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ASSESSMENT OVERVIEW

for the

TOXICOLOGICAL REVIEW OF FORMALDEHYDE – INHALATION

[CASRN 50-00-0]

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ABBREVIATIONS

Acronym	Definition
ADAF	age-dependent adjustment factors
ADME	absorption, distribution, metabolism, excretion
ALS	amyotrophic lateral sclerosis
AML	acute myeloid leukemia
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BBDR	biologically based dose-response
BMC	benchmark concentration
BMR	benchmark response
CASRN	Chemical Abstracts Service Registry Number
CFD	computational fluid dynamics
CFU	colony-forming unit
CML	chronic myeloid leukemia
cRfC	candidate reference concentration
DPX	DNA-protein cross-link(s)
ETS	environmental tobacco smoke
FDR	fecundability density ratio
FEF	forced expiratory flow
FVC	forced vital capacity
GLP	good laboratory practice
GM	granulocyte, monocyte
HEC	human equivalent concentration
HERO	Health and Environmental Research Online
HSPC	hematopoietic stem or progenitor cell
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease
IUR	inhalation unit risk
LEC	lowest effective concentration
LH	luteinizing hormone
LHP	lymphohematopoietic
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LRT	lower respiratory tract

Acronym	Definition
MDA	malondialdehyde
MDS	myelodysplastic syndrome
MLE	maximum likelihood estimate
MOA	mode of action
MOR	mortality odds ratio
NALT	nasal associated lymphoid tissues
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NPC	nasopharyngeal cancer
NRC	National Research Council
NTP	National Toxicology Program
OR	odds ratio
osRfC	organ/system-specific reference concentration
PBL	peripheral blood lymphocyte
PBPK	physiologically based pharmacokinetic
PECO	Populations, Exposures, Comparisons, Outcomes
PEFR	peak expiratory flow rate
PMR	proportionate mortality ratio
POD	point of departure
POE	portal of entry
RfC	reference concentration
ROS	reactive oxygen species
RR	relative risk
SCC	squamous cell carcinoma
SES	socioeconomic status
SMR	standardized mortality ratio
TSCE	two-stage clonal expansion
TSFE	time since first exposure
TTP	time-to-pregnancy
TWA	time-weighted average
UF	uncertainty factor
URT	upper respiratory tract
WBC	white blood cell

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1. SUMMARY AND ASSESSMENT METHODS

This IRIS health assessment presents a systematic evaluation of the publicly available studies relevant to inhalation exposure to formaldehyde and potential adverse health outcomes. The purpose of the review was to identify hazards that may result from formaldehyde inhalation and describe the level of confidence in the supporting evidence (see EPA cancer guidelines and standard IRIS procedures (U.S. EPA, 2020, 2005a). When there was sufficient confidence in the evidence supporting a hazard and appropriate studies and data were available, toxicity values were derived using either analyses of dose-response or selected no-adverse-effect or lowest-adverse-effect levels (NOAEL or LOAEL). The results of the assessment are summarized in Tables 1 and 2.

The evidence identification, evaluation, and integration framework depicted in Figure 1 was used to conduct the assessment. Potential health hazards were evaluated, including sensory irritation; reduced pulmonary function; immune system effects, focusing on allergic conditions and asthma; respiratory tract pathology; nervous system effects; reproductive and developmental toxicity; and cancer. Several well-studied cancer sites were specifically evaluated, including cancers of the upper respiratory tract (i.e., nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx/hypopharynx, and laryngeal cancer) and of the lymphohematopoietic system (i.e., Hodgkin lymphoma, multiple myeloma, myeloid leukemia, and lymphatic leukemia).

Table 1. Evidence integration judgments for noncancer health effects and the reference concentration (RfC)

Noncancer health effect	Confidence in health effect	POD basis	Confidence in POD	UF_C	osRfC (mg/m^3)
Decreased pulmonary function	**evidence indicates [likely]**[c]	Human	*high*	3	0.007
Allergic conditions	**evidence indicates [likely]**	Human	*high*	3	0.008
Current asthma symptoms or degree of asthma control	**evidence indicates [likely]**	Human	*medium*	10[a]	0.006[d]
Sensory irritation	**evidence demonstrates**	Human	*medium*	10	0.009
Female reproductive or developmental toxicity	**evidence indicates [likely]**	Human	*low*	10	0.01
Respiratory tract pathology	**evidence demonstrates**	Rat	*medium*	30[a]	0.003[d]
Male reproductive toxicity	**evidence indicates [likely]**	Rat	*low*	3,000	0.001
Nervous system effects[a]	**evidence suggests**	Not Derived	-	-	-

	Confidence in health effects	PODs basis	Confidence in PODs	UF_C	Confidence in database	RfC (mg/m^3)	Overall confidence
RfC[b]**:**	*Medium or High*	Human	*Medium or High*	3 or 10[d]	*High*	**0.007**	**High**

Abbreviations and definitions: RfC, reference concentration: an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure of a chemical to the human population (including sensitive subpopulations), that is likely to be without risk of deleterious noncancer effects during a lifetime. osRfC, organ-or system-specific RfC: an RfC based on the evidence for effects on that particular organ or system. UF_C: composite (total) uncertainty factor; POD: point-of-departure.

[a]Three separate judgments were drawn for nervous system effects, all **evidence suggests**; specifically, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause increases in amyotrophic lateral sclerosis incidence or mortality, developmental neurotoxicity, and behavioral toxicity.

[b]Basis for RfC—sensory irritation, decreased pulmonary function, current asthma symptoms or degree of asthma control, and allergic conditions. The corresponding osRfCs (i.e., based on human studies with *medium* or *high* confidence in the health effects and PODs) are highlighted in gray, which also have the lowest UF_C values.

[c]For decreased pulmonary function, the judgment **evidence indicates [likely]** was drawn for long-term exposure durations. For acute or intermediate durations (hrs to wks), the **evidence** is **inadequate** to draw judgments.

[d]These two osRFCs and the RfC are based on multiple studies and candidate values, sometimes with different UF_Cs applied. The UF_C values shown in this table reflect the candidate values selected to represent each osRfC [i.e., the

UF_C applied to the POD from Krzyzanowski et al. (1990) for asthma and from Woutersen et al. (1989) for respiratory pathology].

Table 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 (NPC) (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 demonstratese**	Human	3.4×10^{-5}	NA[f]	*low*
Sinonasal cancer	**evidence demonstratesg**	No usable data	-	-	
Oropharyngeal/ Hypopharyngeal cancer	**evidence suggests**	Not derived	-	-	
Multiple myeloma	**evidence suggests**	Not derived	-	-	
Hodgkin lymphoma	**evidence suggests**	Not derived	-	-	
Laryngeal cancer	**evidence inadequate**	Not derived	-	-	
Lymphatic leukemia	**evidence inadequate**	Not derived	-	-	
Cancer descriptor:	***Carcinogenic* to humans**				
Total cancer risk (IUR)[h]**:**	**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 mode of action (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 2.2.1). In addition, cRfCs for one mechanism contributing to nasal cancer development, specifically cytotoxicity-induced regenerative cell proliferation, were estimated to be between 0.006 and 0.018 mg/m^3 based on calculations using animal data. Specifically, this narrow range of cRfCs was estimated based on PODs from a pathology study of hyperplasia, labeling studies of proliferating cells, and BBDR modeling results (see Section 2.2.1).

[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 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 judgment of **evidence demonstrates** for sinonasal cancer is based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels. The strong animal and mechanistic evidence for nasal cancers across species is interpreted to provide *moderate* evidence supportive of sinonasal cancer (a judgment of *moderate* rather than *robust* reflects some uncertainty in interpreting the nasal cavity findings in animals as fully applicable to the specific human disease of sinonasal cancer).

[h]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 $\mu g/m^3$.

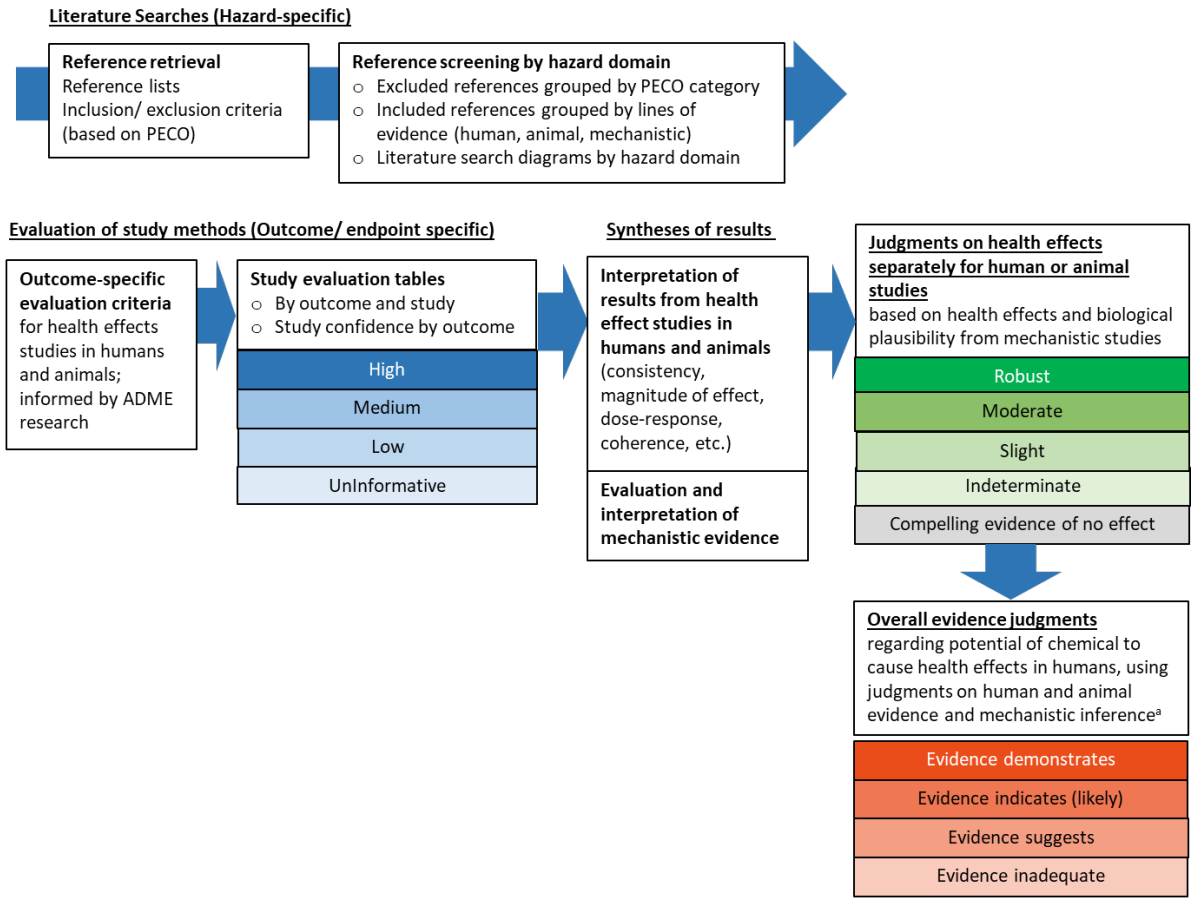

Figure 1. Overview of assessment methods for hazard identification.

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 integration judgments regarding the potential for noncancer health effects and for developing specific types of cancer. *Mechanistic inference considered during evidence integration included biological plausibility, relevance of animal study results to humans, and, in consideration with the available health effect data, identification of susceptible groups. Notes: for this assessment, "compelling evidence of no effect" was not reached for any evidence and, as such, is not discussed further. 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 Section 1.1 below). Abbreviations: HERO, Health and Environmental Research Online; PECO, Populations, Exposures, Comparisons, Outcomes; ADME, absorption, distribution, metabolism, excretion; MOA, mode-of-action.

1.1. ASSESSMENT METHODS

Assessment development was based on EPA guidelines as well as standard IRIS procedures (U.S. EPA, 2020) that were reviewed by the National Academy of Sciences, Engineering, and Medicine (NASEM) (NASEM, 2021). The approaches implemented can be grouped into (1) those used to identify and evaluate individual studies; (2) those used to synthesize the evidence, including interpreting the degree of support for particular human health hazards by integrating different evidence streams (i.e.,

human, animal, and mechanistic studies) and coming to summary conclusions; and (3) selecting and analyzing studies and data to derive quantitative (dose-response) toxicity values. The process involves a successive focusing on the more informative outcomes within each hazard domain as well as the most methodologically robust studies to judge and integrate the evidence within, and across, the human, animal, and mechanistic evidence.

1.1.1. Literature Search and Screening

The literature search strategy used to identify primary research was conducted using the databases and approaches listed in Table 3. A separate, systematic literature search strategy was developed for each health effect considered in the assessment. These strategies are described in detail in Appendix Section A.5, with populations, exposures, comparators, and outcomes (PECO) criteria, and diagrams depicting the search and sorting process. Health effects and search terms were selected after reviewing the draft Toxicological Review for Formaldehyde (U.S. EPA, 2010) and other relevant health assessments or reviews of formaldehyde toxicity. A series of comprehensive literature searches was conducted annually beginning in 2012 through 2016, after which the completed 2017 Step 1 draft IRIS formaldehyde-inhalation assessment was suspended at the request of senior EPA management. When the IRIS assessment was unsuspended in March 2021 (http://www.epa.gov/sites/production/files/2021-03/documents/iris_program_outlook_mar2021.pdf), systematic evidence mapping (SEM) methods were employed to survey the newer literature and expedite updating the unsuspended draft (see Appendix F for the methods and results of the formaldehyde SEM update). In all searches, electronic database queries for published and unpublished studies were supplemented using various approaches to identify additional papers, including review of reference lists in identified publications and national-level health assessments.

Table 3. General approach to literature search strategies

Databases	Health effect-specific searches[b]
Web of Science ToxNet[a] PubMed TSCATS2	[formaldehyde, formalin, paraformaldehyde, OR CASN 50-00-0] AND: Sensory Irritation[c] Pulmonary Function[c] Immune-Mediated Conditions, focusing on Allergies and Asthma Respiratory Tract Pathology Developmental and Reproductive Toxicity Nervous System Effects Cancer Inflammation and Immune Effects (mechanistic information[d])

[a]Toxicology information previously contained in ToxNet were integrated into other NLM products (see https://www.nlm.nih.gov/toxnet/index.html for where to access).
[b]Specific parameters and keywords for each hazard-specific database search strategy are included in Appendix A.5.

[c]A systematic search strategy was not applied to the database of animal studies on this health outcome. Sensory irritation in animals is a well-described phenomenon. For pulmonary function, there was an extensive set of research studies in humans, and therefore, the few studies on this outcome in animals were not reviewed.
[d]This separate, systematic literature search was performed to augment the analyses of mechanisms relevant to other health effect-specific searches. Details are not included in this Overview (see Appendix A.5.6).

The citations for primary health effects studies were screened using inclusion and exclusion criteria based on health effect-specific Populations, Exposures, Comparisons, Outcomes (PECO) considerations. In general, although studies of other routes of exposure might inform the mechanistic understanding of potential health effects, the formaldehyde database is large and the toxicokinetics following inhalation exposure differ significantly from those observed after exposure via other routes (see Section 2 of this Overview); thus, mechanistic descriptions were focused on inhalation exposure studies (an exception includes studies of genotoxicity). Ambient levels of formaldehyde in outdoor air are significantly lower than those measured in the indoor air of workplaces or residences, and the narrow range of exposures (encompassing 0.005 mg/m^3 or less) evaluated in the few epidemiological studies of outdoor exposure limited their sensitivity to find any associations with health outcomes even if they existed. Therefore, the few studies examining health effects in relation to outdoor formaldehyde concentrations were excluded. Other exclusions were based on specific outcome-specific criteria relating to each health hazard, which are summarized in each of the respective health effect-specific PECO tables (see Appendix A.5).

In addition to the health effects listed in Table 3, relevant literature on additional topics (e.g., formaldehyde exposure, toxicokinetics) was identified. The references identified and selected through the literature search process (i.e., all included and excluded studies), including bibliographic information and abstracts, can be found on the Health and Environmental Research Online (HERO) web site: http://hero.epa.gov/hero/index.cfm/project/page/project_id/4051.

For the literature update from 2016–2021 using SEM approaches (overlapping with the searches conducted for the 2017 draft), while the aforementioned description of the search and screening process was largely identical (see Appendix F) a few differences are important to note. Most notably, after screening the studies for PECO relevance, only those studies meeting the PECO criteria and judged as likely to have a potential impact on the conclusions or toxicity values described in the suspended 2017 draft are synthesized in this assessment. Studies meeting PECO criteria that were judged to have no impact on those conclusions or toxicity values are summarized in Appendix F, along with explanations for these decisions. These latter studies are not further discussed or synthesized in the assessment.

1.1.2. Study Evaluation

All human and experimental animal health effect studies identified in the search and included by the screening process described above, without regard to study results, were considered for use in assessing the evidence for health effects potentially associated with inhalation exposure to

formaldehyde. Study methods were evaluated to assign a level of confidence in the results of the study with respect to the health outcome under consideration. These evaluations were performed on a health outcome-specific basis, rather than a study-specific basis; thus, a single study was sometimes evaluated multiple times for different outcomes, sometimes involving slightly different considerations. The evaluations focused on potential sources of bias or other limitations (including reduced sensitivity) that can affect the validity or interpretation of study results. The general procedure involved evaluating specific methodological features, which differed somewhat between observational epidemiology, animal toxicology, and human controlled exposure studies. Sets of studies for each hazard-specific outcome were evaluated by a primary reviewer. The results of the evaluations were then commented on by a second reviewer who also evaluated each study; the evaluation decisions were discussed, and any differences were resolved. A study confidence level was drawn and the evaluation, including relevant study characteristics and an indication of the expected impact of any identified limitations on the results (when possible), was documented in tables (see Appendix A.5).

