Summary of Comments on IRIS Toxicological Review of Formaldehyde-Inhalation

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Author: hvb3 Subject: Sticky Note Date: 12/22/2021 10:56:01 AM
I will be using the acronyms for the comment importance as follows:

T1 = Tier 1
T2- Tier 2
T3- Tier 3

EPA/635/R-21/286a
Interagency Review Draft
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Toxicological Review of Formaldehyde—Inhalation

CASRN 50-00-0

In Support of Summary Information on the Integrated Risk Information System (IRIS)

December 2021

Integrated Risk Information System
Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

evidence inadequate[1]) as to whether formaldehyde inhalation exposure may pose a human hazard for specific types of cancer or individual noncancer health effects, given relevant exposure circumstances. The evidence integration for cancer concludes with a descriptor summarizing the weight of evidence for cancer according to EPA's cancer guidelines (U.S. EPA, 2005a).

Based on the current understanding of the toxicokinetics of formaldehyde inhalation exposure (see Appendix A.2), several practical working assumptions were applied to this assessment. Although some uncertainties remain, the organization and analyses in the assessment assume that inhaled formaldehyde is not distributed to an appreciable extent beyond the upper respiratory tract to distal tissues; thus, it is assumed that inhaled formaldehyde acts via a pathway different from a direct interaction with tissues distal to the portal of entry (POE) to elicit observed systemic effects. Similarly, it is assumed that formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Thus, 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 here to interpreting the human health hazards of inhaled formaldehyde.

The Toxicological Review includes an inhalation reference concentration (RfC) value for lifetime exposure. The inhalation RfC (expressed in units of μg of substance/m^3 air) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous daily exposure of formaldehyde to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. A carcinogenicity assessment was also performed, including derivation of an inhalation unit risk value (IUR), which is an upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/m^3 in air. In addition, organ/system-specific RfCs (osRfCs) were derived for the various noncancer health endpoints, when supported by the available evidence. These may be useful when considering cumulative risk scenarios. Multiple candidate RfCs (cRfCs) were sometimes compared before choosing a representative osRfC. An osRfC was typically selected from cRfCs based on use of higher confidence studies, and higher confidence in the cRfC derivation (including point-of-departure [POD] selection). Where relevant, mechanistic understanding regarding the development of specific health effects (e.g., temporal progression, potential thresholds in dose-response), as well as knowledge of susceptibility, was used to inform approaches to derive points of departure (PODs), uncertainty factors, or confidence levels for the quantitative estimates (e.g., osRfCs, RfC, IUR). Where possible, the assessment attempts to describe the level of response observed across different exposure levels within the range of the data, and to

[1] These level of evidence judgments and their implications are described in detail in the IRIS Handbook (http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086). Note that none of the health effects evaluated in this assessment approached the level of evidence needed to support a judgment of **strong evidence supports no effect**, so this level is not discussed.

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Author: hvb3 Subject: Sticky Note Date: 12/22/2021 10:37:58 AM
Tier 1: Yet, EPA developed systemic RfCs? That doesn't make any sense. In order to make this palatable, inhaled formaldehyde has portal of entry effects and very small amounts are distributed, systemically, to other tissues causing effects that are not from direct interaction with tissues. Or perhaps one could be saying that it is a metabolite of formaldehyde interacting with distal tissues?

Author: hvb3 Subject: Highlight Date: 12/22/2021 10:32:37 AM

Author: hvb3 Subject: Highlight Date: 12/22/2021 10:34:14 AM

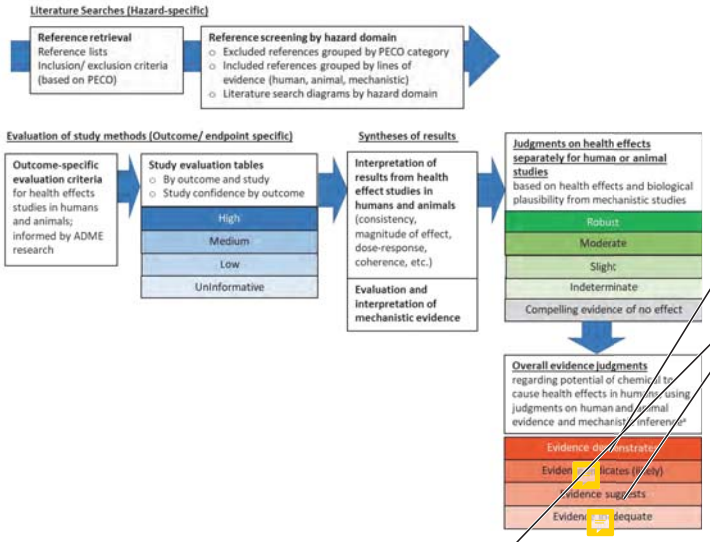

Figure I. Overview of assessment methods for hazard identification.

This figure illustrates the flow of evidence through the assessment, sequentially focusing on the most useful information, as well as the decision-making processes for arriving at evidence judgments regarding the potential for noncancer health effects and for developing specific types of cancer. [a]Mechanistic inference considered during evidence integration included biological plausibility or relevance of animal study results to humans and identification of susceptible groups. Notes: For this assessment, "compelling evidence of no effect" was not reached for any of the human or animal evidence evaluations; as such, criteria for evidence integration when compelling evidence of no effect was present are not discussed in this assessment. Importantly, hazard identification for carcinogenicity includes an additional step of assigning a descriptor regarding the potential for formaldehyde to cause cancer (this step is not shown but is discussed in this section below (see Table IX). Abbreviations: HERO = Health and Environmental Research Online; PECO = Populations, Exposures, Comparisons, Outcomes; ADME = absorption, distribution, metabolism, excretion; MOA = mode of action.

Literature Search Strategy

The literature search strategy used to identify primary research pertaining to formaldehyde inhalation was conducted using the databases and approaches listed in Table I. A separate search strategy was developed for each health hazard considered in the assessment. These strategies are described in detail in Appendix A.5, with PECO criteria, and literature flow diagrams depicting the systematic search and sorting process. Generally, health outcomes and search terms were selected

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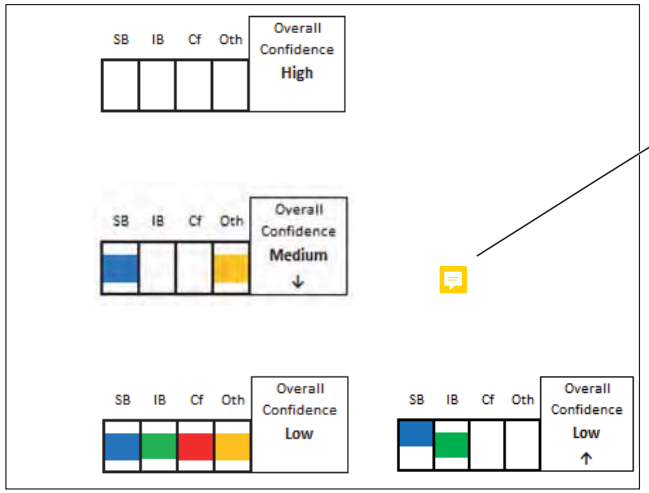
Author: hvb3 Subject: Sticky Note Date: 1/5/2022 9:49:40 AM
Tier 1: "Evidence indicates" is too strong of a category especially since it appears to be used when there is not mechanistic evidence. Suggests the use of only three evidence judgments:
Evidence Demonstrates
Evidence Suggests
Evidence Inadequate

Author: hvb3 Subject: Sticky Note Date: 12/22/2021 10:56:45 AM
T2 - Is this last one supposed to be "Evidence" and not "[vidence"?

Author: hvb3 Subject: Sticky Note Date: 12/22/2021 11:04:09 AM
T2- Revamp the figure to include all the work that was done to include no effect and cancer. I would suggest that no effect and cancer be added to the figure with a cross-out of the box (es) so that the figure explains all that was done and not just part of the work.



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Author: hvb3 Subject: Sticky Note Date: 12/22/2021 11:16:40 AM
T2- there is no labeling of panels in this Figure. Suggest inserting "A, B, C" in the appropriate places for clarity.
T2- An explanation as to why there are different colors would be helpful. I.e. Do the different colors have different meaning? Either that or make all 'shading' the same color.

Figure II. Summary depictions of evaluation of epidemiology studies.

The extent of column shading reflects the degree of limitation. The direction of anticipated bias is indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate). Panel A: *High* confidence study; Panel B: *Medium* confidence study with likely attenuated effect estimate; Panel C: Two possible examples for a *low* confidence study. Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis.

The synthesis of evidence (see next section) focuses on the *medium* and *high* confidence studies, if available, taking into account differences in populations and settings (e.g., children and adults; occupational, residential, or in schools), exposure levels, and other aspects of the studies.

Formaldehyde exposure considerations specific to observational epidemiological studies

All residential or school-based studies with measures of formaldehyde exposure were included in the hazard identification evaluation; because the database of studies with direct measurements is relatively large, residential studies with indirect measures of formaldehyde exposure (e.g., based on age of building or presence of plywood) were not included. Most of the included studies attempted to estimate average formaldehyde levels using area samples placed in one or more locations; measurement periods ranged from 30 minutes to 2 weeks. A few studies included more than one sampling period (e.g., sampling on multiple days in different seasons over

the course of a year). Studies in adults and in children indicate that area-based (e.g., residential or school) samples are highly correlated with personal samples (Hazenby et al., 2012; Gustafson et al., 2005); therefore, the use of measures based on residential (e.g., bedroom) samples rather than personal samples was not considered to be a limitation when evaluating a study.

