards of chemicals and the elimination of the directive barring experts currently receiving EPA grants from serving on EPA advisory committees.**

Furthermore, we would like to note that although we are generally supportive of opportunities for public comment and input, we also acknowledge that a more involved process with greater opportunity for review and comment is a major contributor to delays in finalizing and releasing assessments. We have seen many examples of past assessments where increased opportunity for input not only required more time, but resulted in a process that skews input received by EPA towards the regulated community, such as industry. This is a commonly-utilized delay tactic by industry and the regulated community.[6] In the interest of ensuring the timely completion of IRIS assessments, we strongly encourage the Committee to consider a recommendation of balanced public participation and input into the IRIS process that does not hinder the timeline for completing assessments.

In conclusion, we appreciate the NAS committee efforts to review the recent advances of IRIS and we are optimistic that its final report will lend support to the continuation of an independent chemical assessment program committed to incorporating best scientific practices in the evaluation of data to support chemical risk evaluations.

We appreciate the Committee's consideration of our comments, and welcome follow-up questions or comments.

Sincerely,
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[6] Natural Resources Defense Council (NRDC). 2011. The Chemical Industry Delay Game. https://www.nrdc.org/resources/chemical-industry-delay-game

Detailed Comments

NOTEWORTHY CHANGES AND ACHIEVEMENTS

There are several particularly noteworthy changes and achievements that the IRIS program has recently accomplished that demonstrate the positive direction of the Program:

1) **Current IRIS and NCEA leadership is well-positioned to ensure the success of the Program.**

The IRIS program is located within EPA's National Center for Environmental Assessment (NCEA) in the Office of Research and Development (ORD). The placement of IRIS in its non-regulatory research arm ORD is intentional, to create separation from the agency's program offices responsible for regulatory decisions so IRIS can develop impartial chemical toxicity information independent of its ultimate use by EPA's program and regional offices in risk assessments, risk management decisions, and the development of national regulations and clean-up standards.[7] This critical positioning enables NCEA's experienced and multi-disciplinary scientific teams to interact with both scientific exerts (inside and outside the Agency) at the forefront of their fields ensuring the highest level of scientific expertise as well as EPA program and regional offices that make regulatory, enforcement, and remedial actions and decisions, all while maintaining its independence.

Dr. Kristina Thayer was appointed to lead the IRIS program in January 2017. Previously, Dr. Thayer served as the director of the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT). At OHAT, Dr. Thayer spearheaded efforts to adapt and integrate state-of-the-art systematic review methodology for use in technical assessments of the potential for adverse effects on human health by chemical agents, substances, mixtures, or exposure circumstances. Similar to IRIS, OHAT assessments are typically later combined with additional information, such as current human exposure levels, to inform NTP-issued opinions on whether these substances may be of concern.[8] NTP OHAT was one of the earliest adopters of systematic review and in 2015 under Dr. Thayer's direction it completed the development of an OHAT approach to systematic review,[9,10,11] publishing a Handbook outlining its methodology[12] and protocols for several ongoing case studies implementing systematic review and systematic scoping approaches.[13]

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[7] US EPA. 2018. Basic Information about the Integrated Risk Information System. https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system

[8] U.S. Department of Health and Human Services. 2018. National Toxicology Program Reports & Publications. https://ntp.niehs.nih.gov/results/pubs/index.html

[9] Birnbaum LS, Thayer KA, Bucher JR, Wolfe MS. 2013. Implementing systematic review at the National Toxicology Program: status and next steps. Environmental health perspectives. 121(4):a108.

[10] NTP OHAT. 2015. Fact Sheet: Systematic Review. https://www.niehs.nih.gov/health/materials/systematic_review_508.pdf

[11] Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environmental health perspectives. 122(7):711.

[12] NTP OHAT. 2015. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf

[13] NTP OHAT. 2018. Ongoing Evaluations of the Office of Health Assessment and Translation. https://ntp.niehs.nih.gov/pubhealth/hat/selected/topic.html

Dr. Thayer has substantial expertise in systematic review, machine learning and automation, and chemical evaluations. In her short time at EPA, Dr. Thayer has focused on early partner and stakeholder engagement and input and implemented approaches to foster consistency across the IRIS program, increasing transparency of the IRIS review process, integrating systematic review in IRIS assessments, and modernizing the IRIS program through the utilization and supporting development of automated and machine learning software programs to expedite systematic review and incorporation of emerging data types. With time, we anticipate that Dr. Thayer will continue to propel the Program forward with the adaptation of methodological approaches previously recommended by the NAS and novel software that will ensure the scientific rigor as well as efficiency and timeliness for completion of IRIS assessments.

Dr. Tina Bahadori was appointed to lead NCEA in January of 2017. Previously, Dr. Bahadori was the director of ORD's Chemical Safety for Sustainability National Research Program. Dr. Bahadori has extensive knowledge of computational toxicology and exposure science, and has been a strong supporter of systematic review methodology and its use in the IRIS assessment process.

Collectively, Drs. Thayer and Bahadori are poised with vision and leadership that will serve the IRIS program well, in particular with their dedication to systematic review and incorporation of empirically demonstrated scientific approaches to the IRIS process of assessing chemical hazards. We strongly support their continued roles in the Agency and believe that success of the IRIS program is very promising under their leadership.

2) IRIS is seeking to utilizing collaborative approaches in adapting methodologies for use in chemical assessments.

IRIS' development and integration of systematic review methodology in its chemical assessments involves a network of leading expert collaborators from academia, clinical sciences, environmental health, domestic and international public health agencies. A few examples of these collaborators include:

- National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH)
- Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Department of Health and Human Services (DHHS)
- University of California, San Francisco (UCSF) Program on Reproductive Health and the Environment (PRHE)
- Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES)[14]
- Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE)[15]

[14] CAMARADES is a collaboration located at the University of Edinburgh in Scotland that provides a supporting framework for groups involved in the systematic review and meta-analysis of data from pre-clinical experimental animal studies. http://www.dcn.ed.ac.uk/camarades/default.htm
[15] SYRCLE is a research center located within Radboud University Nijmegen Medical Centre in Nijmegen, Netherlands that aims to develop, apply, and disseminate the methodology of systematic review of animal studies to advance responsible animal-based research

- Science in Risk Assessment and Policy (SciRAP)[16]
- The Cochrane Collaboration[17]
- Grading of Recommendations Assessment, Development and Evaluation (GRADE)[18]
- World Health Organization (WHO)/International Agency for Research on Cancer (IARC)
- Health Canada
- European Food and Safety Administration (EFSA)

These collaborations involve the sharing of health assessment or systematic review outputs, supporting the development or utilization of tools and software, evaluation and analysis of epidemiological, toxicological and mechanistic data, evidence integration, quantitative approaches, or providing/soliciting review and feedback.