Systematic evaluations of individual mechanistic studies were also conducted in relation to several important health hazards where a reasonable number of studies were available, but the mechanistic interpretations were not well established. Specifically, this included: biomarkers of genotoxicity in exposed humans, and mechanistic data related to potential nervous system effects or potential respiratory health effects. For these studies, the literature identification methods and study confidence conclusions were similarly documented (see Appendices A.4 and A.5).

The study confidence levels were *high*, *medium*, and *low* confidence, and *not informative*, and are presented as italicized text in the various assessment documents. *High* confidence studies generally had no significant methodological limitations for an outcome, while *medium* confidence studies were considered well conducted but had specific issues that might introduce some uncertainty about attribution of the results solely to formaldehyde exposure on the health outcome in question. Methodological limitations of *low* confidence studies are considered significant, but the outcome-specific results might still be of limited use (e.g., as support for observations from other studies; to identify potential data gaps). The results of studies identified as *not informative* are not discussed in the Toxicological Review or this Overview.

In some situations, study author(s) were contacted to obtain key study details or results that were not presented. A decision to contact an author was based on whether the missing information might result in the reevaluation of methodological features and possibly change the study confidence level, or if it was useful for dose-response analyses. Any additional study details obtained from the authors are noted.

Evaluation of observational epidemiological studies

For each type of health outcome examined, the studies were evaluated for each of the categories of information relevant to internal validity (bias) that could lead to an under- or overestimate

of risk, and sensitivity, features that could affect the interpretation of the results or limit the ability to detect a true association (e.g., narrow exposure range). The categories used for the epidemiological studies included: population selection, exposure (measurement and levels/range), outcome ascertainment, consideration of confounding, and analytic approach. The potential for selection bias, information bias (relating to exposure and to outcome), and confounding were evaluated. The expected direction of bias was explicitly considered and the impact of a potential bias on effect estimates was incorporated in the determination of overall confidence. Emphasis was placed on discerning a bias that would be expected to produce a substantive change in the estimated effect estimate, which would result in a categorization of *low* confidence. If a study or individual analysis was judged to have multiple severe limitations, or if reporting deficiencies precluded the ability to conduct an evaluation for multiple categories, a study or individual analysis was concluded to be *not informative.*

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. The primary reason that some of these studies were judged to be *low* confidence was if the exposure generation method was interpreted to result in significant exposure to substances other than formaldehyde.

Evaluation of animal toxicological studies

In general, toxicology study evaluations considered categories related to those evaluated for epidemiological studies. The categories were based on the design of a toxicology study, and included test animals, experimental design (e.g., duration of exposure, timing of endpoint evaluations, allocation procedures), exposure conduct, endpoint evaluation procedures, and data presentation and analysis. Since 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 from what would be deemed a potential "confounder" in epidemiological studies. Observations in *low* confidence experimental animal studies were determined to have a high likelihood of being influenced by factors other than formaldehyde exposure alone, or there were significant concerns that the observations were attributable to non-specific effects (e.g., toxicity; irritation).

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, however, were simplified 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 studies were characterized as *high* or *medium* confidence, *low* confidence, or *not informative*. Subsequent to this, 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*. *Robust* evidence required multiple, consistent *high* or *medium* confidence studies, while *moderate* evidence required at least one *high* or *medium* confidence study and some supporting information (see Appendix A.5.6 for additional details). For studies of genotoxicity biomarkers in exposed humans, a confidence level of *high*, *medium*, *low*, or *not informative* was assigned to each study, consistent with evaluations of human health effect studies.

Exposure-specific considerations in experimental studies

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 effects and formaldehyde exposure and, because methanol can be converted to formaldehyde in the body, it can also introduce quantitative uncertainty. Thus, a critical evaluation of exposure quality (with an emphasis on the test article used to generate formaldehyde) was applied to experimental studies, although conclusions about the level of concern varied by health outcome. Specifically, far greater concern was raised for potential impacts of methanol coexposure on nonrespiratory health effects (i.e., nervous system effects, developmental and reproductive system effects, LHP cancers), as compared to respiratory health effects. This disproportionate level of concern was primarily based on two factors: (1) as compared to formaldehyde, which does not appear to be distributed to systemic sites in appreciable amounts, inhaled methanol would be readily transported beyond the URT and could elicit direct effects at distal target tissues; and (2) certain, systemic effects evaluated in this assessment (i.e., nervous system effects; reproductive and developmental toxicity) are known to be a target of methanol toxicity, while other health effects, although they are generally less well studied, have not been clearly associated with methanol exposure. Separately, for some endpoints (e.g., nervous system effects), the study evaluations also considered the potential impact of the irritant and odorant nature of formaldehyde gas, and the inescapable nature of these exposures (animals cannot terminate exposure at irritating levels), which can complicate interpretations of causality. Similarly, uncertainties introduced by phenomena such as reflex bradypnea, an irritant response to formaldehyde that can occur in rodents but not humans, are discussed in the evidence syntheses. Thus, during study evaluation, care was taken

to consider the exposure protocols in detail, including the duration between exposure and testing and whether the tested exposure levels were likely to introduce variables such as reflex bradypnea.

1.1.3. Results Display and Evidence Synthesis

For each hazard category, or specific hazard outcome, and depending on the data available, separate syntheses were developed for each of the three streams of evidence: namely, human and animal health effect studies, and mechanistic studies. One notable exception is the mechanistic evidence related to potential respiratory health effects. Given the abundant data available and the assumed interdependence of the mechanisms involved across these health effects, the data were identified and evaluated in a single overarching analysis (see Appendix A.5.6). For brevity, while detailed discussions and analyses are included in the Appendix, the mechanistic syntheses in the Toxicological Review focus on the primary conclusions that could be drawn from the analysis and any outstanding issues, uncertainties, or data gaps that might remain. The evidence syntheses, which incorporate the evaluations of the strengths and limitations of the available studies, are narrative summaries analyzing the information provided by each stream of evidence regarding the potential for exposure to formaldehyde via inhalation to result in specific health effects. All informative human and animal health effect studies (see above), or mechanistic studies (i.e., when individual studies were evaluated) were considered in assessing the evidence; however, the focus of the synthesis was on the *high* and *medium* confidence studies, when available. *Low* confidence studies supported the evaluation of consistency, or if no or few higher confidence studies were available, *low* confidence studies were considered in greater depth. Descriptive information about study methods and detailed results were generally presented in tabular or graphical displays, with supportive text in the Toxicological Review. The evidence syntheses discuss the nature and breadth of the available literature, highlighting details that contribute to the analysis of the strength of the evidence within and across the three streams of evidence, as described in the next section.

The synthesis of the separate streams 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 considered within each stream of evidence (Table 4). 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, results were summarized, regardless of precision. 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, relevance to humans, susceptibility (considering both apical and mechanistic data), 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).

Table 4. Synthesized information most relevant to drawing evidence integration judgments

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 lifestage 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.

Consideration	Description and synthesis methods
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.
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.

Consideration	Description and synthesis methods
Mechanistic evidence related to biological plausibility	• There are multiple uses for mechanistic information 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, this examines 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).

1.1.4. Evidence Integration

For transparency in the sequential decision steps taken to draw overall evidence integration judgments, a two-step, sequential process was used (see Figure 2). First, judgments regarding the strength of the evidence from the available human and animal studies were made. 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 information on the human relevance of the animal evidence (i.e., based on default assumptions or empirical evidence), coherence across the human and animal evidence streams, and susceptibility.

Human and animal evidence judgments from Step 1 and the overall evidence integration conclusion from Step 2 were reached using decision frameworks based on considerations originally described by Austin Bradford Hill (Hill, 1965).

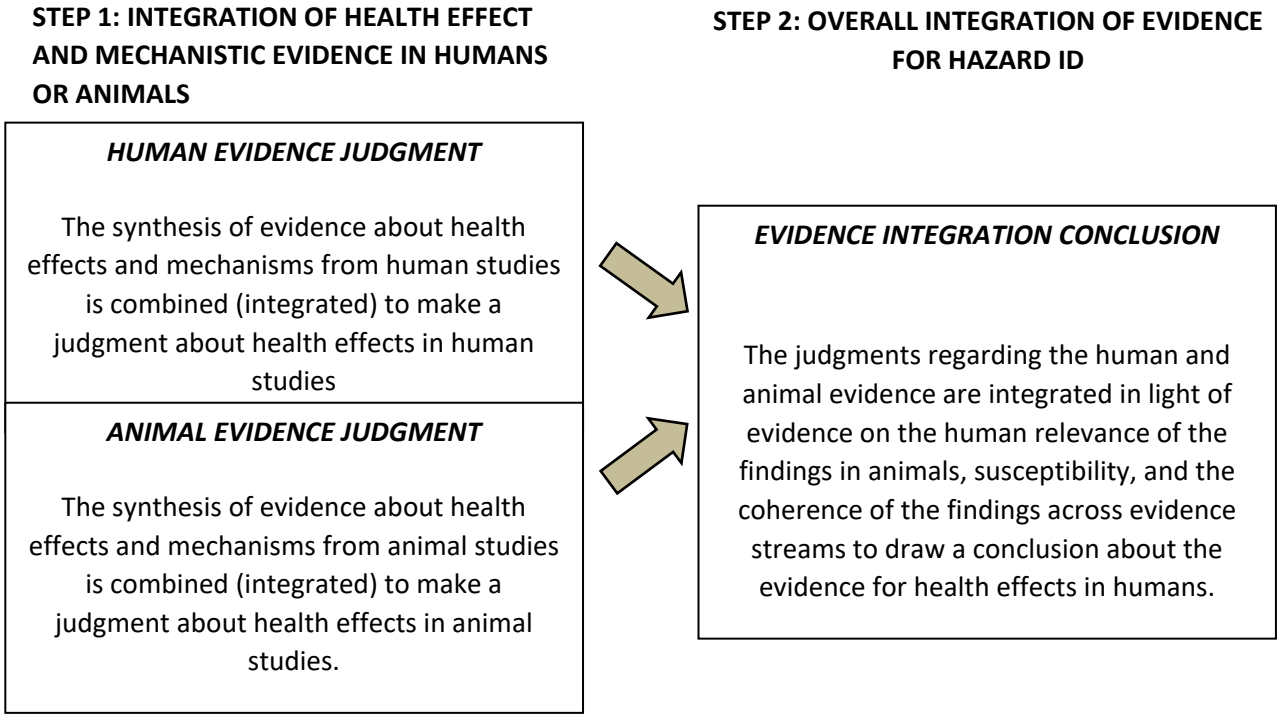

Figure 2. Process for evidence integration.

In the first step, the strength of the human and, separately, the animal evidence for each noncancer health effect (or groups of related effects) and specific cancer type (or groups of related cancer types) was summarized using the following terms: *robust, moderate, slight,* and *indeterminate*, which are presented as italicized text in the various assessment documents. The strength of the human and animal evidence was determined starting from the evidence syntheses that summarized the evidence from the available human and animal health effects studies, respectively, and then considering coherent effects from mechanistic evidence, which could add to or detract from the strength of evidence. 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 (see Table 5).

Table 5. Considerations that inform judgments regarding the strength of the human and animal evidence[a]

Consideration	Increased evidence strength (of the human or animal evidence)	Decreased evidence strength (of the human or animal evidence)
The structured categories and criteria in Tables 6 and 7 will guide the application of strength of evidence judgments for an outcome or health effect. Evidence synthesis scenarios that do not warrant an increase or decrease in evidence strength will be considered "neutral." 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).		
Risk of bias; sensitivity (across studies)	• An evidence base of *high* or *medium* confidence studies increases strength.	• An evidence base of mostly *low* confidence studies decreases strength. An exception to this is an evidence base of studies where the primary issues resulting in *low* confidence are related to insensitivity. This may increase evidence strength in cases where an association is identified because the expected impact of study insensitivity is toward the null. • Decisions to increase strength for other considerations in this table should generally not be made if there are serious concerns for risk of bias.
Consistency	• Similarity of findings for a given outcome (e.g., of a similar magnitude, direction) across independent studies or experiments increases strength, particularly when consistency is observed across populations (e.g., location) or exposure scenarios in human studies, and across laboratories, populations (e.g., species), or exposure scenarios (e.g., duration; route; timing) in animal studies.	• Unexplained inconsistency (conflicting evidence) decreases strength. Generally, strength should not be decreased if discrepant findings can be reasonably explained by study confidence conclusions, variation in population or species, sex, or lifestage, exposure patterns (e.g., intermittent or continuous), levels (low or high), duration or intensity. However, any decisions about decreased strength will be determined by the extent to which residual questions about the evidence may persist.
Strength (effect magnitude) and precision	• Evidence of a large magnitude effect (considered either within or across studies), can increase strength. Effects of a concerning rarity or severity can also increase strength, even if they are of a small magnitude. • Precise results from individual studies or across the set of studies increases strength, noting that biological significance is prioritized over statistical significance.	• The presence of small effects is not typically used to decrease confidence in a body of studies. However, if effect sizes that are small in magnitude are concluded not to be biologically significant, or if there are only a few studies with imprecise results, then strength is decreased. • In animal studies, an example of evidence that can decrease strength involves an effect for which there is a lesser level of concern under some conditions (e.g., rapid reversibility after removal of exposure). Note that many reversible effects are of high concern. Such a decision is informed by factors such as the toxicokinetics of the chemical and the conditions of exposure [see U.S. EPA (1998)], judgments regarding the potential for

Consideration	Increased evidence strength (of the human or animal evidence)	Decreased evidence strength (of the human or animal evidence)
		delayed or secondary effects, as well as the exposure context focus of the assessment (e.g., addressing intermittent or short-term exposures).
Biological gradient/dose-response	• Evidence of dose-response increases strength. Dose-response may be demonstrated across studies or within studies and it can be dose- or 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).	• A lack of dose-response when expected based on biological understanding and having a wide-range of doses/exposures evaluated in the evidence base can decrease strength. • 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 stream, 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 mode-of-action (MOA) in models also increases strength, particularly when support is provided for rate-limiting or	• 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 U.S. EPA (2005a); IARC (2006)]. • 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

Consideration	Increased evidence strength (of the human or animal evidence)	Decreased evidence strength (of the human or animal evidence)
	key events, or conserved across multiple components of the pathway or MOA.	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).

1

Decision frameworks, with criteria described in Tables 6 and 7 were used to develop the judgments concerning the strength of evidence for a health effect within each of the human and animal evidence bases, weighing the strengths and weaknesses of both positive and null studies. These frameworks, which add clarity, consistency, and transparency to the evidence evaluations and conclusions, are consistent with generally accepted principles in epidemiology and toxicology and are meant to convey a distribution of confidence in each body of evidence pertaining to a hazard, a process that relies on expert judgment.

Table 6. Framework for strength of evidence judgments (human evidence)

Strength of Evidence Judgment	Description
Robust *… evidence in human studies*	A set of *high* or *medium* confidence independent studies reporting an association between the exposure and the health outcome, with reasonable confidence that alternative explanations, including chance, bias, and confounding, can be ruled out across studies. The set of studies is primarily consistent, with reasonable explanations when results differ; an exposure-response gradient is demonstrated; and the set of studies includes varied populations. Additional supporting evidence, such as associations with biologically related endpoints in human studies (coherence) or large estimates of risk or severity of the response, may increase confidence but are not required. In exceptional circumstances, a finding in one study may be considered to be *robust*, even when other studies are not available (e.g., analogous to the finding of angiosarcoma, an exceedingly rare liver cancer, in the vinyl chloride industry). Mechanistic evidence from exposed humans or human cells, if available, may add support, informing considerations such as exposure-response, temporality, coherence, and MOA, thus raising the level of certainty to *robust* for a set of studies that otherwise would be described as *moderate*.
Moderate *… evidence in human studies*	A smaller number of studies (at least one *high* or *medium confidence* study with supporting evidence), or with some heterogeneous results, that do not reach the degree of confidence required for *robust.* For multiple studies, there is primarily consistent evidence of an association, but there may be lingering uncertainty due to potential chance, bias or confounding. For a single study, there is a large magnitude or severity of the effect, or a dose-response gradient, or other supporting evidence, and there are not serious residual methodological uncertainties. Supporting evidence could include associations with related endpoints, including mechanistic evidence from exposed humans or human cells, if available, based on considerations such as exposure-response, temporality, coherence, and MOA, thus raising the level of certainty to *moderate* for a set of studies that otherwise would be described as *slight*.
Slight	One or more studies reporting an association between exposure and the health outcome, where considerable uncertainty exists. In general, only *low* confidence studies may be available, or considerable heterogeneity across studies may exist. Supporting coherent

Strength of Evidence Judgment	Description
… evidence in human studies	evidence is sparse. Strong biological support from mechanistic evidence in exposed humans or human cells may also be independently interpreted as s*light*. This also includes scenarios where there are serious residual uncertainties across studies (these uncertainties typically relate to exposure characterization or outcome ascertainment, including temporality) in a set of largely consistent *medium* or *high* confidence studies. This category serves primarily to encourage additional study where evidence does exist that might provide some support for an association, but for which the evidence does not reach the degree of confidence required for *moderate*.
Indeterminate *… evidence in human studies*	No studies were available in humans or situations when the evidence is inconsistent or primarily of *low* confidence.
Compelling evidence of no effect *… in human studies*	Several *high* confidence studies showing null results (for example, an odds ratio of 1.0), ruling out alternative explanations including chance, bias, and confounding with reasonable confidence. Each of the studies should have used an optimal outcome and exposure assessment and adequate sample size (specifically for higher exposure groups and for susceptible populations). The set as a whole should include the full range of levels of exposures that human beings are known to encounter, an evaluation of an exposure-response gradient, and an examination of at-risk populations and lifestages.

Table 7. Framework for strength of evidence judgments (animal evidence)

Strength of evidence judgment	Description
Robust *… animal evidence*	A set of *high* or *medium* confidence experiments includes consistent findings of adverse or toxicologically significant effects across multiple laboratories, exposure routes, experimental designs (e.g., a subchronic study and a two-generation study), or species, and the experiments can reasonably rule out the potential for nonspecific effects (e.g., resulting from toxicity) to have resulted in the findings. Any inconsistent evidence (evidence that cannot be reasonably explained by the respective study design or differences in animal model) is from a set of experiments of lower confidence. At least two of the following additional factors in the set of experiments increases certainty in the evidence for the health outcome(s): coherent effects across multiple related endpoints (may include mechanistic evidence); an unusual magnitude of effect, rarity, age at onset, or severity; a strong dose-response relationship; or consistent observations across animal lifestages, sexes, or strains. Alternatively, mechanistic data in animals or animal cells that address the above considerations or that provide experimental support for a MOA that supports causality with reasonable confidence may raise the level of certainty to *robust* for evidence that otherwise would be described as *moderate* or, exceptionally, *slight or indeterminate*.

