March 10, 2022

The Honorable Michael Regan
Administrator
U.S. Environmental Protection Agency
William Jefferson Clinton Building
1200 Pennsylvania, N.W.
Washington, D.C. 20460

Submitted via email and mail

RE: National Academies of Sciences, Engineering, and Medicine (NASEM) Review of EPA's 2022 Draft Formaldehyde Assessment

Dear Administrator Regan:

Scientific integrity, transparency, and a robust peer review process are critical to the U.S. Environmental Protection Agency's ("EPA" or "the Agency") mission and in developing public confidence in the Agency's use of science in its regulations. In 2011, NASEM reviewed EPA's draft Integrated Risk Information System (IRIS) assessment for formaldehyde and identified fundamental problems in the IRIS assessment and how EPA evaluated the available science for the overall IRIS program.[1] The American Chemistry Council ("ACC")[2] Formaldehyde Panel ("the Panel") reiterates its repeated requests over the last decade[3] that EPA needs to fully and directly address and document its implementation of the 2011 NASEM review recommendations prior to public dissemination of another draft IRIS assessment for formaldehyde. In addition, the Agency should ensure that the 2022 NASEM review of the IRIS assessment verifies that EPA has adequately addressed all the deficiencies identified in the 2011 NASEM review. These issues should be a central element of the Committee's task and charge questions. EPA's failure to scientifically resolve these major deficiencies could violate statutory requirements as well as EPA's own policies as well as undermining the public confidence in the resulting assessment.

We were very concerned that an EPA letter dated February 8, 2022,[4] in response to a letter from ACC and several chief executive officers,[5] minimized the significance of adequately addressing these NASEM critiques. The Agency's letter characterizes EPA's 2021 assessment as being "… developed *de novo* to be fully responsive to the recommendations in the [NASEM] reports." This characterization is inconsistent with past Agency updates and may signal an attempt to sever the draft IRIS assessment and 2022 review from the previous peer review comments by unduly narrowing the scope of the upcoming review. EPA's

[1] National Research Council (2011) Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde, The National Academies Press, Washington, DC https://doi.org/10.17226/13142.
[2] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry.
[3] ACC Formaldehyde Panel Follow-up Letter to EPA Office of Research and Development Regarding the Formaldehyde IRIS Assessment (americanchemistry.com)
[4] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/epa-response-to-acc-stakeholder-letter-on-nasem-review-of-draft-iris-assessment
[5] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-stakeholder-letter-to-epa-on-nasem-review-of-draft-iris-assessment

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attempt to turn the page on the highly relevant NASEM feedback raises concerns about the transparency, independence, and rigor of the 2022 review.

For example, EPA has not planned, issued, nor taken comment on a systematic review protocol for formaldehyde, unlike the other sixteen chemicals to be assessed according to the Agency's February 2022 *IRIS Program Outlook*.[6] However, the Feb. 8 EPA letter claims that "[t]he systematic review methods used in the current draft IRIS formaldehyde assessment formed the basis for the methods presented in the IRIS Handbook, which was favorably reviewed by the NASEM in November 2021." While subsequent process-oriented reviews[7] may offer context to the panel reviewing the 2022 IRIS assessment, they do not resolve NASEM critiques of the previous IRIS assessment of formaldehyde. In addition, EPA's has signaled that, in the formaldehyde risk evaluation under the amended Toxic Substances Control Act (TSCA), it "plans to include information developed from the draft IRIS hazard and dose response assessment."[8] The push to use draft IRIS information in a regulatory setting without finalizing the assessment or addressing comments on the underlying work product runs contrary to EPA policies and ACC comments on the scoping document. It also suggests that the Agency' rush to deploy the draft could short-circuit a rigorous peer review process.

The 2011 review of the 2010 assessment identified significant deficiencies in how EPA evaluated the available science, specifically in the areas of toxicokinetics, mode of action, systemic and port-of-entry health effects, derivation of reference concentrations and unit risk estimates, the systematic review process, and the use of a weight of evidence approach. These fundamental issues are not easily resolved, and it is essential that an independent and impartial panel reviewing the IRIS assessment are tasked with fully evaluating the Agency response to these deficiencies. A summary of the NASEM recommendations to EPA from the 2011 review is provided in Appendix 1.