Another example of IRIS' commitment to collaborative approaches to methods development for chemical assessments is a recent meeting December 16-17, 2015 on "Advancing Systematic Review for Chemical Assessment" held in Arlington, VA.[19] At this meeting, EPA IRIS solicited expertise from a wide range of sectors, including academia, government, and others to examine recent developments and applications of methods for identification, evaluation, and integration of different types of evidence (epidemiology, toxicology, and mechanistic) for use in chemical assessments (see Appendix 1: Agenda for EPA Advancing Systematic Review for Chemical Risk Assessment Meeting, December 16-17, 2015).

These collaborative approaches and interactions with external scientific experts will continue to benefit the Program as they integrate novel scientific methods into their chemical assessment processes, advance framework approaches and guidance documents outlining approaches to chemical assessment, and solicit feedback on their draft chemical assessments.

3) IRIS is actively integrating transparent, objective, and state-of-the-art systematic review methods to summarize existing data on chemical toxicity from diverse evidence streams.

The NAS has reviewed the IRIS program and its assessments several times. A 2011 NAS report reviewing the draft IRIS assessment of formaldehyde offered a number of recommendations to improve the IRIS process generally in approach, scientific methods, and presentation of information, but did not explicitly disagree with the scientific conclusion of the formaldehyde

https://www.radboudumc.nl/en/research/technology-centers/animal-research-facility/systematic-review-center-for-laboratory-animal-experimentation

[16] SciRAP is a web-based reporting and evaluation resource developed to facilitate and increase the use of academic toxicity and ecotoxicity studies in regulatory assessment of chemicals. Their intention is to bridge the gap between academic research and chemicals regulation and policy. http://www.scirap.org/

[17] The Cochrane Collaboration is a world-renowned collaboration that, for the past 20 years, has been working to develop approaches to gather and summarize the best evidence from research to make informed health decisions in the clinical field. http://www.cochrane.org/

[18] GRADE is a working group that, for the past 18 years, has worked to develop a common, sensible and transparent approach to grading quality or certainty of evidence and strengths of recommendations, predominantly for use in the clinical sciences, but use of which has recently expanded to other fields such as environmental health. http://www.gradeworkinggroup.org/

[19] US EPA. 2015. Advancing Systematic Review Workshop (December 2015). https://www.epa.gov/iris/advancing-systematic-review-workshop-december-2015

assessment.[20] Following the release of this report, IRIS undertook several active steps in response to the NAS recommendations to modify its scientific, technical, and general process, in particular through increasing transparency and implementing systematic review methodology. As a result, a 2014 NAS report reviewing the IRIS process reflected support to these changes, noting that substantial progress had been made in a short period of time, and that continuation of implementing the future planned changes, when completed, would result in a beneficial transformation of the IRIS program:

> *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*.[21]

Much of the Program's focus has been on integrating transparent, objective and state-of-the-art systematic review methods in its chemical assessment process. In particular, IRIS has focused on developing an approach that integrates systematic review methods in a pragmatic and feasible way. In this regard, IRIS has developed systematic review protocols outlining its plans for conducting assessments and specific procedures and approaches for each assessment component, designed to accommodate and integrate different evidence streams.[22,23] Further, as IRIS invests in resources and training, it will gain efficiencies in the systematic review process. We are confident that the program will continue to innovate, particularly as their location within the research arm of a government agency will ideally ensure sustainability, which is critical for maximizing efficiency. Although previous IRIS assessments have been critiqued for limitations in the assessment approach,[20] systematic review approaches and corresponding software programs hold great promise for increased efficiencies and greater consistency and transparency.

The NAS also recognized that "…it might be advantageous for EPA to build on systematic reviews that are published in the peer-reviewed literature"[24] and that "…the methods and role of systematic review and meta-analysis in toxicology are evolving rapidly and EPA will need to stay abreast of these developments, strive for transparency, and use appropriate methods to address its questions."[24] These recommendations point to the path forward for IRIS, where strategic incorporation of existing systematic reviews, particularly as they gain more recognition (and, subsequently, publications), in the environmental health field can greatly help reduce the time requirements to completing a systematic review. Furthermore, as discussed below in Point #4, IRIS is already actively seeking opportunities to utilize specialized tools and software

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[20] National Research Council (NRC). 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Washington, DC: The National Academies Press. https://doi.org/10.17226/13142

[21] National Research Council (NRC). 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764

[22] U.S. Environmental Protection Agency. 2018. Systematic Review Protocol for the IRIS Chloroform Assessment (Inhalation). https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=338653

[23] U.S. Environmental Protection Agency. 2018. A Message from the IRIS Program. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=338653

[24] National Research Council (NRC). 2017. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Pg. 157. Washington, DC: The National Academies Press. https://doi.org/10.17226/124758

programs that can greatly reduce the time and resources required to completing a systematic review. This will prove to be a critical aspect to ensure the feasibility of completing chemicals assessments in a timely manner, and also offers hope for opportunities to quickly update existing chemical assessments with the incorporation of updated scientific information as it is made available.

4) **IRIS actively contributes to and supports specialized software programs at the forefront of leading machine learning approaches to increase the efficiency of systematic review processes that will be widely beneficial to the environmental health and systematic review community.**

IRIS is committed to applying systematic review methodology approaches to chemical assessments because, among other reasons, they provide objectivity and transparency to the process of collecting, evaluating, and synthesizing scientific evidence to reach conclusions regarding the strength of the scientific evidence in support of environmental health questions.[25]

Several software programs have been developed to assist with the preparation, implementation, and maintenance of systematic reviews, such as Covidence,[26] Distiller,[27] EPPI-Reviewer,[28] RevMan,[29] and SRDR.[30] However, all of these software programs have been developed and/or utilized in fields other than environmental health—clinical sciences, healthcare research, pre-clinical animal toxicology, etc. As a result, challenges arise when utilizing such tools to a systematic review addressing questions of environmental health interest.