There was also variation in the exposure measurements used within occupational settings. For hazard identification, an accurate characterization of "high" versus "low" exposure or "exposed" versus "nonexposed" may be able to provide a sufficient contrast to examine associations, even if there is considerable heterogeneity within the high exposure group. Exposure assessments in occupational studies involved one or more area samples in specific task areas, personal samples, or a combination of both. Sampling periods ranged from less than 1 hour to an entire work shift over 1 or more days. Concentrations were reported as an average of all samples for a particular location or as a time-weighted average (TWA) over the sampling period. Generally, a TWA concentration from a full-shift measurement using personal sampling was preferred as a more precise estimate of average exposure. Other studies that used a formaldehyde-specific exposure definition or semiquantitative measure (e.g., duration, number of embalmings) also were included, although they were concluded to be limited to some extent by exposure misclassification. Studies that defined certain occupational groups with considerable exposure to formaldehyde (e.g., embalmers, pathologists, wood furniture workers) as formaldehyde exposed were included, even in the absence of sampling data.

Evaluation of controlled exposure studies in humans

A process incorporating aspects of the evaluation approaches used for epidemiological studies and experimental animal studies (see below) was used to evaluate controlled exposure studies in humans. The evaluation categories included exposure generation, outcome classification, consideration of possible bias (i.e., randomization and blinding), consideration of confounding (i.e., adequacy of randomization), and details of analysis and presentation of results. A study was judged to be *low* confidence if the exposure generation method resulted in exposure to substances other than formaldehyde (e.g., emissions from pressed wood products), allocation to the order of exposure categories was not random, or subjects were not blinded to their exposure order.

Evaluation of experimental studies

Classification scheme

Toxicological studies differ systematically from observational epidemiological studies because the former seek to control both the exposure and nonexposure conditions of an experiment. This leads to some differences in approach and interpretation. In general, however, toxicological study evaluations considered similar categories to the epidemiological studies. The categories were based on the design of a toxicological study, including test animals, experimental design (e.g., duration of exposure, timing of endpoint evaluations, allocation procedures), exposure

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 9:50:55 AM
T1: The level of correlation may have an effect on the value obtained from area samples to personal samples. Was any adjustment made? Alternatively, were unadjusted and adjusted compared to find out if they influence results?

Author: hvb3 Subject: Highlight Date: 12/22/2021 11:18:30 AM

Author: hvb3 Subject: Sticky Note Date: 12/22/2021 11:25:25 AM
T1: This appears to be different than method used earlier for 'age of building and plywood' (i.e., indirect measures were not used). If the aforementioned are no good for measures, why would semiquantitative be any good for exposure?

Author: hvb3 Subject: Sticky Note Date: 1/5/2022 9:56:17 AM
T1: Same comment as above. Studies without sampling data should not have been addressed without providing significant justification as to what those studies are providing that cannot be gotten from studies with sampling data.

conduct, endpoint evaluation procedures, and data presentation and analysis. The specifics of the considerations applied were different for each type of health outcome examined (see Appendix A.5).

As the expectation is that experimental studies should attempt to control all variables, any study limitation interpreted as capable of influencing the data was considered to have negatively affected the quality (e.g., validity, accuracy) of the results. Thus, these "confounding factors" differ substantially from what would be deemed a potential "confounder" in epidemiological studies.

Formaldehyde exposure considerations specific to controlled exposure (animal or human) studies

Typical human exposures to formaldehyde can be complex and difficult to translate to experimental systems. Experimental exposure to formaldehyde by inhalation is typically achieved through volatilization of formalin or depolymerization of paraformaldehyde. Methanol, present in aqueous formaldehyde solutions to inhibit polymerization, is a potential confounder of associations between observed health outcomes and formaldehyde exposure via formalin. As experimental studies, including controlled exposure studies in either humans or animals should aim to control all variables other than the exposure or manipulations of interest; coexposure to methanol in these studies introduces uncertainty that the effects were caused by formaldehyde alone. Inhaled methanol could affect health endpoints or introduce quantitative uncertainty. An example of the former would be if methanol were distributed to different locations than inhaled formaldehyde, where it could either directly cause effects or, theoretically, be metabolized to formaldehyde and cause effects. An example of the latter would be that, because methanol is metabolized to formaldehyde in vivo, substantial coexposure to methanol could result in differences in tissue-specific formaldehyde levels at identical external formaldehyde exposure levels when different test articles are used. This limitation typically introduces a bias toward an effect and is of particular concern in studies observing systemic effects after exposure. Thus, the test article used to generate the formaldehyde atmosphere in experimental studies was critically evaluated (see Appendix A.5 for details), including consideration of whether a methanol-only control group was used.[3] Although this evaluation was applied to all experimental systems, conclusions about the level of uncertainty introduced by this coexposure varied by health outcome, with a far greater level of concern for potential impacts on nonrespiratory health effects (see Section 1.3, Nervous System Effects,

[3]While one study used a sprayer in a heated vessel to generate formaldehyde from a formalin solution containing a known concentration of methanol (Kamata et al., 1997), presumably resulting in the release of formaldehyde and methanol in proportions that would be conserved from liquid to gas (i.e., allowing air methanol levels to be relatively accurately estimated based on air formaldehyde levels), the remaining formalin studies generally evaporated formalin from solution. Notably, the liquid:air partitioning of methanol and formaldehyde is influenced by the proportions of these agents in aqueous solutions (Albert et al., 2000). Thus, as chamber methanol levels were not analytically measured in the other identified studies, a methanol control group may not eliminate uncertainty. Unfortunately, a calculation for estimating methanol levels released (e.g., by evaporation) from formalin solutions at different levels of inhaled formaldehyde was not identified.

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Author: hvb3 Subject: Highlight Date: 12/22/2021 11:35:21 AM

Author: hvb3 Subject: Sticky Note Date: 12/22/2021 11:37:14 AM
T1: If methanol is problematic then would also look at the possible toxicities of methanol before making any evidence conclusion for formaldehyde.

developmental and reproductive system effects, and lymphohematopoietic (LHP) cancers), as compared to respiratory health effects (see Section 1.2). This disproportionate level of concern is primarily based on two factors: (1) as compared to formaldehyde, which does not appear to be distributed to distal sites in appreciable amounts, inhaled methanol would be readily transported beyond the portal of entry (POE) and could elicit direct effects at distal target tissues, and (2) certain systemic effects evaluated in this assessment (i.e., reproductive and developmental toxicity, nervous system effects) are health outcomes known to be a target of methanol toxicity, while other health outcomes, although generally less well studied, have not been clearly associated with methanol exposure (U.S. EPA, 2013). These issues are discussed further in each major endpoint discussion in Sections 1.2 and 1.3.

For certain health outcomes, the irritant and odorant nature of formaldehyde gas and the inescapable nature of these exposures (animals cannot terminate exposure at irritating levels), can complicate interpretations of causality. In addition, reflex bradypnea is an irritant response that exists in rodents, typically at formaldehyde concentrations exceeding 1 mg/m^3 (see Section 1.1.3), but not humans and can cause large variations between the administered and internal exposures. Although the understanding of irritation-related responses, including reflex bradypnea in rodents, is incomplete (e.g., responses following repeated and prolonged exposure are not well studied; see Appendix A.3), it is generally assumed that irritation- and odorant-specific changes are either short lived or markedly reduced shortly after formaldehyde exposure is removed. In light of these considerations, care was taken to consider in detail the specifics of the study protocols related to formaldehyde exposure (e.g., determining whether a sufficient duration was allotted between exposure and testing, evaluating whether the exposure levels tested were capable of introducing variables such as reflex bradypnea) for certain health outcomes.

Overall, as in observational studies in humans, considerations related to the quality of the exposure paradigms used in experimental studies typically had the strongest influence on study confidence determinations.

Evaluation of mechanistic studies

For the datasets described previously, evaluations of individual mechanistic studies involving formaldehyde inhalation in experimental animals or in vitro models of gaseous formaldehyde exposure considered the same general features evaluated for more apical measures of toxicity (i.e., evaluations of exposure quality and study design were emphasized). The specific criteria were simplified, however, to accommodate the increased heterogeneity of the available mechanistic studies, as compared to the data available for apical measures of toxicity. Similarly, study evaluations of individual mechanistic studies involving exposed humans emphasized consideration of exposure assessment, study design, outcome ascertainment, and comparison groups for potential sources of bias and their potential impact. For the mechanistic studies related to potential noncancer respiratory effects, given the large number of studies identified, individual experiments were characterized as *high* or *medium* confidence, *low* confidence, or *not informative*.

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T2: effect in animal can be to metabolism. breathing slower than normal.

Author: hvb3 Subject: Highlight Date: 12/22/2021 12:16:38 PM

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Author: hvb3 Subject: Sticky Note Date: 12/22/2021 12:19:12 PM
T2: Looks like table II that is below and not 1-II

Author: hvb3 Subject: Highlight Date: 12/22/2021 12:18:41 PM

Author: hvb3 Subject: Sticky Note Date: 12/22/2021 12:22:06 PM
T2: What are these circles? Need explanation in table footer. Are they bullets that will be used later to identify the evidence judgment?

These evaluations emphasized exposure-related considerations and were designed to identify the mechanistic data most likely to be associated with constant, chronic inhalation exposure to formaldehyde (see Appendix A.5.6 for additional details). As these individual study evaluations were less endpoint specific than the evaluations of the individual health effect-specific studies, these evaluations were generally less rigorous. Subsequently, groupings of studies or related endpoints were evaluated to assess the strength of the evidence for different "mechanistic events" as robust, moderate, slight, or indeterminate. Likewise, potential associations between mechanistic events were judged based on the tissue(s)/region(s) assessed and known biological roles within those tissues for the identified mechanistic events. The criteria and presentation of decisions for the strength of the mechanistic evidence relating to potential respiratory health effects are illustrated in Table 1-II. For studies of genotoxicity biomarkers in exposed humans, conclusions about bias and sensitivity were drawn using the same approach as for other epidemiological studies.

