October 17, 2016

Dr. Michael Slimak
Acting Director of NCEA
U.S. Environmental Protection Agency
109 T.W. Alexander Drive
Mail Code: B243-01
Research Triangle Park, NC 27709

Dear Dr. Slimak,

In July 2016, Deputy Assistant Administrator Thomas Burke responded to an inquiry from the American Chemistry Council's Formaldehyde Panel (Panel) regarding consideration of recently published science and the Agency's application of its Stopping Rules as it develops the revised draft IRIS assessment of formaldehyde. Specifically, Dr. Burke noted the last full literature search of the published formaldehyde science was in September 2015. He further advised us that an update of that literature search would soon be completed to ensure the most recent scientific evidence informs the development of the draft assessment. The Panel has been actively engaged in sponsoring scientific studies to respond to recommendations made by the National Academy of Sciences (NAS) in its review of the previous formaldehyde IRIS draft.[1] I am writing to direct your personal attention, as the recently named Acting Director of NCEA, to those publications and to urge that they be considered and included in the forthcoming updated literature search. This information is both relevant and pertinent to EPA's formaldehyde IRIS assessment and its evaluation of potential human health risk.

The new studies provide key information for evaluating any association between formaldehyde and cancers, understanding the differences between endogenous and exogenous formaldehyde exposure, and improving the application of risk assessment approaches for quantifying risk. Per the IRIS Stopping Rules,[2] new studies can be considered for inclusion in an IRIS assessment until a few months before an assessment is released for review, and may also be included before the public peer review meeting. We have summarized the relevance and importance of these studies below and urge the Agency to include this information as it conducts a full systematic review and weight of the evidence evaluation of the formaldehyde science to draw scientifically justified conclusions. These recent articles, as well as others published since the 2011 NAS review, provide persuasive evidence that formaldehyde cannot and does not cause leukemia (including AML) in humans, as had been suggested in a few, but not most, of the older literature.

[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.
[2] IRIS Stopping Rules. Weblink: https://www.epa.gov/sites/production/files/2014-06/documents/iris_stoppingrules.pdf

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A. Checkoway, Harvey, Dell, Linda D., Boffetta, Paolo, Gallagher, Alexa E., Crawford, Lori, Lees, Peter S.J., Mundt, Kenneth A. (2015). "**Formaldehyde Exposure and Mortality Risks from Acute Myeloid Leukemia and Other Lymphohematopoietic Malignancies in the US National Cancer Institute Cohort Study of Workers in Formaldehyde Industries**" Journal of Occupational and Environmental Medicine 57(7):785-794.

The 2011 NAS review noted that when considering the data in the critical National Cancer Institute (NCI) cohort study (Beane Freeman et al. 2009) that an evaluation of the most specific diagnoses available in the epidemiological data was needed (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). These authors obtained the data from the NCI cohort study via a Technology Transfer Agreement to replicate the findings reported by Beane Freemen et al. (2009) and to conduct additional analysis of associations of specific leukemias and lymphomas, especially acute myeloid leukemia, with formaldehyde exposure. Analyses were conducted including peak exposure as defined by Beane Freeman et al. (2009), as well as using an alternative more standard definition of peak exposure. Associations of cumulative and peak formaldehyde exposures with Hodgkin's Lymphoma previously reported were replicated, as well as an association with chronic myeloid leukemia; however, the authors indicate that these associations have not been reported in other studies and are not considered plausible. No other clear associations for peak or cumulative formaldehyde exposures were observed for any other specific leukemia or lymphoma, including acute myeloid leukemia, which the authors note have been of greatest prior concern.

B. Albertini, Richard and Kaden, Debra. (2016). "**Do chromosome changes in blood cells implicate formaldehyde as a leukemogen?**" Critical Reviews in Toxicology, *in press.* (http://dx.doi.org/10.1080/10408444.2016.1211987).