IRIS, predominantly as a result of the efforts of Dr. Kris Thayer, has been actively contributing to the support of more specialized software programs specifically developed for and targeting applications to systematic reviews in the environmental health fields. These include freely available and open-source software programs such as Sciome Workbench for Interactive computer-Facilitated Text-mining (SWIFT) Review[31,32] and the Health Assessment Workspace Collaborative (HAWC)[33]. These programs offer many advantages, aside from an approach tailored for environmental health assessments, including structured data extraction to promote consistency and completeness, integration with automated data-extraction tools and machine-learning capabilities to prioritize screening, web-based formats to promote and simplify team collaborations, and ability to export data files for independent analysis of findings or making data publicly available.

[25] Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environmental health perspectives. 122(7):711.
[26] The Cochrane Collaboration. 2018. Covidence. https://www.covidence.org/
[27] Evidence Partners. 2018. DistillerSR. https://distillercer.com/
[28] ePPI Centre. 2018. https://eppi.ioe.ac.uk/cms/Default.aspx?alias=eppi.ioe.ac.uk/cms/er4
[29] The Cochrane Collaboration. 2018. http://community.cochrane.org/tools/review-production-tools/revman-5
[30] Brown University Evidence-based Practice Center for the Agency on Healthcare Research and Quality (AHRQ). 2018. Systematic Review Data Repository (SRDR). https://srdr.ahrq.gov/
[31] Howard BE, Phillips J, Miller K, Tandon A, Mav D, Shah MR, Holmgren S, Pelch KE, Walker V, Rooney AA, Macleod M. 2016. SWIFT-Review: a text-mining workbench for systematic review. Systematic reviews. 5(1):87.
[32] Sciome. 2018. SWIFT-Review. http://swift.sciome.com/swift-review/
[33] HAWC. 2018. http://hawc.readthedocs.io/en/latest/

Not only will the use and further advancement of these tools benefit the IRIS program, but they carry benefits to the greater environmental health and systematic review community. The rapid development of these tools over the past several years has already enabled scientists from non-government organizations (NGOs), academia, and other sectors to carry out the steps of systematic review in a transparent, reproducible manner that reduces biases in a way that maximizes efficiency in conducting and managing the review. These benefits will also feed back to IRIS, with the availability of a greater number of systematic reviews being published and available for IRIS to adapt in its own assessments. These software tools overall greatly help to ensure transparency, helping to bridge communication between IRIS and stakeholders and increase clarity regarding the methods and criteria for selecting, evaluating, and integrating the scientific evidence in the chemical assessment.

5) IRIS is committed to including a broad set of potentially affected stakeholders.

In the NAS 2014 report, the committee praised EPA initiatives to involve stakeholders in the IRIS process earlier and more fully.[21] A recent review of the IRIS program from EPA's Science Advisory Board (SAB) noted that "...it is now standard practice for the [IRIS] program to engage stakeholders in an early scoping and problem formulation phase, thereby allowing stakeholders to provide important input at the very beginning of the process."[34]

Recent IRIS activities illustrate the dedication to encouraging the participation of diverse sets of stakeholders. An open call for stakeholder involvement[35] was one of several enhancements to help improve quality of IRIS assessments, while also helping to ensure that its assessments were resulting in products that addressed concerns of all affected stakeholders, such as workers and fence-line communities. In addition to public sessions (virtually all of which are streamed online) and oral (which are available for remote participants during public meetings) and written public comment periods, IRIS also arranged with the NAS to have independent experts attend the IRIS bimonthly public meetings to provide input on the science underlying the assessment. These public experts, speaking on their own behalf, attended the IRIS meetings to contribute to the scientific discussion amongst EPA scientists, stakeholders, and the public.[36]

We strongly support these continued efforts to actively seek and engage participation from various affected stakeholders and incorporate their concerns in IRIS assessments, as many of these stakeholders and members of the public will be the ones handling or using these chemicals and likely most impacted by their adverse health impacts. Further, the contribution of academic experts will benefit the development of IRIS' methodology as applied to these assessments, and ideally also inform the expert's own research. The balance to industry participation is also a necessity to ensure that these assessments serve the general and the most vulnerable populations which the EPA is dedicated to protecting.

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[34] U.S. EPA Science Advisory Board comments on EPA's response to recommendations on the Integrated Risk Information System. September 1, 2017. EPA-SAB-17-008. https://yosemite.epa.gov/sab/SABPRODUCT.NSF/RSSRecentAdditionsBOARD/A9A9ACCE42B6AA0E8525818E004CC597/$File/EPA-SAB-17-008.pdf

[35] U.S. EPA. 2014. A Message to IRIS Program Stakeholders: We Want to Hear From You! https://blog.epa.gov/blog/2014/06/a-message-to-iris-program-stakeholders-we-want-to-hear-from-you/

[36] U.S. EPA. 2014. National Research Council Experts—October 2014. https://www.epa.gov/iris/national-research-council-experts-october-2014

RECOMMENDATIONS

We would like to further take this opportunity to offer several recommendations that we believe are critical to the Program's success:

1) **Fully funding the IRIS program and maintaining its current independent location within the Office of Research and Development (ORD).**

We recommend IRIS remain as a program in ORD. In a recent version of the Senate FY2018 Appropriations Bill posted online by the Committee on Appropriations majority,[37] funding for IRIS is eliminated and a small fraction of its responsibilities and funding was re-allocated to the Office of Chemical Safety and Pollution Prevention (OCSPP). **We are strongly opposed to this proposal.**

As discussed earlier, the placement of IRIS in its non-regulatory research arm ORD is intentional. This creates separation from Agency regulatory decisions to allow IRIS to independently develop impartial chemical toxicity information removed from its ultimate use by EPA's program and regional offices in risk assessments, risk management decisions, and the development of national regulations and clean-up standards. This is a critical aspect of maintaining IRIS' independence and scientific integrity. A shift to OCSPP would disrupt that impartial independence, instead placing the Program within a regulatory policy office that could bias the scientific assessments.

