NATURAL RESOURCES DEFENSE COUNCIL
THE EARTH'S BEST DEFENSE

Comments to the EPA IRIS Program on the NRC Recommendations October, 2014

More information available here:
http://www.epa.gov/iris/irisworkshops/NRC_workshop/wrk_agenda.htm

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- Alaska Community Action on Toxics (Pamela Miller)
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Thank you for the opportunity to present comments. The Natural Resources Defense Council (NRDC) is a national, non-profit environmental organization of lawyers, scientists, and other professionals. NRDC presents these comments on behalf of our 1.3 million members and online activists, and on behalf of the groups and individuals listed above that have signed their support. NRDC does not have any financial interest in the topic of these comments.

The National Academy of Sciences released numerous reports recommending modernization of chemical health evaluations in the United States. Chemical evaluations, including chemical testing and risk assessment, are important because they are used to set allowable levels of human exposure. If the testing or assessments are not done right, or are done too slowly, people can become ill because legally allowable levels of chemical exposures may be unsafe based on outdated or inaccurate science or no data at all.

These comments refer to the following National Academies reports:

Science and Judgment in Risk Assessment. (1994) Washington, DC: National Academies Press.

Understanding Risk: Informing Decisions in a Democratic Society. (1996) Washington, DC: National Academies Press. (The Orange Book)

Toxicity Testing in the Twenty-first Century: A Vision and a Strategy. Committee on Toxicity and Assessment of Environmental Agents. (2007). National Academies Press, Washington D.C.

Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Committee on the Health Risks of Phthalates, National Research Council (2008). National Academies Press, Washington D.C.

Science and Decisions: Advancing Risk Assessment. (2009) National Academies Press, Washington D.C. (The Silver Book)

Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic: Interim Report. (2013) National Academies Press, Washington D.C.

Review of the EPA's Integrated Risk Information System (IRIS) Process. (2014) Washington, DC: National Academies Press.

Systematic Integration of Evidence Streams for IRIS

The NRC (2014, section 6) has recommended that the evidence-integration process consider all lines of evidence (i.e., human, animal, and mechanistic), systematically cover important determinants of strength of evidence (e.g., consistency or exposure-response gradient), use uniform language to describe the strength of evidence (e.g., "sufficient evidence" or "suggestive evidence"), and treat cancer and non-cancer outcomes in a more uniform manner. Section 6 of the NRC Review of the IRIS Process discusses two qualitative approaches for integrating evidence: guided expert judgment and structured processes.

Comments:

Stakeholder engagement must be expanded

The NRC emphasized the importance of expanding stakeholder engagement, and noted various ways that the IRIS program makes this a priority (NRC 2014, p 23). We strongly agree. This engagement should include reaching out to exposed populations, including workers and communities, early in the problem formulation stage to gather their input and ensure that their health concerns are being addressed if possible.[1] However, we recognize that there will be significant challenges due to unequal resources among stakeholders. The metric of success for IRIS should go beyond a head count of how many representatives from various perspectives are in the room, on the phone, or even submitted written comments. Success should be measured to the extent that the IRIS assessment can incorporate how impacted communities, workers, and individuals experience a hazardous exposure – realistic doses, routes of exposure, how it impacts existing (background) exposures, how health status, age, or sex alter the impact of the hazard, etc. Much of this critical information can be made available to IRIS staff if they are pro-active in engaging all stakeholders, and not just the ones that read the federal register notices or check the IRIS online calendar.

As early as 1996, an NRC committee issued what has come to be known as the “orange book”, titled, Understanding Risk: Informing Decisions in a Democratic Society. The report recommended that the participation of impacted populations in the risk analysis is likely to provide greater credibility to the

[1] Comment submitted by Tracey Woodruff to the Office of Health Assessment and Translation, National Toxicology Program Re: draft OHAT approach for systematic review and evidence integration for literature-based health assessments. June, 2013

analysis, as well as facilitate acceptance from the community, and that regulatory agencies benefit from having both technical experts and a broad spectrum of interested and affected parties. That committee noted that, "adequate risk analysis and characterization thus depend on incorporating the perspectives and knowledge of the interested and affected parties from the earliest phases of the effort to understanding the risks." (NRC 1996, p. 3) The primary goal should not be to facilitate acceptance from a community, but rather to expand the very limited purview that risk assessment affords policy-makers.