We expect that EPA and NASEM will take every effort to ensure that any disseminated draft IRIS assessment uses the best available science, a weight of the evidence and mode of action approach and incorporates the most recent scientific studies.

EPA actions that are contrary to recommendations from the 2011 review, or that minimize the significance of those recommendations for the 2022 IRIS assessment, may raise legal, scientific, and procedural issues, especially for the Agency's use of IRIS in subsequent regulatory actions. For example:

- Regulatory use of this assessment without fully responding to 2011 review creates substantial legal risk. Under Section 307(d)(3) of the Clean Air Act (CAA), EPA must "set forth or summarize and provide a reference to any pertinent findings, recommendations, and comments by the… National Academy of Sciences, and, if the proposal differs in any important respect from any of these recommendations, an explanation of the reasons for such differences" if it intends to use IRIS in national air quality regulations.[9] Failure to identify and document responses to the pertinent 2011 NASEM review findings, recommendations, and comments could undermine the assessment and the legality of EPA's use of the results in CAA rules.

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[6] A Message from the IRIS Program IRIS Program Outlook February 2022 (epa.gov)
[7] Summary of activity through 2019 available at: https://www.epa.gov/iris/iris-and-national-academies-sciences-nas; NASEM, Review of U.S. EPA's ORD Staff Handbook for Developing IRIS Assessments: 2020 Version, 2022, https://doi.org/10.17226/26289.
[8] EPA, *Final Scope of the Risk Evaluation for Formaldehyde*, August 2020, 74, https://www.epa.gov/sites/default/files/2020-09/documents/casrn_50-00-0-formaldehyde_finalscope_cor.pdf.
[9] 42 U.S. Code §7607.

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- Under amended TSCA, when undertaking rulemaking and risk evaluations of substances, the Administrator is required to "use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science." The Administrator must consider, among other factors, "the extent to which the variability and uncertainty… are evaluated and characterized" and "the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models."[10] Should the EPA not adequately address the 2011 NASEM recommendations in the 2022 IRIS assessment, and utilize the findings for TSCA purposes, EPA will be in violation of the TSCA mandate requiring the use of the best available science.

- EPA's failure to allow NASEM to exercise their independent judgment in evaluating the 2022 assessment may limit the Agency's ability to use the resulting advice under 1997 amendments to the *Federal Advisory Committee Act.*[11]

- EPA decisions to not fully implement and document 2011 NASEM review recommendations is contrary to Congressional direction. For example, in the U.S. House of Representatives report 112-151[12] accompanying the 2012 Consolidated Appropriations Act,[13] the Committee on Appropriations directed that "EPA shall incorporate… the recommendations of Chapter 7 of the National Research Council's Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde, into the IRIS process" as well as that the Agency specifically document and address recommendations for future assessments. Furthermore, the Committee prohibited funds to be "used to take any administrative action based on any draft or final assessment that does not incorporate the recommendations… as part of the assessment process."[14]

- Not fully addressing and documenting responses to 2011 review comments violates EPA's own peer review requirements. EPA's Peer Review Plan for the "Highly Influential" assessment of formaldehyde commits to "provide significant and relevant public comments to the peer reviewers before they conduct their review…"[15] EPA's current Peer Review Handbook states that "[t]he credibility of the final influential work product is likely to be enhanced if the public understands how the Agency addressed the specific concerns raised by the peer reviewers." It further notes that, for "Highly Influential Scientific Assessments" like this, "EPA offices should prepare a written response to comments in the peer review report explaining (1) the Agency's agreement or disagreement with the views expressed in the report; (2) the actions that have been or will be taken to respond to the report; and (3) the reasons that the EPA office believes those actions satisfy any key concerns or recommendations in the report."[16] Accordingly, EPA must clearly document its responses to the 2011 review for the 2021 assessment in order to inform the public and peer reviewers.