Furthermore, we have concerns that assimilation of IRIS within OCSPP will adversely affect the IRIS program and its chemical assessments. OCSPP implements a select number of statutes, including the Toxic Substances Control Act (TSCA), and its activities over the near terms will be heavily focused on implementing TSCA, as recently amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act.[38] These activities focus on developing full risk assessments of industrial chemicals that fall under the jurisdiction of TSCA and are beholden to the statutory mandates as outlined in TSCA and the Lautenberg Amendments. In contract, IRIS only conducts the hazard identification and dose-response assessment steps of risk assessment for a broader set of chemicals used for a variety of purposes that are not covered by the particular statutes regulated within OCSPP, such as air or water pollutants. IRIS chemical assessments feed into a variety of different regulatory frameworks and contexts, and therefore it is critical that these assessments are completed in a way that support incorporation of these results into a broader context for policy and regulatory use.

Integrating IRIS into OCSPP within the offices responsible for implementing TSCA-related activities would therefore adversely affect the scope and mission of the Program, and will limit the utility of IRIS assessments. Furthermore, over the past year OCSPP has been developing TSCA chemical review procedures that contradict best practices and violate the letter and intent of the Lautenberg Amendments that have garnered sharp criticism from scientists and NGOs. Several lawsuits have been recently filed challenging OCSPP's prioritization framework rule,

[37] November 2017 Senate Appropriations Bill for FY2018. Available at https://www.appropriations.senate.gov/imo/media/doc/FY2018-INT-CHAIRMEN-MARK-BILL.PDF and Minority response: https://www.appropriations.senate.gov/news/minority/summary-fy2018-interior-environment-appropriations-chairmans-mark-released

[38] U.S.C. Title 15, Chapter 53, Subchapter I: Control of Toxic Substances

risk evaluation framework rule, inventory notification rule, and the new chemicals program framework.[39,40,41,42,43]

In light of this, we strongly recommend ensuring the continued, full funding of the IRIS program, maintaining its current location within ORD. Furthermore, given the critical concerns surrounding the frameworks and methodological approaches proposed by the TSCA program in contrast to the recent positive trajectory of IRIS for its chemical assessment process, we also recommend that other Offices within the Agency, such as OCSPP, actively seek collaborative opportunities with the IRIS program and view the IRIS' framework for systematic review and chemical assessment as a model for the Agency for other Offices and Programs to adopt.

2) **IRIS' continued incorporation of scientific best practices in its process for chemical assessment, including but not limited to: the use of systematic review methodology, appropriate evaluation of study risk of bias (not numerical scoring of reporting quality), integrating primary toxicity information and health effects from animal and human studies, supported by mechanistic or other types of data, integrating recommendations to improve risk assessment, and using free and open source collaborative software to facilitate cross-Agency collaborations, communication, and public transparency.**

A recent review of the IRIS program by EPA's Scientific Advisory Board (September 2017) reported favorably, noting that the IRIS program incorporates a number of scientific best practices in their assessment process, including appropriate evaluation of study risk of bias (not numerical scoring of reporting quality); integrating primary toxicity information and health effects from animal and human studies, supported by mechanistic or other types of data; and using free and open source collaborative software to facilitate cross-Agency collaborations, communication, and transparency.[44]

We strongly encourage IRIS to continue incorporating such scientific best practices. Of particular note is the emphasis that tools to evaluate study risk of bias (i.e., internal study validity) should not be used to generate a composite numerical quality score, as it has been well-documented that scoring can lead to bias in the evaluation of the studies.[45] There are several risk

[39] Environmental Defense Fund v. US EPA and Scott Pruitt, Administrator. 2017. Petition for Review Agency Docket No. EPA-HQ-OPPT-2016-0654.
[40] Environmental Defense Fund v. US EPA and Scott Pruitt, Administrator. 2017. Petition for Review Agency Docket No. EPA-HQ-OPPT-2016-0636.
[41] Alliance of Nurses for Health Environmental; Cape Fear River Watch; and National Resources Defense Council, Inc. v. US EPA. 2017. Petition for Review Agency Docket No. EPA-HQ-OPPT-2016-0636.
[42] Safer Chemicals Healthy Families; Alaska Community Action on Toxics; Environmental Health Strategy Center; Environmental Work Group; Learning Disabilities Association of America; Sierra Club; Union of Concerned Scientists; Union Steel, Paper and Forestry, Rubber, Manufacturing, Energy, Allied Industrial and Service Workers International Union; AFL-CIO/CLC; We Act for Environmental Justice; Asbestos Disease Awareness Organization; and Vermont Public Interest Research Group v. US EPA and Scott Pruitt, Administrator. 2017. Petition for Review Agency Docket No. EPA-HQ-OPPT-2016-0654.
[43] Inside EPA. 2018. NRDC Sues Over EPA's 'New' Chemical Framework As Groups Detail Claims. https://insideepa.com/daily-news/nrdc-sues-over-epas-new-chemical-framework-groups-detail-claims
[44] Memo from EPA Scientific Advisory Board to Administrator Pruitt, Sept 1, 2017. *Science Advisory Board comments on EPA's response to recommendations on the Integrated Risk Information System*. https://yosemite.epa.gov/sab/sabproduct.nsf/0/A9A9ACCE42B6AA0E8525818E004CC597/$File/EPA-SAB-17-008.pdf
[45] Jüni, P., Witschi, A., Bloch, R. and Egger, M., 1999. The hazards of scoring the quality of clinical trials for meta-analysis. *Jama*, *282*(11), pp.1054-1060.

of bias tools that have been developed specifically for the streams of evidence anticipated to answer environmental health questions[12,46,47] (i.e., human epidemiology and animal toxicology studies) that draw from tools that had already been developed and empirically demonstrated for decades in the clinical sciences.[48] Proof of concept case studies applying these tools to environmental health questions have repeatedly demonstrated the utility of high-quality human epidemiology studies in making determinations regarding chemical toxicity, and we encourage IRIS to similarly utilize these risk of bias tools to identify high-quality human epidemiology studies that reflect real-world exposure scenarios to assess potential resulting health outcomes.[46,47,49,50,51] Epidemiologic studies present a number of advantages in use for chemical assessment, including: the exposure-response relationships are investigated in humans, the target species, and can be studied in heterogeneous populations; they allow for the possibility to explore interactions between chemical exposure and other factors, such as genetics and lifestyle; they provide data on relevant exposure conditions and routes of exposures; and they allow for the consideration of real-world cumulative exposures to both chemical and non-chemical stressors.[56]

