November 21, 2017

Dr. Jennifer Orme-Zavaleta
Environmental Protection Agency
Deputy Assistant Administrator for Science (principal)
EPA Science Advisor
Office of Research and Development
Mail code: 8101R
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Re: Recent and Ongoing Formaldehyde Science Relevant to Non-Linear Dose Response Modeling

Dear Dr. Orme-Zavaleta:

EPA's Integrated Risk Information System (IRIS) program has been working to revise the 2010 draft formaldehyde IRIS assessment in response to numerous substantive recommendations made by the National Academy of Sciences (NAS) in 2011.[1] Concurrently, the American Chemistry Council's Formaldehyde Panel (the Panel) has supported scientific studies and evaluations of formaldehyde that are directly responsive to key recommendations made by the NAS.

In light of your recent appointment as the Deputy Assistant Administrator for Science in the Office of Research and Development, we write to call your attention to seminal research led by Dr. James Swenberg at the University of North Carolina. Dr. Swenberg's work specifically addresses the NAS recommendation to improve the understanding of when exogenous formaldehyde exposure can alter normal endogenous formaldehyde concentrations. His research findings reconcile the divergent statements made in the published literature, and noted by the NAS, as to whether rat nasal tumors form via a threshold mode of action (MOA) and whether inhaled formaldehyde can be systemically delivered.

Dr. Swenberg's research employs an innovative ultra-sensitive analytical method that can differentiate and measure endogenous versus exogenous formaldehyde DNA adducts or protein crosslinks in tissues throughout the body. This method has been applied in studies conducted in multiple laboratory species, and has been critical in illustrating that the metabolism of inhaled formaldehyde is rapid at the portal of entry so it does not move beyond the portal of entry or reach distal sites in the body including the bone marrow and circulating blood cells.

Dr. Swenberg's recent formaldehyde related publications include:

[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.

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- Edrissi et al. 2017[2] demonstrated formation of exogenous adducts in the nasal epithelium and, to some extent, in trachea of rats, but not in distant tissues of lung, bone marrow, or white blood cells following inhalation of concentrations of 2 ppm formaldehyde for up to 28 days.
- Lai et al. 2016 [3] found exogenous formaldehyde induced DNA protein crosslinks only in the nasal tissue of rats and monkeys, but not in tissues distant to the site of initial contact.
- Yu et al. 2015[4] measured exogenous and endogenous DNA adducts in rats and monkeys and found that exogenous adducts accumulated in the rat nasal epithelium to reach steady state concentrations, with no exogenous adducts measured at tissues distant to the site of initial contact following exposure to concentrations of 15 ppm for up to 4 days. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively.
- Edrissi et al. 2013[5] found that exogenous N6-formyllysine was detected in the nasal epithelium, but was not detected in the lung, liver, or bone marrow following inhalation of concentrations up to 9.1 ppm for 6 hours.
- Lu et al. 2012[6] demonstrated that N(2)-hydroxymethyl-dG is the primary DNA adduct formed in cells following formaldehyde exposure to cells in culture. In addition, the study showed that alkylating agents induce methyl adducts at N(2)-dG and N(6)-dA positions, which are identical to the reduced forms of hydroxymethyl adducts arising from exogenous formaldehyde.
- Moeller et al. 2011[7] found that both exogenous and endogenous adducts were readily detected and quantified in the nasal tissues of groups of monkeys exposed by inhalation to 1.9 or 6.1 ppm formaldehyde for two consecutive days, with an exposure dependent increase in exogenous adducts observed. In contrast, only endogenous adducts were detectable in the bone marrow, even though ~10 times more DNA was analyzed for this tissue than for nasal tissues. These data clearly show the formation of exogenous formaldehyde adducts in nasal DNA of primates and the lack of formation of exogenous DNA adducts in the bone marrow.

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[2] Edrissi, B., Taghizadeh, K., Moeller, B.C., Yu, R., Kracko, D., Doyle-Eisele, M., Swenberg,. J.A., and Dedon, P.C. (2017). N6-Formyllysine as a Biomarker of Formaldehyde Exposure: Formation and Loss of N6-Formyllysine in Nasal Epithelium in Long-Term, Low-Dose Inhalation Studies in Rats. Chemical Research in Toxicology30(8):1572-1576.

[3] Lai, Y., Yu, R., Hartwell, H.., Moeller, B., Bodnar, W., and Swenberg, J. (2016). Measurement of endogenous versus exogenous formaldehyde-induced DNA-protein crosslinks in animal tissues by stable isotope labeling and ultrasensitive mass spectrometry. Cancer Research, 76(9): 2652-2661.

[4] Yu, R., Lai, Y., Hartwell, H. J., Moeller, B. C., Doyle-Eisele, M., Kracko, D., Bodnar, W., Starr, T., and Swenberg, J. A. (2015). Formation, accumulation, and hydrolysis of endogenous and exogenous formaldehyde-induced DNA damage. Toxicological Sciences, 146(1), 170-182.

[5] Edrissi, B., Taghizadeh, K., Moeller, B., Kracko, D., Doyle-Eisele, M., Swenberg, J., and Dedon, P. (2013). Dosimetry of N 6-Formyllysine Adducts Following [13C2H2]-Formaldehyde Exposures in Rats. Chemical Research in Toxicology. 26(10): 1421-1423.