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[10] 15 U.S. Code § 2625(h).

[11] Pub. L. 92–463, §15, as added Pub. L. 105–153, §2(b), Dec. 17, 1997, 111 Stat. 2689.

[12] https://www.congress.gov/112/crpt/hrpt151/CRPT-112hrpt151.pdf.

[13] Pub. L. 112-74, December 23, 2011.

[14] The Committee also stated: "Furthermore, no funds shall be used for action on any proposed rule, regulation, guidance, goal or permit, issued after May 21, 2009, that would result in the lowering or further lowering of any exposure level that would be within or below background concentration levels in ambient air, public drinking water sources, soil, or sediment."

[15] https://cfpub.epa.gov/si/si_public_pra_view.cfm?dirEntryID=352623&Lab=CPHEA.

[16] https://www.epa.gov/sites/default/files/2016-03/documents/epa_peer_review_handbook_4th_edition.pdf (pg. 87)

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- Sidestepping comments from independent peer review raises issues under both EPA and Office of Management and Budget (OMB) requirements for information quality. Under the Information Quality Act (IQA),[17] and subsequent EPA and OMB guidelines and memoranda from 2001 through 2019,[18] EPA is responsible for a pre-dissemination review of its information products like IRIS assessment. EPA must undertake this review in order to ensure that the information adheres to standards for quality, objectivity, utility, and integrity. The IQA and Agency emphasize peer review as the critical tool to determine whether scientific information is fit for dissemination and/or policy. In addition, EPA's Scientific Integrity Policy "requires adherence to applicable Agency information quality, quality assurance, and peer review policies and procedures, ensuring that the Agency produces scientific products of the highest quality, rigor, and objectivity for use in policy decisions."[19]Accordingly, EPA is bound by its own policies to provide the peer reviewers with all the information as to how the NASEM recommendations were addressed in the 2022 IRIS assessment.

- Marginalizing the 2011 NASEM review is also inconsistent with recommendations of other respected institutions. According to long-standing recommendations on Federal Regulation of Cancer-Causing Chemicals, the Administrative Conference of the U.S., an independent federal agency with EPA as a member, states: "When an agency rejects an advisory panel's scientific judgment, it should explain the basis for that rejection. When an agency selects a regulatory approach whose bases appear inconsistent with a panel's advice, it should explain the legal, social, or other reasons that dictate or justify that choice."[20] Similarly, a 2009 report from the Bipartisan Policy Center recommended that agencies should be required to state in the Federal Register "whether it differed with any conclusions of a scientific advisory committee and if so, why, and should be required to explain how the new regulatory policy is consistent with the conclusions that were accepted."[21] Accordingly, principles of scientific integrity dictate that EPA must address the NASEM recommendations explicitly and clearly.

The Panel has actively supported scientific research to improve the understanding and characterization of potential human health risks associated with formaldehyde and address the scientific gaps identified in the 2011 NASEM review. Formaldehyde has a unique and robust dose-response and hazard assessment database that includes decades of published and peer reviewed literature on the differences and role of exogenous and endogenous formaldehyde in adverse health effects, lack of systemic distribution of inhaled formaldehyde, pharmacokinetic modeling, biological plausibility for adverse effects, non-linear dose response, and dose-dependent transitions for endogenous compounds. The experimental evidence demonstrates that inhaled formaldehyde does not move beyond the portal-of-entry, there is a threshold for nasal tumor formation, and the published data (mechanistic, epidemiological, and toxicological) demonstrate a lack of biological plausibility for a causal association between inhaled formaldehyde and

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[17] Treasury and General Government Appropriations Act, 2001, Pub. L. No. 106-554, § 515(a) (2000) (as codified at 44 U.S.C. § 3516, note).

[18] OMB, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Dissemination by Federal Agencies, 66 FR 49718-49723 (September 28, 2011); OMB Memorandum, Improving Implementation of the Information Quality Act, M-19-5 (April 24, 2019); EPA, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency (October 2002).

