

(Date Received by EPA: January 5, 2022)

**Comments from the National Institute for Occupational Safety and Health (NIOSH) on the
Environmental Protection Agency (EPA) IRIS Toxicological Review of
Formaldehyde—Inhalation**

EPA/635/R-21/286a Interagency Review Draft dated December 2021 (780 pages)

File name: Formaldehyde_Maintext_2021Interagency_Dec2021_HEROnet

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Overall comment

EPA has done a fine and transparent job of identifying the relevant studies, assessing the quality of studies, integrating the evidence, and developing the reference concentration (RfC) and inhalation unit risk (IUR). The draft document appears to address many criticisms of past formaldehyde assessments. The scope and quality are impressive.

Specific comments (page numbers refer to the .pdf of 780 pages)

-Page 211, line 24: The study by Horton et al. 1963 has severe limitations—there was no examination of nasal epithelium in its inhalation studies. The mice were exposed to reasonably high concentrations of formaldehyde and yet there was no development of neoplasms. Evidence from this study must be excluded in drawing any conclusions on formaldehyde given the study's weaknesses.

-Page 251, line 25 Nasopharyngeal cancer: It was interesting to see that there was no mention of the meta-analysis studies by Blair et al. 1990 or Partanen 1993—the meta-analyses studies that calculated aggregate risks for nasal and nasopharyngeal cancers from occupational exposure to formaldehyde. These studies support the evidence from animal studies related to carcinogenicity of formaldehyde in the upper respiratory tract.

-Pages 281, 484, and 540: Weaknesses in the study by Stroup et al. 1986 such as lack of information about exposure to other chemicals and actual exposure levels to formaldehyde were not discussed anywhere in the document.

-Page 361, Evaluation of experimental support for the hypothesized mode of action: Chromosomal aberrations are evidence of potential genotoxic effects of formaldehyde. Please cite these studies:

1. Yager et al. 1986: average sister chromatid exchange (SCE) increase and formaldehyde exposure
2. Vasudeva and Anand 1996: chromosomal aberrations in medical students exposed to formaldehyde.
3. Chebotarev et al. 1986: SCE and a 2.67% increase in chromosomal breakage in workers exposed to formaldehyde.

-Page 363, line 4: Please include Lai et al. 2016. The study describes methods to evaluate DNA adducts (marker of genotoxicity) formed by endogenous formaldehyde (an essential metabolite of formaldehyde via detoxification processes).

-Page 484, Myeloid leukemia: It would be valuable to consider the meta-analysis by Zhang et al. [2009] as epidemiological evidence for myeloid leukemia from exposure to formaldehyde. This meta-analysis approached the risk of acute myeloid leukemia (AML) differently than other meta-analyses by suggesting that higher relative risks are not a result of confounding factors.

References for studies mentioned above

Blair A, Saracci R, Stewart PA, Hayes RB, Shy C [1990]. Epidemiologic evidence on the relationship between formaldehyde exposure and cancer. *Scand J Work Environ Health* 16:381–393.

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.

Lai Y, Yu R, Hartwell HJ, Moeller BC, Bodnar WM, Swenberg JA [2016]. Measurement of endogenous versus exogenous formaldehyde-induced DNA-protein crosslinks in animal tissues by stable isotope labeling and ultrasensitive mass spectrometry. *Cancer Res* 76(9):2652–61.

Partanen T [1993]. Formaldehyde exposure and respiratory cancer—a meta-analysis of the epidemiologic evidence. *Scand J Work Environ Health* 19:8–15.

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.

Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT [2009]. Formaldehyde exposure and leukemia: A new meta-analysis and potential mechanisms. *Mutat Res* 681(2-3):150–168.