

(Date Received by EPA: January 5, 2022)

**Office of Management and Budget (OMB) Comments on the Interagency Science Consultation
Draft IRIS Assessment of Toxicological Review of Formaldehyde—Inhalation
dated December 2021**

Date: 01/05/2022

Dear EPA IRIS:

Thank you for the opportunity to provide comments on the draft Toxicological Review of Formaldehyde - Inhalation. We have comments on sections throughout the text.

Major Comments

1. We agree with the current framework of the draft hazard assessment which focuses on the relationship between specific diagnoses of myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma and formaldehyde exposure, rather than drawing causal conclusions between such exposure and the broad categories of “all leukemias” or “all LHP 5 cancers.” However, we are concerned with EPA’s judgement of “evidence demonstrates” for myeloid leukemia. Given the inconsistencies in the epidemiologic data and the lack of proposed MOA, it is not clear that this determination is, as EPA indicates (Overview, page 4), based on “robust human evidence of increased risk in groups exposed to occupational formaldehyde levels, and robust animal evidence of nasal cancers in rats and mice that exhibits steeply increasing incidence at high formaldehyde levels. Strong mechanistic support is provided across species (primarily rats, but also mice, monkeys, and humans), including genotoxicity, epithelial damage or remodeling, and cellular proliferation that are consistent with neoplastic development in a regional, temporal, and dose-related fashion.” Claiming “evidence demonstrates” while the confidence in the unit risk estimate is low and the data are limited may result in an overly conservative appreciation of the degree of hazard for myeloid leukemia, particularly considering no MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia, a disease that results from systemic exposure. The mechanistic information considered by EPA may support associations with local, route-of-exposure, tumors associated with epithelial cells, but does not support the tumorigenesis or carcinogenesis of disease related to systemic exposures.

DRAFT External Peer Review Charge Questions for the IRIS Toxicological Review of Formaldehyde—Inhalation and throughout

Page 6, no line provided. “The evidence demonstrates that formaldehyde inhalation causes an increased risk of myeloid leukemia in humans, based on robust human evidence from observations of increased risk in groups exposed to occupational formaldehyde levels.”

Suggested edit: “The evidence **indicates** that formaldehyde **is likely associated with** an increased risk...”

Nervous system effects (1.3.1)

No suggested edits to the text. This section is very well done.

General comment (no text edits recommended): We agree that the MOA remains unclear regarding possible neurotoxic effects due to uncertainties about systemic exposure. However, we note that there is a

known route of exposure from olfactory bulb, to amygdala, to hippocampus (CA regions and dentate gyrus). Without data demonstrating a concentration gradient, it is uncertain that formaldehyde is taken up via this route. However, the route has been shown to be relevant to other inhalational chemical exposures (e.g. metals and welding).

Developmental and Reproductive Toxicity (1.3.2)

Page 428, line 13. “recognition of pregnancy” is an unusual phrase. Is this different from diagnosis of pregnancy or confirmation of pregnancy? We wonder if this word choice is due retrospective recall of TTP.

No other comments. Also a well done section.