[19] https://www.epa.gov/sites/default/files/2014-02/documents/scientific_integrity_policy_2012.pdf.

[20] https://www.acus.gov/recommendation/federal-regulation-cancer-causing-chemicals.

[21] https://bipartisanpolicy.org/download/?file=/wp-content/uploads/sites/default/files/BPC Science Report fnl.pdf.

lymphohematopoietic cancers. We have been transparent with all of this scientific evidence and shared all peer reviewed studies with the agency once the publications became available.

Thank you for your consideration of the ACC Formaldehyde Panel's request regarding the NASEM committee's review of the EPA's 2022 draft formaldehyde IRIS assessment. Again, on behalf of the regulated community and the public, the Panel expects that EPA's 2022 draft formaldehyde IRIS assessment will reflect significant scientific revisions and improvements, prior to public dissemination and the subsequent peer review, as rigorously recommended by the 2011 NASEM review.

Respectfully,

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On Behalf of the ACC Formaldehyde Panel

cc:
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Kathryn Guyton, Senior Program Officer, NASEM
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Appendix 1: 2011 NASEM review of the 2010 draft formaldehyde IRIS assessment

The following sections summarize the key deficiencies identified in the 2011 NASEM review[22] of the 2010 draft formaldehyde IRIS assessment, issues that should be central to the 2022 NASEM review of the 2021 assessment.

Toxicokinetics

The 2011 NASEM committee reviewed the discussion on toxicokinetics of formaldehyde and focused on several key issues: the implications of endogenous formaldehyde, the fate of inhaled formaldehyde, the systemic availability of formaldehyde, the ability of formaldehyde to cause systemic effects and the use of various models. The issue of whether inhaled formaldehyde can reach the systemic circulation was noted by the committee to be extremely important in assessing any risk of adverse outcomes at nonrespiratory sites. The NASEM committee stated "that the weight of evidence suggests that formaldehyde is unlikely to appear in the blood as an intact molecule except perhaps at concentrations high enough to transiently overwhelm the metabolic capability of the tissue at the site of exposure. Thus, direct evidence of systemic delivery of formaldehyde is generally lacking." (5)

Formaldehyde is a highly reactive chemical that interacts with tissues at the initial site of contact (typically the nose) and does not circulate beyond the portal of entry and therefore, neither systemic nor site-specific effects are expected. This has been demonstrated by peer reviewed scientific toxicokinetic experiments in rats and non-human primates that differentiate between endogenous and exogenous formaldehyde N2-hydroxymethyl-dG adducts, DNA-Protein crosslinks, and N6-formyllysine protein adducts using isotope labeled formaldehyde.

The 2010 draft IRIS assessment contained inconsistent statements regarding systemic delivery of formaldehyde. Specifically, the committee noted that "some parts of the draft assume that the high reactivity and extensive nasal absorption of formaldehyde restrict systemic delivery of inhaled formaldehyde so that formaldehyde does not go beyond the upper respiratory tract, and other parts of the draft assume that systemic delivery accounts in part for the systemic effects attributed to formaldehyde exposure." (5)

> "The strongest data cited by EPA in support of systemic delivery of inhaled formaldehyde come from several studies in which antibodies to formaldehyde-hemoglobin and formaldehyde-albumin were detected in blood from exposed workers, smokers, and laboratory animals. The studies did not definitively demonstrate, however, whether adduct formation occurs at a site distant from the portal of entry. For example, it is not known whether the adducts could be formed in the airway submucosal capillary beds or reflect systemic delivery of formaldehyde. Moreover, the draft IRIS assessment does not evaluate the antibody work as critically as the direct chemical-analysis approaches. The committee found that the draft does not offer a sufficient basis for EPA's reliance on the antibody data to support the hypothesis that formaldehyde (or its hydrated form, methanediol) may reach sites distal to the portal of entry and produce effects at those sites." (34)

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[22] National Research Council, *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*, 2001, https://doi.org/10.17226/13142. Subsequent page references are noted parenthetically.