IRIS has been incorporating aspects of the ROBINS-E tool (Risk Of Bias In Non-randomized Studies of Exposures tool)[52] in its Risk of Bias evaluation process. We think it is more appropriate to use the risk of bias tools that have been developed and tested through the Navigation Guide[54] and NTP OHAT[11], both of which were recently highlighted in a recent NAS report demonstrating an application systematic review methods.[24] We have some concerns with a direct application of this tool for evaluating risk of bias of environmental health studies.[53] We know that IRIS has been looking at the ROBINS-E tool, and evaluating its appropriateness and it appears to be keeping up with current science in this area and incorporating an approach to evaluating epidemiological studies that appropriately acknowledges the range of quality and that well-designed epidemiological studies can provide useful information to addressing study questions. For instance, in rating risk of bias IRIS compares epidemiological studies to an "ideal" epidemiological study, which is not centered around a structured comparison of the observational studies being rated to the "ideal" randomized controlled trial (RCT). This latter approach would be problematic because it assumed that RCTs are methodologically superior and does not take into consideration which study design is best for the type of question being asked—for instance, observational studies can be the best design for answering questions aimed at assessing harm from real-world exposures that are often complex and never controlled fully by the investigator. IRIS' approach instead is a more appropriate application of the tool that aligns with other risk of

[46] Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. 2014. The Navigation Guide—evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environmental health perspectives. 122(10):1028.
[47] Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. 2014. The Navigation Guide—evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. Environmental health perspectives. 122(10):1015.
[48] Higgins JPT, Altman DJ, Sterne JAC, eds. 2011. Chapter 8: Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (Higgins JPT, Green S, eds). http://www.cochrane-handbook.org
[49] Lam J, Lanphear BP, Bellinger D, Axelrad DA, McPartland J, Sutton P, Davidson L, Daniels N, Sen S, Woodruff TJ. 2017. Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis. Environmental health perspectives. 125(8):086001-1.
[50] Johnson PI, Koustas E, Vesterinen HM, Sutton P, Atchley DS, Kim AN, Campbell M, Donald JM, Sen S, Bero L, Zeise L. 2016. Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. Environment international. 92:716-28.
[51] Lam J, Sutton P, Kalkbrenner A, Windham G, Halladay A, Koustas E, Lawler C, Davidson L, Daniels N, Newschaffer C, Woodruff T. 2016. A systematic review and meta-analysis of multiple airborne pollutants and autism spectrum disorder. PLoS One. 11(9):e0161851.
[52] University of Bristol. 2018. The ROBINS-E tool (Risk Of Bias In Non-randomized Studies—of Exposure). https://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-e/
[53] Bero L, Chartres, N. Diong, J. et al. 2018. The Risk of Bias in Observational Studies of Exposures (ROBINS-E) Tool: Theoretical and practical concerns arising from application to observational studies of exposures. Under Review. International Journal of Epidemiology.

bias tools.[54] While these adjustments may make some difference to make the ROBINS-E tool more amenable to observational studies, we still think the underlying approach is problematic and recommend that IRIS should move forward with the OHAT or Navigation Guide approach.

We recommend that IRIS not require knowledge of the mechanism or mode-of-action by which a chemical exerts its toxicity as criteria for determining toxicity. A chemical's mechanism of action or mode of action is not a requirement for science-based decision making. The benefits of hand washing in surgical suites were well described before we understood the underlying mechanism of germs. Similarly, we lack knowledge on the mechanism for the vast majority of pharmaceutical drugs, but this is not a requirement for allowing their use by millions of people.[21] The NAS agreed with this sentiment, stating that:

> *Organizing evidence around mechanism for chemicals on which only some human or animal data are available, however, seems inappropriate…Randomized clinical trials are so successful partly because they bypass the need for mechanistic information and provide an indication of efficacy. Similarly, epidemiologic studies that identify unintended effects are often credible because explanations of an observed association other than a causal effect are implausible. For example, the associations between statins and muscle damage and between thalidomide and birth defects are widely accepted as causal; mechanistic information played a minor role in the determination, if any. The history of science is replete with solid causal conclusions in advance of solid mechanistic understanding*.[21] (page 90)

We therefore instead recommend EPA consistently utilize mechanistic knowledge, when available, as a separate stream of evidence to supplement the human and animal evidence streams but only to upgrade and support evidence of toxicity, similar to how NTP OHAT incorporates mechanistic evidence in their evidence integration.[12]

We recognize that to date there is no existing standard method for assessing risk of bias for mechanistic data. NAS also recognized this in its report and encouraged EPA to advance methods in this nascent field, stating: "Although additional methodologic work might be needed to establish empirically supported criteria for animal or mechanistic studies, an IRIS assessment needs to include a transparent evaluation of the risk of bias of studies used by USEPA as a primary source of data for the hazard assessment. EPA should specify the empirically based criteria it will use to assess risk of bias for each type of study design in each type of data stream."[55] Given the import of mechanistic studies in the evidence integration phase, we strongly recommend that the criteria that EPA will use to judge the quality of mechanistic studies be explicitly stated beforehand in the form of a risk of bias assessment for this evidence stream.

Prior NAS publications have given detailed recommendations for EPA to adopt modern scientific methods and approaches, such as in *Science and Decisions*,[56] *Phthalates and*

[54] Woodruff TJ, Sutton P, Navigation Guide Work Group. 2011. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. Health affairs. 30(5):931-7.
[55] National Research Council (NRC). 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press (pg. 131). https://doi.org/10.17226/18764
[56] National Research Council (NRC). 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press. https://doi.org/10.17226/12209

Cumulative Risk,[57] and *Review of EPA's Integrated Risk Information System (IRIS) Process.*[21] These approaches have been developed and promoted by leading clinical and scientific communities, including doctors and academics in the U.S. and around the world. These publications compile a wealth of expertise and the most current state of the science that can be specifically and efficiently integrated into EPA's chemical assessments. EPA should utilize this existing knowledge and practice and not have to reinvent the wheel, but instead immediately begin incorporating these best practices and lessons learned from other government bodies. This will maximize efficiency and expedite the implementation process, allowing EPA to focus on other aspects of chemical assessment that warrant further attention. In particular, we strongly recommend IRIS incorporate the following specific scientific principles:

1. **Treat cancer and non-cancer health endpoints in a scientifically equivalent manner. Do not assume a 'threshold' response exists for non-cancer outcomes unless there is strong scientific evidence to demonstrate a threshold.** The NAS recommended a unified approach to cancer and non-cancer health assessment, based on understanding of the underlying biology and the lack of a scientific reason supporting the approach to handle the evaluation of these health endpoints differently.[56] For example, under a unified approach IRIS would develop risk estimates for non-cancer health outcomes across the spectrum of potential exposures as it does for carcinogens and not assume that a threshold exists for a chemical unless there is strong evidence documenting that one does. Currently, IRIS does not consistently develop risk estimates for non-cancer health effects. The NAS has identified this weakness, noting "… current RfD-based risk characterizations do not provide information on the fraction of the population adversely affected by a given dose or on any other direct measure or risk." This is problematic because these qualitative results "…are inadequate for benefit-cost analyses or for comparative risk analyses. MOEs and RfDs as currently defined do not provide a basis for formally quantifying the magnitude of harm at various exposure levels… A probabilistic approach to non-cancer assessment, similar to how cancer risks are expressed, would be much more useful in risk-benefit analysis and decision-making."[56] EPA should provide quantitative estimates of the potential risks posed across the range of exposure scenarios, for both cancer and non-cancer outcomes, in order to accurately capture the true value of preventing or reducing health risks. The feasibility of calculating non-cancer risk estimates has been demonstrated.[56,58,59,60]

   The NAS has also recommended use of a continuous dose-response approach that can default to a linear model, specifically recommending "linear conceptual models unless data are sufficient to reject low-dose linearity; and nonlinear conceptual models otherwise"[56] that do not assume a threshold for real world exposure levels and below. With this approach, the default is to assume that no "threshold" or "safe" level of exposure exists below which there is no harm unless strong scientific evidence exists to demonstrate otherwise. Data show that chemicals can increase the risk of many non-

[57] National Research Council (NRC). 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Washington, DC: The National Academies Press. https://doi.org/10.17226/12528
[58] Evans JS, Rhomberg LR, Williams PL, Wilson AM, Baird SJ. 2001. Reproductive and developmental risks from ethylene oxide: A probabilistic characterization of possible regulatory thresholds. Risk Analysis. 21(4):697-718.
[59] Hattis D, Baird S, Goble R. 2002. A straw man proposal for a quantitative definition of the RfD. Drug and chemical toxicology. 25(4):403-36.
[60] Woodruff TJ, Wells EM, Holt EW, Burgin DE, Axelrad DA. 2007. Estimating risk from ambient concentrations of acrolein across the United States. Environmental health perspectives. 115(3):410.

cancer health effects (such as reproductive harm and neurological effects) even at very low doses. Further, people are exposed to multiple chemicals simultaneously, many of which can increase the risk of similar adverse health outcomes. Additionally, vulnerabilities in the population may occur due to life stage, genetics, disease status, or other exogenous factors (e.g. poverty), and these vulnerabilities can contribute to adverse health outcomes. Together, these factors have the effect of lowering any potential threshold in the population that may have theoretically existed in a one-chemical-at-a-time exposure model among healthy individuals to levels of exposure that are trivial or insignificant, thereby essentially negating the existence of a "safe" threshold. In general, current science shows that the real-world scenario of simultaneous exposures to multiple chemicals at current environmental levels and even at several orders of magnitude below are unlikely to reflect a "safe threshold." IRIS' experience with BMD modeling and cancer dose-response can guide an application of these approaches to noncancer effects.

Additionally, IRIS should not use Margin of Exposure (MOE) approaches, as these are simply the point of departure (e.g., LOAELs, NOAELs or BMDLs) divided by exposure values and compared to a combination of the uncertainty factors. The MOE is not an actual estimate of risk, as it does not provide any information about the potential risk at various exposure estimates. Rather, it is another version of the "bright line" approach similar to the RfD, which the NAS recommended moving away from.[56] Furthermore, the EPA cannot conduct a benefits analysis using solely the MOE because there is no accompanying dose-response information. We strongly advise against representing the MOE as an estimate of risk and encourage EPA to utilize available analytical methods to develop quantified estimates of risk that can be more informative and useful to both risk managers and decision-makers.

2. **Assess aggregate risk and cumulative risks to ensure hazard and risk assessment reflect the reality of people's exposures.** People are simultaneously exposed to a multitude of chemicals in the real world, many of which contribute to similar adverse health effects, and they can be exposed to the same chemical through multiple exposure pathways. Not accounting for these well-documented scientific facts inherently biases EPA's assessment, in the direction of systematic underestimation of individual and population risk, which in turn undermines science-based decisions. The federal pesticide law passed in 1996 and the European framework for chemical management (REACH) require aggregate risk assessments.[61,62] Under these laws, regulators must consider all sources of possible exposure to a chemical even when only considering the risk from any one source of that chemical. Assessing "cumulative exposures," i.e., accounting for the fact that people are exposed to a multitude of chemicals simultaneously, because these exposures can have additive effects on increasing the risk of an adverse health effect, was codified in Food Quality Protection Act (FQPA) and recommended by the NAS in 2008.[61,57] This concept was expanded on in *Phthalates and Cumulative Risk* in which NAS recommended that chemicals that contribute to the same common adverse health outcome should be considered as additive to the risk.[57] While *Phthalates and Cumulative*

[61] H.R. 1627—Food Quality Protection Act of 1996. 104th Congress (1995-1996)
[62] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency.

Risk focused on the need to do this for phthalates, the NAS did not limit its recommendation to phthalates. For example, it pointed to the fact that lead and mercury can have an additive effect collectively on brain development. Biomonitoring data clearly support that people are exposed to a myriad of chemicals simultaneously—for instance NHANES data has documented that virtually 100% of pregnant women in the U.S. are simultaneously exposed to measurable levels of at least 43 different chemicals.[63] However, current EPA practices fail to consistently aggregate cancer or non-cancer risks over different exposure pathways (inhalation, ingestion, etc.). EPA should incorporate practices to consider aggregate exposures from all relevant pathways to develop risk metrics that are adequately representative of the true risks faced by the population. When data are lacking, EPA should rely on a default approach to account for all chemicals that contribute to the same common adverse health outcome considered as additive to the risk. The EPA has broached this issue in the past in their draft dioxin risk assessment, which considered the impact of background and cumulative exposure to dioxin-like compounds and the potential impact on low-dose response.[64] We recommend that EPA begin routinely incorporating these considerations in all their chemical assessments.