The 1996 NRC report distinguishes between "getting the science right" and "getting the right science", with the latter requiring broad participation to increase the likelihood that the technical analysis is not only correct, but also appropriate to the needs of interested and affected parties. (NRC 1996, p. 7) The NRC report also distinguishes between, "getting the right participation" and "getting the participation right", with the former noting that all important perspectives must be considered, and the latter stressing that the process must be responsive to the points raised by participants. (NRC 1996, p. 7) The NRC report concludes, "A broad and extensive analytic-deliberative process can lead to better informed and more widely acceptable decisions" (NRC 1996, p. 10).

To facilitate pro-active broad and meaningful public engagement, we strongly support the suggestion by the NRC that substantive and technical assistance for impacted communities would be a valuable and effective way to ensure engagement from under-resourced stakeholders (NRC 1996, p. 23). The inclusion of the knowledge, experience, and participation of impacted communities in a risk assessment based on publicly-available information and data is likely to increase the scientific strength of the risk assessment, increase its utility for impacted communities, and increase public confidence in final decisions based on the risk assessment.

<u>Systematic integration of evidence streams must be clear and transparent</u>

The NRC (2014) was clear that a systematic review approach is to be used. We are strongly supportive of this approach and believe that it will save the Agency resources – both time and money – by finalizing more assessments with less time defending and updating them.

However, the NRC (2014) is vague on how IRIS should evaluate the overall quality of evidence and integrate it to come up with a summary conclusion. We agree with the NRC that IRIS should develop a structured approach, providing clarity about how it will evaluate and integrate data (NRC 2014, Chapter 5 recommendations, p. 74-75).

It is important that IRIS apply the same approach for all data, including the evaluation of mechanistic or high throughput data. These data are often introduced later in the review process by industry, in an attempt to explain – or explain away – evidence of harm. IRIS can find guidance on how to treat these data from the NavGuide or NTP/OHAT approaches. (See our comments for Session 2 for our perspective on mechanistic data). In particular, it is important that IRIS subject mechanistic and high- throughput data to the same level of scrutiny and risk of bias analysis as all other data types. It is possible to misinterpret or even fake mechanistic, modelled, or other non-observational data to avoid seeing a toxic effect. There should be a very high level of scrutiny for the mechanistic, modelled, high-throughput, and other data that is less obvious to interpret than counting tumors, and possibly easier to bias.

<u>Threshold of evidence should support regulatory decisions that prevent harm</u>

There is a considerable degree of expert judgment involved in establishing the level of proof that will be required for the ultimate hazard determination. Where to set the threshold bar for evidence of harm will undoubtedly be a point of intense disagreement among stakeholders. Since EPA is charged with preventing harm to human health and the environment, that bar should be set so as to result in decisions that are health-protective and precautionary, minimizing false negatives (type I errors) and errors that lead to the underestimation of risk. For that reason it is established EPA policy that a single, well conducted study may provide evidence of toxicity or a health effect – even when the mechanism of toxicity is not well understood (there may be more than one). For example, EPA's minimum criteria for animal data for a reproductive or developmental hazard are data demonstrating an adverse reproductive effect in a single appropriate, well-executed study in a single test species. (U.S. EPA, 1996; U.S. EPA, 1991)[2] [3] It is important that IRIS apply judgment in a transparent manner consistent with a well-described systematic review framework.

The labels for the final hazard determinations should not be "causal" since scientists tend to see this language as a very high threshold or bar to achieve, requiring much more evidence than is appropriate for a public health agency charged with making regulatory decisions that prevent harm to human health and the environment. Instead, IRIS should adopt the language used by the International Agency for Research on Cancer (IARC) (known, probable, possible human carcinogens), which has a strong precedent (over 900 agents have been classified since 1971) and is well-understood by scientists and regulators world-wide.

Adapting Systematic Review Methodologies for IRIS

The National Research Council (NRC 2014, section 5) recommended that factors that can lead to bias (i.e., systematic errors that can affect the apparent outcome) be identified and consistently evaluated for individual studies considered in IRIS assessments. They noted that for many of the criteria included in available study evaluation tools, the evidence base is modest and the criteria have not been empirically tested.