The committee noted that "cytotoxicity and compensatory cell proliferation also appear to play important roles in the carcinogenic mode of action of formaldehyde-induced nasal tumors. Substantial nonlinearity in dose-response relationships was observed in animal studies of DPX cross-links, cytotoxicity, and compensatory cell proliferation (Swenberg et al. 1983; Monticello et al. 1996). There is a strong site concordance between formaldehyde uptake, cytotoxicity, cell proliferation, and tumor formation. Furthermore, no tumors were observed at concentrations that did not also cause cytotoxicity. The draft IRIS assessment discusses this alternative mode of action but relies on the mutagenic mode of action to justify low dose linear extrapolations in the assessment of formaldehyde-induced nasal tumors." (45)

The committee recommended that EPA provide alternative calculations that factor in nonlinearities associated with the cytotoxicity-compensatory cell proliferation mode of action and assess the strengths and weaknesses of each approach.

The 2011 NASEM committee stated while computational fluid dynamic (CFD) models were evaluated by EPA, they were not used to extrapolate to low concentrations.

> "The committee disagreed with EPA's findings that CFD models are not useful for low-dose extrapolations [ ] and recommends that the CFD-based approach also be used to extrapolate to low concentrations, that the results be included in the overall evaluation, and that EPA explain clearly its use of CFD modeling approaches." (44)
>
> "In addition, the committee recommended that the biologically based dose-response (BBDR) model that was developed for formaldehyde should be used in the derivation of unit risk estimates and that some of the manipulations performed by the EPA were extreme, may not be scientifically justified, and should not have been used as the basis of rejection of the use of the BBDR model in its assessment." (6)
>
> "In particular, adjustments of parameter values associated with mutation, birth, and death rates of initiated cells used in EPA's analysis of alternative models that yielded the most extreme deviations from the Conolly et al. (2004) low-dose extrapolations also produced unrealistically high added risks for humans at concentrations that have been observed in the environment of occupationally exposed workers (100% incidence at concentrations as low as about 0.1-1 ppm). Thus, the committee recommends that manipulations of model parameters that yield results that are biologically implausible or inconsistent with the available data be discarded and not used as a basis for rejecting the overall model. The committee concludes that the existing BBDR models were developed from an impressive exposure- and time-dependent database on the modes of actions of formaldehyde in rats and monkeys; exquisitely detailed dosimetry models in rats, monkeys, and humans; and sparse data on humans that required scale-up of key model parameter values from animal studies and other biologic data and epidemiologic observations to constrain the human model predictions. The scope of the research makes this one of the best-developed BBDR models to date for any chemical, even with its acknowledged uncertainties." (56)

Mode of Action

EPA based its approach to its cancer assessment primarily on the conclusion that formaldehyde is a genotoxic chemical that causes mutation (a mutagenic mode of action). However, the committee noted,

for nasal tumors attributed to formaldehyde exposure, animal data supports a mode of action characterized by regenerative cellular proliferation that results from cytotoxicity. (6) The committee recommended that "EPA provide additional calculations that factor in regenerative cellular proliferation as a mode of action, compare the results with those presented in the draft assessment, and assess the strengths and weaknesses of each approach." (7)

The IRIS assessment speculated that formaldehyde could reach the bone marrow and cause mutagenic effects, however, "despite the use of sensitive and selective analytical methods that are capable of differentiating endogenous exposures from exogenous ones, numerous studies have demonstrated that systemic delivery of formaldehyde is unlikely at concentrations that do not overwhelm metabolism" (7) and that the "causal determinations are not supported by the narrative provided in the draft" (11) for lymphohematopoietic cancers and leukemias. The NASEM committee raised several issues regarding epidemiological evidence:

1) the Draft IRIS assessment relied upon epidemiological evidence to determine causality and the strengths and weaknesses of the epidemiological studies, and inconsistencies in the epidemiological evidence were not discussed,
2) concerns regarding the interpretation of the exposure metrics in the NCI formaldehyde users and producers cohort and
3) specific diagnoses were not considered (such as acute myeloid leukemia, chronic lymphocytic leukemia, and others).

