Dr. David Dorman
Member, Committee to Review EPA's IRIS Process, National Research Council

Responses to Questions for the Record from Chairman Broun and Chairman Schweikert
"Status of Reforms to EPA's Integrated Risk Information System"

1. The NAS report appears complimentary of EPA's "trajectory" and plans. However, it is not clear which of the EPA documents reviewed by the panel have fully implemented the National Academies' 2011 recommendations or followed the approach NAS supports. Could you please provide the Committee with some examples?

Response: The NRC IRIS committee evaluated several IRIS assessments that were provided by EPA or were publically available, such as EPA's Toxicological Review of Ammonia, Toxicological Review of Methanol (Noncancer), and Toxicological Review of Trimethylbenzenes. The IRIS committee considered each assessment, particularly EPA's documentation of its implementation of the 2011 NRC recommendations that was provided as an appendix to each IRIS assessment. The committee found that implementation of the recommendations from the NRC formaldehyde report was still in process, and none of the reviewed IRIS assessments had fully implemented the 2011 NRC recommendations. However, each of the reviewed IRIS assessments included multiple elements that were consistent with the recommendations from the 2011 NRC formaldehyde report.

2. In 2011, the NAS recommended that EPA provide clear guidance guidelines for study selection. In a true systematic review, one must develop criteria in advance, and use these criteria to evaluate study quality. Is this the correct approach?

Response: It is appropriate for criteria to be established to evaluate study quality and risk of bias. That approach is consistent with the methods used by the Cochrane Collaboration and other organizations. Many different assessment tools are available, and, in some cases, tools can be developed for a specific review. As noted by the NRC IRIS committee, it is appropriate for the IRIS program to define the criteria and tools to be used to assess risk of bias as part of the protocol development process (see page 37 of the NRC report), which is defined in advance of the assessment. However, the IRIS committee recognized that assessment tools for risk of bias should be based on empirical evidence, and that information is often lacking for certain evidence streams used by the EPA IRIS program (e.g., animal and in vitro data streams).

Do the recent draft IRIS assessments that are currently undergoing review or will soon be reviewed (ammonia, trimethylbenzenes, ethylene oxide) transparently provide these criteria?

Response: A review of the EPA's Toxicological Review of Ammonia and the Toxicological Review of Trimethylbenzenes that were provided to the committee do not include a transparent description of how study quality or risk of bias would be evaluated.

Should systematic review be a priority for all draft assessments?

Response: Adoption of systematic review processes is consistent with the recommendations of the 2011 and 2014 NRC reports and is also consistent with the approaches that the IRIS program is developing. Further development of systematic review methods was viewed as a priority for the IRIS program by the 2014 NRC IRIS committee (see pages 137-138, Box 8-1).

3. What is the most significant improvement to the IRIS program, and what continues to be the most pressing challenge?

Response: The committee did not rank the improvements in any tangible way but noted that significant improvements included changes to the IRIS document structure and adoption of systematic-review principles. A pressing challenge that remains relates to EPA's development of methods for evidence integration using a qualitative structured approach or possibly quantitative approaches. Other high-priority items were identified in Box 8-1 in the 2014 NRC IRIS report.

4. Many other federal agencies – including the National Institutes of Health, OSHA, CDC, and other parts of EPA – also conduct chemical risk assessments. Could the NRC's 2014 report recommendations be applied to all federal chemical risk assessment programs, and should they?

Response: The general principles outlined in the 2014 NRC report, in particular steps up to derivation of IRIS specific toxicity values, could be broadly applied to other federal programs. Whether they should be applied represents a policy decision that is beyond the scope of the committee's work.

Further, could the recommendations in Chapter 7 of the NRC's 2011 formaldehyde report be applied to all federal chemical risk assessment programs, and should they?

Response: The general principles outlined in the 2011 NRC report could also be broadly applied to other federal programs. Whether they should be applied represents a policy decision that is beyond the scope of the committee's work.

5. To what extent does having multiple toxicity assessment sources for the same chemical present challenges for ensuring consistent risk management across the nation, and what steps has EPA taken to either minimize or explain reasons for any differences.

Response: Evaluating challenges for consistent risk management given multiple toxicity assessment sources was clearly beyond the scope of the 2014 NRC IRIS report.

6. The NRC recommends that EPA should provide technical assistance to stakeholders who don't have resources to provide input – what stakeholders did NRC have in mind?

Response: The NRC IRIS committee notes (page 23) that "even in the face of expanded transparency and enhanced stakeholder engagement, there is concern about the uneven participation of the first two principal stakeholder groups." Earlier in the NRC report (page 21) these first two stakeholder groups were broadly identified as nongovernment organizations, such as environmental advocacy groups, and the second as industrial and government entities that produce, use, and release chemicals. The committee observed that most comments submitted to the IRIS program were provided by organizations and individuals associated with the chemical industry (page 23), suggesting the need for technical assistance to nongovernment organizations, including environmental advocacy groups.

7. At the Committee's request, the EPA Inspector General issued a report last year on the use of the IRIS database by EPA program officers and regions. According to the IG's report, approximately "one-third (34 percent) of the survey respondents reported that they have used an alternative source for toxicity values when an IRIS value was available. The primary reason selected for using an alternative source was that the alternative source was more up to date with current scientific practice or information." Was the NRC panel aware of this report when it came out last year and did it factor into the panel's discussions as it determined that IRIS was substantially improving?

Response: The committee members were made aware of both the IG report and a GAO report that was critical of EPA (as summarized in Risk Policy Report - 06/11/2013 with links to the original reports). The IG report provided additional information regarding the need for increased efficiency in the IRIS process, which was discussed on pages 24-25 in the 2014 NRC IRIS report.

8. The NRC recently completed its review of the National Toxicology Program's (NTP) listing of formaldehyde in the 12th Report on Carcinogens. In its report, the panel concurred with the NTP's listing of formaldehyde as "known to be a human carcinogen," and it also found "clear and convincing" evidence of "an association between formaldehyde exposure and myeloid leukemia." This is a very different conclusion than the one found by the NRC panel in 2011 which did not find a causal link between formaldehyde exposure and leukemia. Please explain the discrepancy between the two reports, and which report should Congress view as the authoritative one on formaldehyde?

Response: This topic was beyond the scope of the 2014 NRC IRIS report. However, on the basis of my experience as a member of the 2011 NRC formaldehyde committee and as a peer reviewer of the NRC report entitled "Review of the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogen," part of the discrepancy can be explained by the statements of task and approaches of the two committees. The 2014 formaldehyde committee that reviewed the NTP's assessment was asked to independently apply the NTP's listing criteria and make an "independent listing recommendation for formaldehyde and provide scientific justification for its recommendation". In contrast, the 2011 formaldehyde committee was not asked to conduct an independent risk assessment. Per its statement of task, the 2011 formaldehyde committee was asked to "comment on the cancer weight-of-evidence narrative in the draft, developed according to EPA's 2005 Guidelines for Carcinogen Risk Assessment and answer the question, is the weight-of-evidence narrative scientifically supported?" Thus, the 2011 formaldehyde committee did ***not*** *make an independent assessment of whether a causal association existed between formaldehyde exposure and leukemia. It evaluated the evidence and methods used by EPA and concluded that EPA's conclusion of causality was not supported by EPA's narrative provided in the draft formaldehyde assessment. That conclusion was based in part by the lack of a clear framework for causal determinations. Moreover, the two programs (IRIS and NTP) use different criteria and guidelines for listing a chemical as a possible carcinogen.*