Comments:

IRIS' systematic review framework will have to be adapted for *in vitro* and *in silico* data

Adapting clinical systematic review frameworks to environmental health data requires extra attention to be health protective. Unfortunately, many of the existing systematic review frameworks are meant for clinical data, and are fairly silent on how to assess data from animal studies, *in vitro* or *in silico* (computer simulation) studies, and non-clinical observational studies, which are the data that are often

[2] U.S. EPA. Guidelines for Reproductive Toxicity Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, 630/R-96/009, 1996.
U.S. EPA, Risk Assessment Forum. Guidelines for Developmental Toxicity Risk Assessment. Washington, DC, EPA/600/FR-91/001, 1991.

[3] Comment submitted by Tracey Woodruff to the Office of Health Assessment and Translation, National Toxicology Program Re: draft OHAT approach for systematic review and evidence integration for literature-based health assessments. June, 2013

available for environmental health endpoints. The IRIS program will need to be flexible and vigilant to make sure that whatever framework IRIS uses is maximizing its ability to effectively use the datasets to support decision strategies that result in improved environmental and health protections and prevention of harm, minimizing false negatives (type I errors) and errors that lead to the underestimation of risk.

GLP is not a measure of study quality

It is important for IRIS to develop a systematic review framework that measures study quality, and not just reporting quality. If the systematic framework were to only rely on reporting quality as a measure of study quality, it would favor/bias towards GLP-compliant (Good Laboratory Practice) studies, when, ironically, the GLP-compliant studies may actually be the most likely to be insensitive to health endpoints being measured. GLP is a standard for animal care and data collection required for industry laboratories in response to fraudulent practices documented in the 1970s. Industry-funded studies are required by EPA and FDA to follow GLP standards, which include specified approaches to recordkeeping to facilitate audits and reduce fraud (54 Fed. Reg. 34034. August 17, 1989). GLP requirements are not necessarily associated with higher quality research, proper study design or correct statistical analysis.[4] In most cases, GLP studies have not even undergone scientific peer-review and publication. GLP studies are most often designed to identify major toxic effects (apical effects) like cancer. The problem is that major (apical) endpoints will not be predictive or indicate early-warnings of potential toxicity leading to "major" adverse health outcomes. GLP studies don't necessarily use modern methods for evaluating chemicals and aren't designed to grapple with the problems of low- dose exposures, endocrine or hormonal effects, behavioral or learning effects, immunotoxicity, cardiotoxicity, or upstream effects like reduced sperm count or reduced anogenital distance which are predictors of infertility.[5]

The ToxRTool was developed to assess the reporting quality of a study, and is not an appropriate measure of the internal validity of in vitro studies or of risk of bias or overall study quality. The reliability categories utilized in the ToxRTool are the same as the Klimisch codes of reliability (Klimisch et al. 1997).[6] Since the Klimisch codes favor GLP compliant studies, using the ToxRTool would be subject to the same criticism as using either Klimisch codes or GLP as measures of study quality.

IRIS should not require full or raw data for a study

IRIS should contact study authors if it requires more information about a study method or findings, but not require full disclosure of the raw data. Otherwise the framework may presume "the worst" bias where authors fail to fully describe methods, which would be unfair and inaccurate in some cases. Industry's insistence that the full or raw data must be made publicly available will unfairly burden academic researchers with both time and financial costs, while shielding industry data using confidential business information claims (CBI). Goldman and Silbergeld (2012) propose other mechanisms to make data available that address concerns about transparency without unduly burdening non-industry

[4] Myers, J. P., F. S. vom Saal, et al. (2009) "Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A." Environ Health Perspect 117 (3): 309-15.
[5] Myers, J. P., F. S. vom Saal, et al. (2009) "Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A." Environ Health Perspect 117 (3): 309-15.
[6] http://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/bpaprotocoldraft.pdf

researchers.[7] Whatever IRIS chooses, it must ensure that non-industry funded research is available for IRIS assessments – we recommend contacting study authors directly in cases where IRIS staff need clarification or additional information.

Mechanistic data could upgrade the hazard classification, but should not be used to explain away hazard evidence

The IRIS systematic review framework should consider – but, not require – mechanistic data as part of the overall evaluation, but not as any more or less valuable than other evidentiary data. We agree with the NRC (2014) that mechanistic (or mode of action, MOA) data should be treated as a parallel stream of data, and can be very helpful in interpreting human and animal data or in suggesting a chemical's potential toxicity or putative mechanism (often inferred from structurally similar compounds) (NRC 2014 p. 32-33, 82).