Strength of evidence judgment	Description
Moderate *… animal evidence*	A set of evidence that does not reach the degree of certainty required for *robust*, but which includes at least one *high* or *medium* confidence study and information strengthening the certainty in the evidence for the health outcome(s). Although the results are largely consistent, notable uncertainties remain. However, while inconsistent evidence or evidence indicating nonspecific effects (e.g., toxicity) may exist, it is not sufficient to reduce or discount the level of concern regarding the positive findings from the supportive experiments or it is from a set of experiments of lower confidence. The set of experiments supporting the effect provide additional information supporting causality, such as consistent effects across laboratories or species; coherent effects across multiple related endpoints (may include mechanistic evidence); an unusual magnitude of effect, rarity, age at onset, or severity; a strong dose-response relationship; or consistent observations across exposure scenarios (e.g., route, timing, duration), sexes, or animal strains. Mechanistic data in animals or animal cells that address the above considerations or that provide information supporting causality with reasonable confidence may raise the level of certainty to *moderate* for evidence that otherwise would be described as *slight*.
Slight *… animal evidence*	Scenarios in which there is a signal of a possible effect, but the evidence is conflicting or weak. Most commonly, this includes situations where only *low* confidence experiments are available and supporting coherent evidence is sparse. It also applies when one *medium* or *high* confidence experiment is available without additional information increasing the certainty in the evidence (e.g., corroboration within the same study or from other studies). Lastly, this includes scenarios in which there is evidence that would typically be characterized as *moderate*, but inconsistent evidence (evidence that cannot be reasonably explained by the respective study design or differences in animal model) from a set of experiments of higher confidence (may include mechanistic evidence) exists. Strong biological support from mechanistic studies in exposed animals or animal cells may also be independently interpreted as *slight*. Notably, to encourage additional research, it is important to describe situations where evidence exists that might provide some support for an association but is insufficient for a conclusion of *moderate*.
Indeterminate … animal evidence	No animal studies were available, or a set of *low* confidence animal studies exist that are not reasonably consistent or are not informative to the hazard question under evaluation.

Strength of evidence judgment	Description
Compelling evidence of no effect *… in animal studies*	A set of *high* confidence experiments examining a reasonable spectrum of endpoints relevant to a type of toxicity that demonstrate a lack of biologically significant effects across multiple species, both sexes, and a broad range of exposure levels. The data are compelling in that the experiments have examined the range of scenarios across which health effects in animals could be observed, and an alternative explanation (e.g., inadequately controlled features of the studies' experimental designs; inadequate sample sizes) for the observed lack of effects is not available. The experiments were designed to specifically test for effects of interest, including suitable exposure timing and duration, postexposure latency, and endpoint evaluation procedures, and to address potentially susceptible populations and lifestages.

The second stage of evidence integration combined the animal and human evidence judgments, while also considering mechanistic information on the human relevance of the animal evidence, relevance of the mechanistic evidence to humans (especially in cases where animal evidence was lacking), coherence across streams of evidence, and information on susceptible populations, to arrive at an overall evidence integration judgment regarding the evidence for causation (see Table 8). This evidence integration framework interprets the instructions and examples provided in the cancer guidelines (U.S. EPA, 2005a) to allow clarity and consistency in the evaluation of each hazard. The evidence integration framework illustrates the principle that evidence in humans generally has greater weight than evidence in animals. In the absence of sufficiently justifiable MOA information, effects in animal models are assumed to be relevant to humans. In this assessment, for potential health hazards where the evidence from animal models influenced the overall evidence integration judgment, the available mechanistic evidence was considered in light of human relevance.

For each potential health effect evaluated, a narrative summary and evidence integration judgment regarding the available evidence were developed. The overall evidence integration judgments: **evidence demonstrates, evidence indicates [likely], evidence suggests**, and **evidence inadequate** (to judge hazard) are presented as bolded text throughout the assessment and are accompanied by a description of the conditions of expression (e.g., exposure levels, exposure patterns) in the studies that served as the basis for the judgment. For each credible hazard identified (in this assessment, judgments of **evidence demonstrates** or **evidence indicates** [likely]), the "appropriate exposure circumstances" alluded to during hazard identification are more fully evaluated and defined through dose-response analysis (including, when possible, the derivation of toxicity values).

Importantly, for the purposes of this assessment, the same evidence integration approach was used to draw evidence integration judgments for both noncancer health effects and specific cancer types. This approach uses the methods and considerations and described in the EPA cancer guidelines (U.S. EPA, 2005a). Consistent with these guidelines, for carcinogenicity, a final step of categorizing the totality of the evidence using a "descriptor" was performed, as described below.

Table 8. Overall evidence integration judgments for characterizing the integrated evidence for noncancer health effects and cancer outcomes

Overall evidence integration judgment in narrative	Explanation and example scenarios
Evidence demonstrates	This signifies a very high level of certainty that formaldehyde exposure caused the health effect. For this assessment, if the data were amenable, a toxicity value was estimated. • This category was[a] used if there was *robust* human evidence supporting an effect. • This category could also be used with *moderate* human evidence and *robust* animal evidence if there was strong mechanistic evidence that MOAs and key precursors identified in animals were anticipated to occur and progress in humans.
Evidence indicates [likely][b]	This reflects a reasonable certainty that the relationship between formaldehyde exposure and the health outcome was causal, although there may be some outstanding questions that remain. For this assessment, if the data were amenable, a toxicity value was estimated. • This category was used if there is *robust* animal evidence supporting an effect and *moderate*-to-*indeterminate* human evidence when strong mechanistic evidence was lacking. • This category was also used with *moderate* human or animal evidence supporting an effect and *slight or indeterminate* evidence from the opposite evidence stream. In these scenarios, any uncertainties in the *moderate* evidence were not sufficient to reduce or discount the level of concern, or mechanistic evidence in the opposite evidence stream (e.g., precursors) existed to increase confidence in the *moderate* evidence.
Evidence suggests (but is not sufficient to infer)[c]	This conveys some concern that formaldehyde may cause a particular health outcome, but there were very few studies that contributed to the evaluation, the evidence was very weak or conflicting, or the methodological conduct of the studies was poor. Given the substantial degree of uncertainty, additional research would provide valuable information for future evaluations. Although it may sometimes be possible to develop toxicity values for evidence in this category, given the particulars of the available data in this assessment, toxicity values were not estimated. • This category was used if there was *slight* human or animal evidence. • This category could also be used with *moderate* human or animal evidence and *slight or indeterminate* evidence in the opposite evidence stream. In these scenarios, there were outstanding issues regarding the *moderate* evidence that reduced the level of concern or confidence in the reliability of the findings, or mechanistic evidence from the opposite evidence stream (e.g., null results in well-conducted evaluations of precursors) existed to decrease confidence in the *moderate* evidence. • Exceptionally, when there is general scientific understanding of mechanistic events that result in a hazard, this category could also be used if there was strong mechanistic evidence that is sufficient to identify a cause for concern—in the absence of adequate conventional studies in humans or in animals (i.e., *indeterminate* evidence in both).

Overall evidence integration judgment in narrative	Explanation and example scenarios
Evidence inadequate[d]	This conveys either a lack of information or an inability to interpret the available evidence. A toxicity value was not estimated. • 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 guidelines. 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, 2005a)]. 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 is summarized using descriptors, consistent with EPA guidelines (U.S. EPA, 2005a) (see Table 9). For this assessment, the descriptors build upon the overall evidence integration judgments for individual cancer types, as described in Table 8; however, this does not alter or supersede any EPA guidelines.

Table 9. Criteria for applying cancer descriptors to evidence integration judgments 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 for 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 tumors at another site is supported by animal evidence, consistent with EPA

Cancer descriptor	Criteria
	guidelines (U.S. EPA, 2005a) that site-concordance is not required). Such a decision would depend on mechanistic understanding (i.e., in this example, the decision would consider differences in tumor types or ADME across species).
Likely to be carcinogenic to humans	• This descriptor was used if the **evidence indicates** that, for at least one cancer type, formaldehyde inhalation exposure likely caused the increase in cancer incidence or mortality. • Similar to the rationale provided above, this descriptor could also be used in rare instances when the **evidence suggests** formaldehyde inhalation exposure may cause multiple tumor types, depending on mechanistic inference.
Suggestive evidence of carcinogenic potential	This descriptor was used if, for the evidence relating to carcinogenicity, the **evidence** was only **suggestive** that formaldehyde inhalation exposure may cause any of the observed increases in cancer incidence or mortality for any cancer type. This would reflect a substantial degree of uncertainty in any potential causal inference.
Inadequate evidence to assess carcinogenic potential	This descriptor was used if the **evidence** was **inadequate** to draw a conclusion regarding cancers of any type with any confidence. This might reflect a lack of information or highly conflicting information.
Not Likely to be carcinogenic to humans	This descriptor conveys a high degree of certainty that there is negligible concern for carcinogenic effects. A substantial amount of evidence would be required to support this descriptor [see (**U.S. EPA, 2005a**)].

1.1.5. Dose-response Analysis

The Toxicological Review includes an inhalation reference concentration (RfC). The RfC is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous daily inhalation 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 cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/m^3 in air for a lifetime. In addition, organ/system-specific RfCs (osRfCs) were derived for the various noncancer health endpoints, when supported by the available evidence, which may be useful when considering cumulative risk scenarios. Multiple candidate RfCs (cRfCs) were sometimes compared before choosing a representative osRfC. 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). A confidence level of *high*, *medium*, or *low* was assigned to each osRfC and the RfC based on the reliability of the associated POD and cRfC calculation(s). Confidence in the completeness of the database for each osRfC and the overall RfC was also assigned. These decisions were used to draw an overall level of confidence in the RfC. Likewise, an overall level of

confidence was assigned to the IUR. Where possible, the assessment attempts to describe the level of response observed across different exposure levels within the range of the data and transparently discusses the uncertainties and assumptions when deriving and applying the different toxicity value estimates (e.g., cRfCs, IUR).

2. SUMMARY OF TOXICOKINETICS

Several detoxification and removal processes exist for inhaled formaldehyde, including at the site(s) of first contact (e.g., human nasal passages). Much of what is known regarding the uptake and distribution of inhaled formaldehyde is based on experiments using monkeys and rats. Species differences in the structure of the airways and breathing patterns, as well as the composition of the surface epithelium at various nasal locations, are important considerations when interpreting results in experimental animals and extrapolating observations to humans. While the nasal passages in humans are generally similar to other mammalian species, one key difference is that humans and non-human primates have nasal passages adapted for both oral and nasal (oronasal) breathing, as opposed to obligate nasal breathing in rodents. A second key difference regards the shape and complexity of the nasal turbinates, with relatively simple shapes in humans, and complex, folded patterns in rodents. In general, these differences provide better protection of the rodent lower respiratory tract (LRT) against inhaled toxicants than is provided to the human LRT (Harkema et al., 2006).

Uptake of inhaled formaldehyde is based on rough estimates determined from the amount of formaldehyde removed from the air and indicates that the vast majority of formaldehyde is removed from inhaled air by the upper respiratory tract (URT) in monkeys (Casanova et al., 1991; Monticello et al., 1989), dogs (Egle, 1972), and rats (Kimbell et al., 2001b; Chang et al., 1983; Heck et al., 1983; Kerns et al., 1983). Further, dosimetric modeling studies in humans have shown close agreement with observations of exposed rodents. Overall, a concentration gradient of inhaled formaldehyde follows an anterior to posterior distribution, with high concentrations of formaldehyde distributed to nasal squamous, transitional and respiratory epithelium, and less uptake by olfactory epithelium, and very little formaldehyde reaching more distal sites such as the larynx or lung. The possibility that more extensive distribution to the LRT may occur when people are breathing through the mouth during exercise or when they have an upper respiratory tract infection has not been investigated.

As inhaled formaldehyde enters the URT, it interacts with the mucociliary apparatus, the first line of defense against inhaled materials in the nose. In nasal mucus, most of the formaldehyde is rapidly converted to methanediol (~99.9%) and a minor fraction remains as free formaldehyde (~0.1%) (Bogdanffy et al., 1986; Fox et al., 1985). Formaldehyde levels are reduced through interactions with components of the mucus and through mucociliary clearance; through reactions with cellular materials

at the plasma membrane of the respiratory epithelium; via interactions with glutathione (GSH) and other macromolecules in the intracellular and extracellular space; through localized metabolism and conjugation reactions; and through reversible interactions with intracellular materials. This results in the formation of a gradient of formaldehyde across the tissue space, with the greatest formaldehyde concentration at the apical surface of the mucosa, and the lowest levels of formaldehyde at deeper components of the tissue, such as the nasal associated lymphoid tissues (NALT) and blood vessels. Models developed by Schroeter et al. (2014) and Campbell et al. (2020) demonstrate that at sufficiently low levels of exogenous formaldehyde, the uptake of exogenous formaldehyde is reduced due to the presence of endogenous formaldehyde. These results add to the characterization of the uncertainty in formaldehyde dose-response at low exposure concentrations (discussed in further detail in Section 1.1.3 and 2.2.1 of the Toxicological Review).

Several of the key considerations for evaluating the distribution of inhaled formaldehyde to the portal-of-entry (the rat nose is depicted) and systemic sites are represented in Figure 3.

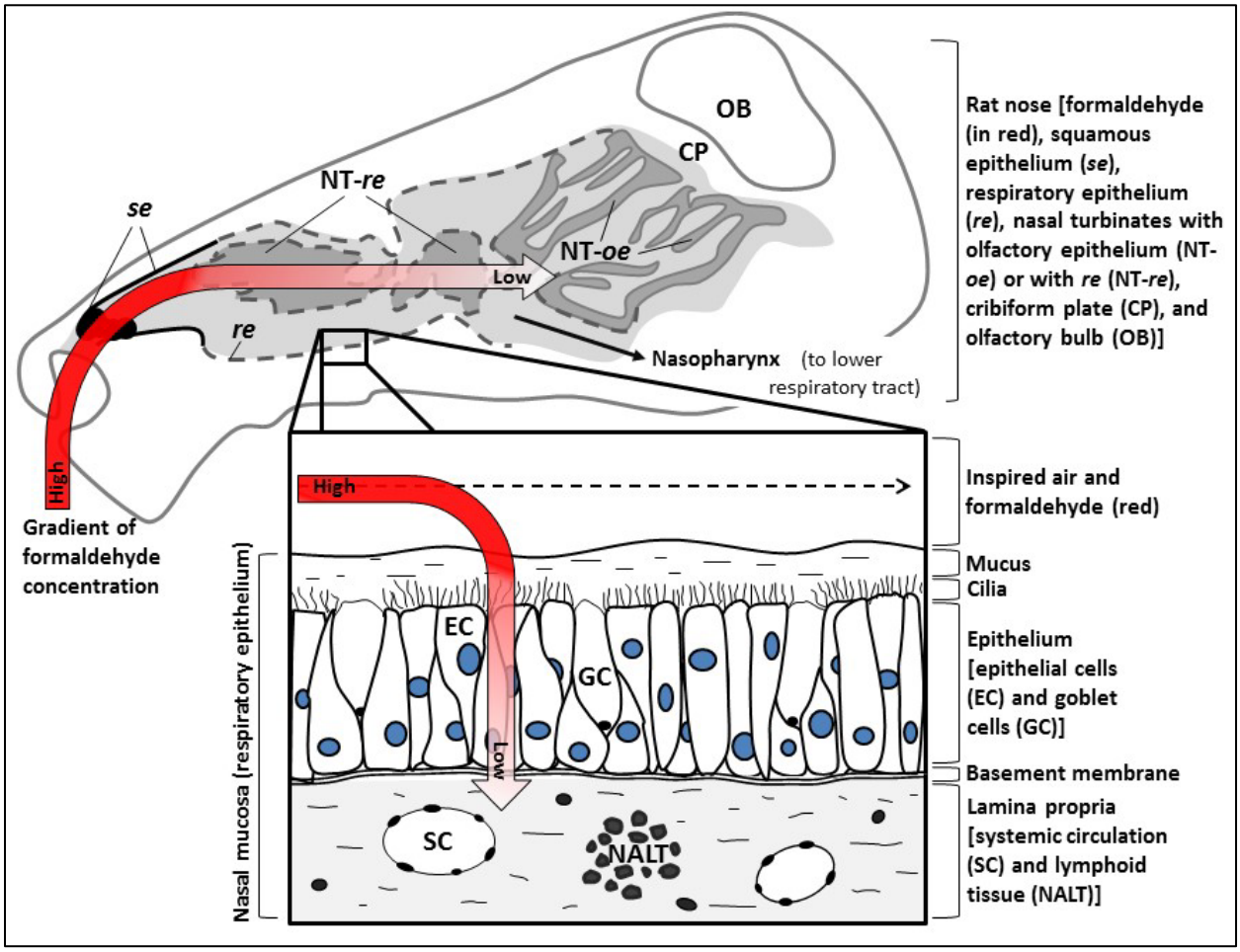

Figure 3. Schematic of the rat upper respiratory tract depicting the gradient of formaldehyde concentration formed following inhalation exposure.

The gradient both from anterior to posterior locations, as well as across the tissue depth is depicted. Modeling based on observations in rodents predicts a similar pattern of distribution in humans. Drawn based in part on images by NRC (2011) and Harkema et al. (2006).

