THE HAMNER INSTITUTES FOR HEALTH SCIENCES
WHERE GREAT MINDS & MEDICINE MEET

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RE: Comments on the Recommendation from the Expert Panel Report (Part B) on Formaldehyde, 74 Fed. Reg. 67,883 (December 21, 2009).

Dear Dr. Lunn,

You will remember that I made a presentation to the Expert Panel meeting to discuss formaldehyde in Research Triangle Park, NC November 2-4, 2009. I had a chance to read the report and see the Panel's conclusions. While I strongly disagree with the Panel's conclusion to list formaldehyde, a natural component of every cell in the body, as a human carcinogen, I specifically wanted to respond to the section on page 26, outlining the topic of "Toxicokinetics". In the section below from the report, I italicized the sentence: *It is also well recognized that formaldehyde exists in equilibrium with methanediol and with S-hydroxymethylglutathione, both of which offer possible mechanisms for formaldehyde to enter the blood and be transported to other tissues.* The sentence shows a lack of understanding of the chemistry and biochemistry of formaldehyde in tissues and should be corrected.

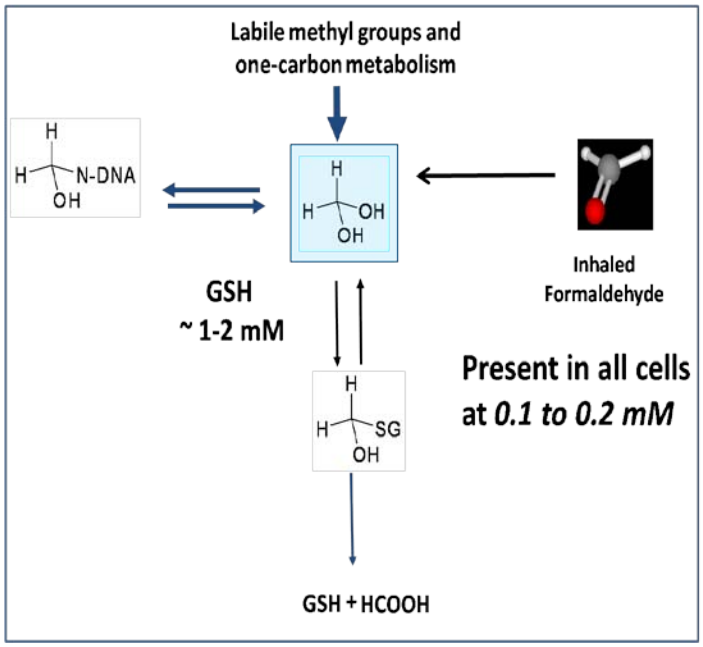
The report reads:

"Toxicokinetics

Insofar as there are at least three cancer types associated with formaldehyde exposure in humans, namely, sinonasal adenocarcinoma, nasopharyngeal cancer, and myeloid leukemia, the toxicokinetic issues are somewhat different. For tumors occurring at the point of contact (sinonasal adenocarcinoma and nasopharyngeal cancer), it is clear that formaldehyde is absorbed at the site of contact (via inhalation) and causes damage to cells in the sinonasal-pharyngeal areas. Regarding myeloid leukemia, the toxicokinetic issues relate to distribution of formaldehyde from the nasal and pharyngeal passages to the blood and possibly to the bone marrow. The only direct evidence that formaldehyde enters the blood following inhalation is the study of Pala *et al*. (2008) who measured formaldehyde human-

serum albumin (HSA) adducts in people exposed to formaldehyde. There is also indirect evidence that formaldehyde produced formaldehyde-DNA adducts in the blood of smokers (Wang *et al.* 2009) and DNA-2003, Shaham *et al.* 1996, Shaham *et al.* 1997). *It is also well recognized that formaldehyde exists in equilibrium with methanediol and with S-hydroxymethylglutathione, both of which offer possible mechanisms for formaldehyde to enter the blood and be transported to other tissues.* The panel recognized that the endogenous levels of formaldehyde methanediol in human blood are high (about 0.1 mM, Heck and Casanova 2004) and that this represents a significant challenge for low-dose extrapolations."

My comments on this section:



Chemistry: As shown in the figure to the right from my presentation, formaldehyde, as a non-hydrated aldehyde, predominates only in the air phase. Whether in the extracellular spaces or within cells, free formaldehyde will be present at extremely low concentrations. It first reacts reversibly with water to form an acetal (i.e., formaldehyde acetal shown in the blue box). The equilibrium constant for acetal versus free formaldehyde is somewhere between 5,000 and 10,000. The acetal reacts with a variety of other tissue nucleophiles, preferentially interacting with glutathione (GSH) to form what a chemist would call thioacetal. The text refers to the acetal as methanediol and the thioacetal as S-hydroxymethylglutathione. Both of these are natural constituents of every cell in the body – in the nose, in the blood, in the bone marrow, everywhere. Importantly, each tissue has an endogenous rate of formaldehyde production due to various pathways involved in single carbon metabolism. The combined steady-state concentration of thioacetal and acetal in cells is large, about 0.1 to 0.2 mM, a very significant concentration that exists without causing toxicity or pathology. With a dissociation constant of 1.5 mM for the GSH-thioacetal, approximately 60% of formaldehyde in any tissue is expected to be in the S-hydroxymethylglutathione pool.

Mammalian cells have robust processes to insure that the endogenous formaldehyde acetal is tightly controlled. The thioacetal formed with glutathione is the substrate for formaldehyde dehydrogenase that converts the thioacetal to formic acid with release of free GSH. When we speak of formaldehyde in tissues, we actually mean a mixture of acetal, thioacetal, other reversible interaction products and extremely small amounts of free formaldehyde (CH_2O) at any time. Of these forms, the thioacetal is the major cellular form of formaldehyde under normal conditions.

In the nose, most inhaled formaldehyde is absorbed into the first epithelial surfaces encountered by the gas during inspiration. In these areas concentrations of the acetal increase leading to higher tissue reactivity and toxicity due to complexing of all available GSH and partial saturation of FDH. Some acetal will diffuse to adjacent tissues where it becomes diluted and enters into the pool of acetal and especially thioacetal. At all times and in all tissues, there is a high concentration of the acetal and thioacetal. Small amounts of these forms of formaldehyde, i.e., the methanediol and S-hydroxymethyglutathioine, moving from the contact site to distant tissue will have no appreciable influence on total levels of formaldehyde in these distant tissues. Neither will they serve as a delivery for unreacted formaldehyde to these tissues.

With formaldehyde, low dose linear extrapolations are unwarranted since these methodologies completely ignore the basic biology of this important endogenous compound. At the highest tolerable inhaled concentrations of formaldehyde, there will be responses at the site of contact and not in distant tissues. At concentrations only slightly below those causing toxicity, the risks of any response even in the nose falls rapidly as the increment of tissue formaldehyde – acetal, thioacetal, etc. - from inhalation becomes small with respect to normal background production in tissues.

In summary, the concluding sentences of the toxicokinetics section in the report are incorrect and misleading. Neither the acetal nor the thioacetal represent ways in which significant amounts of formaldehyde could enter the circulation and reach distant tissues. The panel needs to justify this statement since it is contrary to our extensive understanding of formaldehyde chemistry and biochemistry. In addition the comment in the last sentence says that high endogenous levels represent a challenge for extrapolation. They certainly do. The challenge for the panel should have been to provide any reasonable argument that inhaled formaldehyde can in any way cause biologically appreciable increases in tissue concentration at sites remote from the epithelial cells lining the respiratory tract. There was no attempt at justification because none is possible.

Respectfully submitted,

[Redacted]

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