Table II. Criteria and presentation of strength of the evidence for each mechanistic event and for potential associations between events relating to potential respiratory health effects

	Evidence judgment[a]	Mechanistic events		Associations between mechanistic events	
		Criteria for conclusions	Presentation[b]	Criteria for conclusions	Presentation[b]
Strongest	Robust	Direct evidence supporting an effect in multiple, consistent *high or medium* confidence studies[b]	Emphasized in Text	Formaldehyde-specific data demonstrate a linkage (i.e., inhibition of mechanistic event "A" prevents or reduces the occurrence of event "B"; events "A" and "B" are linked by concentration, location, or temporality)	→
	Moderate	Direct or indirect (e.g., genetic changes) evidence supporting an effect in at least one *high or medium* confidence study, with supporting evidence (e.g., consistent changes suggesting an effect in *low* confidence studies)[b]	Emphasized in Text	• An association between events "A" and "B" is known based on established (basic) biology • An association has been demonstrated for similar chemicals or effects	⇢
	Slight	• Evidence supporting an effect in one hypothesis-generating *high or medium* confidence study	Minimal Discussion in Text	An association is justifiable, or even expected, based on underlying biology, but it has not been well established (note: events for which a biological	⇢

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outcome. Thus, hazard conclusions were developed for consolidated sets of related health endpoints within an overall hazard category in some instances (e.g., male reproductive toxicity).

For each hazard category, or hazard subdivision, and depending on the data available, separate syntheses were developed for each of the three lines of evidence: namely, human and animal health effect studies and mechanistic studies. These evidence syntheses, which incorporate the evaluations of the strengths and limitations of the available studies as well as considerations related to the toxicokinetics of inhaled formaldehyde, provide a discussion of the information provided by each line of evidence regarding the potential for exposure to formaldehyde via inhalation to result in specific health effects. All informative studies (see above), regardless of the magnitude or direction of results (i.e., whether yielding positive or null results) were considered in assessing the evidence; however, the focus of the synthesis was on the *high* and *medium* confidence studies, when available. Descriptive information about study methods and detailed results are generally presented in tabular or graphical displays, with supportive text. The narrative summaries discuss the nature and breadth of the available literature, highlighting details that contribute to the analysis of the strength of evidence regarding causality in the next section.

The syntheses of the separate lines of evidence—human health effect studies, animal health effect studies, and mechanistic studies—involved related considerations that differed due to the nature of the study designs and applicability of the data (see Table III). Consistency, magnitude of effects, and dose-response gradients were emphasized in the synthesis of results of epidemiological and controlled human exposure studies. While the precision of effect estimates could add to the strength of evidence for a health effect, all of the results were summarized. Consistency between studies was examined by comparing study results by confidence level, specific methodological features that contributed to potential bias, exposure setting, and level of exposure. The primary considerations for synthesizing the results of animal studies were consistency (e.g., across species and across research groups, with consideration of study confidence), magnitude and severity of the effects, dose-response, and coherence of findings for related effects. The information from mechanistic studies in humans or animals relevant to each apical outcome was synthesized, highlighting information that could inform either biological plausibility, coherence, susceptibility, relevance to humans or an improved understanding of dose-response. Given the exposure-related issues specific to formaldehyde and the abundance of data available, the mechanistic evaluations in this assessment focused almost exclusively on in vivo studies of inhalation exposures, with rare exception (e.g., evaluation of in vitro genotoxicity studies).

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Table III. Information most relevant to describing primary considerations informing causality during evidence syntheses

Consideration	Description and synthesis methods
Consistency	• Examines the similarity of results (e.g., direction; magnitude) across studies. When inconsistencies exist, the synthesis considers whether results were "conflicting" (i.e., unexplained positive and negative results in similarly exposed human populations or in similar animal models) or "differing" (i.e., mixed results explained by differences between human populations, animal models, exposure conditions, or study methods) (U.S. EPA, 2005a) based on analyses of potentially important explanatory factors such as: • Confidence in studies' results, including study sensitivity (e.g., some study results that appear to be inconsistent may be explained by potential biases or other attributes that affect sensitivity, resulting in variations in the degree of confidence accorded to the study results) • Exposure, including route (if applicable), levels, duration, etc. • Populations or species, including consideration of potential susceptible groups or differences across lifestages at exposure or endpoint assessment • Toxicokinetic information as an explanation for any observed differences in responses across route of exposure, other aspects of exposure, species, or lifestages The interpretation of the consistency of the evidence and the magnitude of the reported effects will emphasize biological significance as more relevant to the assessment than statistical significance. Statistical significance (as reported by p-values, etc.) provides no evidence about effect size or biological significance, and a lack of statistical significance will not be automatically interpreted as evidence of no effect.
Strength (effect magnitude) and precision	• Examines the effect magnitude or relative risk, based on what is known about the assessed endpoint(s), and considers the precision of the reported results based on analyses of variability (e.g., confidence intervals; standard error). In some cases, this may include consideration of the rarity or severity of the findings (in the context of the health effect being examined). Syntheses will analyze results both within and across studies, and may consider the utility of combined analyses (e.g., meta-analysis). While larger effect magnitudes and precision (e.g., $p < 0.05$) help reduce concerns about chance, bias or other factors as explanatory, syntheses should also consider the biological or population-level significance of small effect sizes. Thus, a lack of statistical significance should not be automatically interpreted as evidence of no effect.
Biological gradient/dose-response	• Examines whether the results (e.g., response magnitude, incidence, severity) change in a manner consistent with changes in exposure (e.g., level, duration), including consideration of changes in response after cessation of exposure. Syntheses will consider relationships both within and across studies, acknowledging that the dose-response (e.g., shape) can vary depending on other aspects of the experiment, including the outcome and the toxicokinetics of the chemical. Thus, when dose-response is lacking or unclear, the synthesis will also consider the potential influence of such factors on the response pattern.

Consideration	Description and synthesis methods
Coherence	• Examines the extent to which findings are cohesive across different endpoints that are known/expected to be related to, or dependent on, one another (e.g., based on known biology of the organ system or disease, or mechanistic understanding such as toxicokinetic/dynamic understanding of the chemical or related chemicals). In some instances, additional analyses of mechanistic evidence from research on the chemical under review or related chemicals that evaluate linkages between endpoints or organ-specific effects may be needed to interpret the evidence. These analyses may require additional literature search strategies. Syntheses will consider potentially related findings, both within and across studies, particularly when relationships are observed within a cohort or within a narrowly defined category (e.g., occupation, strain or sex, lifestage of exposure). Syntheses will emphasize evidence indicative of a progression of effects, such as temporal- or dose-dependent increases in the severity of the type of endpoint observed.
Mechanistic evidence related to biological plausibility	• There are multiple uses for mechanistic information (see 9.2), and this consideration overlaps with "coherence." This examines the biological support (or lack thereof) for findings from the human and animal health effect studies and becomes more impactful on the hazard conclusions when notable uncertainties in the strength of those sets of studies exist. These analyses can also improve understanding of dose- or duration-related development of the health effect. In the absence of human or animal evidence of apical health endpoints, the synthesis of mechanistic information will drive evidence integration conclusions (when such information is available). Syntheses can evaluate evidence on precursors, biomarkers, or other molecular or cellular changes related to the health effect(s) of interest to describe the likelihood that the observed effects result from exposure. This will be an analysis of existing evidence, and not simply whether a theoretical pathway can be postulated. This analysis may not be limited to evidence relevant to the PECO, but may also include evaluations of biological pathways (e.g., for the health effect; established for other, possibly related, chemicals). The synthesis will consider the sensitivity of the mechanistic changes and the potential contribution of alternative or previously unidentified mechanisms of toxicity.
Natural experiments	• Specific to epidemiological studies and rarely available, these examine effects in populations that have experienced well-described, pronounced changes in exposure to the chemical of interest (e.g., blood lead levels before and after banning lead in gasoline).

Evidence Integration and Integration Judgments for Noncancer and Cancer Health Outcomes

For transparency in the sequential decision steps taken to draw overall evidence integration judgments, a two-step, sequential process was used (Figure III). First, judgments regarding the strength of the evidence from the available human and animal studies were made in parallel. These judgments incorporated mechanistic evidence (or MOA understanding) in exposed humans and animals, respectively, that informed the biological plausibility and coherence of the available human or animal health effect studies. Second, the animal and human evidence judgments were combined to draw an overall conclusion(s) that incorporated inferences drawn based on

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Author: hvb3 Subject: Sticky Note Date: 12/22/2021 12:37:11 PM
T1: How is EPA separating out the two (coherence and mechanistic-biological) so that bias is not introduced because related factors were given additional weight?

Author: hvb3 Subject: Sticky Note Date: 12/22/2021 12:40:38 PM
T2: Do you mean separately instead of parallel? Parallel typically signifies a distance from one another (in the english language).

reliable evidence (e.g., mechanistic events and associations with robust evidence are preferred). Based on the known or presumed linkages, these events are organized from a "plausible initial effect of exposure" (e.g., a potential direct interaction between inhaled formaldehyde and biological materials) to each apical toxicity endpoint in a linear fashion, regardless of tissue region. Additional details and other mechanistic changes that might contribute to the observed health effects are discussed in Appendix A.5.6. Note, however, that the lack of mechanistic data explaining an association did not discount results from human or animal health effect studies. To draw these judgments, a modified set of considerations was applied to evidence from studies in humans and animals (Table III). Examples of ways that mechanistic evidence was used in causal analyses and derivation of toxicity values are described in Table IV.

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T1: This needs to be a reason to down-grade the evidence findings. It is significant.