In the respiratory tissue, formaldehyde can be metabolized to formate, which can either enter the one-carbon pool leading to protein and nucleic acid synthesis, or be further metabolized to CO_2 and eliminated in expired air or excreted in urine unchanged. Alternatively, upon interactions with cellular macromolecules, it can form DNA-protein cross-links (DPX), protein adducts (Edrissi et al., 2013b; Edrissi et al., 2013a), or other products, as demonstrated by concentration-dependent increases in DPX formation in rat and monkey nasal passages. Recently, analytical methods have been developed that can distinguish between N^2-hm-dG adducts from exogenous (inhaled) formaldehyde and N^2-hm-dG adducts from endogenous formaldehyde (Lu et al., 2012; Lu et al., 2011; Moeller et al., 2011; Lu et al., 2010). DNA monoadducts (Leng et al., 2019; Yu et al., 2015; Lu et al., 2011; Moeller et al., 2011; Lu et al., 2010) and DPX (Leng et al., 2019; Lai et al., 2016) derived from exogenous formaldehyde were detectable in nasal tissues, but not in distal tissues (including the bone marrow) of experimental animals exposed by inhalation, supporting that exogenous formaldehyde is not systemically distributed. Also, toxicokinetic studies demonstrate that labeled carbon from inhaled formaldehyde measured in bone marrow of rats was the result of metabolic incorporation from the 1-Carbon (1C) pool, not covalent binding, further supporting the lack of transport of formaldehyde or metabolites of formaldehyde to the distal tissues (Casanova-Schmitz et al., 1984). Finally, inhalation exposure to formaldehyde does not appear to alter blood formaldehyde levels (approximately 0.1 mM across different species), suggesting that inhaled formaldehyde is not significantly absorbed into blood (Kleinnijenhuis et al., 2013; Casanova et al., 1988; Heck et al., 1985).

The toxicokinetics of formaldehyde may be influenced by certain formaldehyde-related effects, such as altered mucociliary clearance [e.g., (Morgan, 1983)], reflex bradypnea in rodents (Chang et al., 1983; Chang et al., 1981), and dynamic changes in tissue structure (Kamata et al., 1997), which have the potential to modulate formaldehyde uptake and clearance. For example, during repeated inhalation exposure to formaldehyde, mice, and to a lesser extent rats, lower their minute volume thereby restricting the intake of the gas (Chang et al., 1983; Chang et al., 1981), which may impact dosimetric adjustment if the dose-response results from these studies are extrapolated to humans.

3. NONCANCER HEALTH EFFECTS

Based on the current understanding of the toxicokinetics of formaldehyde inhalation exposure, 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 respiratory tract to systemic sites; thus, it is assumed that inhaled formaldehyde is not directly interacting with tissues distal to the portal-of-entry to elicit effects. Similarly, it is assumed that formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Thus, for the purposes of this assessment, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts measured in distal tissues and health outcomes are not considered relevant to inhaled formaldehyde.

Research on several noncancer respiratory health effects was evaluated: sensory irritation; pulmonary function; immune-mediated conditions, focusing on allergic conditions and asthma; and respiratory tract pathology. An overarching evaluation of the mechanistic information pertinent to any or all potential noncancer respiratory system health effects was performed (see Appendix A.5.6), with the most pertinent results summarized within each section. Evaluations were also performed for noncancer systemic (i.e., non-respiratory) health effects: nervous system effects; reproductive or developmental toxicity.

3.1. SENSORY IRRITATION

Individuals exposed to formaldehyde in indoor air reported symptoms of irritation in the eyes, nose, and throat; eye irritation is the most sensitive effect. Controlled human exposure studies evaluated frequency and severity of symptoms during brief periods of exposure, and a few studies also evaluated objective measures, such as conjunctival redness or frequency of eye blinking. Epidemiological studies of exposure to indoor formaldehyde among residential populations evaluated symptoms of irritation, including burning and watering eyes, sneezing and rhinitis, sore throat, and coughing. This review of sensory irritation focused on symptoms and other measures of eye irritation, which is an immediate response to formaldehyde exposure (Andersen and Molhave, 1983; Andersen, 1979).

3.1.1. Literature Identification

While the review focused on the more informative controlled human exposure studies and observational studies in residential populations, occupational studies and studies of students exposed to embalming fluid during dissection labs were also reviewed. The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.2, as are the specific PECO criteria and the methods for identifying literature from 2016–2021 are described in Appendix F. Mechanistic studies relevant to sensory irritation were separately identified (and evaluated) as part of the overarching review of mechanistic data informing respiratory effects (see Appendix A.5.6 for additional details and supporting analyses).

3.1.2. Study Evaluation

The controlled human exposure studies were able to evaluate symptoms in a controlled environment; therefore, the dose-response relationship was more precise and potential confounders were less of a 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 between 0.01 (LOD) to approximately 1 mg/m^3, with a large proportion of residences 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 had existing respiratory and other health conditions.

3.1.3. Synthesis of Human Health Effect Studies

The controlled human exposure studies showed that the irritant response to formaldehyde is an immediate phenomenon apparent at concentrations of 0.1 mg/m^3, the lowest concentration evaluated, and higher, and resolves when exposure is removed (Sauder et al., 1986; Andersen and Molhave, 1983). Both prevalence and severity of symptoms were associated with concentration. In addition, a large variability in sensitivity to the irritant properties of formaldehyde at specific concentrations was observed (Mueller et al., 2013; Berglund et al., 2012). Because of the wide variability in responses, it has been difficult for experimental studies to characterize the exposure-response relationship in the lower range of concentrations experienced by the general population.

Only a few studies evaluated whether symptom prevalence or severity changed over the course of the exposure period. Controlled exposure studies by one research group indicate that irritant responses to 2.46 mg/m^3 do not differ across groups as a result of previous, routine formaldehyde exposure (Schachter et al., 1987; Schachter et al., 1986). Studies that examined change in response during exposures at relatively high levels (>1 mg/m^3) reported higher symptom scores initially with subsequent declines suggestive of acclimation during exposure (Green et al., 1987; Schachter et al., 1986; Andersen and Molhave, 1983). However, at lower concentrations (0.3 and 0.5 mg/m^3), the initiation of symptoms was delayed and symptom severity continued to increase during the exposure period (Andersen and Molhave, 1983). Overall, these few studies suggest that some acclimatization may occur over a few hours at higher concentrations, however this phenomenon may not be apparent when concentrations are lower (<1 mg/m^3).

Two studies investigating the prevalence of symptoms of irritation in relation to residential formaldehyde exposure observed a statistically significant relationship between increasing formaldehyde concentration (from approximately 0.01 to >0.60 mg/m^3) and symptoms of irritation using logistic regression models with adjustment for age, gender, smoking behavior and other potential confounders (Liu et al., 1991; Hanrahan et al., 1984). Data were collected on symptoms occurring since participants had moved into their homes (Hanrahan et al., 1984) or those that occurred during the two weeks prior to the end of the one-week formaldehyde sampling period (Liu et al., 1991). Although the

sampling period used by Hanrahan et al. (1984) was short (1 hour), the study ruled out several exposure sources that might contribute to variability in concentrations. Other emissions released from the same sources as formaldehyde that also may contribute to eye irritation, including phenols, pinene, and terpenes, were not adjusted for in the analysis, but were present at lower levels compared to formaldehyde. A strong dose-response relationship with formaldehyde, as a cumulative measure (ppm-hour) or a one-hour concentration, was reported by these two *medium* confidence studies, indicating that the associations are unlikely to be entirely explained by unmeasured confounding from coexposures. Although the studies were limited by low participation rates, a potential source of selection bias if related to formaldehyde concentrations, participants were randomly selected for recruitment and the investigators noted that the characteristics of respondents and non-respondents, such as age of housing stock, demographics, and formaldehyde concentrations, were comparable.

Figure 4 graphs prevalence of eye irritation (or burning eyes) by formaldehyde concentration reported by controlled human exposure studies and residential studies that evaluated concentrations below 1 mg/m^3. These results are complementary for the most part and indicate a consistent pattern in response to formaldehyde concentrations between 0 and 1 mg/m^3. The study by Bender et al. (1983) used a protocol that involved exposure to the eyes only, although the concentration-response pattern was similar to the studies that evaluated exposure via inhalation. Two controlled human exposure studies that also evaluated concentrations below 1 mg/m^3 reported results using a different metric, a subjective symptom score rather than symptom prevalence (Mueller et al., 2013; Lang et al., 2008). The results of the two studies differed. Lang et al. (2008) reported an increase in symptom scores for eye irritation at 0.3 mg/m^3, whereas Mueller et al. (2013) reported no effect related to formaldehyde exposure.

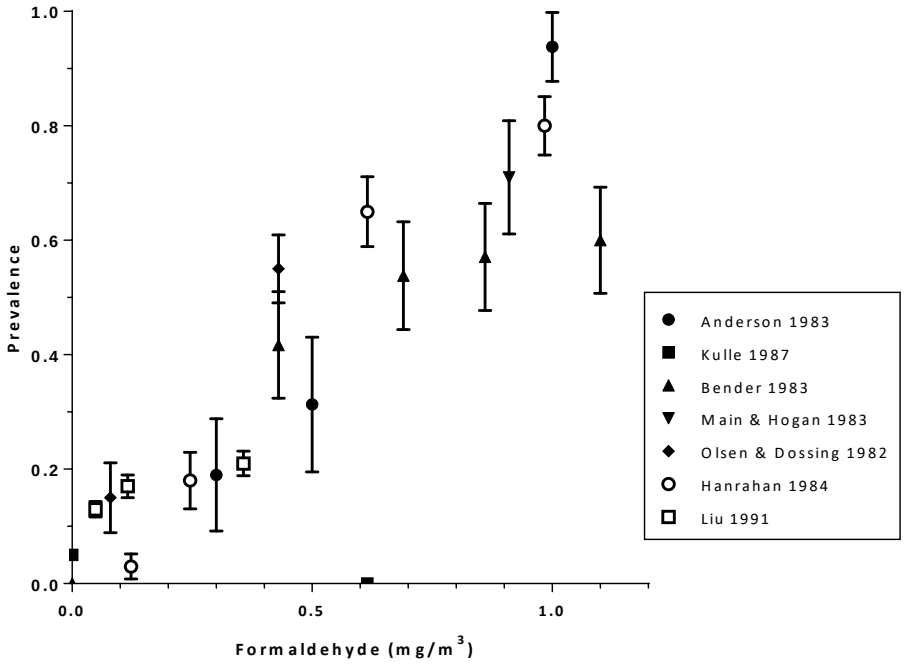

Figure 4. Prevalence of eye irritation among study groups exposed to formaldehyde in residential settings and controlled human exposure studies.

Exposure in these studies was either in mobile trailer offices or residential mobile homes. Prevalence at formaldehyde concentrations measured among comparison groups is graphed if reported (Holness and Nethercott, 1989; Holmström and Wilhelmsson, 1988; Horvath et al., 1988; Olsen and Dossing, 1982). Error bars are standard error (SE) calculated by EPA. Average weekly concentrations in three categories for Liu et al. (1991) were estimated from the midpoint of each category of reported weekly cumulative exposure (ppm-hour) and an assumption that individuals spent 60% of a 24-hour period at home.

3.1.4. Mode-of-action Information

Sensory irritation is understood to occur as a result of direct interactions of formaldehyde with cellular macromolecules in the nasal mucosa leading directly or indirectly to stimulation of trigeminal nerve endings located in the respiratory epithelium (see Figure 5; see Appendix A.5.6 for additional details, related analyses, and discussion). This potential mechanism is most directly supported by studies demonstrating increases in afferent nerve activity after acute exposure to approximately 0.5 mg/m^3 formaldehyde or lower (Tsubone and Kawata, 1991; Kulle and Cooper, 1975), although several related findings provide additional confirmation. While other mechanistic changes (e.g., oxidative stress; airway inflammation; damage or dysfunction of the respiratory epithelium, not shown) and biological differences (e.g., nasal morphology; underlying allergy, infection, or other respiratory conditions) are expected to be strong modifiers of this sequence of events, this pathway is interpreted as likely to be the dominant mechanism by which formaldehyde exposure causes sensory irritation. All of the mechanistic events in this pathway are supported by robust or moderate evidence, and the relationships described are largely well-understood biological phenomena or have been demonstrated

following formaldehyde exposure. This mechanistic understanding provides strong support for the biological plausibility of this effect. Although the primary support for an MOA reliant on stimulation of receptors on nasal trigeminal nerve endings is from studies in experimental animal models, the mechanistic events presumed to be driving sensory irritation after formaldehyde exposure are expected to be conserved in humans.

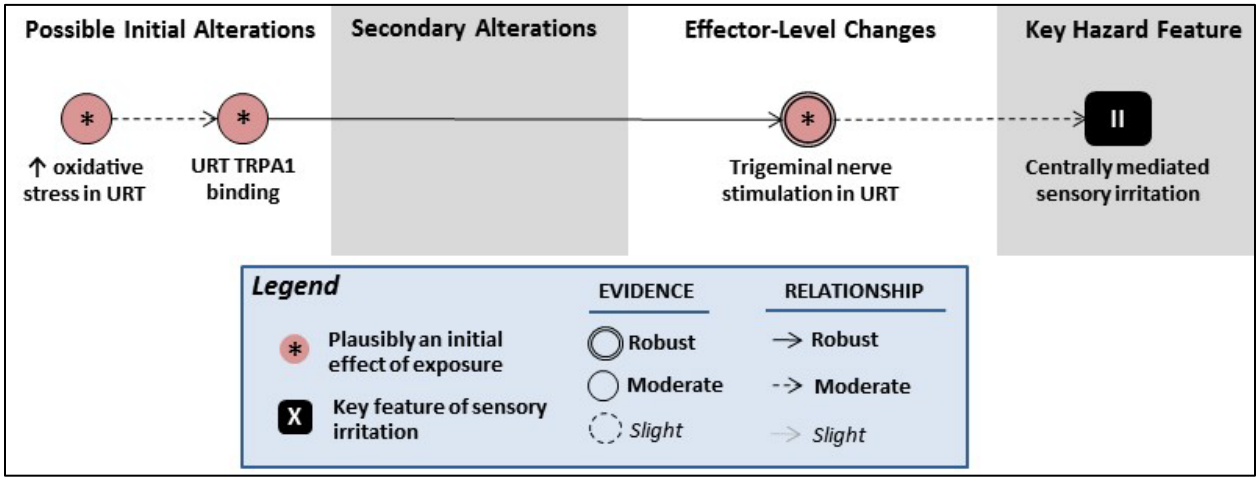

Figure 5. Likely mechanistic association between formaldehyde exposure and sensory irritation.

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

3.1.5. Overall Evidence Integration Judgment and Susceptibility for Sensory Irritation

Studies in humans provide *robust* evidence of sensory irritation based on the controlled human exposure studies and observational epidemiological studies, and this effect also is well described and accepted across a range of experimental animal species (*robust*), as well as in an established MOA based on mechanistic evidence in animals (this MOA is interpreted to be operant in humans). Overall, the **evidence demonstrates** that inhalation of formaldehyde causes sensory irritation in humans, given appropriate exposure circumstances (see Table 10). The primary basis for this conclusion is based on residential studies with mean formaldehyde concentrations >0.05 mg/m^3 (range 0.01–>1.0 mg/m^3) and controlled human exposure studies testing responses to concentrations 0.1 mg/m^3 and above.

Table 10. Evidence integration summary for effects on sensory irritation

Evidence	Evidence judgment	Hazard determination
Human	*Robust*, based on: *Human health effect studies*:	The **evidence demonstrates** that formaldehyde inhalation causes

	• Four *high* and *medium* confidence studies of symptom prevalence (eye, nose, throat) among adults and children in residential settings (mean >0.05 mg/m^3 formaldehyde, range 0.01 to approximately 1.0 mg/m^3) • Numerous *high* and *medium* confidence studies involving acute exposure (controlled human exposure studies) • Numerous *high* and *medium* confidence studies with longitudinal designs (occupational, panel studies of medical school pathology/ anatomy lab courses) • Consistent observations of irritation symptoms in all studies; clear exposure-response trends *Biological Plausibility*: No directly relevant human mechanistic studies were found	sensory irritation in humans given appropriate exposure circumstances[a] Primarily based on well-conducted residential studies with mean formaldehyde concentrations >0.05 mg/m^3 and controlled human exposure studies testing ≥0.1 mg/m^3
Animal	*Robust*, based on: *Animal health effect studies*: Although animal studies were not formally evaluated, formaldehyde inhalation-induced sensory irritation in rodents is a well-documented phenomenon (e.g., reflex bradypnea in mice and rats; see Appendix A.3). *Biological Plausibility*: Robust and moderate evidence for mechanistic events from animal studies identifies stimulation of the trigeminal nerve as the dominant MOA	*Potential susceptibilities*: Potentially large variations in sensitivity are expected, depending primarily on differences in nasal health (including allergy or inflammatory status) and physiology
Other inferences	• *Relevance to humans*: Assumed, based on similarities in systems mediating the identified MOA across species • *MOA*: Trigeminal nerve stimulation is likely to be the dominant mechanism • *Other*: This effect does not appear to worsen with longer exposure durations, although uncertainties remain	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis (see below).

3.1.6. Dose-response Analysis

Because of the rapid nature of the irritant response generated by inhalation of formaldehyde, the studies considered to be the most informative for derivation of a cRfC were those where the exposure assessment was concurrent with the outcome assessment. Data from studies in humans involving residential populations with continuous exposure, as well as controlled human exposure studies evaluating acute effects, were determined to be pertinent to the derivation of a cRfC.

Study selection

The *high* and *medium* confidence studies that included information about dose-response relationships for sensory irritation are presented in Table 11, which indicates for each study whether the study was used to develop a POD or the rationale for why the study was not suitable.