3. **Use science-based defaults and incorporate factors that reflect the range of variability and susceptibility in the population to ensure that risks are not underestimated.** The use of defaults is a typical component of risk assessment to handle the common issue of missing data. Historically, IRIS has relied on standard default values ("uncertainty" or "safety" factors) that have been applied across the board to various chemicals and health outcomes. However, science has since evolved and there are now more scientifically-based values that can be used when specific information is missing. For example, science has shown that developmental life stages, including the fetus, infancy, and childhood, are more vulnerable periods of exposure to chemicals. However, typical IRIS age-dependent adjustment factors account for other life stages but NOT fetal exposures. This is a critical point to address, as fetal development is the most sensitive time period of one's life and has implications for healthy development and outcomes that can persist into adulthood. IRIS should evaluate this rich body of literature to identify the most up-to-date scientific knowledge regarding human variability and susceptibility and incorporate these scientifically-based default values in their assessments when specific data are lacking. For example, the California EPA has developed child-specific risk values for chemicals (i.e., atrazine, chlorpyrifos, lead, nickel, manganese, heptachlor, etc.) that specifically address child-specific routes of exposure and differences in children's susceptibility compared to adults. IRIS should review this body of evidence and incorporate these values as appropriate.[65] Furthermore, a default guidance principle should be that animal findings are relevant to humans unless there is sufficient and compelling information to support otherwise.

[63] Woodruff TJ, Zota AR, Schwartz JM. 2011. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environmental health perspectives. 119(6):878.
[64] U.S. Environmental Protection Agency. 2004. Exposure and human health reassessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds National Academy of Sciences (NAS) review draft. U.S. Environmental Protection Agency: Washington, DC.
[65] California Environmental Protection Agency Office of Environmental Human Health Assessment. 2010. Table of all Child-Specific Reference Doses (chRDs) Finalized to Date. http://oehha.ca.gov/risk-assessment/chrd/table-all-chrds

IRIS should also incorporate the real-world experience and perspective of communities who are overburdened by pollution, environmental hazards, and social and economic stressors. These communities are exposed to a disproportionate share of pollution and subsequent adverse health impacts. These communities are often made up of people of color and lower income who are exposed to a multitude of pollution exposures that collectively increase the risk of harm, combined with synergistic effects with other health stressors in their daily lives such as limited access to quality health care.[66,67,68,69] IRIS should incorporate guidance for their risk assessments that advance environmental justice and truly protect the whole of public health by reducing environmental exposures and resulting health impacts in these overburdened communities. At a minimum, this includes updating risk assessment guidelines to account for cumulative impacts of multiple exposures and underlying vulnerabilities, in particular by incorporating alternate methods to assess risk that better capture and represent those faced by overburdened and underserved communities.

Lastly, as discussed above the utilization of open source software programs for the implementation of systematic review offers many advantages, including increased transparency for chemical assessments and the ability to export data files for independent analysis of findings or making data publically available. We strongly encourage IRIS to continue pursuing avenues to ensure transparency and active communication with the public and other stakeholders for each of its chemical assessments.

3) **Continued efforts to actively include a broad set of stakeholders that can inform assessments or are potentially affected by the chemicals that are being assessed, including but not limited to non-government organizations (NGOs), academics, members of the general public, tribal communities, and representatives from environmental justice communities. Stakeholders should be required to disclose financial conflicts of interest.**

As highlighted above, IRIS has undertaken an active role in seeking participation from various stakeholders, such as environmental groups, public health groups, other federal agencies, states, trade associations, union representatives, and academics. However, often missing from the list of participants are members of the public such as fence-line communities living near industries, processing plants, recycling facilities, or Superfund sites; other concerned members of the public, such as susceptible and vulnerable populations; occupational workers; or tribal communities. We strongly encourage IRIS to actively seek the participation and input of these groups and incorporate their concerns in their chemical assessments. These particular members

[66] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. 2011. Understanding the cumulative impacts of inequalities in environmental health: implications for policy. Health affairs. 30(5):879-87.
[67] Brulle RJ, Pellow DN. 2006. Environmental justice: human health and environmental inequalities. Annu. Rev. Public Health. 27:103-24.
[68] Payne-Sturges D, Gee GC, Crowder K, Hurley BJ, Lee C, Morello-Frosch R, Rosenbaum A, Schulz A, Wells C, Woodruff T, Zenick H. 2006. Workshop Summary: Connecting social and environmental factors to measure and track environmental health disparities. Environmental research. 102(2):146-53.
[69] Vesterinen HM, Morello-Frosch R, Sen S, Zeise L, Woodruff TJ. 2017. Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. PloS one. 12(7):e0176331.

of the population are those who will be handling, using and/or the most highly exposed to these chemicals and likely the most burdened and impacted by their adverse health impacts.

As noted by the NAS, "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."[70] IRIS' efforts to increase opportunities through stakeholder involvement included, among other things, the addition of bimonthly meetings with open registration and option for remote participation. As the NAS report predicted, these meetings are now overwhelmingly dominated by industry speakers with vested financial interests in the chemicals under assessment (as an example, see Appendix 2: Agenda for IRIS bimonthly public meeting, October 29-30, 2014). IRIS' approach to contract with the NAS to increase participation by independent scientific experts was in part an attempt to offset this imbalanced participation, a laudable approach which we fully support. However, this approach remains inadequate to address the issue of balanced participation—one significant reason being that many individuals providing comments to IRIS fail to disclose their financial ties to industry or trade associations that have clear financial and other vested interests in the topics that they are addressing in their comments. Dr. Richard Denison from the Environmental Defense Fund outlined several examples of egregious undisclosed conflicts of interest, using an example of IRIS' June 2014 bimonthly meeting.[71]

We strongly recommend that IRIS require all registrants for its meetings and submitters of comments (either oral or written) to disclose critical information regarding potential or actual conflicts of interest, including but not limited to the organization they are presenting or submitting on behalf of and any funding they have received from an organization with financial conflicts of interest for the chemical or scientific issue under discussion. As outlined by Dr. Denison,[71] there is strong support and precedent already set forth by various federal agencies[72,73] and scientific journals[74,75,76,77] that demonstrate the importance of disclosure of conflicts of interest. Disclosure of financial conflicts of interest are also routinely done in the medical education, research, and clinical practice.[78,79,80] These illustrate examples that could be adapted by IRIS to ensure the reduction of bias towards the perspective of regulated industries that have a vested interest in minimizing EPA's regulation of hazardous materials and products.