The NRC (2014) identified various uncertainties with mechanistic data, making it inappropriate to dismiss evidence of harm in animal or human data on the basis of mechanistic data. For example, numerous hazardous materials share the same mechanism of toxicity, and a single material can have numerous mechanisms of toxicity, different mechanisms at high or low doses, differences between acute or chronic responses, or differences across species (NRC 2014 p. 83, 84). For these reasons, we strongly believe that mechanistic data should not be seen as a requirement for interpreting or evaluating other data.

However, the NRC noted that "when human data are nonexistent, are mixed, or consistently show no association and an animal study finds a positive association, the importance of mechanistic data is increased" (NRC 2014, p. 85). That is, strong evidence from mechanistic/MOA studies could support a conclusion and raise it to a level of increased concern. This is consistent with the OHAT-NTP systematic review framework.

The fact is that the mechanistic understanding of how a chemical leads to cancer often comes much later than the evidence that it does so. But when there is scientific evidence showing a statistically significant causal link between an exposure and an adverse effect, science accepts that evidence even without a full mechanistic explanation. For example, science still cannot fully explain exactly how lead damages kids' brains, but we know it does and we banned lead from house paint in 1978 and from gasoline in 1986. Congress banned PCBs long before scientists understood how they caused cancer. Since then we've learned more about the mechanism, but if we'd waited, many more kids would have had permanent lead-induced brain damage and more people would have had PCB-related cancer. Science is still exploring the mechanism of how smoking causes cancer, but we no longer allow smoking in most public places. In fact, we now know that the tobacco industry hid evidence for decades that cigarette smoking caused premature death, that tobacco was addictive, and that its own health research was a sham.[8] [9]

[7] Goldman LR, Silbergeld EK. Assuring access to data for chemical evaluations. Environ Health Perspect. 2013 Feb;121(2):149-52. http://www.ncbi.nlm.nih.gov/pubmed/23229062

[8] Cummings MK, Brown A, O'Connor R. The cigarette controversy. Cancer Epidemiol Biomarkers Prev. 2007 June;16:1070

[9] Glantz SA, Barnes DE, Bero LA, Hanauer P, Slade J. Looking through a keyhole at the tobacco industry: the Brown and Williamson documents. *JAMA 1995*;*274*:*219*–24

The chemical industry's unscientific position that no conclusion can be reached about a chemical's hazard and no regulation should take place until we fully understand the mechanism of action is a self-interested effort – based upon the precedent of the tobacco industry's historic efforts to disregard evidence, delay regulations, and deny harm.

IRIS should exclude underpowered studies that fail to find an effect (null-association), but not studies that find an effect despite being underpowered

For a continuous endpoint, the IRIS framework should determine if the study was adequately powered, and if the results are consistent across studies. If there is inconsistency across studies, and it's the underpowered studies that are showing null association, than they should be excluded from consideration. In other words, the framework should eliminate null-association studies that are inconsistent and underpowered, but not eliminate studies that may be underpowered if they do find an effect. This is because an underpowered study that fails to find an effect cannot be interpreted, but an underpowered study that finds an effect indicates that the effect is more likely to be real. As an analogy, if you reach into a haystack a few times (an underpowered study) and don't find a needle (a null study), you cannot conclude whether or not there may be needles in the haystack, whereas if you do find a needle (an underpowered study that finds an effect), there is at least one needle, and probably more, in the haystack (the effect is real). The NTP-OHAT framework incorporates this in its approach, and represents the state of the science – IRIS should adopt this into its framework as well.[10]

Risk of bias analysis

Risk of bias is only one part of evaluating overall quality of evidence. Studies may have bias, but if they have other important features (consistency of effect, very little uncertainty, etc.) they could inform the assessment and should be included in the assessment as appropriate. Bias should be a consideration, but not necessarily an eliminating factor.

NRC (2014) was clear that financial conflicts, including study sponsorship, should be considered a form of bias. The NRC wrote that:

> "Reviews of human clinical studies have shown that study funding sources and financial ties of investigators are associated with research outcomes that are favorable for the sponsors (Lundh et al. 2012). Favorable research outcomes were defined as increased effect sizes in drug-efficacy studies and decreased effect sizes in studies of drug harm. One study (Krauth et al. 2014) has demonstrated funding bias in preclinical studies of statins. Although selective reporting of outcomes is considered an important source of bias in clinical studies (Rising et al. 2008; Hart et al. 2012) and one study (Tsilidis et al. 2013) suggests that there is selective outcome reporting in animal studies of neurologic disease, further research is needed to determine the importance of

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Glantz SA, Slade J, Bero LA, Hanauer P, Barnes DE. The cigarette papers. Berkeley (CA): University of California Press; 1996.

