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Dr. Thomas Burke
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Mr. Lek Kadeli
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Dear Dr. Burke and Mr. Kadeli:

In the four years since the National Academy of Sciences (NAS) called for improving the scientific quality of the EPA's Integrated Risk Information System (IRIS) program, generally, and the draft IRIS Toxicological Review of Formaldehyde, specifically, we have seen little in the way of full implementation of many of those recommendations.[1] As key stakeholders, this is very frustrating. The NAS requested improvements to the overall process and approaches utilized by the entire IRIS program to evaluate scientific data and determine human health hazards. Notably, the NAS also found that EPA's assessment of formaldehyde was not consistently developed, did not sufficiently document methods to identify or evaluate relevant scientific studies, and did not integrate the lines of evidence from the available animal, human, and mechanistic data. The NAS also called EPA's formaldehyde IRIS assessment subjective and potentially problematic given the inconsistencies in the available scientific data.

Although the Agency has offered assurances to Congress that the critically needed reforms of the IRIS program are underway, we are concerned with the lack of transparency as to whether or how EPA has addressed the numerous scientific recommendations for the draft formaldehyde IRIS assessment. To date, it is still unclear what changes, if any, have been completed that should result in significant improvements to the scientific quality of IRIS assessments, in general, as well as those specific improvements that must be made to the formaldehyde assessment. Given that there has been a significant amount of formaldehyde science generated over the past several years that directly addresses the NAS recommendations, it is particularly essential that the Agency demonstrate how it has systematically evaluated and integrated the different lines of scientific evidence in a revised formaldehyde IRIS assessment.

Formaldehyde occurs naturally in living cells, and is exhaled in human breath. It also is one of the most common and extensively studied compounds in commerce. It is produced and used in the manufacture of a variety of commercial, consumer, and industrial products. Given that the 2011 NAS report identified

[1] National Academy of Sciences (NAS). National Research Council (NRC). 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. Board of Environmental Studies and Toxicology. Division of Earth and Life Sciences.

significant concerns with the EPA's draft IRIS assessment of formaldehyde, the continued credibility of the IRIS program depends on a scientifically defensible assessment developed through a fully transparent process. We are deeply concerned that a less than robust assessment could propagate unwarranted concern by the public, prompt regulatory actions that do not benefit public health, and unjustifiably disrupt commerce.

It is particularly essential that the scientific basis for the formaldehyde IRIS assessment be able to stand up to the full breadth of scientific scrutiny and critique. The revised assessment must fully and transparently implement all of the recommendations identified by the NAS for the IRIS program. Further, the revised assessment must also fully incorporate the formaldehyde specific NAS recommendations and be based on a comprehensive review of all the newly published science.

Again, we request a full update on the status of the IRIS Toxicological Review of Formaldehyde, including answers to the following key questions.

1. Is EPA still considering newly published scientific studies and evaluations for inclusion in the revised formaldehyde IRIS assessment?

    a. If so, up to what date will EPA accept newly published data for inclusion in the revised formaldehyde IRIS assessment?
    b. If not, what criteria will EPA use to determine if a new study is a "game changer" and should be evaluated for inclusion in the revised formaldehyde IRIS assessment?

2. Given that the science around formaldehyde is complex and diverse, what type of framework is the Agency using to integrate the epidemiology, toxicology and mechanistic data? What steps is EPA taking, specifically in the formaldehyde IRIS assessment, to ensure integration of the scientific literature to avoid over-reliance on any one study?

3. In 2014, EPA hosted a scientific workshop on the epidemiology studies that are relevant to the formaldehyde IRIS assessment. At that time, the Agency expressed a commitment to hold a second epidemiology workshop. Considering the significant divergent interpretations of the findings of the available formaldehyde epidemiology studies, why has EPA not conducted a second workshop? Why can't such a workshop be convened before the revised draft formaldehyde IRIS assessment is released?

4. Recognizing that many epidemiology studies are conducted on foreign populations with different work environments, dietary and nutrition habits, etc., please explain how the Agency extrapolates or adjusts those study findings to make them relevant to U.S. populations.

5. Scientists, including the National Institutes of Health (NIH) Director Francis Collins[2], are increasingly calling for replication of study findings, particularly in those instances where the findings are novel. Under what circumstances, if at all, will EPA base the establishment of risk

[2] Collins, Francis S., and Lawrence A. Tabak. "NIH plans to enhance reproducibility." Nature 505.7485 (2014): 612.

values in IRIS assessments, in whole or in part, on studies whose findings have not been replicated?

6. What 2011 and 2014[3] NAS recommendations are being applied to the revised formaldehyde IRIS assessment?

   a. When EPA is evaluating the available scientific data, what criteria is the Agency using in determining the quality and limitations of the key studies? What methods are being used to weigh, synthesize and integrate evidence to scientifically substantiate any conclusions it may draw about formaldehyde toxicity and carcinogenicity (especially leukemogenicity)?
   b. EPA has committed to the application of tools such as systematic review to identify studies to be evaluated in an IRIS assessment. While the currently available tools may help ensure the inclusion of studies, they may not address the quality of those studies. Recognizing the NAS has called for the establishment of study quality criteria, what steps has EPA taken to address that recommended reform and how will this be implemented in the revised formaldehyde IRIS assessment?

7. What steps remain in the peer review process for the revised formaldehyde IRIS assessment? Does EPA plan to submit the revised IRIS assessment to peer review by the Chemical Assessment Advisory Committee? In light of the previous engagement by the NAS and in the interests of closure with the NAS recommendations, is EPA considering asking the Academy to be the peer review body for the revised formaldehyde IRIS assessment?

Formaldehyde is one of the most commonly used building block chemicals, utilized in numerous applications. Given that the 2011 NAS report was critical of the 2010 draft IRIS Toxicological Review of Formaldehyde, we again submit it is essential that EPA take the necessary time to implement the corrective measures to ensure a scientifically sound and defensible product.

Sincerely,

Kimberly Wise White, PhD
American Chemistry Council (ACC)
Senior Director
Chemical Products & Technology Division

cc to Dr. Ken Olden and Dr. Vince Cogliano

[3] National Academy of Sciences (NAS). NRC (National Research Council). 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Board of Environmental Studies and Toxicology. Division of Earth and Life Sciences. Available at http://www.nap.edu/catalog.php?record_id=18764.