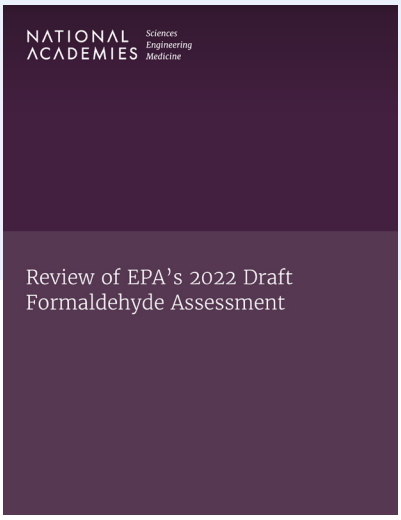
REVIEW OF EPA'S 2022 DRAFT FORMALDEHYDE ASSESSMENT



Formaldehyde is widely present in the environment and is one of the highest production chemicals by volume, used in manufactured goods including wood products, permanent press fabrics, and household products. It is also formed by combustion sources and is present in smoke from cigarettes and other tobacco products, and in emissions from gas stoves and open fireplaces. In carrying out its mission to protect human health, the U.S. Environmental Protection Agency (EPA) identifies and characterizes the health hazards of chemicals found in the environment through its Integrated Risk Information System (IRIS) Program, which has reviewed the human health hazards resulting from formaldehyde exposure in several assessments.

This report is a continuation of guidance from the National Academies on draft IRIS assessments of formaldehyde and other aspects of the IRIS program. A 2011 report recommended that EPA improve documentation of the methods and rationale for decisions made in an earlier draft formaldehyde assessment. A 2014 report encouraged the IRIS Program to adopt systematic review methods, to develop a staff handbook with general guidance on the methods used in IRIS assessments, and to develop an a priori protocol for each major IRIS assessment. EPA received further guidance from National Academies reports (NASEM 2018 and 2022) that informed the EPA's most recent IRIS Toxicological Review of Formaldehyde (2022 Draft Assessment).

This report reviews the 2022 Draft Assessment with regard to its adequacy and transparency in evaluating the scientific literature, use of appropriate methods to synthesize the current state-of-the science, and presentations of conclusions that are supported by the scientific evidence. The report concludes that the 2022 Draft Assessment follows the advice of prior National Academies reports and that its findings on hazard and quantitative risk are supported by the evidence identified. However, revisions are needed to ensure that users can find and follow the methods used in each step of the assessment for each health outcome.

The committee that authored the report was not asked to conduct its own hazard risk assessment of formaldehyde and did not address any broader aspects of the IRIS program. In addition, the committee was not asked to provide a recommendation for a safe level of formaldehyde exposure for humans.

DRAFT ASSESSMENT REVIEW PROCESS

The IRIS program supports EPA by "identifying and characterizing the health hazards of chemicals found in the environment…IRIS assessments are an important source of toxicity information used by EPA, state and local health agencies, other federal agencies, and international health organizations." This review of the 2022 Draft Assessment is organized by the systematic review approach that EPA uses to make hazard determinations and to derive toxicity values, as shown in Figure 1. The report prioritized its recommendations in three Tiers: Tier 1—changes that EPA should make to improve critical scientific concepts, issues, or narrative; Tier 2—changes EPA is encouraged to make to help strengthen or clarify the scientific concepts, issues, or narrative in the assessment but are not critical; and Tier 3—changes that might inform future evaluations or assessments.

SUMMARY OF THE COMMITTEE'S FINDINGS AND RECOMMENDATIONS

Overall, the 2022 Draft Assessment responds to the broad intent of the guidance in the National Academies 2011 and 2014 reports. However, protocols were not developed in advance of conducting the assessment, and EPA's assessment methods were described in several places across 2022 Draft Assessment: the Main Assessment (789 pages), accompanying Appendices (1059 pages), and an Assessment Overview (192 pages).

The committee's only Tier 1 recommendation focuses on the revisions needed to ensure that the methods used for each outcome can easily be found.