[10] NTP Health Assessment and Translation (OHAT) Approach For Systematic Review and Evidence Integration For Literature-Based Health Assessments (78 FR 37 published February 25, 2013)

biases—for example, related to funding and selective reporting—in the animal-toxicology literature." (NRC 2014, p. 67)

We agree with the NRC that "Funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are part of an IRIS assessment" (NRC 2014 p. 75). It is included in both the GRADE and NavGuide criteria for evaluating and integrating evidence (NRC 2014 p. 94). However, we believe that, like all sources of bias, financially conflicting sources of funding should be publicly disclosed and considered in the risk of bias analysis, but should not *a priori* or in itself necessarily be an eliminating factor.

In addition to financial conflicts, IRIS should consider rights of review – even without financial conflicts – in its risk of bias analysis. That is, researchers should disclose any parties that reviewed or edited a submission if those parties had a financial or other interest in the outcome of the study. Reviewer bias can be equally or even more problematic than funder bias. For this reason, a recent OSHA proposed regulation on occupational exposure to crystalline silica requested that all commenters disclose information on funding sources and any parties that reviewed or edited the submission that may have had an interest or be affected by the results of the rulemaking.11 Medical journals are now requiring that authors verify that funders did not review or edit the final reports. For example, the International Committee of Medical Journal Editors notes that, "Agreements between authors and study sponsors that interfere with the authors' access to all of a study's data or that interfere with their ability to analyze and interpret the data and to prepare and publish manuscripts independently may represent conflicts of interest, and should be avoided."[12]

Advancing Dose-Response Analysis—Combining Multiple Studies

The NRC (2014, section 7) has recommended that EPA use formal methods for combining multiple studies to derive toxicity values in a transparent and replicable process. They further recommended that EPA develop both central estimates and bounds (lower bounds for reference values and upper bounds for cancer slope factors).

Comments:

Previous NRC reports made important recommendations for advancing risk assessments, and we raise those recommendations here for IRIS to consider when combining information from studies to develop dose-response estimates.

<u>Identify and incorporate variability in human exposure and vulnerability into health assessments, so that all people are better protected</u>

[11] Finkel A. Regulatory Transparency Should be a Two-Way Street. RegBlog. May 12, 2014. http://www.regblog.org/2014/05/12/12-finkel-regulatory-transparency/

[12] ICMJE Author Responsibilities – Conflict of Interest. http://www.icmje.org/recommendations/browse/roles-and-responsibilities/author-responsibilities--conflicts-of-interest.html

In the 2009 report, Science and Decisions: Advancing Risk Assessment, the NAS recommended that in addition to providing a more robust characterization of the population at risk, special attention should be directed to vulnerable individuals and populations that may be particularly susceptible and/or more highly exposed.

For cancer assessments, the NRC (2009) committee recommended that EPA add a factor of 25 to account for differences in median versus higher end response to carcinogens.[13] This value is not likely to fully address the full range of sensitivities, and only addresses the identifiable subpopulations among the general populations. The unknown variabilities and highest risk populations are likely unidentified and unaccounted for in these factors. The NRC pointed out that variability is distinct from uncertainty (data gaps), and each of these important issues should be addressed separately, with separate additional adjustment factors.

NRDC has more detail in our 2012 report, Strengthening Toxic Chemical Risk Assessments to Protect Human Health.[14]

<u>In assessing the risk of chemicals, incorporate information about the potential impacts of exposure to multiple chemicals. In addition, consider other factors, such as exposure to biological and radiological agents and social conditions</u>

In the 2009 report, Science and Decisions, the NRC underscored the key recommendations of the NRC Phthalates and Cumulative Risk Assessment report (2008), and added: "There is a need for cumulative risk assessments (CRA) …—assessments that include combined risks posed by aggregate exposure to multiple agents or stressors; aggregate exposure includes all routes, pathways, and sources of exposure to a given agent or stressor."[15] The NRC definition of "agent or stressor" includes not only chemicals, but also biological agents, radiologic agents, physical agents, and psychosocial stressors.[16] The committee recognized that a broad variety of factors can increase individual vulnerability to toxic chemicals, and these factors – and the variability in them across a population – need to be considered in risk assessment in order to protect public health. EPA should develop databases and scientifically-based default approaches to allow the incorporation of key non-chemical stressors in the absence of population-specific data to make the process more efficient.[17] NRDC has more detail in our 2012 report, Strengthening Toxic Chemical Risk Assessments to Protect Human Health.[18]