[6] Lu, K., Craft, S., Nakamura, J., Moeller, B., and Swenberg, J. (2012). Use of LC-MS/MS and stable isotopes to differentiate hydroxymethyl and methyl DNA adducts from formaldehyde and nitrosodimethylamine. Chemical Research in Toxicology. 25(3): 664-675.

[7] Moeller, B., Lu, K., Doyle-Eisele, M., McDonald, J., Gigliotti, A., and Swenberg, J. (2011). Determination of N 2-hydroxymethyl-dG adducts in the nasal epithelium and bone marrow of nonhuman primates following 13CD2-formaldehyde inhalation exposure. Chemical Research in Toxicology. 24(2): 162-164.

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These results consistently demonstrate that formaldehyde is not systemically delivered. In addition to this research, other agencies have also sought to evaluate the potential impacts of exogenous exposures. A 2014 European Food Safety Authority (EFSA) scientific report[8] evaluated endogenous formaldehyde turnover and background levels from food sources. EFSA (2014) cited literature demonstrating steady state formaldehyde concentrations in blood of 2.6 mg/L and daily endogenous turnover of 878-1310 mg formaldehyde/kg bw/day. The EFSA evaluation found that the relative contribution of exogenous formaldehyde compared to that which is systemically produced as part of normal metabolism was negligible and illustrates the utility of conducting reality check calculations to determine if exogenous formaldehyde exposures present an appreciable risk.

To further add to the weight of the scientific evidence, the Panel is currently supporting, Dr. Swenberg's research to identify threshold levels above which exogenous formaldehyde exposure alters normal endogenous formaldehyde concentrations. Specifically, this research includes a 28 day *in vivo* (nose only) inhalation study where rats were exposed to radio-labeled formaldehyde at 0, 1, 30 or 300 ppb. Following exposures, tissue samples were collected from the nasal and upper respiratory tract, lung, bone marrow, liver, cerebrum, hippocampus, olfactory bulb, blood and plasma, for analysis. The in-life portion of the study is complete and sample analysis is underway, with results expected by the end of January 2018.

Previous scientific research has supported a threshold for formaldehyde effects and has called into question EPA's use of a linear dose-response model for the estimation of an Inhalation Unit Risk (IUR) for formaldehyde. In the 2010 draft formaldehyde IRIS assessment, EPA utilized a linear dose-response model to develop an IUR. According to the EPA's 2005 Guidelines for Carcinogen Risk Assessment, [9] the linear approach is used when there is an absence of sufficient information on MOAs for carcinogenicity or the MOA information indicates that the dose-response curve at low doses is expected to be linear. However, where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. In the case of formaldehyde, significant mechanistic data informs the formaldehyde MOA and provides evidence of an exposure threshold in the dose-response curve for carcinogenicity. The available toxicity literature provides considerable additional evidence in animals of observed thresholds for effects from formaldehyde exposure (Woutersen et al. 1989[10]; Casanova-Schmitz et al. 1984[11]; Heck et al. 1990[12]; Swenberg et al. 2013[13]; and Starr and Swenberg 2016[14]). The work currently being

[8] European Food Safety Authority (EFSA) 2014. Scientific Report. Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources. EFSA Journal. 12(2):3550.
[9] EPA Guidelines for Carcinogen Risk Assessment (March 2005).
[10] Woutersen, R.A., Garderen-Hoetmer, V., Bruijntjes, J.P., Zwart, A. and Feron, V.J. (1989). Nasal tumours in rats after severe injury to the nasal mucosa and prolonged exposure to 10 ppm formaldehyde. Journal of Applied Toxicology, 9(1): 39-46.
[11] Casanova-Schmitz, M., Starr, T.B., and Heck, H.D. (1984). Differentiation between Metabolic Incorporation and Covalent Binding in the Labeling of Macromolecules in the Rat Nasal Mucosa and Bone Marrow by Inhaled [14C] - and [3H] Formaldehyde. Toxicology and Applied Pharmacology, 76(1): 26-44.
[12] Heck, H.D., Casanova, M., and Starr, T.B. (1990). Formaldehyde Toxicity—New Understanding. Critical Reviews in Toxicology, 20(6): 397-426.
[13] Swenberg, J.A., Moeller, B.C., Lu, K., Rager, J.E., Fry, R. and Starr, T.B. (2013). Formaldehyde Carcinogenicity Research: 30 Years and Counting for Mode of Action, Epidemiology, and Cancer Risk Assessment. Toxicologic Pathology, 41(2): 181-189.

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conducted by Dr. Swenberg will further add to the weight of evidence regarding effect thresholds for formaldehyde exposure. We consider the magnitude and quality of Dr. Swenberg's work to be truly "game changing" and critical to the fuller understanding of the effects of chronic formaldehyde exposure.

The Panel has endeavored to keep staff in the IRIS program informed of relevant new scientific data as it becomes available and we will continue to do so moving forward. Panel representatives would like to meet with you in January 2018 to discuss this important science on formaldehyde and how the results support use of a non-linear approach for formaldehyde dose- response modeling. I will contact your office next week to arrange a mutually convenient time.

Sincerely,

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

[14] Starr, T.B. and Swenberg, J.A. (2016). The bottom-up approach to bounding potential low-dose cancer risks from formaldehyde: an update. Regulatory Toxicology and Pharmacology, 77: 167-174.

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