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

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Introduction

The U.S. Environmental Protection Agency (EPA) is seeking a scientific peer review of a draft *IRIS Toxicological Review of Formaldehyde—Inhalation* developed in support of the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's Center for Public Health and Environmental Assessment within the Office of Research and Development.

IRIS is a human health assessment program that evaluates scientific information on effects that could result from exposure to specific chemicals or pollutants in the environment. Through IRIS, EPA provides high-quality science-based human health assessments to support the Agency's regulatory activities and decisions to protect public health. IRIS assessments contain information that can be used to support hazard identification and dose-response assessment, two of the four steps in the human health risk assessment process. When supported by available data, IRIS provides health effects information and toxicity values for health effects (including cancer and effects other than cancer) resulting from chronic exposure. When used by risk managers in combination with information on human exposure and other considerations, IRIS assessments support the Agency's regulatory activities and decisions to protect public health.

An existing assessment for formaldehyde includes an oral reference dose (RfD) posted on IRIS in 1990, and a cancer weight of evidence descriptor and inhalation unit risk (IUR) for cancer posted on IRIS in 1989. A draft IRIS formaldehyde assessment was reviewed by the National Academy of Sciences (NAS) in 2011 (NRC, 2011). The IRIS Program decided to conduct a reassessment of formaldehyde inhalation from scratch on the basis of that review, using transparent and predefined systematic review methods. The draft *Toxicological Review of Formaldehyde—Inhalation* is based on a comprehensive review of the available scientific literature informing the noncancer and cancer health effects in humans exposed to formaldehyde via inhalation, including human and animal health effect studies, as well as extensive mechanistic analyses. Two other documents provide supporting information, the S*upplemental Information to the Toxicological Review of Formaldehyde—Inhalation* (i.e., Appendices) and the *Assessment Overview for the Toxicological Review of Formaldehyde—Inhalation*. The draft assessment was developed according to EPA guidelines and technical reports and contains conclusions on the noncancer human health hazards and carcinogenicity potential posed by formaldehyde inhalation, including a standardized cancer descriptor to express formaldehyde's human carcinogenic potential. The assessment also derives noncancer toxicity values, including a reference concentration (RfC) for chronic inhalation, and a cancer IUR estimate.

Charge Questions on the Draft Toxicological Review of Formaldehyde—Inhalation

In response to the numbered charge questions below, the advice provided as part of this peer review would be most useful when prioritized to indicate its relative importance as follows:

- Tier 1: *Recommended Revisions* – Key major recommendations necessary for strengthening the scientific basis for the Toxicological Review. The implication of such key Tier 1 recommendations is that the assessment conclusions are not adequately supported without addressing the recommendations and need to be reconsidered or better substantiated. For Tier 1 recommendations, please describe the specific revisions necessary to modify or better substantiate the most scientifically appropriate assessment conclusions.
- Tier 2: *Suggestions* – Recommendations that are encouraged to strengthen the scientific analyses and conclusions in the Toxicological Review. That other factors (e.g., timeliness) also could be considered before deciding to address or incorporate Tier 2 suggestions is understood. For Tier 2 recommendations, please provide specific suggestions to strengthen the scientific basis for assessment conclusions or improve the clarity of the analyses and presentation.
- Tier 3: *Future Considerations* – Scientific exploration that might inform future work. These recommendations are outside the immediate scope or needs of the current document under review but could inform future toxicological reviews or research efforts.

1. **Assessment Development Methods and Organization.** The Toxicological Review describes and applies a systematic review process for identifying, screening, and evaluating pertinent studies, and then for prioritizing the evidence to inform hazard and dose-response decisions. This process is described in the Toxicological Review's *Preface on Assessment Methods and Organization*, with documentation primarily in Appendix A.5. Please answer parts (a) and (b).
    a. Please comment on whether the methods for assessment development (*Preface on Assessment Methods and Organization*) and the organization of the assessment are clear and transparent.
    b. Please comment on whether there is sufficient documentation on methods and criteria for the following:
        - Identification of epidemiologic, experimental, and mechanistic studies (please identify any additional peer-reviewed studies that the assessment should consider).
        - Critical evaluation of individual studies or sets of studies.
        - Assessment of the weight of evidence (i.e., evidence integration).
        - Selection of studies and data sets for deriving toxicity values.
2. **Toxicokinetics.** Several assumptions and interpretations were applied in the Toxicological Review that were based on current research. Please answer parts (a), (b), and (c) considering the extent to which the available science on the toxicokinetics of inhaled formaldehyde is clearly presented and appropriately applied in the assessment of potential respiratory and systemic (i.e., nonrespiratory) health hazards.
    a. Please comment on the Toxicological Review conclusion that inhaled formaldehyde is not likely to be distributed in appreciable amounts beyond the upper respiratory tract to distal tissues. This conclusion underpins the organization of the assessment and several key assumptions.
    b. Please comment on the Toxicological Review assumptions (based on [a]) that:

- Inhaled formaldehyde is not directly interacting with tissues distal to the portal-of-entry (POE) to elicit systemic effects.
- Formaldehyde levels in the blood or at systemic sites are not changed as a result of formaldehyde from exogenous sources (inhalation).
- Inhaled formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Therefore, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts in tissues distal to the POE (e.g., formate in blood or urine; brain formaldehyde levels) and health outcomes are not considered relevant to interpreting the human health hazards of inhaled formaldehyde.

c. Please comment on the Toxicological Review evaluation of the potential impact of normal levels of endogenous formaldehyde on the penetration and distribution of inhaled formaldehyde in the respiratory tract, on the basis of available dosimetric models and data.

3. Respiratory System Health Effects (Noncancer). For each noncancer POE health effect considered in the assessment and outlined in (a) to (e), below, please comment on whether the evidence integration decisions for hazard identification are clearly described and scientifically justified (considering the extent to which the available data have been appropriately synthesized to describe the strengths and limitations). In addition, please separately comment on whether the dose-response decisions are transparent and scientifically justified, including study selection for dose-response analyses; point of departure (POD) estimates, including modeling choices and assumptions, and dosimetric adjustments; selection of uncertainty factors and derivation of candidate values; selection of organ- or system-specific RfCs (osRfCs); and confidence in the calculated values. For these well-studied health effects, confidence was consistently judged as either *medium* or *high*.

a. Sensory irritation
   - The assessment concludes that the **evidence demonstrates** that inhalation of formaldehyde causes increased sensory irritation in humans, given the appropriate exposure circumstances. Well-conducted studies in humans and animals support this hazard conclusion, and strong mechanistic evidence in animals provides plausible modes of action (MOAs) for the identified endpoints.
   - A POD from Hanrahan et al. (1984), a human study, was ultimately selected to calculate an osRfC of 0.009 mg/m^3 for eye irritation. A composite uncertainty factor (UF_C) of 10 was applied to address intraspecies uncertainty (UF_H). The assessment also considers PODs from controlled human exposure studies and discusses their utility for developing an RfC for lifetime exposure as well as their potential increased utility for purposes outside the scope of the current assessment (e.g., derivation of an acute RfC).

b. Pulmonary function
   - The assessment concludes that the available **evidence indicates** that formaldehyde inhalation likely causes decreased pulmonary function given the appropriate exposure circumstances. This conclusion was supported primarily by evidence in

exposed humans, with supportive mechanistic evidence indicating that formaldehyde inhalation results in biological changes related to these outcomes in exposed animals.

- A POD from Krzyzanowski et al. (1990), a human study, was ultimately selected to calculate an osRfC of 0.007 mg/m^3 for pulmonary function. A UF_C of 3 was applied to address UF_H. This UF_H value was selected using an evidence-based analysis.

c. Respiratory tract pathology
   - The assessment concludes the **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans, given the appropriate exposure circumstances. Well-conducted studies in humans and animals support this hazard conclusion, and strong mechanistic evidence in animals provides plausible MOAs for the identified endpoints.
   - PODs from the Kerns et al. (1983) and Woutersen et al. (1989) rat studies were ultimately selected to calculate an osRfC of 0.003 mg/m^3 for squamous metaplasia. This POD was estimated using dosimetric simulations of formaldehyde flux to the nasal lining using a computational fluid dynamics model to extrapolate from results in rats to humans. A UF_C of 30 or 100 was applied to address UF_H, subchronic (UF_S) and interspecies (UF_A) uncertainties.

d. Allergy-related conditions
   - The assessment concludes that the available **evidence indicates** that formaldehyde inhalation likely causes increased allergic responses in humans, given the appropriate exposure circumstances. This conclusion was supported primarily by evidence in exposed humans, with supportive mechanistic evidence indicating that formaldehyde inhalation results in biological changes related to these outcomes in exposed animals.
   - A POD from Annesi-Maesano et al. (2012), a human study, was ultimately selected to calculate an osRfC of 0.008 mg/m^3 for allergy-related conditions. A UF_C of 3 was applied to address UF_H. This UF_H value was selected using an evidence-based analysis.