Table 11. Eligible studies for POD derivation and rationale for decisions to not select specific studies

Reference	Endpoint	POD derived?	Rationale for decision not to advance
(Hanrahan et al., 1984)	Eye irritation: Prevalence	Yes	
(Liu et al., 1991)	Eye irritation: Prevalence	No	Incomplete reporting of modeling results; provided support for analyses using Hanrahan et al.
(Kulle et al., 1987)	Eye irritation: Prevalence	Yes	
(Andersen and Molhave, 1983)	Eye irritation: Prevalence	Yes	
(Mueller et al., 2013)	Eye irritation: Tear film break-up time, symptom score using visual analogue scale (VAS)	No	An exposure-response trend was not observed for either endpoint. Difficult to define an adverse response level cutoff for these endpoints
(Lang et al., 2008)	Eye irritation: Conjunctival redness, blinking frequency, symptom score	No	Difficult to define an adverse response level cutoff for these endpoints and appeared to less sensitive than symptom score

Derivation of PODs

The PODs and supporting information from the studies are presented in Table 12. Two studies involving adults and children in a residential exposure setting, for which there was *medium* confidence, presented results based on responses at multiple exposure levels, although only the study by Hanrahan et al. (1984) provided the quantitative results of statistical analyses necessary for dose-response analysis (Liu et al., 1991; Hanrahan et al., 1984). Hanrahan et al. (1984) used one-hour average formaldehyde measurements taken in two rooms in the mobile homes of a group including teenagers and adults, and presented the predicted concentration-response for prevalence of "burning eyes" experienced by the participants since moving into the homes from a logistic regression model that adjusted for age, gender, and smoking. The mathematical expression for the dose-response pattern and a $BMCL_{10}$ was determined from a graph of the predicted prevalence and upper and lower 95% confidence bounds for several concentrations between 100 and 800 ppb (0.12–0.98 mg/m^3).[1] The concentration corresponding to a 13% prevalence of "burning eyes" was calculated from the model based on a 10% increase in irritation as a result of formaldehyde exposure in addition to an assumed background prevalence of 3%. The background prevalence of 3% was considered to be a reasonable estimate, but the impact of using alternative estimates (1% and 2%) was evaluated and was found to be minimal.

PODs also were determined using two controlled human exposure studies of formaldehyde for which there was *medium* confidence that evaluated multiple levels of exposure (Kulle et al., 1987;

[1]EPA estimates that 44% of the average measured concentrations were below 100 ppb (see Appendix B.1.2 for modeling details and supporting rationale).

Andersen and Molhave, 1983). Kulle et al. (1987) evaluated results for participants exposed for 3 hours once a week to five concentration levels (including a clean air exposure), while Andersen and Molhave (1983) exposed subjects for 5-hour periods to four concentration levels with a 2-hour clean air exposure prior to each trial. The occurrence of irritation symptoms during the clean air exposure was not reported. Two sets of models were evaluated using the data from (Andersen and Molhave, 1983) and estimates of 0% and 3% for prevalence of irritation during the clean air exposure. The BMC of 0.37 mg/m^3 derived from the model using a baseline prevalence of 3% was selected.

Table 12. Summary of derivation of PODs for sensory irritation

Endpoint and reference	Population	Observed effects by exposure level[a]	POD (mg/m^3)
Residential exposure			
Symptom prevalence (Hanrahan et al., 1984)	Teenage and adult (M and F), *n* = 61	Third degree polynomial model fit to ln prevalence odds using presented results of logistic regression analysis: upper 95% confidence bound for predicted prevalence between <0.123–0.98 mg/m^3, $BMC_{10\%}$: concentration where an increased prevalence of 10% over a 3% background prevalence is anticipated.	BMC_{10}[b] 0.19 $BMCL_{10}$ 0.09[c]
Controlled human exposure			
Symptom prevalence (Kulle et al., 1987)	Nonsmoking, healthy, *n* = 10–19, Mean age 26.3 yr, (M and F)	Exposure and proportion responding *mg/m^3*: 0 / 0.62 / 1.2 / 2.5 / 3.7 *%*: 5 / 0 / 26 / 53 / 100 trend, $p < 0.05$ Probit model BMC = 0.69 ppm	BMC_{10} 0.85[c] BMC/2[d] 0.42
Symptom prevalence (Andersen and Molhave, 1983)	Healthy students, *n* = 16, age 30–33 years, 31.2% smokers (M and F)	Exposure and percentage responding (prevalence at the end of exposure) *mg/m^3*: 0.3 / 0.5 / 1.0 / 2.0 *%*: 19 / 31 / 94 / 94 Assuming prevalence for clean air dose 0% LogLogistic model BMC = 0.26 mg/m^3 3% LogLogistic model BMC = 0.37 mg/m^3	BMC_{10} 0.37[c] BMC/2[d] 0.19

[a]Concentrations reported in publication converted to mg/m^3

[b]BMC_{10} benchmark concentration at 10% increase in prevalence over estimated 3% background prevalence. An increase of 10% was selected consistent with EPA guidelines (U.S. EPA, 2012) because the endpoint, burning eyes with mild to moderate severity, was considered a minimally adverse outcome.

[c]The POD was not adjusted for a 24-hour equivalent concentration because the timing of formaldehyde measurements was concluded to be appropriate to the timeframe of reported symptoms.

[d]The BMD models did not account for the correlated measures between concentration levels (each participant was exposed to each concentration). Therefore the 95% confidence limit for the BMC estimated by the model is too narrow to use as the POD. A factor of 2 was used to adjust the BMC to identify a lower estimate that approximates the BMDL.

Derivation of cRfCs

Table 13 describes the uncertainty factors used to adjust the POD to derive the cRfC for each of the three studies. For the cRfC for sensory irritation in adult (and teenage) populations (residential exposures) in Hanrahan et al. (1984), a UF_H of 10 was used. Although the study population in Hanrahan et al. (1984) comprised randomly selected households in mobile homes with individuals representing a range of age, gender, health behavior, occupational status, and health status, the identified PODs were not based on evaluation of differential susceptibility among subgroups with conditions or characteristics that may contribute to variation in response. For the controlled human exposure studies (Kulle et al., 1987; Andersen and Molhave, 1983), a factor of 10 was applied to account for variation in the broader human population not represented by participants in controlled human exposure studies. No other uncertainty factors greater than one were applied.

Table 13. Derivation of cRfCs for sensory irritation

Endpoint (*reference*; population)	POD	POD basis	UF_A	UF_H	UF_L	UF_S	UF_D	$UF_{COMPOSITE}$	cRfC (mg/m^3)
SENSORY IRRITATION									
Eye irritation symptoms *(*Hanrahan et al., 1984*)*; adult M+F, *n* = 61, residential, prevalence at POD 13%)	0.09	$BMCL_{10}$	1	10	1	1	1	10	**0.009**
Eye irritation symptoms *(*Kulle et al., 1987*)*; adult M+F, *n* = 10, controlled exposure)	0.42	BMC/2	1	10	1	1	1	10	**0.04**
Eye irritation symptoms *(*Andersen and Molhave, 1983*)*; adult M+F, *n* = 16, controlled exposure)	0.19	BMC/2	1	10	1	1	1	10	**0.02**

Organ system-specific RfC (osRfC)

The POD was derived using the dose-response model using prevalence data from the residential population in Hanrahan et al. (1984) is 0.09 mg/m^3. The study by Hanrahan et al. (1984) is pertinent to the U.S. general population because (1) the population was randomly selected from the general population in the study area; (2) the exposure levels were concluded to reflect the usual, relatively constant formaldehyde concentrations in the residences; and (3) exposed individuals included a range of ages (teenagers and adults), men and women, some with chronic disease. Moreover, a significant proportion of the study population was estimated to be exposed to average formaldehyde concentrations below 0.05 mg/m^3.

The PODs based on the two controlled human exposure studies were 0.19 and 0.42 mg/m^3 (Kulle et al., 1987; Andersen and Molhave, 1983), less than an order of magnitude greater than the BMCL estimated from residential exposure. There is less confidence in the PODs based on these studies because (1) the study participants were young, healthy volunteers, not representative of the age

distribution and health status in the general population; (2) the PODs are based on small sample size, more subject to random variation; and (3) formaldehyde concentrations were high, imposing substantial uncertainty regarding responses at the low tail of the exposure distribution.

Therefore, the cRfC of 0.009 mg/m^3 based on Hanrahan et al. (1984) was chosen as the osRfC for sensory irritation. Confidence in the POD is *medium* because of uncertainties in the concentration measurements relative to the study period for which the symptoms were being assessed. There is extensive literature on this response to formaldehyde and the completeness of the database is *high*. Because sensory irritation is an immediate response to exposure, the osRfC is applicable to short-term as well as long-term exposure scenarios.

3.2. PULMONARY FUNCTION

Several studies in humans examined the effect of formaldehyde inhalation on pulmonary function in various populations using different study designs. The systematic review process assigned controlled human exposure studies of acute exposure involving healthy individuals to the review of pulmonary function and the studies involving asthmatic volunteers to the review of effects on immune-mediated conditions and their results are summarized there (see Section 1.2.3 of the Toxicological Review). However, since all of these studies involved measurements of pulmonary function, the results of the studies involving participants with asthma have been integrated with the evidence from studies of acute exposure in healthy individuals in this section. The few animal studies of analogous endpoints (all acute exposure) were not included in the hazard evaluation. Changes in pulmonary function measures involving acute or intermediate-duration exposures have been evaluated using experimental study designs (controlled human exposure studies), panel studies of medical school anatomy students, and occupationally exposed populations. In addition, occupational groups with long-term exposures are available, which compared effects in exposed groups to effects in referents using different exposure metrics, such as time-weighted average (TWA) or cumulative measures. Population-based studies of adults and children that analyzed cross-sectional associations with average indoor formaldehyde concentrations also have been conducted. Generally, groups exposed to formaldehyde at work experienced TWA concentrations above 0.2 mg/m^3 with intermittent peaks above 1 mg/m^3. Students meeting once or twice a week in anatomy labs experienced fluctuating concentrations during dissections averaging between 0.1 and >1.0 mg/m^3. Formaldehyde concentrations in residential or primary school settings are much lower and less variable (<0.1 mg/m^3). EPA included both the higher exposure and the lower exposure studies in its evaluation of pulmonary function effects.

Poor pulmonary function as well as a decrease in pulmonary function is an important health endpoint, associated with the development of chronic respiratory disease, coronary heart disease, and mortality (Clayton et al., 2014; Menezes et al., 2014; Young et al., 2007; Sin et al., 2005; Schroeder et al., 2003; Schunemann et al., 2000; Sorlie et al., 1989). Spirometric measures (the focus of this section) are commonly used diagnostic criteria. EPA considered a decrease in mean values to suggest a shift toward

a decline in the respiratory health status of the population. Consistent with this, the American Thoracic Society (ATS) evaluated the clinical significance of small average declines in pulmonary function observed in a population in response to air pollutants and concluded that although the magnitude of the observed declines may not be clinically relevant to an individual, a shift in the population distribution toward lower pulmonary function, assuming the association is causal, may have a large impact on public health (ATS, 2000).

3.2.1. Literature Identification

This review focused on standard quantitative measures of pulmonary function (i.e., spirometry; peak flow measurements). The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.3, as are the specific PECO criteria and the methods for identifying literature from 2016–2021 are described in Appendix F. Mechanistic studies relevant to pulmonary function were separately identified (and evaluated) as part of the overarching review of mechanistic data informing respiratory effects (see Appendix A.5.6 for additional details and supporting analyses).

3.2.2. Study Evaluation

Forty-two observational epidemiological studies and eleven controlled human exposure studies were evaluated for sources of bias and sensitivity. Pulmonary function is assessed using spirometry, which measures the volume and speed of air that is exhaled or inhaled. Several parameters can be measured during spirometric testing to characterize an individual's respiratory health. The measurement of pulmonary function outcomes used by the studies in this section was considered to be adequate if they followed the guidelines published by the American Thoracic Society (Tepper et al., 2012; Miller et al., 2005a; Miller et al., 2005b; Pellegrino et al., 2005), or provided a description of the protocols and reference equations that were used. In addition to the use of conventional spirometric equipment to measure forced expiratory volume (FEV_1), forced vital capacity (FVC), and forced expiratory flow (FEF), peak expiratory flow (PEF) has been measured in research settings using portable flow meters operated by study participants trained in their use. Although it requires careful training and monitoring, this method has the advantage that it can be used in large epidemiological studies and multiple measurements can be obtained over time. Studies of residential exposure to formaldehyde were conducted in this way (Krzyzanowski et al., 1990).

Lung function varies by race or ethnic origin, gender, age, and height, and is best compared when normalized to the expected lung function based on these variables (Pellegrino et al., 2005; Hankinson et al., 1999). Analyses were considered to be limited if they did not adjust or otherwise account for these variables. Smoking status also was considered as a potential confounder. FEV_1 and peak expiratory flow rate (PEFR) exhibit diurnal variation and this complicates the interpretation of changes across a work shift or during a laboratory session if no comparisons were made with an

unexposed group (Tepper et al., 2012; Lebowitz et al., 1997). Studies with no comparison group were given less weight in evaluating the results of studies that measured short-term changes.

The healthy worker effect and survivor (lead time) bias was a concern for several cross-sectional occupational studies, some of which had no other major limitations. Removal of individuals more sensitive to the irritant effects of formaldehyde from jobs or tasks with formaldehyde exposure likely occurred in industries with high formaldehyde exposures, and this type of selection bias might result in an attenuation of risk estimates or a null finding if these individuals also experienced effects on pulmonary function.

3.2.3. Synthesis of Human Health Effect Studies

While studies involving acute exposure either observed no change or inconsistent responses, studies of occupational populations exposed over long periods and children exposed in residential settings reported declines in pulmonary function. The controlled human exposure studies of healthy or asthmatic volunteers consistently did not observe changes even at high concentrations, although two studies by one research team observed small decrements (<5%) when longer exercise components (15 minutes) were included. Studies using shorter exercise components (8−10 minutes) reported no changes. One exception among asthmatic participants was a heightened response to a dust mite challenge in the formaldehyde inhalation arm compared to the clean air exposure in one study that used nose clips, although a different study did not observe an increased response in a study with a similar design but using a pollen challenge and no nose clip. Many of the studies of occupational groups or anatomy students observed pulmonary function declines over the course of the work day or lab; however, most did not account for diurnal changes, limiting the interpretation of these results. The few studies of exposure during dissection labs that included an unexposed comparison group generally reported that referent groups also experienced a change (increase or decrease) in pulmonary function. A panel study using repeated peak expiratory flow measures taken by students trained in the procedure at multiple points during dissection lab sessions found that PEF declined during the labs, and these declines became attenuated over successive weeks (Kriebel et al., 2001).

The review of the epidemiological literature provides evidence that long-term formaldehyde exposure is associated with declines in pulmonary function, including FEV_1, FVC, FEF, and PEF. Although precision was low for most studies, pulmonary function was generally lower in highly exposed occupational groups employed at exposed jobs for long durations compared to their nonexposed or lesser-exposed comparison groups. The occupational groups under study were exposed to high average formaldehyde concentrations (≥0.2 mg/m^3) in a variety of industries with different formaldehyde sources. Employees had worked at these jobs for at least 5 years, and in a few studies, for more than 10 years. While a few studies conducted longitudinal analyses, most of the occupational studies were cross-sectional in design, recruiting only current employees, and likely were limited by lead time bias, a selection bias that results in attenuated effect estimates.

Three studies conducted longitudinal analyses of small groups of workers with continued exposure over 4−6 years (Löfstedt et al., 2011; Nunn et al., 1990; Alexandersson and Hedenstierna, 1989). For FEV_1 (only one study tested multiple parameters), all the longitudinal studies reported no change in the full cohorts over the study period; however, one (Nunn et al., 1990) reported that among exposed nonsmokers, the annual decline was −45 mL/year (95% CI: −28, −62 mL/year), which is 50% greater than the expected rate of decline in FEV_1 in nonsmokers [29 mL/year; (Redlich et al., 2014; Lee and Fry, 2010)]. In addition, Alexandersson and Hedenstierna (1989) reported a decline in FEF_{25-75} at a TWA concentration of 0.42−0.5 mg/m^3, with FEF_{25-75} percentage declining by −168 ± 46 mL/second (10.1 L/minute) for each year of exposure over a 5-year period ($p < 0.001$). The annual decrease was corrected for normal aging and reference pulmonary function spirometry values. Consistent with the results for FEV_1, there was a larger decrease among nonsmokers compared to smokers, likely reflecting the already reduced FEV_1 in smokers (−212 mL/sec/yr and −60 mL/sec/yr, respectively).

The longitudinal studies were limited with respect to duration of follow-up and sample size. Given the large amount of within-person variability in these measures when assessed over time, these studies would have had limited sensitivity to detect a small longitudinal change. Loss to follow-up of exposed participants with symptoms also was evident. This type of selection bias also could result in an attenuated effect estimate. Overall, the longitudinal analyses appear to be inconsistent, but while hindered by a lack of sensitivity, seem to support a conclusion that occupational exposure may result in declines in FEV_1 and FEF over time.

Most of the occupational studies adjusted for smoking in statistical analyses or otherwise addressed potential confounding by smoking, and two studies found no correlation between pulmonary function measures and cigarette smoking indicating that smoking was not a confounder in the cohorts (Malaka and Kodama, 1990; Holmström and Wilhelmsson, 1988). Potential confounding by coexposures is an uncertainty for this review. However, many independent associations with formaldehyde for one or more pulmonary function measures were found using statistical models that addressed potential confounding (e.g., dust), and, since a pattern of reduction in pulmonary function was observed across several different exposure settings (all involving high formaldehyde exposure), confounding by a coexposure becomes less compelling as an alternative explanation for the observed associations.

Results among four studies of residential exposure among adults are difficult to compare because different methods were used to assess pulmonary function and two of the studies did not report results quantitatively (Norback et al., 1995; Broder et al., 1988). A cross-sectional study of residential formaldehyde exposure in a large, randomly selected sample in Arizona observed an association with declines in PEFR among adult smokers at formaldehyde concentrations between 0.049 and 0.172 mg/m^3, but not among the group as a whole (Krzyzanowski et al., 1990). Another study among elderly nursing home residents observed an elevated risk of low pulmonary function defined as values falling in the lower 20% of the distribution associated with formaldehyde concentrations above the median level measured in each nursing home [overall median and range: 0.007 mg/m^3 and

0.001−0.021 mg/m^3; (Bentayeb et al., 2015)]. Two additional studies in primarily adult residential populations exposed to concentrations between 0.009 and 0.279 mg/m^3 reported no associations, although the outcomes evaluated by each study were not equivalent (Norback et al., 1995; Broder et al., 1988).