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Author: hvb3 Subject: Highlight Date: 12/22/2021 12:44:41 PM

Consideration	Increased evidence strength (of the human or animal evidence)	Decreased evidence strength (of the human or animal evidence)
	duration dependent. It may also not be a monotonic dose-response (monotonicity should not necessarily be expected), and the analysis will consider the extent to which this might be explained by the available evidence (e.g., different outcomes may be expected at low versus high doses due to activation of different mechanistic pathways or induction of systemic toxicity at very high doses). • Decreases in a response after cessation of exposure (e.g., symptoms of current asthma) also may increase strength by increasing certainty in a relationship between exposure and outcome (this is applicable to human observational studies, but not experimental studies).	• In rare cases, and typically only in toxicology studies, the duration of exposure might reveal an inverse association with effect magnitude (e.g., due to tolerance or acclimation). Similar to the discussion of reversibility above, a decision about whether this decreases strength depends on the exposure context focus of the assessment and other factors. • If the data are not adequate to evaluate a dose-response pattern, then strength is neither increased nor decreased.
Coherence	• Biologically related findings within an organ system, or across populations (e.g., sex) increase strength, particularly when a temporal- or dose-dependent progression of related effects is observed within or across studies, or when related findings of increasing severity are observed with increasing exposure.	• An observed lack of expected coherent changes (e.g., well-established biological relationships), particularly when observed for multiple related endpoints, will typically decrease evidence strength. The decision to decrease depends on the strength of the expected relationship(s), and considers factors (e.g., dose and duration of exposure) across studies of related changes.
Mechanistic evidence related to biological plausibility	• Mechanistic evidence of precursors or health effect biomarkers in well-conducted studies of exposed humans or animals, in appropriately exposed human or animal cells, or other relevant human or animal models (for the human or animal evidence, respectively) increases strength, particularly when this evidence is observed in the same cohort/population exhibiting the health outcome. • Evidence of changes in biological pathways, or providing support for a proposed MOA in models also increases strength, particularly when support is provided for rate-limiting or key events, or conserved across multiple components of the pathway or MOA.	• Mechanistic understanding is not a prerequisite for judging the evidence, and thus absence of knowledge should not be used a basis for decreasing strength (NTP (2015); NRC (2014a).The human relevance of animal findings is assumed unless there is sufficient evidence to the contrary [see IARC (2006b); U.S. EPA (2005a)]. • Mechanistic evidence in well-conducted studies that demonstrates that the health effect(s) are unlikely to occur, or only likely to occur under certain scenarios (e.g., above certain exposure levels), can decrease evidence strength. A decision to decrease depends on an evaluation of the strength of the mechanistic evidence supporting vs. opposing biological plausibility, as well as the strength of the health effect-specific findings (e.g., stronger health effect data require more certainty in mechanistic evidence opposing plausibility).

[a]These ideas build upon the discussion for assessing causality of disease in Hill (1965), although there are some differences in the use or interpretations of the terms (see Toxicological Review).
[b]While humans are "exposed" and not "dosed," and nor are animals "dosed" via inhalation, "dose-response" is used for convention throughout the assessment, although it is acknowledged that 'exposure-response' may be more appropriate in many contexts.
[c]There is a clear overlap in the use of mechanistic evidence to interpret coherence (e.g., informing the relatedness or comparability of potentially coherent health findings) and biological plausibility. The available mechanistic information is also considered during the subsequent step of evidence integration across lines of evidence (see Table VIII).
[d]Although it is not separately listed, Hill's consideration of 'analogy' (information for a similar but different association that supports causation) is indirectly encompassed by the evaluation of coherence during the review of environmental health studies; however, this use of analogous chemicals or exposure scenarios is less common.

Overall evidence integration judgment in narrative	Explanation and example scenarios
	absence of adequate conventional studies in humans or in animals (i.e., *indeterminate* evidence in both).
Evidence inadequate[d]	This conveys either a lack of information or an inability to interpret the available evidence. • This category was used if there was *indeterminate* human and animal evidence. • This category could also be used with *slight*-to-*robust* animal evidence and *indeterminate* human evidence if strong mechanistic information indicated that the animal evidence was unlikely to be relevant to humans. A conclusion of **inadequate** is not a determination that the agent does not cause adverse health outcomes or is safe. It generally indicates that further research is needed.

Note: This table does not supersede or alter any EPA guidance. It is meant only to provide added transparency for conclusions drawn regarding the level of evidence from human, animal, and mechanistic studies.
[a]Terminology of "was" refers to the default option; terminology of "could also be" refers to alternative options.
[b]For some applications, such as benefit-cost analysis, to better differentiate the categories of **evidence demonstrates** and **evidence indicates (likely)**, the latter category should be interpreted as evidence that supports an exposure-effect linkage that is likely to be causal.
[c]Health effects characterized as having evidence demonstrates and evidence indicates (likely) (and, in some cases, evidence suggests) are evaluated for use in dose-response assessment. When the database includes at least one well-conducted study and a judgment of evidence suggests is drawn, quantitative analyses may still be useful for some purposes (e.g., providing a sense of the magnitude and uncertainty of estimates for health effects of potential concern, ranking potential hazards, or setting research priorities), but not for others [see related discussions in U.S. EPA (2005c)]. It is critical to transparently convey the extreme uncertainty in any such estimates.
[d]Specific narratives for each of the health effects with an evidence integration judgment of **evidence inadequate** may be deemed unnecessary.

For carcinogenesis only, the weight of evidence as to whether formaldehyde inhalation exposure is carcinogenic to humans was summarized using descriptors, consistent with EPA guidelines (U.S. EPA, 2005a) (Table IX). For this assessment, the descriptors build upon the overall evidence integration judgments for individual cancer types, as described in Table VIII; however, this does not alter or supersede any EPA guidance. These descriptors are bolded and italicized.

Table IX. Criteria for applying cancer descriptors to overall confidence conclusions for cancer types

Cancer descriptor	Criteria
Carcinogenic to humans	This descriptor was used if the **evidence demonstrates** that, for at least one cancer type, formaldehyde inhalation exposure caused the increase in cancer incidence or mortality. This descriptor could also be used in rare instances if the **evidence indicates** that formaldehyde inhalation exposure likely causes different cancer types across evidence bases (e.g., when one type of cancer is based on human evidence and

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Author: hvb3 Subject: Highlight Date: 12/22/2021 12:55:17 PM
T2: What is this stating with 'is drawn'? One cannot 'drawn' a judgment. Suggest sentence edit. Consider "and produces an 'evidence suggests' judgment."

Author: hvb3 Subject: Highlight Date: 12/22/2021 12:56:52 PM
T3: There is a different font size here. Revise for consistency.

reproductive toxicity, male reproductive toxicity, respiratory tract cancers (i.e., nasopharyngeal cancer), and lymphohematopoietic cancers (i.e., myeloid leukemia). In some cases, estimates considered information from mechanistic studies (see Table ES-2, footnote c for examples of how these data were considered quantitatively). Specifically, for some outcomes (i.e., nasal cancers; noncancer respiratory tract pathology), analyses included efforts to apply dosimetry models estimating the uptake of inhaled formaldehyde, including an evaluation of modeling efforts to account for the potential contribution of endogenous formaldehyde on uptake (see Section 2.2). Candidate osRfCs or cancer unit risk values were estimated for each of these noncancer or cancer health outcomes, respectively, and the associated uncertainties were discussed. In addition to the overall evidence integration judgment for concluding that formaldehyde inhalation results in specific health effects (which incorporates the individual study confidence), a confidence level of **high**, **medium**, or **low** was assigned to each osRfC regarding the reliability of the associated POD calculation(s). Confidence in the completeness of the database for each osRfC was also assigned. These judgments were used to select the RfC, draw an overall level of confidence in the RfC, and determine the completeness of the formaldehyde literature database. For noncancer health hazards, multiple graphical depictions were developed to display PODs, uncertainty factors, and candidate osRfCs across outcomes and studies, as well as the context of these estimates (e.g., in relation to the study-specific results, in relation to known human exposures to formaldehyde). Organ/system-specific RfCs, a single, overall RfC, and unit risk were selected; the specific rationale is described in Section 2, Dose-Response Analysis. For the derivation of the cancer inhalation unit risk (IUR) estimate, exposure-response analyses for nasopharyngeal cancer (NPC) from an occupational cohort study and cancers of the nose across two bioassays in rats, and for lymphohematopoietic malignancies from an occupational cohort study, were considered. The IUR was based on the preferred unit risk estimate for NPC and application of age-dependent adjustment factors (see Section 2.2.6). An overall level of confidence was assigned to the IUR. For one mechanism that contributes to cancer risk, cytotoxicity-induced regenerative proliferation, a contributing mechanism which appears to involve a threshold, cRfCs were derived using different data sets from rat bioassays.

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Author: hvb3 Subject: Sticky Note Date: 12/22/2021 1:01:30 PM
T3: Is EPA supposed to be using plain language writing? Paragraphs that span a page are not acceptable in plain language. Plain language paragraphs are typically 3 to 5 sentences.

Table X. Considerations for study selection for quantification of dose-response and derivation of toxicity values

Factor	Considerations
Overall Confidence Conclusion	For this assessment, if the data were amenable, a toxicity value was estimated for health effects with evidence integration judgments of **evidence demonstrates** or **evidence indicates [likely]**. Although it may sometimes be possible to develop toxicity values for judgments of **evidence suggests**, given the particulars of the available data in this assessment, toxicity values were not estimated.
Study Confidence	Studies with appropriate study designs (e.g., long-term bioassays were preferred for animal studies of most health effects), reasonably complete reporting of results, and with no identified sources of selection bias, information bias, or confounding that would substantially alter interpretation of study results.
Population	Human studies were preferred over animal studies. Dose-response information for the most susceptible subgroups was evaluated, if appropriate.
Exposure information	Studies with risk estimates for multiple exposure levels or regression coefficients per unit of formaldehyde concentration were generally preferred over LOAELs or NOAELs because they provided information about the shape of the concentration-response curve and allowed for benchmark dose modeling.