e. Prevalence of current asthma and degree of asthma control
   - The assessment concludes that the available **evidence indicates** that formaldehyde inhalation likely causes an increased frequency of current asthma symptoms or difficulty controlling asthma, given the appropriate exposure circumstances. This conclusion was supported primarily by evidence in exposed humans, with supportive mechanistic evidence indicating that formaldehyde inhalation results in biological changes related to these outcomes in exposed animals.
   - PODs from the Annesi-Maesano et al. (2012), Krzyzanowski et al. (1990), and Venn et al. (2003) human studies were ultimately selected to calculate an osRfC of 0.006 mg/m^3 for current asthma or degree of asthma control. A UF_C of 3 or 10 was applied to address UF_H. The UF_H value applied to the POD from Annesi-Maesano et al. (2012) was selected using an evidence-based analysis.

4. **Systemic (i.e., nonrespiratory) Health Effects (Noncancer).** For each noncancer systemic health effect considered in the assessment and outlined in (a) to (c), below, please comment on whether the evidence integration decisions for hazard identification are clearly described and scientifically justified (considering the extent to which the available data have been appropriately synthesized to describe the strengths and limitations). In addition, please separately comment on whether the dose-response decisions are transparent and scientifically justified, including study selection for dose-response analyses; POD estimates, including modeling choices and assumptions, and dosimetric adjustments; selection of uncertainty factors and derivation of candidate values; selection of osRfCs; and confidence in the calculated values. Confidence was consistently lower for these effects as compared with POE effects.

    a. Female reproductive or developmental toxicity:
        - The assessment concludes that the **evidence indicates** that inhalation of formaldehyde likely causes female reproductive or developmental toxicity, given the appropriate exposure circumstances. The conclusion for female reproductive or developmental toxicity is supported by evidence in humans, specifically, increases in time-to-pregnancy (TTP) and spontaneous abortion risk; mechanistic evidence explaining such effects without systemic distribution of formaldehyde is lacking.
        - A POD from Taskinen et al. (1999), a human study, was ultimately selected to calculate an osRfC of 0.01 mg/m^3 for TTP. A UF_C of 10 was applied to address UF_H.

    b. Male reproductive toxicity
        - The assessment concludes that the **evidence indicates** that inhalation of formaldehyde likely causes reproductive toxicity in men, given the appropriate exposure circumstances. The conclusion for male reproductive toxicity is supported primarily by coherent evidence of several alterations to the male reproductive system in animals exposed to very high levels of formaldehyde (>6 mg/m^3), with some corroborative changes in an occupational epidemiological study; although no MOA is available, some relevant mechanistic changes have been observed in well-conducted studies of the male reproductive organs of exposed rodents.
        - A POD from Özen et al. (2002), a rat study, was ultimately selected to calculate an osRfC of 0.01 mg/m^3 for testis weight. A UF_C of 3,000 was applied to address UF_H, LOAEL (UF_L), UF_S, and UF_A.

    c. Nervous system toxicity
        - While many studies reporting evidence of potential neurotoxic effects were available—including developmental neurotoxicity, multiple manifestations of behavioral toxicity, and an increased incidence of, or mortality from, the motor neuron disease amyotrophic lateral sclerosis—due to limitations identified in the database (e.g., poor methodology, lack of consistency), it was ultimately determined that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might pose a human health hazard. The evidence integration narrative emphasizes that additional study is warranted.
        - The available data on potential nervous system effects were considered insufficient for developing quantitative toxicity estimates.

5. **Noncancer RfC.** An RfC was selected based on the grouping of osRfCs for sensory irritation, reduced pulmonary function, allergy-related conditions, prevalence of current asthma, and degree of asthma control. Please comment on whether the approach and selection of the proposed RfC was clear and scientifically justified, including consideration of other potentially sensitive health effects.