There are few studies of residential exposure among children; however, Krzyzanowski et al. (1990) found a clear dose-response relationship among the children in their Arizona study where most household concentrations were less than 0.045 mg/m^3. A linear relationship between increased formaldehyde exposure and decreased PEFR among children exposed to average concentrations of 0.032 mg/m^3 was reported by this large, population-based, cross-sectional study of residential formaldehyde exposure. The investigators reported a statistically significant decrease of −1.28 ± 0.46 L/minute in PEFR per ppb household mean formaldehyde for all children. Figure 6 shows the incremental decrement in PEFR measured at bedtime versus morning and shows differences in the morning among asthmatics and nonasthmatics. Asthmatic children (15.8% of the total) showed a steeper decline in PEFR in the morning at formaldehyde concentrations less than 0.049 mg/m^3 (40 ppb). The analysis of multiple PEFR measurements for each individual resulted in an increased statistical power to detect an association at the lower formaldehyde levels present in the homes. The statistical model adjusted for potential confounders including asthma status, smoking status, SES, NO_2 levels, episodes of acute respiratory illness, and the time of day. Two other studies among children exposed to similar levels of formaldehyde, but with limitations that reduced their sensitivity, did not find an association for either FVC or FEV_1 (Wallner et al., 2012; Franklin et al., 2000).

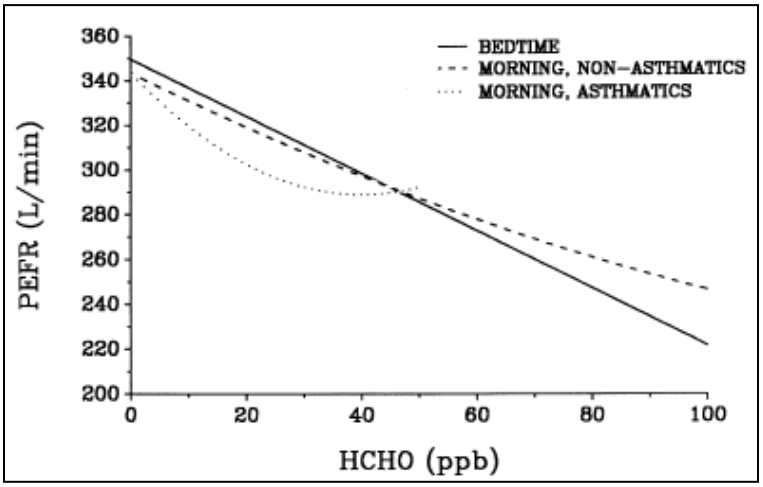

Figure 6. Association of PEFR measured at bedtime and in the morning with household mean formaldehyde concentration among children less than 15 years of age (Krzyzanowski et al., 1990).

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3.2.4. Mode-of-action Information

There is mechanistic support, primarily from studies in animals, although a definitive MOA(s) has not been fully defined (see Figure 7; see Appendix A.5.6 for additional details, related analyses, and discussion). Overall, the most relevant mechanistic events included inflammatory structural alterations and eosinophil increases in the lower airways that appear to be at least partially related to indirect activation of sensory nerve endings. Inflammatory changes in the lower airways are supported most directly by evidence from short-term studies of rodents at 0.3–2.5 mg/m^3 formaldehyde (Fujimaki et al., 2004; Riedel et al., 1996), although indirect effects (e.g., biomarkers of airway oxidative stress) at lower levels have been suggested in human studies (Flamant-Hulin et al., 2010; Franklin et al., 2000). However, the initial cellular or tissue modifications that ultimately lead to these later events are not understood, and it is unclear whether and to what extent certain events would be triggered with chronic, low-level exposure. Although other important mechanistic events would likely be identified with additional study, the available data provide reasonable support for the biological plausibility of the observed associations and identify what is likely to be an incomplete mechanism by which formaldehyde inhalation could cause decreased pulmonary function. Variation in sensitivity is likely to be affected by underlying respiratory health status.

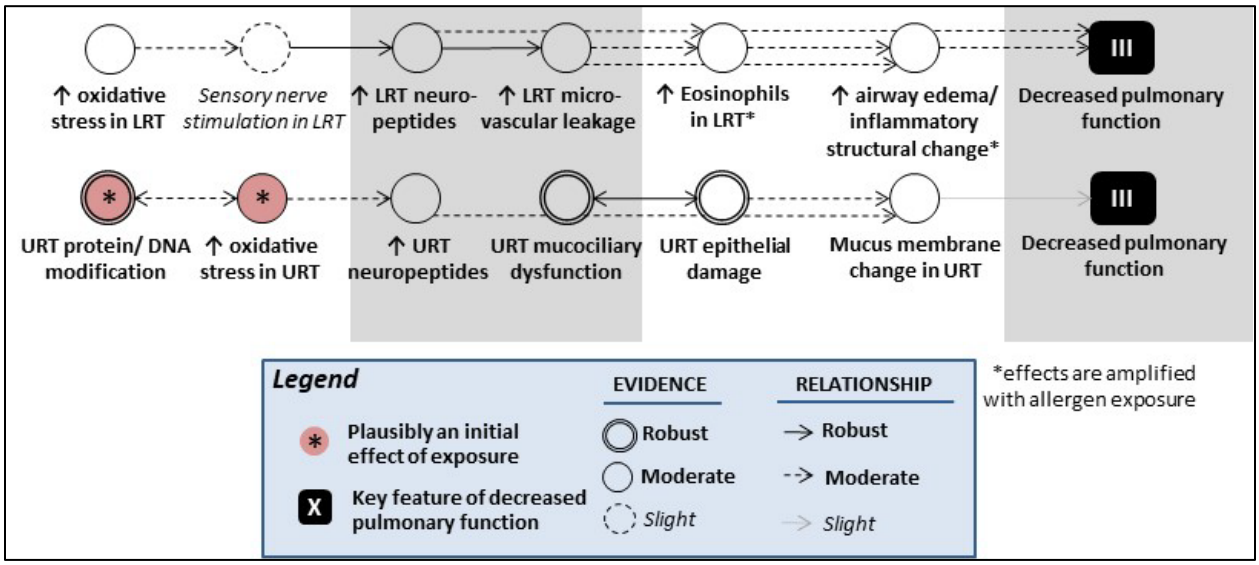


Figure 7. Possible mechanistic associations between formaldehyde exposure and decreased pulmonary function.

An evaluation of the formaldehyde exposure-specific mechanistic data informing the potential for formaldehyde exposure to cause respiratory health effects identified these sequences of mechanistic events as those most directly relevant to interpreting effects on pulmonary function. Evidence of airway inflammatory changes, including eosinophil recruitment to both the upper and lower respiratory tract (URT and LRT; upper pathway), is considered as likely to represent an incomplete mechanism by which formaldehyde inhalation could cause decreased pulmonary function, although whether certain events occur at lower exposure levels is unclear, and other unexplored mechanistic events are expected to

contribute. URT modifications, primarily structural changes (bottom pathway), may also contribute; however, this is not interpreted as likely to be a significant contributing mechanism.

3.2.5. Overall Evidence Integration Judgment and Susceptibility for Pulmonary Function

Overall, based on the *moderate* human evidence from observational epidemiological studies, as well as *slight* animal evidence from mechanistic studies supporting biological plausibility, the **evidence indicates** that long-term inhalation of formaldehyde likely causes decreases in pulmonary function in humans given appropriate exposure circumstances (see Table 14). The primary basis for this conclusion includes a study of children and adults in a residential setting (mean, 0.03 mg/m^3, maximum 0.17 mg/m^3) and several studies of workers with long-term exposure to >0.2 mg/m^3. The **evidence** is **inadequate** to interpret whether acute or intermediate-term (hour to weeks) formaldehyde exposure might cause this effect.

Table 14. Evidence integration summary for effects on pulmonary function

Evidence	Evidence judgment	Hazard determination
Long-term Exposure (years)		
Human	*Moderate for Long-Term Exposure (years)*, based on: *Human health effect studies:* • 1 *high* and two *medium* confidence studies in residential and school populations indicating that susceptible individuals may experience reduced pulmonary function at lower average concentrations (<0.05 mg/m^3). • Numerous *high* and *medium* confidence studies showing a pattern of reduced mean pulmonary function in formaldehyde-exposed occupational groups across a variety of exposure settings and countries. However, some inconsistencies were noted for specific measures; possible explanations may be random variation and low study sensitivity. • Concentration-related associations from four *high* and *medium* confidence adjusted analyses indicate an independent association for formaldehyde exposure suggesting confounding is not an alternative explanation. • Longitudinal declines were reported for one occupational population and a panel study of medical students, but null or equivocal associations were identified from other studies, all with possible differential loss to follow-up and low sensitivity. *Biological Plausibility:* Some indirectly supportive mechanistic information from well-conducted human studies exists related to increased lower airway oxidative stress following exposures likely to span months to years.	The **evidence indicates** that long-term inhalation of formaldehyde likely causes decreased pulmonary function in humans given appropriate exposure circumstances[a] Primarily based on a study of children and adults in a residential setting (mean, 0.03 mg/m^3, maximum 0.17mg/m^3) and several studies of workers with long-term exposure to >0.2 mg/m^3 *Potential Susceptibilities:* Variation in sensitivity is anticipated to depend on age and respiratory health, with the potential for children to be more sensitive.
Animal	*Slight*, based on: *Biological Plausibility:* Robust and moderate evidence for several mechanistic events, primarily from experimental animal studies, provides support for inflammatory changes in the lower airways, including eosinophil increases, which appear to be at least partially dependent on indirect stimulation of sensory nerve endings. While evidence exists for some changes in the range of	

	0.3−0.5 mg/m^3 with exposure for several weeks, some potential associations in the identified, incomplete MOA pathway have only been tested at higher (i.e., >1 mg/m^3) levels and with shorter-term exposures. *Animal health effect studies*: Not formally evaluated.	
Other inferences	*Relevance to humans:* The observed mechanistic changes are expected to occur in humans, given similarities across species in the systems that appear to be involved, and some support is based on studies in both humans and animals (e.g., lower airway oxidative stress). *MOA*: Not established, but likely to involve airway eosinophil increases and stimulation of airway sensory nerve endings.	
Acute or Intermediate-Term Exposure (hours to weeks)		
Humans	*Indeterminate for Acute or Intermediate-Term Exposure (hours to weeks),* based on: *Human health effect studies*: Small reductions in two controlled human exposure studies of healthy volunteers (1 lab) with longer exercise periods (15 min), but no associations with other exposure protocols (including those with ≤10 min exercise periods) in studies involving healthy subjects or asthmatics (see discussion above and Section 1.2.3 for pulmonary function results in asthmatics); inconsistent results among studies of medical school dissection labs and cross-shift measurements in occupational studies. *Biological Plausibility:* Increases in lower airway eosinophils were not observed in the few *low* confidence acute studies in humans available.	The **evidence** is **inadequate** to draw judgments regarding acute or intermediate-term exposure (hours to weeks)
Animals	*Indeterminate*, based on: *Biological Plausibility:* Although some mechanistic changes relevant to pulmonary function, including most of the immunogenic effects, were altered after short-term exposure in animals, given the dependence of some of the key mechanistic events (e.g., URT damage or dysfunction; LRT oxidataive stress) on exposure duration, it remains unclear whether the potential mechanistic pathways would be relevant to interpreting acute or short-term exposure scenarios. *Animal health effect studies*: Not formally evaluated.	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis (see below).

3.2.6. Dose-response Analysis

Study selection

The *high* and *medium* confidence studies that included information about dose-response relationships for decreased pulmonary function are presented in Table 15, which indicates for each study whether the study was used to develop a POD or the rationale for why the study was not suitable.

Table 15. Eligible studies for POD derivation and rationale for decisions to not select specific studies

Reference	Endpoint	POD derived?	Rationale for decisions to not select

Krzyzanowski et al. (1990)	PEFR	Yes	
Malaka and Kodama (1990)	FEV_1, $FEF_{25–75}$	No	Incomplete reporting of modeling results
Kriebel et al. (2001)	PEFR	No	Difficult to use modeling results because of covariance in model coefficients
Wallner et al. (2012)	$FEF_{25–75}$	No	Incomplete reporting of modeling results

Derivation of PODs

Declines in PEFR were associated with increases in 2-week average indoor residential formaldehyde concentrations, with greater declines observed in children (5–15 years of age) compared to adults (Krzyzanowski et al., 1990). This study of effects in a residential population used the most thorough exposure assessment protocol and repeated measurements of PEFR, thus enhancing the ability to detect an association at lower concentrations. Mean formaldehyde levels were 26 ppb (0.032 mg/m^3), and more than 84% of the homes had concentrations 40 ppb (0.049 mg/m^3) and lower. A BMC_{10} of 0.033 mg/m^3 and a $BMCL_{10}$ of 0.021 mg/m^3 were determined from the regression coefficient from a random effects model of PEFR among children with and without asthma reported by the study authors. Table 16 summarizes the study and the derivation of the POD for pulmonary function.

Table 16. Summary of derivation of PODs for pulmonary function

Endpoint and reference	Population	Results by exposure level[a]	BMC and BMCL (mg/m^3)	POD_{ADJ}[b] (mg/m^3)
PEFR (Krzyzanowski et al., 1990) Residential, prevalence	202 households, 298 children aged 5−15 yrs, current asthma prevalence 15.8%; 613 adults and adolescents >15 yr, 24.4% current smokers, current asthma prevalence 12.9%	Random effects model; decreased PEFR, children -1.28 ± 0.46 L/min-ppb (95% upper bound −2.04 L/min-ppb) Formaldehyde concentrations: Mean 0.032 mg/m^3, maximum 0.172 mg/m^3	BMC_{10}[c] 0.033 $BMCL_{10}$ 0.021	0.021

[a]Concentrations reported in publication converted to mg/m^3.
[b]The POD was not adjusted for a 24-hour equivalent concentration because formaldehyde is present in all indoor environments and time-activity information for participants was not reported.
[c]BMC_{10} benchmark concentration at 10% increase in prevalence over background prevalence. A BMR of 10% reduction in PEFR was selected as a cut-off point for adversity, based on rationales articulated by the American Thoracic Society (see Appendix B.1.2 for details on the rationale).

Derivation of cRfCs

Table 17 describes the uncertainty factors used to adjust the POD and the resulting cRfC. For the POD for decreased PEFR among children from Krzyzanowski et al. (1990), a UF_H of 3 was used with support from the model results reported by the authors. While the BMC was defined as the concentration where a 10% decrease in PEFR among all the children in the study was predicted to occur,

the model results also predicted the degree of response among asthmatic and healthy children. Multiple observations in the study indicate that a UF_H of 3 applied to the endpoint can be expected to be protective of asthmatic children and other susceptible individuals. EPA used the published regression coefficients from the random effects model to calculate the predicted decrease in PEFR from the baseline level (i.e., formaldehyde concentration equal to zero) for each group. At the BMC corresponding to a 10% decrease overall (0.033 mg/m^3), the asthmatic children experienced a decrement in PEFR that was 1.5-fold greater than that of the nonasthmatic children. Further, at the BMCL selected as the POD (0.021 mg/m^3), the decrease in PEFR among asthmatic children was 10.5% while that in nonasthmatic children was 7.2%, a 1.5-fold difference. The authors stated that other characteristics affecting variability, such as acute respiratory illness episodes during the observation period, environmental tobacco smoke in the home, or socioeconomic status, did not increase sensitivity. These observations indicate that a UF_H of 1 is not appropriate since the asthmatic children experienced a larger decline in PEFR compared to the healthy children. However, a UF_H of 3 can be expected to be protective of asthmatic children and other susceptible individuals.

Table 17. Derivation of the cRfC for pulmonary function

Endpoint (*reference*; population)	POD	POD basis	UF_A	UF_H	UF_L	UF_S	UF_D	$UF_{COMPOSITE}$	cRfC (mg/m^3)
PULMONARY FUNCTION									
Peak expiratory flow rate (Krzyzanowski et al., 1990); Children M + F, *n* = 298, residential)	0.021	$BMCL_{10}$	1	3	1	1	1	3	**0.007**

Selection of osRfCs

The cRfC for pulmonary function of 0.007 mg/m^3 (Krzyzanowski et al., 1990) was chosen as the osRfC. This population-based study used a thorough exposure assessment based on two-week average measurements in multiple rooms and two different seasons. Hence, confidence in the POD value is *high*. The hazard conclusion is based on several studies in diverse exposure settings, and the completeness of the database is considered *high*.

3.3. IMMUNE-MEDIATED CONDITIONS, FOCUSING ON ALLERGIES AND ASTHMA

This section examines the evidence pertaining to the effect of formaldehyde exposure on immune-mediated responses, primarily in the respiratory system, including allergy-related conditions (e.g., rhinitis; rhinoconjunctivitis) and asthma; sensitization related to dermal exposure is not a focus of this review. Epidemiological studies have investigated potential associations between formaldehyde and outcomes relevant to various exposure durations and time windows in children and in adults using formaldehyde measurements conducted in occupational, residential, and school-based settings. A few studies described other respiratory conditions in infants and toddlers, but these outcomes were not the

focus of the review. Controlled human exposure studies also are available that evaluated pulmonary function responses to formaldehyde among subjects with asthma, but their results are most informative to the pulmonary function outcome and are included in the integration of evidence in that section (see Section 1.2.2). Only two of these studies are relevant to the evaluation of effects on immune-related endpoints; these studies assessed responses to an allergen challenge during formaldehyde exposures: dust mite in Casset et al. (2006) and grass pollen in Ezratty et al. (2007). While exposures were high in occupational settings (>0.1 mg/m^3), formaldehyde concentrations measured in schools and homes averaged between 0.03 and <0.1 mg/m^3.

Experimental animal studies were ultimately concluded to be unsuitable models (*indeterminate*) for evaluating allergy-related conditions and asthma as apical endpoints. However, in the context of the health effects data available, these findings, as well as a few studies that indirectly suggest that respiratory immune function could be affected by formaldehyde exposure, are discussed within the wider context of potential mechanistic changes that might explain respiratory health hazards.

