National Institute for Occupational Safety and Health
Comments on the Interagency Science Discussion (Step 6)
Draft IRIS Toxicological Review of Formaldehyde—Inhalation
June 2024

Date: 07/22/2024

-Page 302 (3-162), lines 25–28
Section: Anatomical location of lesions in the upper respiratory tract

Although an explanation was added to explain why Horton et al. [1963] is still considered (in relation to the anatomical location of lesions), the explanation does not state clearly that the nasal epithelium was not examined. Absence of neoplasms even after exposure to a very high concentration of formaldehyde for 35 weeks could be explained by several mechanisms. However, a mechanism cannot be determined without nasal epithelium examination. The authors might want to state clearly what useful information is derived from this study.

-Page 342 (3-202), lines 12–13
Section 3.2.5 Respiratory tract cancers

"Epidemiological evidence is *slight* for oropharyngeal/hypopharyngeal cancers, …": NIOSH suggests replacing the word "slight" with "limited." Use of the phrase "slight evidence" in an epidemiological context is unusual.

-Page 343 (3-203), lines 5–6

"Although uncertainties remain, the nasal cancer MOA, including mutagenicity, is interpreted as relevant to this cancer type."

This statement is not clear. Are the uncertainties pertaining to the entire MOA(s) or to mutagenicity alone? The sentence could be rewritten to provide clarification.

-Page 432 (3-292), lines 3–6
Section: Respiratory Tract Cancers in Animal Studies

"Although the bioassays in mice, hamsters, and rats represent similar exposure concentrations and duration of exposure, clear species differences in the severity of lesions are present."

The sentence mentions differences in toxicity outcomes in difference species and within sex, when exposed to similar concentration of formaldehyde and for the same duration. If the evidence is collected from different experimental animal studies, and there is a clear indication of differential toxicity due to anatomical and metabolism related differences, NIOSH recommends stating how this issue has been addressed when extrapolating to human adverse outcomes (not just application of uncertainty factors).

-Page 686 (3-546)
Section: Evidence on Mode of Action

During Step 3 NIOSH recommended including key evidence provided by the three studies listed below. In EPA's response to the comment (pages F-115–F-116), the non-English study (Chebotarev et al. 1986) was mentioned to have been removed because its contribution was not significant to the evaluation. It is not clear why the other relevant studies were not considered.

Chromosomal aberrations are evidence of potential genotoxic effects of formaldehyde. Please cite Yager et al. [1986] which looked at an average increase in sister chromatid exchange (SCE) and formaldehyde exposure and Vasudeva and Anand [1996] which evaluated chromosomal aberrations in medical students exposed to formaldehyde.

-Chebotarev AN, Titenko NV, Selezneva TG, Fomenko VN, Katosova LM [1986]. Comparison of the chromosome aberrations, sister chromatid exchanges, and unscheduled DNA synthesis when evaluating the mutagenicity of environmental factors. *Cytol Genet* 20(2):109–115.

-Vasudeva N, Anand C [1996]. Cytogenetic evaluation of medical students exposed to formaldehyde vapor in the gross anatomy dissection level. *J Am Coll Health* 44:177–179.

-Yager JW, Cohn KL, Spear RC, Fisher JM, Morse L [1986]. Sister-chromatid exchanges in lymphocytes of anatomy students exposed to formaldehyde-embalming solution. *Mutat Res* 174(2):135–139.

Thank you for the opportunity to review.