The role of endogenously generated formaldehyde in human diseases is largely unknown. This includes endogenous formaldehyde generated during normal cellular metabolic processes, as well as formaldehyde produced endogenously within cells (e.g., in the liver) as a breakdown product of external exposures to other chemicals, including ingestion of caffeine (Summers et al., 2012; Hohnloser et al., 1980) and methanol-rich foods or beverages, such as fruit-based liquors (Riess et al., 2010). The mode of action by which toxicity at distal sites, such as bone marrow or reproductive tissues, may occur in response to inhalation of formaldehyde over long periods, also is not known. Once formaldehyde is inhaled and interacts with extracellular aqueous matrices such as mucus in nasal passages and is hydrated, the biochemical reactivity of inhaled formaldehyde and endogenous formaldehyde are likely to be very similar, given that there are no differences in

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 9:58:51 AM
T1: Um, these processes are both endogenous (originating from within an organism) but it seems EPA is trying to separate these. Suggest rewrite to 'Endogenous generation includes the metabolic formation of formaldehyde and breakdown of other chemicals to formaldehyde.' Continue with sentences having examples.

chemical structure. However, no specific data are available to inform whether there may be differences in interactions with specific extracellular or intracellular macromolecular targets in vivo. While the rate of cellular detoxification of exogenous formaldehyde remains unknown, the production and subsequent detoxification of endogenous formaldehyde appears to be kept under strict control and has been well described (Burgos-Barragan et al., 2017b).

Although understanding of the contribution of endogenous formaldehyde levels on health is minimal, the Toxicological Review assumed that these impacts on background incidence of prevalence of cancer or other health hazards were accounted for because the focus of the assessment is to estimate the extra risk that results from exogenous exposure over background risk. Endogenous formaldehyde might be responsible for some portion of background risks for some health outcomes, particularly when normal detoxification pathways are deficient (e.g., Pontel et al., 2015); but that possibility is not the purpose of this review. This assessment does consider and discuss the potential impact of normal levels of endogenous formaldehyde on the penetration and distribution of inhaled formaldehyde, based on recent dosimetric models Schroeter et al. (2014) and Campbell Jr et al. (2020); see Section 2.2). In addition, efforts to incorporate the unknown contribution of endogenous formaldehyde to background cancer incidence in an attempt to bound low-dose human cancer risks from formaldehyde exposure have been published using a measure of internal dose for inhaled formaldehyde. These papers are discussed in Section 2.2 and Appendix B.2.3.

OVERVIEW AND FLOW OF EVIDENCE INCLUDED IN THE TOXICOLOGICAL REVIEW

The organization, decision process, and conclusions of the Toxicological Review are presented in Table XI. This table summarizes the results of the various evidence identification and evidence analysis steps performed for each health hazard. Table XI portrays how a large body of identified literature (well over 15,000 articles) was distilled to those studies most germane to the potential health effects of inhaled formaldehyde, as well as how the databases for the various health hazards vary (e.g., a large number of nonspecific, as well as lower quality, studies were identified for reproductive and developmental toxicity and nervous system effects), highlighting potential data gaps/deficiencies. The conclusions in this assessment are based on a large set of published research studies (~300). Only a few of the most informative studies in each health hazard category were considered best suited for dose-response analyses to develop candidate RfCs and cancer unit risks.

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Author: hvb3 Subject: Sticky Note Date: 12/22/2021 1:16:15 PM
T1: Surely there is in vitro work that looks at differences in macromolecular targets. The in vitro work then would be able to produce hypotheses applicable to in vivo.

Author: hvb3 Subject: Sticky Note Date: 12/22/2021 1:22:21 PM
T3: Is there a consistent use of comma at one thousand or not? Doesn't appear so in this table with articles identified. Suggest revision for consistency.

Table XI. Evidence flow for information on the potential health effects of formaldehyde inhalation exposure

Noncancer health effects	Articles identified[a]	Considered for use in hazard identification[b]	Considered in dose-response	cRfC derived?	Overall RfC
Sensory Irritation (humans[c])	857	58	6	Yes	Yes
Pulmonary Function (humans[c])	342	53	4	Yes	**Yes**
Immune-Mediated Conditions, focusing on Allergies and Asthma	4,709	52	9	Yes	**Yes**
Respiratory Tract Pathology	2687	88	4	Yes	No
Neurological Effects	6531	100	0	No	No
Developmental or Reproductive Toxicity	10,154	55	5	Yes	No
Carcinogenicity	**Articles identified**	**Considered for use in hazard identification[b]**	**Considered in dose-response**	**cIUR derived?**	**Overall IUR**
Cancers (all) in Humans[d]	722	59	3	(see below)	N/A
Upper Respiratory Tract (URT) Cancers (humans)	(see above)	(see above)	2	Yes	**Yes**[d]
Lymphohematopoietic (LHP) Cancers (humans)	(see above)	(see above)	2[e]	Yes	No[e]
Other Cancers (humans[d])	(see above)	(see above)	0	No	No
URT Cancers (animals)	285	19	2	Yes	No[f]
LHP Cancers (animals)	49	4	0	No	No

N/A = not applicable.
[a]A subsequent literature update using SEM approaches from 2016-2021 (overlapping with the searches used for the 2017 draft) identified additional articles. A small number considered "possibly impactful" have been included in the draft assessment (see Appendix F).
[b]These articles were all determined to be relevant and are discussed in the assessment or appendices.
[c]Animal studies were not systematically searched for evidence related to these outcomes.
[d]Human epidemiological studies were screened for relevant evidence on any cancer, then subdivided by cancer type.
[e]An overall IUR is derived using URT cancers. An attempt to estimate a unit risk value for myeloid leukemia from the available data is provided for comment during peer review.
[f]Human epidemiological studies were preferred over animal studies.

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:02:11 AM
T2: Is this naopharyngeal cancer? If so, put in table (first row) the abbreviation.

Table ES-2. Cancer evidence integration judgments, carcinogenicity descriptor, and inhalation unit risk (IUR) for cancer incidence

Cancer type investigated	Evidence integration judgment for cancer type risk	Unit risk estimate basis	Unit risk estimate (per µg/m³)	ADAF-adjusted unit risk estimate (per µg/m³)[a]	Confidence in the unit risk estimate
Nasopharyngeal cancer (or nasal cancer in animals)	**evidence demonstrates**[b]	Human	6.4×10^{-6}	1.1×10^{-5}	*medium*
		Animal[c]	8.9×10^{-6} to 1.8×10^{-5}	NA[d]	*medium*
Myeloid leukemia	**evidence demonstrates**[e]	Human	3.4×10^{-5}	NA[f]	*low*
Sinonasal cancer	**evidence indicates [likely]**	No usable data	-	-	
Oropharyngeal/Hypo-pharyngeal cancer	**evidence indicates [likely]**	No usable data	-	-	
Multiple myeloma	**evidence indicates [likely]**	No usable data	-	-	
Hodgkin lymphoma	**evidence suggests**	Not derived	-	-	
Laryngeal cancer	**evidence inadequate**	Not derived	-	-	
Lymphatic leukemia	**evidence inadequate**	Not derived	-	-	
Carcinogenicity Descriptor:	***Carcinogenic* to Humans**				
Total cancer risk (IUR)[g]:	**1.1×10^{-5} per µg/m³;** Confidence in the IUR is **Medium**				

Abbreviations and definitions: IUR = inhalation unit risk: the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/m³ in air; ADAF = age-dependent adjustment factor.

[a]ADAF adjustments are recommended for cancers for which there is sufficient evidence that formaldehyde has, at least in part, a mutagenic MOA (see Section 2.2.4).

[b]The judgment of **evidence demonstrates** for NPC cancer is 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.

[c]While the preferred unit risk estimate for NPC is based on a cancer mortality study in humans, several estimates in general agreement with each other were also derived based on animal nasal tumor incidence. These estimates used multiple mechanistic and statistical models, including biologically based dose-response (BBDR) modeling (see Section 2.2.2). In addition, an RfC for one mechanism contributing to nasal cancer development, specifically cytotoxicity-induced regenerative cell proliferation, was estimated to be between 0.006 and 0.018 mg/m³ based on calculations using animal data. Specifically, this narrow RfC range was estimated based on cRfCs from a pathology study of hyperplasia, labeling studies of proliferating cells, and BBDR modeling results (see Section 2.2.2).

[d]NA = not applicable; an ADAF-adjusted value was not calculated for the unit risk estimates based on the animal data on nasal cancer, as the human unit risk estimate for NPC was the preferred estimate.

[e] The judgment of **evidence demonstrates** for myeloid leukemia is based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels. Supporting mechanistic evidence consistent with leukemia development is provided across numerous studies of peripheral blood isolated from exposed workers, including evidence of mutagenicity and

other genotoxic damage in lymphocytes and myeloid progenitors, and perturbations to immune cell populations. The animal evidence is *inadequate* and the findings to date suggest that there may be a lack of concordance across species for leukemia, as leukemia was not increased in two well-conducted chronic bioassays of rats or mice, and the available animal data provide weak mechanistic support for LHP cancers. No MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution (inhaled formaldehyde does not appear to be distributed to an appreciable extent beyond the upper respiratory tract to distal tissues).

[f]NA = not applicable; no ADAF adjustment is recommended for myeloid leukemia because the MOA is unknown (see Section 1.3.3).

[g]The full lifetime (ADAF-adjusted) IUR estimate is based on the ADAF-adjusted estimate for nasopharyngeal cancer (which includes a mutagenic MOA; see Section 1.2.5). Less-than-lifetime exposure scenarios with a very large fraction of exposure during adulthood may not warrant ADAF adjustment, and one may choose to use the unadjusted unit risk estimate of 6.4×10^{-6} per $\mu g/m^3$. Otherwise, see Table 2-39 for an illustration of how to apply the ADAFs to obtain total cancer risk estimates for less-than-lifetime exposure scenarios (see Section 2.2.4).

ES.2 HAZARD ASSESSMENT SUMMARY

ES.2.1. Noncancer Effects

Overall, the **evidence** integration **demonstrates** that inhalation of formaldehyde causes increased sensory irritation and respiratory tract pathology in humans, given the appropriate exposure circumstances. Well-conducted studies in humans and animals support these hazard conclusions, and strong mechanistic evidence in animals provides plausible modes of action (MOAs) for the identified endpoints.

The available **evidence indicates** that formaldehyde inhalation likely causes decreased pulmonary function, an increased frequency of current asthma symptoms or difficulty controlling asthma, and increased allergic responses in humans, given the appropriate exposure circumstances. These conclusions were 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. In addition, the evidence **indicates** that inhalation of formaldehyde likely causes female reproductive or developmental toxicity and reproductive toxicity in men, 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. 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.