3.3.1. Literature Identification

The focus of this search was on studies with a direct measure of formaldehyde exposure in relation to measures of allergic respiratory conditions, eczema, or current asthma, reflecting the question of whether formaldehyde exposure influences the sensitization response to respiratory allergens. The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.4, as are the specific PECO criteria and the methods for identifying literature from 2016–2021 are described in Appendix F. Additionally, mechanistic studies relevant to immune-mediated conditions, including potential immunological changes in distal tissues and blood, were separately identified (and evaluated) as part of the overarching review of mechanistic data informing respiratory effects (see Appendix A.5.6 for additional details and supporting analyses). Ultimately (see Section 1.2.3 of the Toxicological Review for details), the animal hypersensitivity studies were included as part of the overarching review of respiratory system-related mechanistic information (see Appendix A.5.6) rather than as apical health effect studies; thus, they provided information about potential mechanisms for the reviewed outcomes in the human studies.

3.3.2. Study Evaluation

The category of allergic sensitization and allergies includes allergic sensitization based on skin prick tests and history of allergy-related symptoms. Because the time windows for exposure assessments used in the studies had uncertain relevance to when sensitization may have occurred, lower confidence was placed in the results of skin prick tests for studies in adults than in children (these studies are not discussed in this Overview). For symptoms, International Study of Arthritis and Allergies in Children (ISAAC) questionnaires for rhinitis or rhinoconjunctivitis were considered to provide an adequate basis for case ascertainment in studies in Europe and the United States; in studies in other

areas (i.e., areas that have not been included in ISAAC), specific mention of validation of the questionnaire was needed to receive a *high* confidence rating.

Studies that ascertained asthma outcomes using American Thoracic Society (ATS)-based questionnaires or subsequent variations [ISAAC, European Community Respiratory Health Survey (ECHRS)] for prevalence of current asthma that include questions on medication use and symptoms were considered to provide an adequate basis for case ascertainment in studies in Europe and the United States; in studies in other areas (i.e., areas that have not been included in ISAAC), specific mention of validation of the questionnaire was needed to receive this level of confidence. Some studies included results for more than one asthma measure; in this assessment, outcomes that were defined over a recent period were included (e.g., symptoms in the past 12 months), but outcomes defined over a lifetime (e.g., ever had asthma) were not, as the formaldehyde measures available do not reflect cumulative exposures that could be related to cumulative risk. Studies that did not clearly delineate the period of ascertainment were included, but lower confidence was placed in these studies.

The age of study participants is an important consideration in the interpretation of various measures. Specificity of symptom questions is reduced in the very young (<5 years) because wheezing can occur with respiratory infections in infants and young children, and specificity is reduced at older ages (e.g., >75 years) because of the similarities in symptoms and medication use for chronic obstructive pulmonary disease and asthma (Abramson et al., 2014; Taffet et al., 2014). Rumchev et al. (2002), a study of emergency room visits for asthma in children ages 6 months to 3 years, and two other studies that examined wheezing episodes among infants (Roda et al., 2011; Raaschou-Nielsen et al., 2010), were thus classified as not informative with respect to asthma.

The evaluation of controlled exposure studies of responses among asthmatic subjects examined four primary elements: the type of exposure (paraformaldehyde preferred over formalin or undefined test articles), use of randomization procedures to allocate exposure, blinding of the participant and of the assessor to exposure, and the details regarding the analysis and presentation of results.

3.3.3. Synthesis of Human Health Effect Studies

Allergic conditions and sensitization

The general population studies in children and adults provide evidence of an association between formaldehyde exposure and prevalence of rhinitis or rhinoconjunctivitis (Figure 8). The exposure range was similar in these studies (0.04–0.06 mg/m^3) and estimated RRs were comparable for rhinitis endoints ranging from 1.14 to 1.21 for comparisons of the higher exposed to the referent groups. These studies were conducted in school children in France (Annesi-Maesano et al., 2012), Romania (Neamtiu et al., 2019), and Korea (Yon et al., 2019), and in adults in France (Billionnet et al., 2011) and Japan (Matsunaga et al., 2008). The classification of rhinoconjunctivitis by Annesi-Maesano et al. (2012) is the most sensitive and specific of the measures, and the narrower confidence intervals in this study reflect the larger sample size. No other pollutants (e.g., NO_X, $PM_{2.5}$, acetaldehyde, acrolein,

and environmental tobacco smoke) analyzed by this study were associated with rhinoconjunctivitis. Although the effect size is small, these are relatively common conditions and could result in a large impact in the population. A stronger association with formaldehyde inhalation (2-fold risk) was seen in the only study of atopic eczema (Matsunaga et al., 2008). Eczema, while not indicative of an allergic respiratory response, is often associated with other allergic disorders, including those affecting the respiratory system. Consistent results are seen in studies in both children and adults in school and residential settings (see Figure 8). Two of the studies had sufficient sample size and range of exposure to examine dose-response patterns and observed the highest relative risk estimates in the highest exposure groups. Further, an analysis by categories of rhinitis severity in children observed a statistically significant increasing trend in risk (Yon et al., 2019). Two population-based studies evaluated atopy based on skin prick tests (Garrett et al., 1999; Palczynski et al., 1999), but confidence in these analyses was lower than for the studies of allergy symptoms. It was not certain that the time frame represented by the exposure measurements were relevant to the development of sensitization as measured by skin prick tests. Overall, the evidence indicates that formaldehyde exposure at levels seen in the general population studies can enhance the immune hypersensitivity response to allergens.

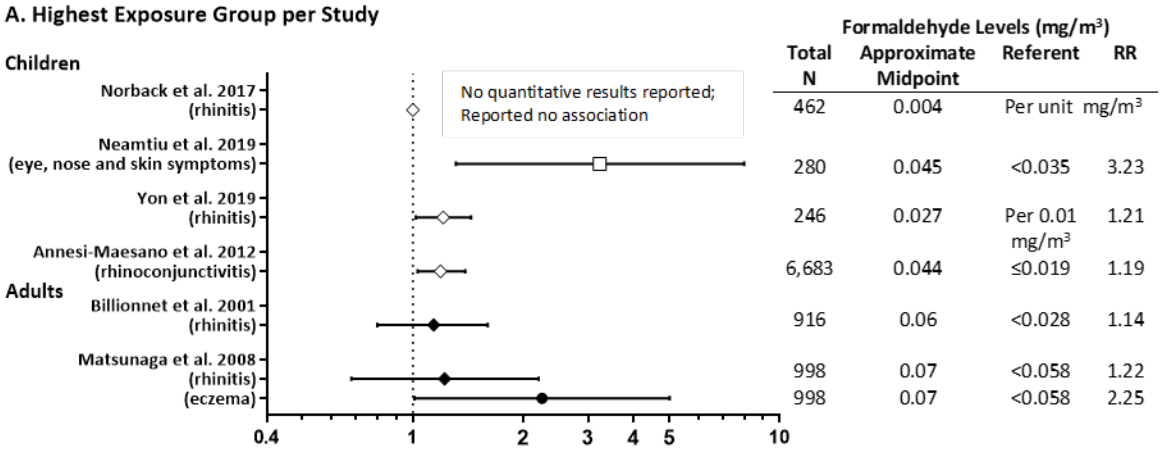


Figure 8. Relative risk estimates for prevalence of allergy-related conditions in children and adults in relation to formaldehyde in residential and school settings.

High and *medium* confidence studies are depicted for rhinitis (diamond) and eczema (circle) and symptom combinations (square). Open symbols are for studies in children; closed symbols are for studies in adults. Results from the highest exposure group in each study are depicted.

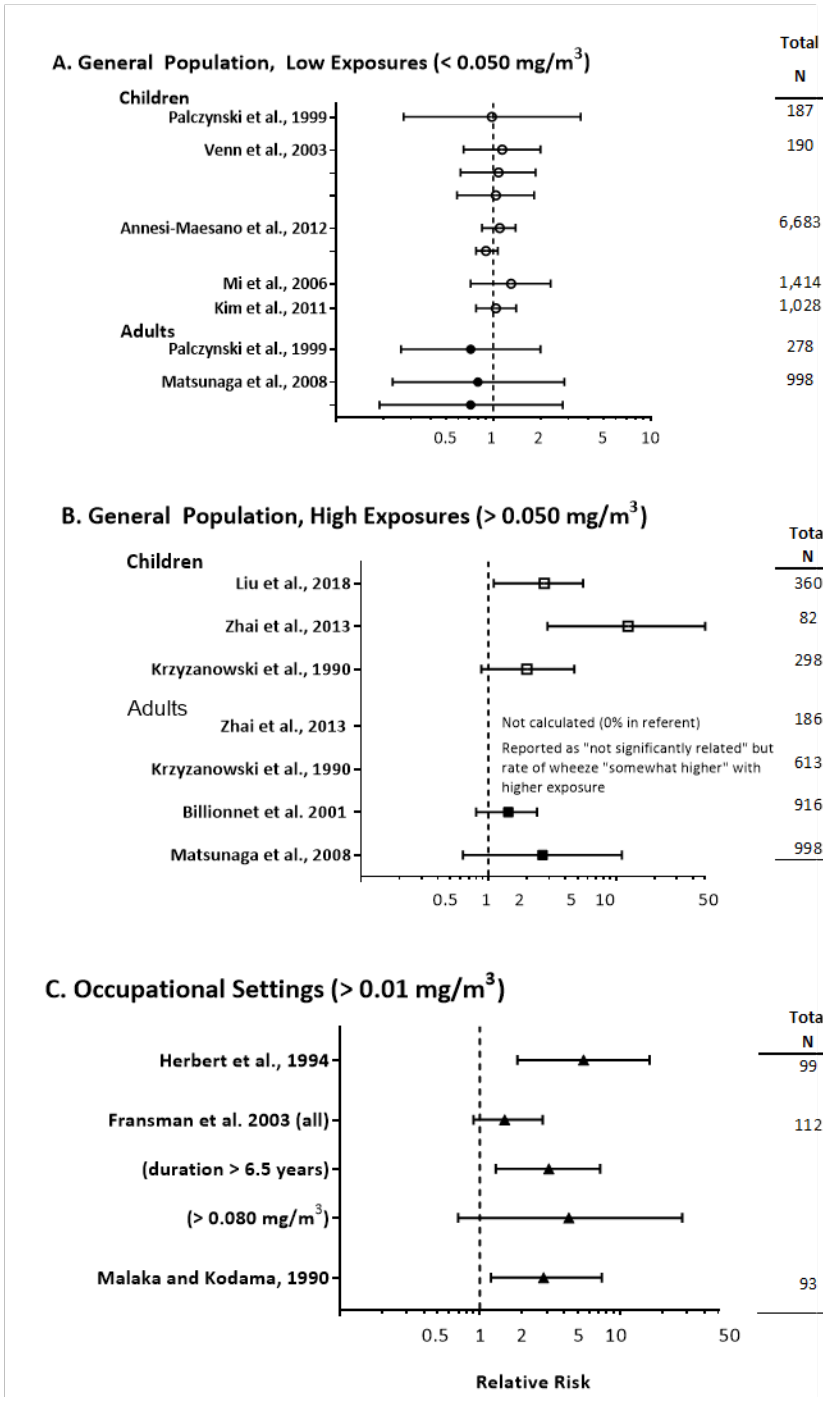
Asthma

The available general population studies also provide evidence of an association between formaldehyde exposure and prevalence of current asthma, as determined by symptoms or medication use in the past 12 months in studies with higher exposures (e.g., above 0.05 mg/m^3), but associations are not seen in settings with a lower exposure range (see Figure 9). The six *medium* or *high* confidence studies in homes or schools with relatively low exposures (<0.05 mg/m^3, most from approximately

0.02−0.04 mg/m^3) report relative risks around 1.0. This set of studies includes a variety of designs and populations; the school-based studies are relatively large (from 1,014 to 6,683 total participants). Six *medium* confidence general population studies in children or adults where a proportion of the study sample had exposures of 0.05−0.1 mg/m^3 were available. Two of these included both children and adults (Zhai et al., 2013; Krzyzanowski et al., 1990), and each provides evidence of a greater susceptibility in children. A limitation of the Krzyzanowski et al. (1990) analysis is the relatively small number in the highest exposure group (n = 21). The summary RR in children calculated for this review combining these two studies was 4.5 (95% CI: 0.76, 27). One other study of children (mean age 10 years) was a hospital-based case-control study that calculated an OR of 2.74 per quartile increase in formaldehyde concentration (95% CI: 1.098, 5.516) using a more specific diagnosis for prevalent asthma including symptoms over the previous 3 or more months, and an FEV_1 increase of 15% in response to β-agonist inhalation (Liu et al., 2018). Exposure levels in the highest quartile ranged from 0.05 to 0.14 mg/m^3. Of note, a Canadian intervention study of impacts on symptom exacerbation among asthmatic children from increasing ventilation rates in homes reported that a 50% reduction in formaldehyde concentrations in the bedroom was associated with a 14 to 20% decrease in the annual change in some symptoms or medical care in the intervention group (Lajoie et al., 2014). However, other coexposures also were reduced by the intervention resulting in uncertainty in the independent effect of formaldehyde, although the reductions were to a lesser extent and separate effects of the other factors were not analyzed. Two other *medium* confidence studies with exposures above 0.05 mg/m^3 were conducted only in adults (Billionnet et al., 2011; Matsunaga et al., 2008); EPA has lower confidence in the results of Matsunaga et al. (2008) because of the lower sensitivity and specificity of the asthma ascertainment (self-report of medication use for asthma). The pattern of results is indicative of an elevated risk, as none of the point estimates are below 1.0; however, the confidence intervals around each of the estimates is relatively wide.

Relatively strong associations were seen in three studies examining prevalence of current asthma in relation to formaldehyde exposure in occupational settings (i.e., >0.10 mg/m^3). A greater than 3-fold increased risk of asthma was seen in each of these studies; the summary RR calculated for this review was 3.79 (95% CI: 1.98, 7.28). One of the wood worker studies addressed potential confounding by dust exposure by the inclusion of this variable in the analysis (Malaka and Kodama, 1990), and another study specifically noted that the measured dust levels were not related to high formaldehyde exposure and that the asthma symptoms were not strongly related to other exposures (Fransman et al., 2003). The results from these studies may represent underestimates of risk, primarily because these were prevalent cohorts with 2 or more years of work duration who would have lost affected individuals prior to the study. In addition, in two of the studies, the comparison group included workers who may have also been exposed to formaldehyde or other respiratory irritants, resulting in an underestimate of the relative risks (Fransman et al., 2003; Herbert et al., 1994). Overall, given the strength of the relative risks, the consistency of the associations seen in the three different workplaces

and populations, and the likelihood that the observed associations were underestimates of the true associations, these studies collectively support a strong association between formaldehyde concentrations above 0.10 mg/m^3 in occupational settings and increased prevalence of current asthma.



Formaldehyde Levels (mg/m³)			
Total N	Approximate Midpoint	Referent	RR
187	0.037	<0.025	0.98
190	0.019	<0.016	1.14
	0.027		1.08
	0.041		1.04
6,683	0.025	≤0.019	1.10
	0.044		0.90
1,414	0.010	per 0.010 mg/m³	1.30
1,028	0.030	per 0.010 mg/m³	1.04
278	0.037	<0.025	0.72
998	0.028	≤0.022	0.80
	0.046		0.72

Formaldehyde Levels (mg/m³)			
Total N	Approximate Midpoint	Referent	RR
360	0.05	per quartile	2.74[a]
82	0.115	<0.08	12
298	0.09	<0.049	2
186	0.115	<0.08	
613	0.09	<0.049	
916	0.046	<0.028	1.43
998	0.07	<0.058	2.65

[a] OR

Formaldehyde Levels (mg/m³)			
Total N	Approximate Midpoint	Referent	RR
99	0.20	<0.08	12
112	0.08	<0.049	1.5
	0.08	<0.08	3.1
	0.16	<0.049	4.3
93	0.12	<0.058	2.65

Figure 9. Relative risk estimates for prevalence of asthma in children and adults in relation to formaldehyde by exposure level in general population and occupational studies.

High and *medium* confidence studies in the general population with highest exposure categories at midpoints of <0.05 mg/m^3 (Panel A) and >0.05 mg/m^3 (Panel B), and occupational populations with exposures >0.1 mg/m^3 (Panel C). Lajoie et al. (2014) was not included in the figure because the study assessed percent change in current asthma symptoms over 12 months, not relative effect.
Levels for most of the participants in the study groups in Panel A, low exposure, were < 0.05 mg/m^3. The exposure value for Liu et al. (2018) is the 75% percentile concentration, which resulted in classifying the study as high exposure. Exposure levels in Billionnet et al. (2011) ranged to a maximum of 0.09 mg/m^3, which resulted in classifying the study as high exposure. Effect estimates are RR or OR.

Two studies examined symptom frequency and medication use in the past 4 weeks, a measure of asthma control among children with asthma. This population could represent a group with greater susceptibility or vulnerability than the general population. Venn et al. (2003) reported a 2- to 3-fold increased risk of frequent symptoms associated with the highest quartile of exposure (>0.032 mg/m^3) compared with <0.016 mg/m^3, with some evidence of an increased risk at even lower exposures. For nighttime symptoms, which may be most relevant with respect to measurements taken in the bedroom, the relative risk estimate was 3.33 (95% CI: 1.23, 9.02). The case definition of wheezing during the past year is interpreted as relevant to the definition of current asthma as used in this assessment, since 88% of the cases also reported using a reliever inhaler in the past year. These results were not impacted by inclusion of measures of room dampness in the models. In a smaller study of 37 low-income children in Boston, Dannemiller (2013) observed higher formaldehyde levels in homes of children with poor asthma control compared to those with better asthma control (geometric mean 0.066 and 0.042 mg/m^3, p = 0.078).

