June 15, 2018

Dr. Tina Bahadori
Director, NCEA
USEPA Headquarters
Ariel Rios Building
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Mail Code: 8601P
Washington, DC 20460

Re: 2018 Commentary on New Formaldehyde Studies in Trp53 Haploinsufficient Mice: Further Support for Nonlinear Risks From Inhaled Formaldehyde

Dear Dr. Bahadori:

I am writing to call to your attention a June 2018 article by C. Thompson titled: "Commentary on New Formaldehyde Studies in Trp53 Haploinsufficient Mice: Further Support for Nonlinear Risks From Inhaled Formaldehyde." The article discusses the relevance of a 2017 final report by the U. S. National Toxicology Program (NTP) that explored the potential involvement of p53 mutation in formaldehyde-induced nasal tumors and lymphohematopoietic cancers. The NTP study demonstrated that inhalation of a maximum tolerated dose of formaldehyde did not cause nasal tumors, did not cause an increased prevalence of leukemia or lymphohematopoietic cancer, and did not cause any other type of cancer in $Trp53^{+/-}$ mice. It provides additional support for utilizing a non-linear threshold model for the dose-response analysis of formaldehyde.

The commentary reinforces that the mode of action of inhaled formaldehyde must be foundational for characterizing the hazard and dose-response assessment. The 2017 NTP report adds to the overall weight of the evidence illustrating that inhaled formaldehyde is not leukemogenic. The 2017 NTP report is consistent with results from available mode of action studies demonstrating that nasal tumors observed in rodent studies following inhalation exposure to formaldehyde are limited to the nasopharyngeal region and are only associated with exposure to high concentrations of formaldehyde. Moreover, the 2017 NTP report lends further support that formaldehyde-induced nasal tumors are highly unlikely to be caused via a mutagenic mode of action as is typically assumed in linear dose-response modeling for cancer assessments.

Consideration of mode of action information is critical in establishing the biological plausibility of carcinogenicity and understanding how inhalation of formaldehyde may impact normal physiological levels and processes. The 2011 NAS report[1] called for selecting outcomes on the basis of available evidence and an understanding of mode of action. The application and integration of this information is essential to reduce uncertainty in characterizing potential human health risk from formaldehyde exposures and its importance cannot be overstated. The

[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.

Panel continues to urge the Agency to apply mode of action research as the foundation for a scientifically defensible hazard characterization and dose-response analysis for formaldehyde.

Feel free to contact me by phone Ex. 6 or email (Kimberly_White@americanchemistry.com) with any questions related to this letter. Additionally, a full copy of the commentary is attached for your reference.

Sincerely,

Kimberly Wise White, PhD
American Chemistry Council (ACC)
Senior Director
Chemical Products & Technology Division
On Behalf of the ACC Formaldehyde Panel

Cc:
Kris Thayer, Director of the Integrated Risk Information System Division
Richard Yamada, Deputy Assistant Administrator for the Office of Research and Development.
Jennifer Orme-Zavaleta, Principal Deputy Assistant Administrator for Science for the Office of Research and Development, and EPA Science Advisor

Attachment 1 – Thompson, C. M. (2018). Commentary on New Formaldehyde Studies in Trp53 Haploinsufficient Mice: Further Support for Nonlinear Risks From Inhaled Formaldehyde. Dose-Response, 16(2), 1559325818777931.