Lastly, while a number of 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 (ALS), due to limitations identified in the database (e.g., poor methodology, lack of consistency), the integration of the evidence ultimately resulted in the determination that formaldehyde inhalation may pose a human health hazard, and additional study is warranted. The

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:02:29 AM
T3: The info on repro evidence really does need to be a separate paragraph.

T1: Without supportive mechanistic evidence for female reproductive toxicity, I believe the allover evidence finding should be down-graded to evidence suggests. Disagree completely with "evidence indicates" category (see comment on earlier figure).

Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:02:44 AM
T2/T3: I would be specific here and say additional neurological study is warranted.

available data on potential nervous system effects were considered insufficient for developing quantitative toxicity estimates.

ES.2.2. Cancer

Formaldehyde is ***Carcinogenic to Humans by the Inhalation Route of Exposure***. This conclusion is supported by two lines of evidence:

- 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).

- The **evidence demonstrates** that formaldehyde inhalation causes an increased risk of myeloid leukemia in humans, based on observations of increased risk in groups exposed to occupational formaldehyde levels. This evidence integration judgment is further supported by other studies of human occupational exposure that provide strong and coherent mechanistic evidence identifying clear associations with additional endpoints relevant to 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, including genotoxicity (i.e., **inadequate evidence**).

Additional support:

- This carcinogenicity conclusion is corroborated by several other lines of evidence for which the integration of the **evidence indicates** that formaldehyde inhalation likely causes that cancer type in humans, namely sinonasal cancer, oropharyngeal/hypopharyngeal cancer, and multiple myeloma.

- 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 nasopharyngeal and sinonasal cancers. The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.

The hazard conclusion for cancer is consistent with those drawn by other expert review panels. Formaldehyde was classified as a known carcinogen by the NTP (NTP, 2011) and a Group 1 carcinogen by IARC (IARC, 2012a, 2006a) , both based on evidence for nasal cancers in humans and animals and myeloid leukemia in humans, with supporting data on mechanisms of carcinogenesis. In addition, an expert committee convened by the NAS confirmed the conclusions of the NTP 12th Report on Carcinogens (RoC) and conducted an independent review of the literature through 2013,

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:08:18 AM
T1: Reproductive toxicity and LHP? Mechanistically a reach. What lines of evidence is there for reproductive toxicity and LHP? Recommend separating the findings for these two endpoints since at least one (LHP) has an evidence conclusion.

Author: hvb3 Subject: Highlight Date: 1/4/2022 9:50:25 AM

Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:09:03 AM
T2: The yellow highlighted statement is confusing since the bullet is about 'evidence demonstrates'. Try "However" (not generally), evidence supporting...
2) Could it just be said that animals studies don't support the conclusion but that the mechanisms between human and other animals species may be different enough to be causing the anomaly? This instead of the highlighted. Refer the reader to where more information is found too.

Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:09:26 AM
T2: If NPC is going to be separated from these other cancer types, I would not have put this as supporting evidence as it leads to confusion. Instead make strong evidence conclusions on the other cancer types just as has been done for NPC.

concluding that formaldehyde is a known carcinogen. The European Union and Health Canada concluded that formaldehyde is a genotoxic carcinogen with a cytotoxic MOA (SCOEL, 2017; ECHA, 2012; Health Canada, 2006, 2001).

ES.3 DOSE-RESPONSE ASSESSMENT SUMMARY

ES.3.3. Inhalation Reference Concentration (RfC) for Noncancer Effects:

The reference concentration (the RfC) of 0.007 mg/m^3 is the concentration one can breathe every day for a lifetime that is not anticipated to cause any harmful noncancer health effects.

Organ- or system-specific reference concentrations (osRfCs)

In this assessment, the RfC is based on several osRfCs, which are themselves based on candidate reference concentrations (cRfCs). The cRfCs are estimates for a specific endpoint based on a single, specific study within an organ- or system-specific hazard domain. The osRfCs differ from the associated cRfCs only when there are multiple cRfCs for the same organ system.

The osRfCs that were used to calculate the overall RfC in this assessment were all based on epidemiological studies and were interpreted with either *high*- or *medium-confidence* based on (1) the study results (i.e., confidence in the individual studies used to derive the osRfC), (2) the point of departure (POD) and the cRfC derivation, and (3) the hazard determination (the strongest, highest confidence judgment of **evidence demonstrates** was preferred) (see Table ES-1). In general, the studies preferred as the basis for the derivation of the RfC were those human studies that best represented the general population, including sensitive subgroups. An osRfC was typically selected from those cRfCs that had a greater degree of certainty with regard to both reliability of study results and cRfC derivation (including POD selection). In addition, candidate RfCs with lower composite uncertainty factors (UF_Cs) were preferred.

The overall RfC is within the narrow range (0.006–0.009 mg/m^3) of the group of respiratory system-related osRfCs (sensory irritation, pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control). The health effects generally were observed in the range of indoor formaldehyde concentrations in population studies (effects were observed in studies at approximately 35–40 µg/m^3) and these were used to arrive at the osRfCs associated with the lowest UF_Cs. Thus, the selected RfC is at the upper end of the range of outdoor formaldehyde levels recorded in some locations (average or median levels of formaldehyde in outdoor air typically range from 0.4 to 10 µg/m^3), and it would be expected that levels in indoor air would exceed this concentration in many situations. However, as the RfC is interpreted to be without appreciable risk, even in sensitive subgroups, it is important to note that the potential for health effects in individuals at concentrations between the RfC (0.007 mg/m^3) and levels at which health effects have been observed in the available population studies (~35–40 µg/m^3) is unknown.

Although the RfC is designed to apply to exposures over a lifetime, the relevant window of exposure for some of the effects observed in the contributing studies may be less than a lifetime.

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Author: hvb3 Subject: Highlight Date: 1/4/2022 10:29:12 AM

Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:09:42 AM
T2: osRfC or cRfC for each respiratory type? If there are mulitiple cRfCs making one respiratory type then it is oSRfC if not it is the other.

Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:10:03 AM
T2: Look at sentence again, ignoring the info in parentheses. Does it make sense? Suggest a rephrase of it. The selected (indoor air levels) RfC exceeds the outdoor formaldehyde air levels.
If there were population based studies at the lower outdoor range with health effects, it would be more protective to base an RfC on those. If there are no outdoor studies with health effects at the lower concentrations than I would state that or explain why they cannot be used.

Author: hvb3 Subject: Highlight Date: 1/4/2022 10:38:40 AM

Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:10:17 AM
T2: This sentence may be trying to relay too much. Are you trying to say that sensitive subgroups were not taken into account in developing the RfC? If it is not important (i.e., sensitive subgroups were accounted for) then remove "even in sensitive subgroups" from sentence. If that is the case then the most important thing to relay would be that we don't know if there are effects between RfC and indoor population study concentrations.

µg/m³ (see Table ES-2). EPA guidance recommends that ADAFs be used when estimating the risk of NPC from childhood inhalation exposures to formaldehyde because the NPCs are judged to be due, at least in part, to a mutagenic MOA. In the absence of information to support a chemical-specific age adjustment factor, EPA's default ADAFs should be applied. Thus, the unit risk estimate was adjusted using age-dependent adjustment factors (ADAFs) to address expected increased susceptibility from early-life exposures (see Table ES-1).

Overall confidence in the IUR is **medium**. The availability of suitable human data from which to derive unit risk estimates eliminates one of the major sources of uncertainty inherent in most unit risk estimates—the uncertainty associated with interspecies extrapolation. The NCI longitudinal cohort study used as the basis for the preferred unit risk estimate is a well-conducted study for the purposes of deriving unit risk estimates and there is *high* confidence in the study's results. However, it was the only independent study with adequate exposure estimates for the derivation of unit risk estimates.

There are some uncertainties that could result in an underestimation of the IUR. An important uncertainty is the inability to derive unit risk estimates for all cancer sites with conclusions of **evidence demonstrates** or **evidence indicates** that formaldehyde inhalation exposure is likely to cause these cancer types given relevant exposure circumstances, resulting in an underestimate of the IUR, Since industrial workers are healthier than the general population overall, the unit risk estimates derived from the NCI worker cohort data could underestimate the cancer risk for the general population to an unknown, but likely small, extent. Given the high survival rates for NPC, cancer incidence risk estimates were calculated using the dose-response relationships from the NCI mortality study to reduce the potential to underestimate the unit risk. However, the calculation required certain assumptions, thus, the estimates may under- or overpredict the true risk by an amount expected to be relatively small.

Because a mutagenic MOA was established for NPC, the IUR was calculated using linear low-dose extrapolation from the 95% lower bound on the exposure level associated with the extra risk level serving as the benchmark response, which is considered to be a plausible upper bound on the risk at lower exposure levels. The low dose extrapolation is a source of uncertainty potentially resulting in overestimation of the IUR, possibly by a substantial (e.g., over an order of magnitude) extent.

ES.4 SUSCEPTIBLE POPULATIONS AND LIFESTAGES

Overall, the most extensive research on the health effects of inhaled formaldehyde and susceptible groups indicates a greater susceptibility among children to respiratory disease, manifested as reduced pulmonary function, increased prevalence of current asthma, and greater asthma severity (reduced asthma control). More research is needed to investigate the role of sex, race, nutrition, exercise, and coexposures that may modulate susceptibility to formaldehyde toxicity. Increased early-life susceptibility for cancer is assumed because of the mutagenic MOA for NPC carcinogenicity. Health status and disease, particularly related to the respiratory system, are

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:10:40 AM
T2: If this is the case (overestimation), wouldn't using the BMD (not BMDL) be a more reasonable choice?

likely to be modifying factors of formaldehyde toxicity. Studies suggest that asthmatics are more susceptible than nonasthmatics to declines in respiratory function following formaldehyde exposure. Based on multiple mechanistic studies of respiratory hypersensitivity, it also appears likely that persons with preexisting respiratory allergies would be more sensitive to the respiratory health effects of formaldehyde exposure, although the data informing potential associations between more generalized atopy and respiratory effects in the available human studies were inconsistent. In addition, epidemiological and toxicological studies identify female reproductive or developmental toxicity as a hazard of formaldehyde exposure. At this time, it is not clear whether increased time to pregnancy and spontaneous abortion rates seen in occupationally exposed women are due to reproductive system toxicity or to toxicity to the developing fetus. Finally, reproductive toxicity in males has been associated with formaldehyde inhalation, although this association has only been tested in well-conducted studies of rodents at very high formaldehyde concentrations.