The 2011 NAS review also indicated concerns with EPA's evaluation and synthesis of the lines of evidence for leukemia and specifically noted that there was a lack of support for the hypothesized modes of action for Hodgkin's lymphoma and multiple myeloma. The hypothesized modes of action include DNA damage in circulating lymphocytes that may impact hematopoietic cells or lymphoid precursors of hematopoietic stem cells that circulate to the nasal epithelium where they can be exposed to formaldehyde and then result in the development of leukemias or lymphomas. Moreover, new research published by Albertini and Kaden (2016) within the past several months focused on the critical review and integration of the available peer-reviewed literature addressing the potential genotoxicity of formaldehyde. This publication also addressed the potential involvement of chromosome changes in blood cells suggested to be key events in proposed modes of action for the development of leukemia following formaldehyde exposure as suggested by Zhang et al.[3] and colleagues.[4] EPA's 2010 draft formaldehyde IRIS assessment relied heavily on modes of action proposed by Zhang et al. Recently, both the methodology and results of these studies have been called into question (Gentry et al. 2013; Mundt et al., *in preparation*). Albertini and Kaden (2016)

[3] Zhang, L; Freeman, LE; Nakamura, J; et al. (2010b) Formaldehyde and leukemia: epidemiology, potential mechanisms, and implications for risk assessment. Environ Mol Mutagen 51:181-191.
[4] Zhang, L; Freeman, LE; Nakamura, J; et al. (2010b) Formaldehyde and leukemia: epidemiology, potential mechanisms, and implications for risk assessment. Environ Mol Mutagen 51:181-191.

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concluded that reported genetic changes in circulating blood cells do not provide convincing support for classifying formaldehyde as a leukemogen. This conclusion was based on a lack of evidence that exogenous exposures to formaldehyde alone, and specifically exposures by inhalation, induce mutations at sites distant from the portal of entry. The authors also noted that recent studies reporting changes in human bone marrow or hematopoietic precursor cells either have had confounding exposures or could not distinguish *in vivo* from *in vitro* occurrences.

C. Lai, Yongquan, Yu, Ru, Hartwell, Hadley J., Moeller, Benjamin C., Bodnar, Wanda M., and Swenberg, James A. (2016). "**Measurement of endogenous versus exogenous formaldehyde-induced DNA-protein crosslinks in animal tissues by stable isotope labeling and ultrasensitive mass spectrometry.**" Cancer Research: canres-2527.

Characterization of exogenous vs. endogenous exposures of formaldehyde is central to understanding the potential human health risk from formaldehyde. The 2011 NAS Committee reviewing the draft formaldehyde IRIS assessment explicitly noted that "An improved understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations is needed." There have been multiple studies that have been conducted since the completion of the 2010 draft formaldehyde IRIS assessment that add to the increasing evidence that exogenous formaldehyde does not move beyond the portal of entry using multiple markers of exposure (Lu et al. 2011; Moeller et al. 2011; Edrissi et al. 2013; Yu et al. 2015). Notably a publication by Lai et al. (2016) examined the formation, accumulation, and hydrolysis of DNA-protein crosslinks of both exogenous and endogenous formaldehyde. The results show that inhaled formaldehyde only reached rat and monkey noses, but not tissues distant to the site of initial contact (i.e. bone marrow or white blood cells). The research provides clear evidence that exogenous formaldehyde does not reach sites distant from the portal of entry.

D. Marsh, Gary M., Morfeld, Peter, Zimmerman, Sarah D., Liu, Yimeng, and Balmert, Lauren C. (2016). "**An updated re-analysis of the mortality risk from nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study**." Journal of Occupational Medicine and Toxicology 11, no. 1: 1.

In the 2011 NAS review of the draft formaldehyde IRIS assessment, the Committee noted limitations with the NCI studies used for dose-response and exposure analysis associated with nasopharyngeal cancer (NPC). Specifically, the Committee had concerns regarding the clustering of seven of nine NPC deaths in a single plant (Hauptman et al. 2004) and missing death reports (Beane-Freeman et al. 2009). New research published in 2016 by Marsh et al. evaluated NCI study data and the suggestion by NCI of a persistent increased mortality risk for NPC from formaldehyde exposure. The researchers used cohort data provided by NCI that was updated through 2004, and they computed rate-based standardized mortality ratios and internal cohort rate-based relative risks in relation to four formaldehyde exposure metrics (highest peak, average intensity, cumulative, and duration of exposure). Marsh et al. (2016) found little to no evidence in support of an association between formaldehyde exposure and mortality from NPC. They indicated that NCI's findings were driven primarily by anomalous findings in one study plant, were based on inappropriate regression analyses and failed to account for an important interaction structure between the plant group and the exposure

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variable. Marsh et al. (2016) also noted that the limitations in the NCI's findings prohibited a generalization of formaldehyde effects both within the NCI cohort and beyond the NCI cohort. The Marsh et al. (2016) findings cast considerable additional uncertainty regarding the validity of NCI's conclusions regarding an association between NPC and formaldehyde.

