Comparing risk science choices underpinning formaldehyde exposure levels established by independent regulatory and advisory bodies.

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Rationale

Many occupational exposure limits exist for formaldehyde. In 2024, the U.S. Environmental Protection Agency issued two documents recommending health-protective exposure levels: a final formaldehyde Integrated Risk Information System (IRIS) assessment and a draft formaldehyde Toxic Substances Control Act (TSCA) Risk Evaluation. In its review of the draft TSCA Risk Evaluation, the TSCA advisory board, the Science Advisory Committee on Chemicals (SACC), recommended a comparison of the conclusions reached in the draft TSCA Risk Evaluation with the decisions made by other global regulatory authorities along with a coherent technical explanation of the differences.

Formaldehyde Uses

https://www.americanchemistry.com/industry-groups/formaldehyde/benefits-applications

Approach / Methods

Risk science choices (i.e., key studies, critical effect, uncertainty factor application) in the final IRIS and draft TSCA assessments are compared to US peer review panels and other authorities:

- Scientific Advisory Committee on Chemicals (2024). Docket ID: EPA-HQ-OPPT-2023-0613.
- EPA Human Studies Review Board (HSRB). (2023). Report from May 18 and July 26 meetings.
- National Academies of Sciences, Engineering, and Medicine (NASEM) (2023). Review of EPA's 2022 Draft Formaldehyde Assessment.
- European Commission (2016). REC/125 Formaldehyde – Recommendation from the Scientific Committee on Occupational Exposure Limits.
- WHO (2010) Guidelines for Indoor Air Quality.
- National Research Council (2007). Emergency and Continuous Guidance Levels for Selected Submarine Contaminants, vol 1.

The scope was limited to risk choices contributing to chronic non-cancer endpoints and values since this endpoint serves as the basis of the TSCA draft occupational exposure value. As such, SACC recommendations were limited to charge question 1.2 (chronic, non-cancer inhalation toxicity value).

Study design considerations

EPA Reports

- IRIS: **Observational epi.** High confidence, Selection bias and confounding unlikely, Diverse population.
- TSCA: **Observational epi.** Consistent with IRIS.

US Peer Review Reports

- SACC: Raised concerns on study selection.
- HSRB: **Controlled chamber** studies have greater scientific rigor vs obs. studies
- NASEM: Favoring well-reported and well-documented **observational epi** studies is justifiable

Reports from Other Authorities

- SCOEL: **Controlled chamber** studies cited as POD basis
- WHO: **Controlled chamber** studies cited as POD basis
- NRC: **Controlled chamber** studies cited as most reliable data for POD

Critical effect choice

EPA Reports

- IRIS: **Respiratory system-related effects** …were interpreted with the highest confidence and had the lowest UF_Cs".
- TSCA: **Respiratory system-related effects** Consistent with IRIS.

US Peer Review Reports

- SACC:"EPA should consider using **sensory irritation** as the key effect for concerns pertinent to chronic exposure…to formaldehyde."
- HSRB: "EPA should consider that PODs for **sensory irritation** could be used as a lower bound for potential adverse effects."
- NASEM: No comment provided.

Reports from Other Authorities

- SCOEL: TWA and STEL are based on **sensory irritation**
- WHO: Short-term guideline based on **sensory irritation**
- NRC: **Irritation** is the end point of greatest concern for subchronic and chronic exposures

Uncertainty Adjustment

EPA Reports

- IRIS: **UF=3** (interindividual variability)
- TSCA: **UF=3** (interindividual variability)

US Peer Review Reports

- SACC: "There were disagreements within the Committee about the uncertainty factors to be applied."
- HSRB: "EPA should consider their previous approach to derive exposure criteria for chloropicrin whereby **uncertainty factors were removed."**
- NASEM: No comment provided.

Reports from Other Authorities

- SCOEL: **No adjustment**. Sufficiently robust coverage of individuals; Effect is concentration-driven, not cumulative dose-driven.
- WHO: **No adjustment**. No evidence of increased sensitivity; No indication of accumulated effects over time.
- NRC: **No adjustment**. Robust data set from controlled studies; Does not appear to follow Haber's law.

Discussion

TSCA section 26 specifies that the EPA must base decisions on the best available science, which includes, in part, consideration of the extent to which methodologies are reasonable for their intended use.

In this analysis, most scientific panels recommended:

- To use **controlled chamber studies** for POD basis
- To **use sensory irritation as the critical effect** to protect against both short-term (eg, tissue irritation) and long-term effects (eg, tumor incidence)
- **Not to apply uncertainty adjustments** due to human variability or exposure duration.

The following key issues were identified as contributing to the different risk science choices:

- Approach to reconcile disparate effect levels by study type
- Differing scientific confidence in relying on short-term effects to protect against long-term exposure.

Conflict of interest

KG and SH are employed by companies or organizations that are members of the American Chemistry Council's Formaldehyde Panel.

This poster represents an update to a previous publication by these authors, published prior to availability of the final IRIS assessment, draft TSCA Risk Evaluation, and the SACC report:

- Goyak and Holm, 2024, Reg Tox Pharm, 148: 105587. https://www.sciencedirect.com/science/article/abs/pii/S0273230024000028X