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:10:59 AM
T1: This reproductive link needs to have a mechanism at least that or some hypotheses on a mechanism.

systematic searches for studies of sensory irritation in experimental animals were not conducted. However, mechanistic data informing this health effect were identified and evaluated as part of the overarching review of mechanistic data relevant to potential respiratory health effects (see Appendix A.5.6 for details). Epidemiological studies describing reports of sensory irritation based on questionnaire responses or objective measures, such as eye blink frequency or conjunctival redness, were included. Articles reporting on case reports, illness investigations, and surveillance studies were not included because the studies were not designed to derive an effect estimate of the association between measures of irritation and formaldehyde exposure. The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.2 and A.5.6, as are the specific PECO criteria. Literature flow diagrams summarize the results of the sorting process using these criteria and indicate the number of studies that were selected for consideration in the assessment through 2016 (see Appendix F for the identification of newer studies through 2021). The relevant health effect studies in humans, as well as the mechanistic data informative to sensory irritation, were evaluated to ascertain the level of confidence in the study results for hazard identification (see Appendix A.5.2 and A.5.6).

Methodological issues considered in evaluation of studies

This review focused on the results of controlled human exposure studies and observational studies of exposure to residential populations. The relevant period for the assessment of irritant responses was considered to be concurrent with the time period of the exposure assessment because the symptoms associated with irritation occur immediately (Krakowiak et al., 1998; Andersen and Molhave, 1983; Andersen, 1979). The controlled human exposure studies were able to evaluate symptoms in a controlled environment; therefore, the exposure-response relationship was more precise, and potential confounders were of less concern. However, the study groups were selected for age (younger adults) and were healthy enough to conform to study protocols. These studies evaluated formaldehyde concentrations above 0.1 mg/m^3, while exposure levels in the residential studies ranged from 0.01 (the limit of detection [LOD] in the available studies) to approximately 1 mg/m^3, with a large proportion of residences having levels less than 0.1 mg/m^3. The studies of residential formaldehyde exposure included a wider range of ages (adults and children) and potentially susceptible individuals, some of whom had existing respiratory issues and other health conditions. Evaluations of individual mechanistic studies emphasized consideration of issues related to exposure conduct, as previously described (see Preface and Appendix A.5.6).

Sensory Irritation Studies in Humans

The following discussion is organized by exposure setting, starting first with evidence from controlled human exposure studies, followed by studies of residential exposure, and then laboratory and occupational studies. Evidence tables for each exposure setting (see Tables 1-1 and 1-2) are organized by level of confidence in the study's results and then by publication year.

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:11:35 AM
T2: Why is this a however statement? It seems like sentence before and this one are both positives to study design. Suggest edit.

Clarify. Controlled human exposure studies evaluated above 0.1 mg/m3 and observational (residential) studies at between 0.01 to 1 mg/me3...

constant formaldehyde exposure (Mueller et al., 2013; Lang et al., 2008). Lang et al. (2008) found that increased eye blink frequency and conjunctival redness occurred at 0.62–1.2 mg/m^3 among subjects who also reported symptoms of eye irritation at 0.37 mg/m^3. Mueller et al. (2013) found no exposure-related effect on blinking frequency and conjunctival redness, although total symptom scores increased beginning at 0.37 mg/m^3 with peaks of 0.7 mg/m^3 in a group with nasal hypersensitivity. Studies using objective measures of nasal irritation reported variable results including no change in nasal flow and resistance between 0.19 and 0.62 mg/m^3 (Lang et al., 2008), a decrease in nasal mucus flow at a concentration of 0.37 mg/m^3 and higher (Andersen and Molhave, 1983), and an increase in nasal flow rate among hypersensitive participants at 0.86 mg/m^3 (Mueller et al., 2013). Subjects exhibited a large degree of individual variability in sensitivity for both objective and subjective responses (Mueller et al., 2013; Berglund et al., 2012; Lang et al., 2008).

Table 1-1. Summary of controlled human exposure studies of formaldehyde and human sensory irritation

Study and design	Results
Mueller et al. (2013) **Design:** *N* = 41, age 32 years, nonsmoking, healthy male volunteers; categorized into hyposensitive and hypersensitive based on CO_2 sensitivity measurements in nasal mucosa (cutpoint median 80.3 mm on visual analogue scale [VAS]). Exposure order randomly assigned; repeated measures cross-over design; blinding not described. Five 4-hour exposure conditions, 1 per day, over 5 days. Four 15-minute cycle exercise segments during exposure period. **Outcome:** Irritation assessed by conjunctival redness (digital photographs), blinking frequency (blinks counted in 60-second segments from 5-minute video, two counters blind to concentration), tear film break-up time (time to first close of eyelid while staring at mark on wall), nasal flow and resistance (rhinomanometry), and validated symptom questionnaire (SPES German translation) measured before and 15 minutes before end of exposure. Severity rated using VAS with 100-mm scale. **Exposure:** 4 hours in groups of 2. Clean air, 0.3 + 4 peaks of 0.6 ppm, 0.4 + 4 peaks of 0.8 ppm, 0.5 ppm and 0.7 ppm (0.0, 0.37 + 0.74, 0.49 + 0.98, 0.62, and 0.86 mg/m^3).[a] Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported. Confidence: ***High***	Results presented in graphs of difference between pre- and end of test values. Large variability in scores between subjects for all measures. Blinking frequency and conjunctival redness—no exposure-related effect, tear film break-up time—increased in 0.4/0.8 ppm and 0.5 ppm ($p < 0.05$), nasal flow rate increased in hypersensitive 0.7 ppm ($p < 0.01$); total symptom score increased in hypersensitive at 0.3/0.6 ppm ($p < 0.001$) and 0.4/0.8 ppm ($p < 0.01$), perception of impure air increased in hypersensitive at all exposure levels (including clean air, 0.01 ppm). Control for "negative affectivity" did not alter associations. Combined eye symptom score reported to be increased with higher scores among hypersensitives at all exposures except 0.7 ppm (0.86 mg/m^3). Changes in scores were not statistically significant and no exposure-response was observed (results in online supplemental resource 10 in Mueller et al). Severity measured using VAS ranged between −0.2 and 2.1 mm). **SPES Symptom Score (SD)—Eye Irritation** mg/m^3 Average/peak / Hypo-sensitive[a] / Hyper-sensitive[a] 0 / −0.17 (2.02) / 1.96 (7.59) 0.37/0.74 / 0.23 (2.65) / 2.13 (4.71) 0.49/0.98 / 0.62 (5.71) / 1.43 (5.31) 0.62 / −0.09 (2.14) / 1.24 (2.84) 0.86 / 0.94 (4.56) / 0.52 (4.14) [a]Sensitivity categorized as above or below median for nasal sensitivity to CO_2 irritation.

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:11:43 AM
T2: Suggest inclusion as to why some studies have medium confidence. What caused the lower rating?

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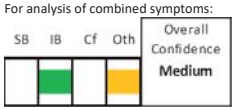
Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:12:12 AM
T2: I prefer the evaluation mini chart because it tells the reader what areas resulted in lowered confidence. That could be added to tables that are missing it. For this table, I would suggest adding a footnote that say what the colors mean on the mini-tables. For instance, green = good/high, yellow = medium, and red = bad. What about when the box does not have a color? Does that mean not assessed?

Table 1-2. Summary of epidemiological studies of residential exposures to formaldehyde and human sensory irritation

Study and design	Results
Zhai et al. (2013) Jan 2008–Dec 2009 (China) (prevalence) **Population:** 186 homes in Shenyang surveyed, homes were decorated in past 4 years and occupied within the past 3 years; randomly selected one adult from each house, plus 82 children (assisted by parents); characteristics of participants were not described. **Outcome:** Reported symptoms and disorders via questionnaire Ferris (1978). **Exposure:** Cited code for indoor environmental pollution control of civil building engineering (GB50325-2001); sampling period not reported. Samplers in breathing zone in bedroom, living room, and kitchen; *N* = 558 in 186 homes; exposure groups "polluted" homes: >0.08 mg/m^3, mean 0.09–0.13 mg/m^3, range 0.01–0.55 mg/m^3, in three rooms; nonpolluted ≤0.08 mg/m^3, mean 0.04–0.047 mg/m^3. **Analysis:** Compared symptom prevalence for children and adults by exposure category (reported *p*-values); multivariate logistic regression of respiratory system symptoms (all) in children and adults, adjusting for age, gender, smoking in family, occupation, education, ventilation frequency, domestic pets, house facing, family history of allergy, height, weight. **Evaluation:**[a] For analysis of combined symptoms:  Combined analysis does not distinguish URT irritation symptoms from asthma-related symptoms; sampling period not reported.	**Respiratory system symptoms and disorders by exposure group (*N* = 186 adults, 82 children)** Symptom / >0.08 mg/m^3 (%) / ≤0.08 mg/m^3 (%) Cough, adults: 16.0* / 4.5 Cough, children: 25 / 8.1 Phlegm, adults: 6.7 / 3.0 Phlegm, children: 15 / 6.7 Wheeze, adults: 5.0 / 3.0 Wheeze, children: 10 / 6.6 Nasal irritation, adults: 52.1** / 16.4 Odor disorder, adults: 21** / 3.0 Throat irritation, adults: 31.9* / 13.4 *p < 0.05, **p < 0.01 **Association of formaldehyde exposure with respiratory system symptoms in adults and children (*N* = 186 adults, 82 children)** Odds Ratio / 95% CI Adults[a]: 2.6 / 1.8, 3.8 Children[b]: 4.3 / 2.1, 8.8 [a]Other statistically significant covariates were ventilation frequency (OR = 1.6) and domestic pets (OR = 1.5) [b]Other statistically significant covariates were ventilation frequency (OR = 1.8) and family history of allergy (OR = 1.9)
Liu et al. (1991); Sexton et al. (1986) (California) Prevalence survey, 1984–1985. 2,203 randomly selected mobile home occupants recruited, 44% response (836 of 1,895 contacted). 1,394 residents in 663 mobile homes in summer and 1,096 residents in 523 mobile homes in winter. 20–64 years of age. **Outcome:** Symptoms (occurrence during 1 week prior to end of sampling period) from mailed questionnaire, questionnaire not described. **Exposure:** Formaldehyde sampling using passive monitors mailed to participants, 7-day samples, two rooms. Average concentration: 0.091 (SD 0.069, range <0.01 (LOD)–0.464) ppm in summer and 0.091 (SD 0.052, range 0.017–0.314) in winter. (0.11 (SD 0.095), range <0.012–0.57 mg/m^3) Cumulative formaldehyde: formaldehyde concentration × hours spent in the residence (ppm-hr). **Analysis:** Logistic regression adjusting for age, gender, smoking status, time spent at home, and chronic respiratory/allergy status.	Significant associations with burning/tearing eyes, stinging/burning skin in summer, and burning/tearing eyes, chest pain, sore throat in winter (effect estimates from logistic regression model were not presented). **Prevalence Burning/Tearing Eyes** ppm-hr / Summer (%) / Winter (%) <7.0: 13.3 / 10.8 7.0–12: 17.1 / 14.7 >12.0: 21.4 / 20.6 Burning/tearing eyes higher among females in regression models.