<u>Because the population is exposed to multiple chemicals and there is a wide range of susceptibility to chemical exposures, it cannot be presumed that exposures - even low ones - are risk free. It should therefore be assumed that low levels of exposures are associated with some level of risk, unless there are sufficient data to reject this assumption</u>

[13] Science and Decisions, p. 168.
[14] http://www.nrdc.org/health/files/strengthening-toxic-chemical-risk-assessments-report.pdf
[15] Phthalates and Cumulative Risk Assessment, p. 9-10.
[16] Phthalates and Cumulative Risk Assessment, pp. 224-229.
[17] Phthalates and Cumulative Risk Assessment, p. 236.
[18] http://www.nrdc.org/health/files/strengthening-toxic-chemical-risk-assessments-report.pdf

According to the NRC (2009), "small chemical exposures in the presence of existing disease processes and other endogenous and exogenous exposures can have linear dose response relationships at low doses".[19] In other words, although the individual response to chemicals is variable and includes thresholds, at the population level the individual variability balance out resulting in a linear dose response for the population. That is, there may be no "safe" threshold in the human population for many chemicals.

Science and Decisions recommended that agencies use the same approach for addressing risks from both cancer and non-cancer health effects (such as developmental or reproductive effects). The committee concluded that "scientific and risk management considerations both support unification of cancer and non-cancer dose response assessment approaches."[20] They called for a "unified-dose response framework" that includes a systematic evaluation of factors such as background exposures, disease processes and inherent vulnerabilities. This evaluation will inform the choice of the appropriate dose-response model. The NRC also pointed out that there are multiple differences in the population due to age, disease status, nutrition, and other factors. Due to these differences, and the fact that people are exposed to multiple chemicals, the science supports using a model that does not have an assumption of a "threshold" below which exposures cause zero risk in the population. The NRC recommended that a conceptual model be developed that is "from linear conceptual models unless data are sufficient to reject low-dose linearity; and nonlinear conceptual models otherwise."[21] In essence, the NRC (2009) recommended approach is to assume that all exposures, even low ones, are associated with some level of risk, unless there are sufficient data to reject this assumption, after accounting for background chemical exposures, biological additivity, and population variability. NRDC has more detail in our 2012 report, Strengthening Toxic Chemical Risk Assessments to Protect Human Health.[22]

The argument as to whether or not there are thresholds below which exposure to a hazardous chemicals is safe or not is a diversion from the more meaningful question of whether or not there are thresholds in the exposure range that populations experience. Industry representatives are arguing *ad nauseum* – and often with scant little scientific evidence - about whether or not a person can drown in a pool that is 1 millionth of an inch deep – when Dr. Adam Finkel points out that risk managers must determine whether reducing the depth from six to five feet will save lives.[23] We can argue about whether a regulatory intervention to reduce exposure will reduce disability, disease, or death, and whether the cost to industry or the economy is worth exposure reduction measures. But, the reality is that the debate over "small risks" misses the fact that bigger risks from toxic chemical exposures continue every day.

Advancing Dose-Response Analysis—Uncertainty Analysis

The NRC (1994; 2009; 2014, section 7) distinguished between scientific uncertainty and population variability and recommended expansion and harmonization of approaches for characterizing uncertainty and variability.

[19] Science and Decisions, p. 158.
[20] Science and Decisions, p. 9.
[21] Science and Decisions, p. 144.
[22] http://www.nrdc.org/health/files/strengthening-toxic-chemical-risk-assessments-report.pdf
[23] Finkel, A. 1996. Who Is Really Crying Wolf? American Scientist, Vol 84, 491-493

Comments:

IRIS must not lose the value of timeliness in its quest for comprehensiveness

The value of the IRIS program is its ability to provide potency estimates – even in the face of uncertainty - that can be used in rapid decision-making or further refined risk assessments. To provide these in a timely way, IRIS must continue to rely on default-based values. If the IRIS program is also intending to provide more extensive, time-consuming "gold-plated" values, then it should not do so at the expense of the useful, default-based 'silver-plated' values based on existing, well-established, scientifically-accepted, and peer-reviewed methods (see comments below). Further, the "gold-plated" values should be immediately usable by regulators with no further justification. We support the comments of Dr. Adam Finkel in this regard.

