

**Department of Defense Comments on the Toxicological Review Of Formaldehyde Inhalation Toxicity**

Comments submitted by: Office of the Secretary of Defense Chemical and Material Risk Management Directorate	Organization: Department of Defense	Date Submitted: 19 April 2010
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\*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Page & Paragraph or Global	Comment	Suggested Action	Category*
1		Global	Formaldehyde is a natural metabolite. The toxicity values in this document appear to be in the range of normal concentrations in the body and in foods. If formaldehyde is toxic at normally occurring concentrations it seems that leukemia rates should be much higher than they are.	A reality check of formaldehyde in the diet and in healthy individuals compared with lifetime risks of leukemia should be presented. Although an estimated 1 to 10 mg per day ingestion is cited (page 2-11), it is not in proximity to, nor compared with, neither the existing data on risk of leukemia from all sources nor with the unit cancer risk of $8.1 \times 10^{-2}$ per ppm ( $6.6 \times 10^{-5}$ per $\mu\text{g}/\text{m}^3$ ).	S/M
2	4.5.3.	Global	None of the hypothesized modes of action are presented in the manner envisioned in the EPA's 2005 cancer guidelines. Moreover, none of the data required for a mode of action analysis are presented in the discussion of the potential modes of action. Thus, it is not possible to judge if there are sufficient data to support any or all of the modes of action presented.	The assessment would be more defensible if the cancer guidelines were better adhered to. Not only does this procedure provide a scientifically defensible procedure for establishing modes of action and causation, but it also is consistent with other methods for determining a mode of action. In particular, those modes of action for which no references are cited for the key events hypothesized should be deleted. EPA's cancer guidelines state that mode-of-action analyses must be based on data.	S

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3	4.5.3.	4-427	The document does not present sufficient information to determine that the cancers have a mutagenic mode of action. The observation of potential for systemic mutagenicity is necessary but not sufficient for demonstrating a mutagenic mode of action at any particular site of carcinogenesis, as has been discussed in EPA's external review draft of a framework for mutagenic mode of action and in peer-reviewed publications from those authors. Since demonstration of a mutagenic mode of action changes the risk estimates for early-life exposures, this determination is critical and must be documented appropriately.	Recommend that the framework outlined in the 2005 cancer guidelines be followed to determine whether formaldehyde has a mutagenic mode of action. If the relevant data to support the determination are available in this document, they are not in the appropriate section, and the analysis in that section is neither complete nor transparent with regard to the criteria set forth in EPA's cancer guidelines.	S/M
4	4.5.3	Global	The data used, and the mode of action hypothesized, for developing the cancer potency for formaldehyde is based primarily on very recent data from one laboratory. Possibly one of the modes of action, it is in conflict with current, evidence-based medical opinion. The current medical consensus is that aplastic anemia is necessary for chemically induced leukemia, as was discussed by Dr. Bernard Goldstein at recent meetings (2009 SRA and 2010 Navy and Marine Corps Public Health Center annual meeting). As such, it would be expected to have a threshold and thus to have a nonlinear extrapolation from the point of departure. (See also: Lu et al. 2010. <i>Distribution of DNA Adducts Caused by Inhaled Formaldehyde is Consistent with Induction of Nasal Carcinoma but not Leukemia</i> . Toxicol Sci. 2010 Feb 22 and Rava et al. 2009. <i>Cause-specific Mortality in Populations Exposed and Unexposed to Outdoor Emissions of Formaldehyde and Wood Dust: the Viadana study</i> . (Epidemiol Prev. 33:176-83.) Furthermore, EPA's	While EPA's hypothesized mode of action has sufficient support to be presented in this document, the more universally accepted, evidence-based medical mode of action should also be presented and a quantitative analysis for risk assessment proffered. Otherwise, if the current data are not replicated or if the weight of evidence continues to support the aplastic anemia basis for the mode of action, this four volume analysis would have to be withdrawn until such an analysis were done. By supplying both analyses, the IRIS document would be more robust and allow decision makers to use either value as more data become available.	S/M

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			<p>cancer guidelines recommends that modes of action that are biologically plausible be carried forward quantitatively to the risk characterization section of the risk assessment so that risk managers can include them in their evaluations. Certainly, the current medical, evidence-based, consensus assessment qualifies.</p> <p>If the medical consensus is accurate, carcinogenesis requires killing of stem cells and therefore is low-dose nonlinear. At a minimum, the analysis should present both risk extrapolations, as the Zhang et al. hypothesis may be shown not to be accurate, and we don't want to have to redo a multivolume assessment.</p>		
4	4.5.3.1.1	4-443 Line 28	There are several Zhang et al. 2010's in the literature, and although this is a critical reference, none are in the reference list.	References should be provided.	E