Tier 1 Recommendation: EPA should revise its assessment to ensure that users can find and follow the methods used in each step of the assessment for each health outcome. EPA should eliminate redundancies by providing a single presentation of the methods used in the hazard identification and dose-response processes. A central roadmap and cross-references are also needed to facilitate access to related sections across the different elements of the assessment (e.g., appendixes, main document) for the different outcomes analyzed. Related Tier 2 recommendations would amplify the impact of this Tier 1 recommendation in improving the assessment.

Tier 2 recommendations, which are summarized below and organized by the steps in EPA's systematic review process, focus on ways to further clarify the evidence review and conclusions for each health

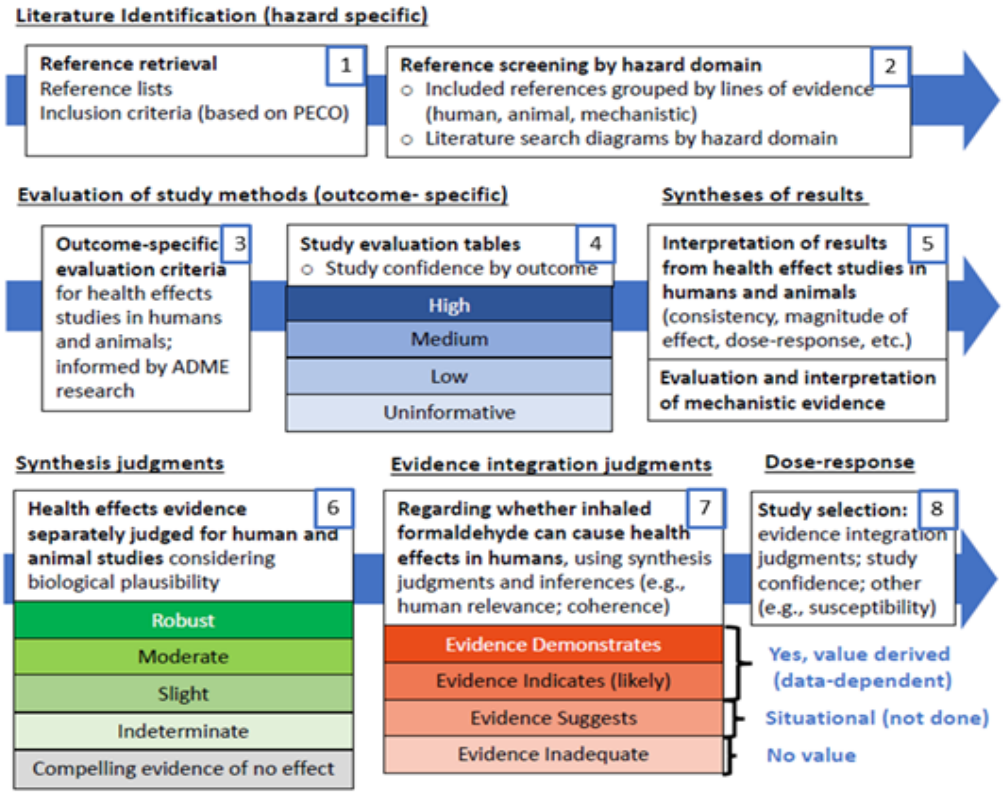


FIGURE 1: Systematic review approach used by EPA to complete the 2022 Draft Assessment

NOTE: Modified from EPA's presentation to the committee on October 12, 2022.

outcome, define key terms, move lengthy but not essential text to appendices, and edit to improve consistency of the use of terms across the health outcomes.

EVIDENCE IDENTIFICATION (STEPS 1 AND 2)

Generally, the literature searches are adequate. Although the search strategies are adequately documented, the origins of the various population, exposure, comparator, and outcome (PECO) statements are less clear. In particular, across noncancer outcomes, the rationale for excluding studies on the basis of the populations, exposures, and outcomes studied is not well documented. The report recommends that EPA expand the text explaining the choices of the elements of the PECO statements for several health outcomes.