Moreover, a "gold-plated" assessment should include consideration of multiple exposures, inherent vulnerabilities, background exposures, biological additivity, population variability, developmental sensitivity, and other impacts on disease outcomes. As IRIS moves towards addressing these NRC recommendations (NRC 2009), it must continue to rely on scientifically-based default assumptions to address limitations, uncertainties, and data gaps so that its assessments support regulations that protect human health and the environment, and prevent harm.

Use scientifically-based default assumptions that will protect health and prevent harm

In Science and Decisions (NRC 2009), the committee concluded that "established defaults need to be maintained for the steps in the risk assessment that require inferences".[24] Most default factors are based on data, including extensive data sets in some cases, across many chemicals; they are not purely policy, as is sometimes alleged. EPA and other agencies could update the default factors and assumptions based on the best current science, identify where unstated or implicit assumptions are used, and replace these with explicitly stated ones. NRDC has more detail in our 2012 report, Strengthening Toxic Chemical Risk Assessments to Protect Human Health.[25]

With these recommendations the NRC is pushing EPA to "continue and expand use of the best, most current science to support or revise its default assumptions"[26] – making them stronger, rather than reducing reliance on them. In fact, the committee specifically recommended that EPA develop "clear standards for departures from defaults".[27] The committee notes that establishing, "clear criteria for departure from defaults can provide incentives for third parties to produce research" that can support alternative assumptions and over time drive more accurate assessments. Importantly, by using the established defaults more often, EPA avoids "the paralysis of having to re-examine generic information with every new risk assessment".[28] The agency should also evaluate and quantify, where possible, the impact of the uncertainty associated with the use of a default assumption, including a description of

[24] Science and Decisions, p. 7.
[25] http://www.nrdc.org/health/files/strengthening-toxic-chemical-risk-assessments-report.pdf
[26] Science and Decisions, p. 207.
[27] Science and Decisions, p. 199.
[28] Science and Decisions, p. 191.

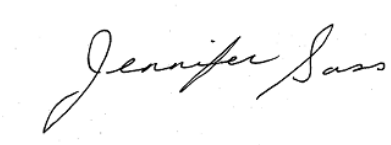
how use of the default, versus the chosen alternative assumption, impacts the decisions that protect the environment and public health.

Whatever framework IRIS develops for its systematic review, it should clearly support the use of established defaults to protect human health and the environment and to prevent harm, in accordance with EPA's guidelines.

Members of the SAB CAAC should be evaluated for conflicts

We are concerned that the IRIS program has established a Chemical Assessment Advisory Committee (CAAC) under its Scientific Advisory Board (SAB) for the purposes of consulting it on chemical-specific and broader issues relevant to the IRIS chemical assessments. Worse, the NRC (2014) has encouraged use of the CAAC to solicit expert judgment and advice (NRC 2014, pp. 20, 25). We believe this may introduce a financial bias because the SAB has elected to evaluate the impartiality of Chemical Assessment Advisory Committee (CAAC) members only in relation to their committee work on specific chemicals. This is not appropriate and contrary to the Federal Advisory Committee Act (FACA), 5 U.S.C. app. 2, et seq. The CAAC will address broad issues, having a significant and lasting impact on future IRIS assessments. These overarching issues are of great interest to the chemical industry as a whole, including to the American Chemistry Council (ACC), the trade organization representing most corporate chemical manufacturers. By declining to consider financial and other conflicts of committee members at the outset of the CAAC's work, SAB greatly undermines its credibility. As a result of SAB's failure to properly evaluate CAAC members, the committee is likely to be "inappropriately influenced" by its members with financial conflicts.

If industry representatives have specific knowledge or expertise of value to the deliberations of a committee, then invitations to address the committee during public meetings are appropriate. However, individuals with financial conflicts should not serve as members of an SAB committee convened pursuant to FACA. While we do not impugn the integrity or qualifications of any of the CAAC members, we remain deeply concerned about certain members' potential biases and conflicts of interest, and are alarmed that a financially-conflicted advisory committee would have such an influential role in steering the development of IRIS chemical assessment approaches.[29]



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[29] Comments from NRDC to the SAB Chemical Assessment Advisory Committee (CAAC) on the IRIS program and the development of IRIS toxicological reviews April, 2013