E. Starr, Thomas B., and Swenberg, James A (2016). "**The bottom-up approach to bounding potential low-dose cancer risks from formaldehyde: an update**." Regulatory Toxicology and Pharmacology 77: 167-174.

The 2011 NAS Committee encouraged EPA to consider the use of alternative extrapolation models for the analysis of cancer data. Another recent paper by Starr and Swenberg (2016) improves a previously proposed method (Starr and Swenberg 2013). This approach has useful applications for substances, like formaldehyde, where there is a substantial endogenous exposure in potential target tissues and little or no empirical evidence of a positive dose-response at low exogenous exposure levels. The "bottom up" approach in the Starr and Swenberg paper uses background cancer risk estimates from available formaldehyde data, endogenous and exogenous DNA adducts measurements in relevant target tissues, and metabolism information to quantify potential risk. It provides valid bounding estimates of added risk from exposure to all airborne formaldehyde concentrations up to and including 2 ppm.

F. Van Landingham, Cynthia, Mundt, Kenneth A., Allen, Bruce C., and Gentry, P. Robinan (2016). "**The Need for Transparency and Reproducibility in Documenting Values for Regulatory Decision Making: The Example of Formaldehyde.**" Regulatory Toxicology and Pharmacology (accepted with minor revisions), August, 2016

The 2011 NAS Committee noted many uncertainties in the approach used in the IRIS document to estimate risk values, recommending that an independent analysis of the dose-response models be conducted to confirm the degree to which the models fit the data appropriately, as well as consider the use of alternative extrapolation models for the analysis of the cancer data. This manuscript documents the methods and results of an attempt to duplicate the IRIS (2010) unit risk values, as well as conduct alternate and independent analyses to address questions raised by NAS (2011).

G. D. L. Morgan, D. Dixon, M. P. Jokinen, D. H. King, H. Price, G. Travlos, R. A. Herbert, J. E. French, M. P. Waalkes. **Evaluation of a potential mechanism for formaldehyde-induced leukemia in C3B6.129F1-Trp53tm1Brd mice.** 2014 Society of Toxicology Annual Meeting, Poster Board -129. and D. L. Morgan, D. Dixon, M. P. Jokinen, D. H. King, H. Price, G. Travlos, R. A. Herbert, J. E. French, and M. P. Waalkes. **Evaluation of a potential mechanism for formaldehyde-induced leukemia in p53-haploinsufficient mice.** 2015 Society of Toxicology Annual Meeting, Abstract #1637.

Scientists at the National Institute of Environmental Health Sciences (NIEHS) have conducted research to explore the mode of action for leukemia in mice exposed to formaldehyde. The research, conducted in mice genetically predisposed for leukemia, found that formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia in these genetically predisposed mice. This

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research was presented at the 2014 and 2015 Society of Toxicology meetings and in 2015 the Panel formally requested that NIEHS work to publish the research in a peer reviewed scientific journal. We have learned from the study authors that the work, while submitted, has not yet been accepted by a journal for publication. We believe this work is important to understanding the mode of action for formaldehyde and informing the EPA's formaldehyde IRIS assessment. Therefore the Panel is also requesting that NIEHS make a public technical report available on the research while the decision regarding publication acceptance is pending. We urge EPA also to request access to the NIEHS technical report for use in the review of EPA's formaldehyde IRIS assessment.

The new science discussed above provides relevant and timely information regarding formaldehyde exposure and are possible "game changers" in understanding the potential for human health effects. The Panel looks forward to continuing a dialogue with the Agency on the relevant science and we would welcome the opportunity to meet with you to discuss the most recently published formaldehyde science and the EPA's planned next steps for the formaldehyde IRIS assessment.

We thank you for your consideration of this information and feel free to contact me with any questions (email: Kimberly_White@americanchemistry.com or phone: 202-249-6707).

Regards,

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American Chemistry Council (ACC)
Senior Director
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cc: Vincent Cogliano
Thomas Burke

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