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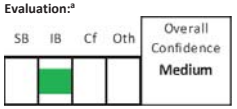
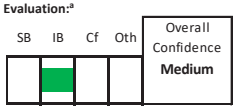
Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:12:25 AM
T2: We only have green here so why is this only medium confidence? Text would be needed.

Study and design	Results
Evaluation:[a] 	
Hanrahan et al. (1984) (Wisconsin) Prevalence survey, 1979 61 teenage and adult occupants from 65 of 208 randomly selected mobile homes. Mean age 48 yrs, 61% female. Participants blinded to exposure status. **Outcome:** Current symptoms with occurrence since moving into home from self-administered questionnaire, questionnaire not described. **Exposure:** Formaldehyde measurements: 1-hour samples, average of measurements in two rooms. Median: 0.16 ppm. Range: <0.1 ppm to 0.80 ppm. Outdoor mean (SD) = 0.04 (0.03) ppm. Windows closed, smoking banned, gas appliances turned off for 30 minutes prior to measurements. **Analysis:** Logistic regression adjusting for age, gender, and smoking. **Evaluation:**[a] 	A statistically significant concentration-response relationship was reported individually for burning eyes and eye irritation; no regression coefficients provided. **Burning Eyes** Concentration (ppm) — Prevalence (%)[a] 0.1 — <5 0.2 — 17.5 0.5 — 65 0.8 — 80 [a]Predicted response estimated by EPA from graphical presentation of logistic regression results normalized to mean age. Formaldehyde concentration not associated with presence of smoker in home or gas appliances. Regression model showed higher prevalence of eye irritation in younger persons.
Olsen and Dossing (1982) (Denmark) Prevalence survey, 1979. Exposed: 66 of 70 employees of seven mobile day care centers (average of 6 months old) paneled indoors with urea formaldehyde glued particle board; mean age 29 years, 10/90 percentiles 19/40 years. Referent: 26 of 34 employees randomly selected from three control (nonmobile home) centers with no materials containing formaldehyde. Mean age 32 years, 10/90 percentiles 25/38 years. All worked in day care centers for >3 months. **Outcome:** Prevalence (yes/no), Severity of symptoms experienced within 1 month measured in centimeters on scale from 0 to 10, "linear" analogue self-assessment method." **Exposure:** Formaldehyde measurements taken after questionnaire study: 2-hour samples in 2–4 locations in the homes. Mean mobile units = 0.43 mg/m^3 (range 0.24–0.55 mg/m^3). Mean referent = 0.08 mg/m^3 (range 0.05–0.11 mg/m^3). **Analysis:** Prevalence and average impact scores compared.	The average frequency of mucous membrane irritation of eyes, nose, and throat was 3× higher among staff of mobile units vs. stationary institutions ($p < 0.01$). Symptoms disappeared after end of work. **Percentage with affirmative answer**[a] Exposed (%) — Referent (%) Eye — 56 — 14.6 Nose/throat — 74 — 25 [a]Estimated by EPA from bar chart in Figure 1 in the paper.

Study and design	Results
Evaluation:[a] SB IB Cf Oth Overall Confidence **Medium**	
Main and Hogan (1983) Prevalence survey 21 exposed individuals working in two mobile trailers for 34 months (mean [SD] age 38 [9] years, 76% male) 18 referent staff members who did not work in the trailers (mean [SD] age 30 [6] years, 50% male) **Outcome:** Modified ATS questionnaire **Exposure:** Three 1-hour area samples taken on four occasions (August, September, December, April) always on a Monday. At least one sample was taken from each office in both trailers. Concentration range 0.12–1.6 ppm (0.15–1.97 mg/m^3)[a] **Analysis:** Group comparisons, χ^2 statistic **Evaluation:**[a] SB IB Cf Oth Overall Confidence **Low** Potential dissimilarity between comparison groups; more exposure to ETS among referent; small sample size	**Symptom Prevalence While at Work** Symptom / Exposed (n = 21) / Referent (n = 18) / χ^2 (p-value) Eye irritation: 0.71 / 0.0 / 20.9 (<0.001) Nasal symptoms: 0.33 / 0.0 / 7.3 (0.01) Throat irritation: 0.48 / 0.0 / 11.5 (0.001)

LOD = limit of detection; RD50 = concentration resulting in a 50% reduction in the respiratory rate; RIL = recommended indoor limit; VOC = volatile organic compound.

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.2). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:12:28 AM
T2: An explanation like this is needed for the medium confidence studies that show only green. What downgraded from high?

Laboratory and occupational exposure

The studies of anatomy students and formaldehyde-exposed workers provide further evidence that formaldehyde exposure is associated with symptoms of eye, nose, and throat irritation. These studies are summarized in tables in the appendix for sensory irritation (Appendix A.5.2). Exposure levels experienced during anatomy laboratory courses and in occupational settings were high and variable. Formaldehyde levels during anatomy courses generally averaged 0.9 mg/m^3 and above during the lab, with short-term peaks above 5 mg/m^3 (Takahashi et al., 2007; Kriebel et al., 2001; Wantke et al., 2000; Kriebel et al., 1993; Uba et al., 1989). These exposures were episodic, one to two sessions per week, for 1–4 hours. Study designs that analyzed reported symptoms and formaldehyde levels measured in close temporal proximity were considered less subject to information bias. The intensity of symptoms (Kriebel et al., 2001)

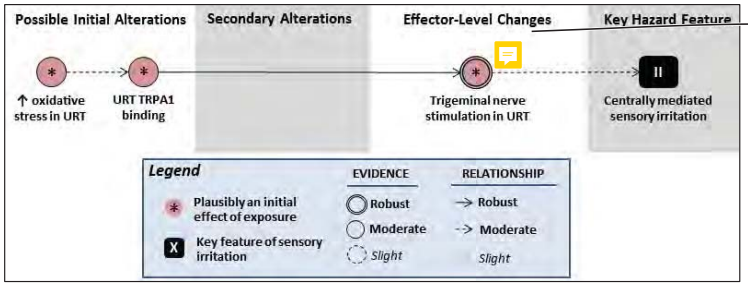

Figure 1-4. Possible mechanistic associations between formaldehyde exposure and sensory irritation.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects (see Appendix A.5.6 for clarifying details) identified this sequence of mechanistic events as likely to be the dominant mechanism by which formaldehyde inhalation could cause sensory irritation.

As illustrated in Figure 1-4, formaldehyde exposure appears to result in activation of chemosensory afferents, likely C fibers, in the URT, presumably in the anterior third of the nasal cavity, based on the pattern of chemosensory activation and consistent with the distribution of inhaled formaldehyde (see Appendix A.5.6). This activation initiates central signals that result in the burning sensation characteristic of sensory irritation. The rapid detection of these sensations in exposed individuals, as well as insights from other irritants, suggest a receptor-mediated event that is dependent on formaldehyde penetration to the nerve endings, which may not have an exposure duration threshold. In vitro and ex vivo studies suggest that activation of the trigeminal nerve by formaldehyde is mediated, at least in large part, through cation channels, primarily the Transient Receptor Potential A1 channel (TRPA1). Alongside the centrally mediated physiological response, the initial activation of the trigeminal nerve is also known to cause a localized release of neuropeptides, such as substance P, from nerve terminals (not shown in Figure 1-4), which can affect local inflammatory and immune responses. Observations of these local neuropeptide changes have been reported at slightly higher formaldehyde levels than those shown to activate the trigeminal nerve, generally at >1 mg/m^3, although the data suggest that they too may be dependent on TRPA1 activation. All of these direct and indirect interactions could act independently or together in a concentration- and duration-dependent manner.

While the response to some irritant chemicals exhibits desensitization or fading of the irritant response over time (e.g., through receptor downregulation) (Nielsen, 1991), it is not clear this is the case with formaldehyde. As previously discussed, results from acute, controlled human exposure studies indicate that some acclimatization may occur over exposures of a few hours at

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Author: hvb3 Subject: Sticky Note Date: 1/5/2022 10:13:01 AM
T2: I am not sure, logically, how moderate evidence can lead to robust evidence; is it because the two moderates sum to robust? Table 1-3 does better at explaining and I don't think this figure is particularly intuitive.