6. **Cancer.** The assessment concludes that formaldehyde is ***Carcinogenic to Humans by the Inhalation Route of Exposure***. Please comment on whether the judgments in (a) to (e), below, are clearly described and scientifically justified. Note that the judgments in (a) and (b) outline the primary support for this conclusion across two lines of evidence, each of which would independently substantiate the carcinogenicity conclusion.

    a. The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer (NPC) in humans, based on observations of increased risk of NPC in groups exposed to occupational formaldehyde levels and nasal cancers in animals, with strong, reliable, and consistent mechanistic evidence in both animals and humans (i.e., *robust* evidence for both the human and animal evidence, and strong mechanistic support for the human relevance of nasal cancers observed in animals).
    b. 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. This judgment is supported by other studies of human occupational exposure that provide strong and coherent mechanistic evidence identifying clear associations with additional endpoints relevant to lymphohematopoietic (LHP) cancers, including an increased prevalence of multiple markers of mutagenicity and other genotoxicity in peripheral blood cells of exposed workers, other perturbations to immune cell populations in blood (primarily from human studies), and evidence of other systemic effects (i.e., developmental or reproductive toxicity). Generally, evidence supporting the development of LHP cancers after formaldehyde inhalation has not been observed in experimental animals (i.e., rodents), including a well-conducted, chronic cancer bioassay in two species, a similar lack of increased leukemias in a second rat bioassay, and multiple mechanistic evaluations of relevant biological changes such as genotoxicity in systemic tissues of exposed rodents (resulting in an judgment that the animal evidence is *indeterminate*).
    c. This carcinogenicity conclusion is corroborated by several other lines of evidence for which the **evidence indicates** that formaldehyde inhalation likely causes that cancer type in humans, namely sinonasal cancer, oropharyngeal/hypopharyngeal cancer, and multiple myeloma.
    d. Formaldehyde is genotoxic in several test systems and operates, at least in part, through a mutagenic MOA. Specifically, a mutagenic MOA was identified in association with the development of nasal (including nasopharyngeal and sinonasal) cancers, while a mutagenic MOA was not identified for other cancer types. The mechanistic evidence was sufficient to conclude that both mutations and cellular proliferation play a role in nasal carcinogenesis.
    e. The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.

7. **Inhalation unit risk for cancer.** An IUR for cancer is derived on the basis of nasal cancers using data on nasopharyngeal cancers (NPCs) in a human study from the National Cancer Institute (NCI), specifically the results reported in (Beane Freeman et al., 2013). In addition, comparative estimates are provided on the basis of modeling of nasal tumors in exposed rodents. Finally, although not included in the draft IUR, an estimate for myeloid leukemia is presented. Please comment on the clarity and scientific justification for each specific decision in the draft cancer dose-response analyses outlined in (a) to (d), below, including study selection; POD estimates, including modeling choices and assumptions, dosimetric adjustments, and extrapolations; any other adjustments; and confidence in the calculated values. Part (e) includes a specific, additional question on myeloid leukemia.

    a. The NCI study results on NPCs were ultimately selected and used to develop the draft IUR estimate. A lifetable analysis was used to develop a POD and, given the assumption of a mutagenic MOA for this cancer type, a linear extrapolation was applied. Age-dependent adjustment factors (ADAFs) were applied to this estimate, in accordance with EPA guidelines when a mutagenic MOA is supported. This draft IUR is interpreted to be of medium confidence.
    b. As a comparison with the modeling of the human data, data from two chronic rat bioassays were used to develop an estimate of nasal cancer risk. Dosimetric simulations of formaldehyde flux to the nasal lining using a computational fluid dynamics model were used to extrapolate the results in rats to a POD in humans. The analysis also evaluates several published models related to this extrapolation and impacts on the estimates if a different MOA were concluded (ultimately, the draft concludes that the mutagenicity-based decisions are best supported). As above, a linear extrapolation was applied.
    c. Given the lack of quantifiable data, the draft IUR does not incorporate potential contributions to risk for sinonasal cancer, oropharyngeal/hypopharyngeal cancer, or multiple myeloma. For each of these cancer types, the draft draws an evidence integration judgment of **evidence indicates** (likely).
    d. For myeloid leukemia, a unit risk estimate is presented using the NCI study results (Beane-Freeman et al., 2009). In line with recommendations from the NAS (NRC, 2011), this reassessment draws hazard conclusions and derives a unit risk estimate at the most specific cancer type supported by the available data. The selected data set used to derive the myeloid leukemia estimate combined the results from myeloid leukemia with results for other/unspecified leukemias. ADAFs were not applied to this estimate, as the assessment concludes that the MOA is unknown.
    e. Although the draft concludes that the **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia, the only data available to develop a unit risk estimate for myeloid leukemia are uncertain. The draft Toxicological Review discusses the strengths and limitations of the myeloid leukemia estimate in detail. Please comment specifically on how the unit risk estimate for myeloid leukemia should inform the IUR for cancer, if at all.
    f.

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