STUDY EVALUATION (STEPS 3 AND 4)

EPA provides overall and outcome-specific evaluation criteria that are generally consistent with the common domains for risk-of-bias analysis. However, the information is presented in several different locations in the documents, and in some cases is inconsistently presented and integrated across the documents. As a result, for several noncancer outcomes, it is difficult to reconstruct the study evaluation approach and how the criteria were applied for study evaluation. The considerations listed for study confidence classification and evaluation of each study by at least two independent experts are adequate. However, there are inconsistencies in how evaluation criteria are described and applied in EPA's evaluation of human and animal studies across noncancer outcomes.

Overall, while outcome-specific criteria for evaluating the human and animal studies were generally appropriate, the committee could not satisfactorily identify the final criteria that were applied, as well as the judgments made in determining overall study confidence for both human and animal studies. Inconsistencies between the stated criteria and the rationale for conclusions on study confidence were evident and should be amended.

EVIDENCE SYNTHESIS (STEPS 5 AND 6) AND INTEGRATION (STEP 7)

For evidence synthesis, the strength-of-evidence categories and how they were applied to the overall evidence judgments are generally clear and appropriate for the human and animal evidence streams. However, while drawing on long-established methods for inferring causation, the 2022 Draft Assessment deviates in several respects, including (1) blurring of the boundary between evidence synthesis and integration; and (2) the choice of terminology used to describe the strata in the four-level schema for classifying strength of evidence. EPA should more sharply demarcate the synthesis and the integration of evidence discussions and expand the narrative descriptions of the evidence integration step.

Regarding mechanistic evidence, EPA is thorough and transparent in identifying the relevant information. However, some key terms including "impactfulness" and "other inferences" need to be clarified and better explained. Regarding toxicokinetics, EPA could enhance transparency by explicitly identifying the models used to derive flux values in the summary tables, and by improving documentation of the dosimetry approaches in the tables and text. For noncancer outcomes comprising effects on pulmonary function, respiratory pathology, allergy and asthma, reproductive and developmental toxicity, and neurotoxicity and sensory irritation, EPA presents hazard identification conclusions supported by the available scientific evidence from humans, experimental animals, and mechanistic studies. The assessment could be strengthened by clarifying the basis for summary judgments, such as by referencing the specific studies relied upon in reaching conclusions.

With respect to cancer hazard identification, EPA used its state-of-practice methods to synthesize the current state of the science and presents hazard identification conclusions supported by the available scientific evidence from humans, experimental animals, and mechanistic studies. For lymphohematopoietic cancers, EPA was responsive

to previous recommendations from the National Academies and focused on the most specific diagnoses of myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma. As noted above, clarification with respect to the summary statements and some terminology (e.g., "other inferences") is needed.

DOSE-RESPONSE ASSESSMENT (STEP 8)

Considerations for selection of dose-response studies are reasonable, although having the discussion in multiple places in the documents makes it difficult to determine what the considerations were and how they were applied. EPA provides criteria for study inclusion in the dose-response assessment but does not include any discussion of how these criteria were applied to the specific studies chosen for dose-response. EPA should clarify and clearly state the criteria used to select the studies for dose-response analysis of noncancer endpoints.

Regarding the dose-response assessment for cancer endpoints, EPA's approaches are consistent with its state-of-practice methods to derive the inhalation unit risk estimates. The analyses generally followed the process outlined in the 2022 IRIS Handbook and were consistent with the 2005 Guidelines for Carcinogen Risk Assessment. Specific recommendations regarding the cancer dose-response assessment concern the criteria for study selection, the procedure and justification for pooling the data from two animal studies into one analysis, the discussion of uncertainties and variabilities, and the characterization of the inhalation unit risk estimate.

THE PATH FORWARD

EPA's formaldehyde Draft Assessment has been revised over a period spanning more than a decade and has been improved substantially. A major focus of the committee's recommendations is the need to provide a clearer description of the methods used in order to facilitate their consideration by readers. At present, the description of methods in several places throughout three lengthy documents is perhaps the most critical area for structural and editorial revisions. Implementation of the committee's recommendations would strengthen EPA's conclusions on the many noncancer outcomes reviewed, as well as the cancer hazard identification and dose-response conclusions. Because formaldehyde is a widely used, high-volume production chemical, EPA should undertake these recommendations expeditiously to complete a revised assessment document that can be implemented without delay.

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