Portal-of-Entry Health Effects

EPA evaluated a wide array of outcomes that the committee characterized as portal-of-entry health effects or systemic health effects. The portal-of-entry effects included irritation, decreased pulmonary function, respiratory tract pathology, asthma, and respiratory tract cancers. The committee noted that EPA identified relevant studies for its assessment, but EPA did not discuss or evaluate literature on mode of action that could have supported its conclusions, critical evaluations of the strengths and weaknesses of the studies were generally deficient, and clear rationales for many conclusions were not provided. (7) The committee identified and discussed specific outcomes for the portal-of-entry effects and the EPA's selection and advancement of particular studies used to calculate the candidate reference concentrations (RfCs) and provided detailed recommendations on studies that should be included or excluded for derivation of RfCs. In the review of the human and animal studies, the committee found that EPA did not thoroughly present the study details, critically evaluate the study weaknesses, consider bias or the possibility of confounding by other pollutants. (66)

Systemic Health Effects

The systemic effects evaluated by EPA included immunotoxicity, neurotoxicity, reproductive and developmental toxicity and lymphohematopoietic (LHP) cancers. The committee noted that "the weight of the evidence suggests that it is unlikely for formaldehyde to appear in the blood as an intact molecule, except perhaps when exposure doses are high enough to overwhelm the metabolic capability of the tissue at the site of exposure. Thus, systemic responses are unlikely to arise from the direct delivery of formaldehyde (or its hydrated form methanediol) to a distant site in the body." (92) The committee found that "EPA overstated the evidence in concluding that formaldehyde is neurotoxic; the human data are insufficient, and the candidate animal studies deviate substantially from neurotoxicity-testing guidelines

and common practice." (10) No mode of action was postulated for formaldehyde-induced neurological effects (99) and "the committee does not support EPA's conclusion that behavior changes observed in animals exposed to formaldehyde are not likely to be caused by the irritant properties of formaldehyde." (10)

The committee disagreed with EPA's overall conclusion regarding the totality of the epidemiological evidence related to the reproductive and developmental effects of formaldehyde and the draft IRIS assessment statement that epidemiologic studies provide evidence of a convincing relationship between occupational exposure to formaldehyde and adverse reproductive outcomes. (103) The committee concluded that the overall database on developmental and reproductive effects of inhalation exposure to formaldehyde in animal studies is suggestive of an effect, but not conclusive. (106)

The draft IRIS assessment concluded that there is no framework for establishing causation on the basis of the weight and strength of the evidence (111) between formaldehyde exposure and mortality from all LHP cancers, all leukemias as a group, myeloid leukemias, Hodgkin lymphoma and multiple myeloma. (11) The committee concluded that EPA's conclusions regarding the association between formaldehyde exposure and LHP appear to be subjective, given the limitations and variability of the epidemiologic data, the weak animal data, and the lack of mechanistic data. Although EPA provided an exhaustive description of the studies and speculated extensively on possible modes of action, the causal association between inhaled formaldehyde and lymphohematopoietic cancers, including myeloid leukemia, was not supported. (11)

Derivation of Reference Concentrations and Unit Risk

The NASEM committee found the 2010 draft IRIS assessment lacked clear links to an underlying conceptual framework and did not contain sufficient documentation on methods and criteria for identifying evidence from epidemiologic and experimental studies, for critically evaluating individual studies, for assessing the weight of evidence, and for selecting studies for derivation of the RfCs and unit risk estimates. The committee noted that EPA's dose-response assessments for cancer and noncancer effects have evaluated some end points for which there may not be adequate evidence to support the conclusion of a causal relationship between that end point and formaldehyde exposure. (118) The committee agreed with EPA's assessment of a causal relations between formaldehyde and portal-of-entry noncancer effects with the exception of asthma, but noted the evidence was not sufficient to support a causal relationship between formaldehyde exposure and systemic noncancer effects on the immune system, the reproductive system, and development. (120)