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[70] National Research Council (NRC). 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press (pg. 5). https://doi.org/10.17226/18764

[71] Environmental Defense Fund. 2014. Time to Come Clean: IRIS Needs to Required Stakeholders Attending Its Meetings to Disclose Their Conflicts of Interest. http://blogs.edf.org/health/2014/11/07/time-to-come-clean-iris-needs-to-require-stakeholders-attending-its-meetings-to-disclose-their-conflicts-of-interest/

[72] Administrative Conference of the United States (ACUS) Recommendation 2013-3, Science in the Administrative Process Item #11, pg.7. https://www.acus.gov/sites/default/files/documents/Science%20Recommendation%20APPROVED-FINAL_1.pdf

[73] U.S. Occupational Safety and Health Administration (OSHA). 2013. Proposed rule on Occupational Exposure to Respirable Crystalline Silica. 78 Fed. Reg, Sept 12, 2013, pg. 56274. https://www.osha.gov/laws-regs/federalregister/2013-10-31

[74] Nature. 2014. Full Disclosure: Regulatory Agencies Must Demand Conflict-of-Interest Statements for the Research They Use. http://www.nature.com/news/full-disclosure-1.14817

[75] Environmental Health Perspectives. 2018. https://ehp.niehs.nih.gov/instructions-to-authors/#about

[76] Toxicological Sciences. 2018. https://academic.oup.com/toxsci/pages/Conflict_Of_Interest

[77] Environmental Science & Technology. 2018. http://pubs.acs.org/page/policy/ethics/index.html

[78] Institute of Medicine. 2009. Committee on Conflict of Interest in Medical Research, Education, and Practice; Lo B, Field MJ, editors. Washington (DC): National Academies Press.

[79] Perlis RH, Perlis CS, Wu Y, Hwang C, Joseph M, Nierenberg AA. Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. American Journal of Psychiatry. 2005 Oct 1;162(10):1957-60.

[80] Lenzer J, Hoffman JR, Furberg CD, Ioannidis JP. Ensuring the integrity of clinical practice guidelines: a tool for protecting patients. BMJ: British Medical Journal (Online). 2013 Sep 17;347.

4) **EPA's selection of scientific advisors who represent support for the protection of human health and the environment, consistent with the mission of the Agency. This includes ensuring a transparent vetting process to identify financial conflicts of interest that could bias towards undervaluing the scientific evidence on health hazards of chemicals and the elimination of the directive barring experts currently receiving EPA grants from serving on EPA advisory committees.**

In general, we strongly recommend that EPA select scientific advisors who represent support for the protection of human health and the environment, consistent with the mission of the Agency, to serve on its 22 advisory committees to advise various aspects of Agency research and activities (such as the Board of Scientific Counselors (BOSC), that provide scientific advice and recommendations to ORD research programs). As such, each selected member must be transparently vetted for any financial conflicts of interest that could bias them towards undervaluing the scientific evidence on health effects from exposure to hazardous chemicals, such as those working for or financially supported by industry.

By law, EPA committees must be composed to ensure that industry bias is publicly disclosed, minimized, and eliminated if possible. The Federal Advisory Committee Act (FACA)[81] requires federal agencies to ensure the advisory committee is "in the public interest" and is "fairly balanced in terms of points of view represented and the function to be performed," and does not contain members with inappropriate special interests. We strongly encourage EPA to exclude financially conflicted members, so that committees are composed of individuals who are not beholden to the industry that funds them, and are able to provide a fair and complete review of all relevant data or issues.

We recognize, however, that there may be situations when a member of industry with financial conflicts of interest would be invited to be an EPA scientific advisor. In this event, we strongly recommend EPA strictly enforce its own disclosure and conflict policies. Effective disclosure policies play an essential role in protecting EPA and committee work products. If such interests are discovered later, it may seem that either the EPA or the individual was intentionally hiding this information from the public, thereby casting doubt on the work products, and on EPA's ability to identify conflicts and enforce its own policies. Every scientific advisor should be screened up front for potential financial COI and these should be explicitly and publicly identified to increase transparency. Declarations of financial conflicts of interest are a routine part of many scientific proceedings and conferences because of the importance of transparency. Other scientific committees (e.g., the National Academy of Sciences and Institute of Medicine) all require complete transparency of financial conflicts of interest and similar guidelines should be adopted and consistently applied by EPA.

Furthermore, a recent directive issued by EPA Administrator Scott Pruitt announced a decision to bar scientific experts currently receiving EPA grants from serving on any EPA advisory committee.[82] We are deeply troubled and concerned about the implementation[83] of this directive.

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[82] U.S. EPA. 2017. News Release: Administrator Pruitt Issues Directive to Ensure Independence, Geographic Diversity & Integrity in EPA Science Committees. https://www.epa.gov/newsreleases/administrator-pruitt-issues-directive-ensure-independence-geographic-diversity

[83] E&E News. 2017. Pruitt Sweeps More Scientists Off Advisory Panels. https://www.eenews.net/stories/1060069799

This directive undermines all EPA advisory panels by effectively purging independent academic scientists from serving on advisory boards, simply because they currently receive EPA grants. This also is a false premise, as EPA intentionally issues its grants through its extramural research program which is placed in its non-regulatory arm, ORD (similar to the placement of the IRIS program), thereby creating separation from those at EPA tasked with making funding decisions from those making regulatory decisions. Meanwhile, those employed by or receiving funding from private industry or trade associations that stand to financially gain from EPA actions are not precluded from serving on advisory committees, in spite of their apparent biases and conflicts of interest. In response, groups of scientists have filed suit against EPA challenging the directive.[84,85]

These advisory committees are critically important to ensuring the scientific integrity and focus areas of EPA. We strongly encourage the Agency to appropriately address and transparently document potential conflict of interest of advisory committee members, and to rescind its policy of barring EPA grantees from serving on these committees.

[84] Union of Concerned Scientists and Elizabeth Anne Sheppard v. Scott Pruitt. 2018. Civil Action No. 18-10129.
[85] Physicians for Social Responsibility; National Hispanic Medical Association; International Society for Children's Health and the Environment; Jos Arvai; Robyn Wilson v. Scott Pruitt. 2017. Case: 1:17-cv-02742