Most of the acute formaldehyde exposure studies among adults with asthma provide little or no evidence of short-term effects; no controlled exposure studies have been conducted in children with asthma. Only two of these studies included an assessment of the response to an allergen challenge, with effects on FEV_1 observed in one study (Casset et al., 2006) but not the other (Ezratty et al., 2007). One difference in these studies is that the Casset et al. (2006) protocol used a nose clip, thus resulting in inhalation solely by mouth.

3.3.4. Mode-of-action Information

The mechanistic information that may inform the potential for formaldehyde to affect allergic conditions or asthma includes animal models using ovalbumin as an experimental allergen, which can provide insight into some of the mechanistic changes that are relevant to these human conditions, while not fully capturing the phenotype of human asthma or allergy-related conditions (see Section 1.2.3 of the Toxicological Review for details on the decision to use animal hypersensitivity studies as mechanistic support). The mechanistic evidence that provides the most direct information regarding the potential role of formaldehyde in respiratory hypersensitivity responses consists of a set of *high* or *medium* confidence studies (Larsen et al., 2013; Fujimaki et al., 2004; Ito et al., 1996; Riedel et al., 1996;

Swiecichowski et al., 1993).[2] These studies differed in the conditions under which formaldehyde affected the relevant endpoints, specifically increased bronchoconstriction and airway hyperresponsiveness, using short-term and acute exposures in sensitized and nonsensitized animals. The data do not indicate that formaldehyde is itself immunogenic, but instead suggest that formaldehyde may augment immune responses to other allergens.

As shown in Figure 10, the analysis identified several pathways describing potential associations between the most relevant mechanistic data available, with several of the initial or early events in these hypothesized pathways (e.g., oxidative stress and inflammatory changes) generally observed to occur at lower formaldehyde levels than other downstream changes (see Appendix A.5.6 for additional details, related analyses, and discussion). The mechanistic evidence indicates that formaldehyde exposure can induce bronchoconstriction and lead to the development of hyperresponsive airways,[3] particularly with allergen sensitization. These heightened responses may be due to a combination of potentially progressive changes, including neurogenic increases in tachykinins and eosinophil recruitment and activation in the lung; however, there was an absence of reliable data supporting mechanistic changes that are typically thought to be essential for sensitization (e.g., IgE). The mechanistic studies also provide consistent evidence that formaldehyde may stimulate a number of immunological and neurological processes related to asthmatic responses; however, a molecular understanding of how formaldehyde exposure favors asthmatic Th2 responses has not been experimentally established.

[2]Note: Swiecichowski et al. (1993) and Leikauf (1992) are considered to involve the same cohort of animals.
[3]Hyperresponsive airways (or hyperresponsiveness) represents a mechanistic event (supported by *robust* evidence) and a potential key feature of respiratory health hazards that is defined to encompass any of a range of relevant airway features, including hyperreactivity (exaggerated response) and hypersensitivity (lower dose to elicit response).

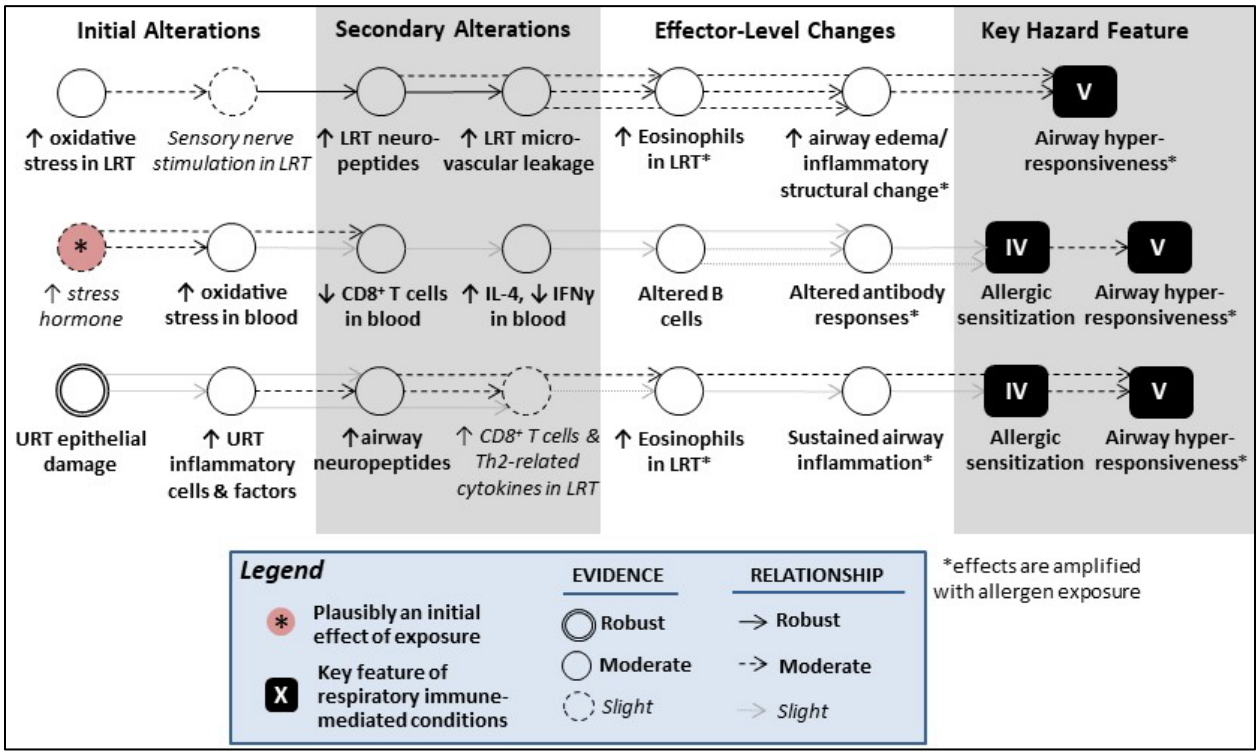


Figure 10. Possible mechanistic associations between formaldehyde exposure and immune-mediated conditions, including allergic conditions and asthma.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects identified these mechanistic pathways. Similar to effects on pulmonary function, events related to indirect stimulation of lower respiratory tract (LRT) sensory nerve endings (top pathway) were considered as likely to represent an incomplete mechanism by which formaldehyde inhalation could cause airway hyperresponsiveness, although whether certain events occur with chronic, low-level exposure remains unclear. While the observed alterations to circulating antibodies (i.e., primarily IgG, not IgE) after formaldehyde exposure might contribute to the development of both allergic sensitization and airway hyperresponsiveness (middle pathway), in the absence of additional clarifying data, this was not identified as a likely mechanism for these effects. Likewise, the slight evidence of altered T cell-related airway responses and, secondarily, inflammatory eosinophil responses might be useful for explaining allergic sensitization (bottom pathway) if additional data were available to better explain the pattern and strength of these associations. Conversely, sustained airway inflammation, at least in animals previously sensitized to an allergen, was considered likely to be an incomplete explanatory mechanism for airway hyper-responsiveness. It is expected that there would be overlap between the top and bottom pathways for airway hyperresponsiveness.

3.3.5. Overall Evidence Integration Judgments and Susceptibility for Immune-mediated Conditions including Allergies and Asthma

Overall, based primarily on *moderate* human evidence as well as *slight* animal evidence from mechanistic studies supporting biological plausibility (including molecular and cellular inflammatory changes and evidence of hypersensitivity), the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of prevalent allergic conditions and prevalent asthma symptoms, as well as decreased control of asthma symptoms given appropriate exposure circumstances (see Table 18). The primary basis for this conclusion includes studies of occupational settings (>0.1 mg/m^3) and population studies where formaldehyde concentrations measured in schools and homes averaged between 0.03 and <0.1 mg/m^3.

Table 18. Evidence integration summary for effects on immune-mediated conditions, including allergies and asthma

Evidence	Evidence judgment	Hazard determination
Allergic Conditions		
Human	*Moderate for* Allergic Conditions, based on: *Human health effect studies*: Small elevated risks in five out of six *high* and *medium* confidence studies of prevalence of rhinitis, conjunctivitis, and eczema among adults and children in residential and school settings with exposures in the range of 0.04−0.06 mg/m^3 formaldehyde. Very low formaldehyde concentrations were measured in the one insensitive null study. *Biological Plausibility (both conditions)*: Studies in humans do not provide robust or moderate evidence for mechanistic events that clearly support the development of asthma, although effects in the blood, such as cytokine, cell, and antibody changes, might contribute	The **evidence indicates** that inhalation of formaldehyde likely increases the prevalence of allergic conditions in humans, given the appropriate exposure circumstances[a] This judgments is primarily based on studies of occupational settings (>0.1 mg/m^3) and population studies where mean formaldehyde concentrations measured in schools and homes were between 0.03 and 0.1 mg/m^3 *Potential Susceptibilities*: Variation in sensitivity is anticipated depending on respiratory health, physiologic changes during pregnancy, age, and exposure to tobacco smoke
Animal	*Slight for* Immune-Mediated Respiratory Effects based on: *Biological Plausibility*: Robust evidence for mechanistic events exists in relation to formaldehyde-induced augmentation of responses to allergens and airway bronchoconstrictor effects in animal models. Although several events typically associated with asthma were not corroborated (i.e., slight or inadequate evidence exists for these events), moderate evidence for mechanistic events exists for stimulation by formaldehyde of important immunological and neurological processes. These include airway eosinophil increases and other inflammatory changes in the airways and systemic circulation that can be reasonably associated with effects on airway hyperreactivity or other responses relevant to the development of allergic conditions and, potentially, asthma. *Animal health effect studies:* Experimental animal models are generally considered to be unable to reproduce the overt manifestations of allergic conditions and are not interpreted to provide direct support.	

<table>
<tr><td>Other inferences</td><td>• Relevance to humans: The most relevant mechanistic findings in animals involve neurological and immunological constituents present in both human and rodent airways.
• MOA: Several incomplete MOAs involving airway inflammatory changes are considered likely to be involved.</td><td></td></tr>
<tr><td colspan="3"><u>Prevalence of Current Asthma</u></td></tr>
<tr><td>Humans</td><td>Moderate for <u>Asthma</u>, based on:

Human health effect studies:
• Elevated risks in eight medium confidence studies of prevalence of current asthma in adults and children, change after an intervention to reduce exposure, or reduced symptom control in children in residential settings including homes with >0.05 mg/m^3 formaldehyde; greater susceptibility among children
• Inconsistencies in study results appear to be explained by exposure levels. No elevated risk of current asthma in six high and medium confidence studies with relatively low exposures (<0.05 mg/m^3), but associations with adequacy of asthma control were observed in one study at this lower exposure level
• Strongly elevated risks in three medium confidence studies in occupational settings with exposures from 0.100 to >0.500 mg/m^3
Biological Plausibility (both conditions):
Studies in humans do not provide robust or moderate evidence for mechanistic events that clearly support the development of asthma, although effects in the blood, such as cytokine, cell, and antibody changes, might contribute</td><td>The evidence indicates that inhalation of formaldehyde likely increases the prevalence of asthma symptoms in humans, as well as decreased control of asthma symptoms, given appropriate exposure circumstances[a]

This judgment is primarily based on studies of occupational settings (>0.1 mg/m^3) and population studies where mean formaldehyde concentrations measured in schools and homes were between 0.03 and 0.1 mg/m^3</td></tr>
<tr><td>Animals</td><td>Slight for <u>Immune-Mediated Respiratory Effects</u> based on:

Biological Plausibility:
In the same way the available mechanistic data are interpreted to provide slight animal evidence supporting the development of allergic conditions in humans, this evidence provides slight evidence supportive of asthma.
Animal health effect studies:
Experimental animal models are generally considered to be unable to reproduce the overt manifestations of asthma and are not interpreted to provide direct support.</td><td>Potential Susceptibilities:
Variation in sensitivity is anticipated depending on respiratory health, physiologic changes during pregnancy, age, and exposure to tobacco smoke</td></tr>
<tr><td>Other Inferences</td><td>• Relevance to humans: For the animal mechanistic data, while several events (e.g., amplified bronchoconstriction; eosinophil increases) have an unclear direct linkage to complex human diseases like asthma, these findings inform the potential for exposure to result in changes to relevant neurological and immunological constituents present in both human and rodent airways.
• MOA: Several incomplete MOAs involving airway inflammatory changes are considered likely to be involved.</td><td></td></tr>
</table>

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis (see below)

3.3.6. Dose-response Analysis

Study selection

The *high* and *medium* confidence studies that included information about dose-response relationships for allergic conditions and current asthma are presented in Table 19, which indicates for each study whether a POD was developed or the rationale for why the study was not suitable.

Table 19. Eligible studies for POD derivation and rationale for decisions to not select specific studies

Reference	Endpoint	POD derived?	Rationale for decisions to not select
Respiratory immune-mediated conditions: Allergic conditions			
Annesi-Maesano et al. (2012)	Rhinoconjunctivitis prevalence: Children	Yes	
Matsunaga et al. (2008)	Atopic eczema	Yes	
Yon et al. (2019)	Rhinitis prevalence	No	Minimal details provided on formaldehyde distribution
Neamtiu et al. (2019)	Allergy-like symptoms (eyes, nose and skin)	No	Provided support for use of Annesi-Maesano et al. (2012)
Garrett et al. (1999)	Atopy prevalence (skin prick tests): Children	No	Uncertain window of exposure with respect to skin prick test results
Palczynski et al. (1999)	Atopy prevalence (skin prick tests): Children	No	Uncertain window of exposure with respect to skin prick test results; too few individuals in third tertile
Respiratory immune-mediated conditions: Current asthma			
Krzyzanowski et al. (1990)	Current asthma prevalence: Children	Yes	
Annesi-Maesano et al. (2012)	Current asthma prevalence: Children	Yes	
Matsunaga et al. (2008)	Current asthma prevalence: Adults	No	Definition of current asthma was narrow and resulted in ascertainment of fewer cases than would be expected
Palczynski et al. (1999)	Current asthma prevalence: Children and adults	No	Uncertainty regarding asthma definition (current, ever?); few cases in third tertile ($n \leq 5$)
Kim et al. (2011)	Current asthma prevalence: Children	No	Provided support for use of Annesi-Maesano et al. (2012)
Mi et al. (2006)	Current asthma prevalence	No	Provided support for use of Annesi-Maesano et al. (2012)
Respiratory immune-related conditions: Asthma control			
Venn et al. (2003)	Asthma control: Children	Yes	
Dannemiller et al. (2013)	Asthma control: Children	Yes	

Derivation of PODs

Allergic conditions and sensitization

The selected *high* confidence studies presented a dose-response analysis using formaldehyde as three (Annesi-Maesano et al., 2012) or four groups (Matsunaga et al., 2008). NOAELs and LOAELs were identified in each of these studies based on the pattern of risk seen across the exposure groups; the PODs were based on NOAELs. The study by Annesi-Maesano et al. (2012) used a relatively long exposure period (5 days) and was a very large study in a school-based sample of children in France (*n* = 6,683) with analysis presented by tertile. Matsunaga et al. (2008) used 24-hour personal samples in a study of 998 pregnant women in Japan. The primary limitation of the Matsunaga (2008) study was that it was conducted only among adults, and so was less able to address the variability in susceptibility that would be anticipated within a population. However, it is a study of pregnant women, a sensitive population for eczema prevalence.

For allergy-related conditions (rhinoconjunctivitis), EPA selected NOAEL and LOAEL values of 0.024 and 0.040 mg/m^3, respectively, in the Annesi-Maesano et al. (2012) study. Higher values (NOAEL = 0.046, LOAEL = 0.062) were selected based on the study in adults by Matsunaga et al. (2008).

Current asthma

Several residential and school-based exposure studies examined prevalence of current asthma in relation to formaldehyde exposure in adults and children in relatively low exposure settings. The six *medium* or *high* confidence studies at exposures of ≤0.050 mg/m^3 do not indicate risk at these lower exposure levels. Several of the relative risk estimates from the individual studies at these exposure levels were limited by low statistical power. However, the consistency of the results, and the absence of an increased risk in the study by Annesi-Maesano et al. (2012), a large school-based study (*n* = 6,683) that used a 5-day sampling period for formaldehyde measurement, strengthens the basis for interpreting this set of studies as indicating an absence of risk of current asthma below 0.05 mg/m^3. Based on the study by Annesi-Maesano et al. (2012) and this collection of studies, EPA selected a NOAEL of 0.042 mg/m^3 for risk of current asthma.

Krzyzanowski et al. (1990) examined prevalence of current asthma in children (5–15 years of age) in higher exposure residential settings (>0.05 mg/m^3). These results are based on a relatively large sample size, with a comprehensive exposure assessment protocol. An increased prevalence of current asthma was seen in the highest exposure group in a categorical analysis. The exposure range in this group was 0.075–0.172 mg/m^3, but the study notes that few values were above 0.11 mg/m^3. Based on this information, EPA selected a LOAEL based on the midpoint of the range estimated as 0.075 to 0.11 mg/m^3 (midpoint of 0.092 mg/m^3). The middle exposure category was selected as a NOAEL, although confidence in this NOAEL is less, given the imprecision of the estimate (*n* with asthma = 1).

EPA identified two studies that examined degree of asthma control in children with asthma in relation to formaldehyde measures in the home (Dannemiller et al., 2013; Venn et al., 2003). The larger sample size, longer sampling period, and more detailed dose-response analysis makes Venn et al. (2003) a stronger basis for providing a POD. EPA selected a NOAEL of 0.027 mg/m^3 (no or weak relative risks seen below this value) and a LOAEL of 0.041 mg/m^3 (2- to 3-fold increased risk of symptoms was seen). The Venn et al. (2003) analysis also evaluated dose-response trends using logistic regression, and EPA used the reported odds ratio per quartile exposure for frequent nighttime symptoms indicating poor asthma control and the median exposure values for each quartile to estimate the concentration associated with a 5% increase in prevalence of symptoms above that observed in the referent group (for modeling details, see Appendix B.1.2). A BMR of 5% was selected because asthma attacks are overt effects, generally requiring the use of drugs to control symptoms (i.e., a frank or adverse effect) (U.S. EPA, 2012).

Table 20 presents the studies with the epidemiology data and sequence of calculations leading to the derivation of a point of departure for each data set with effects relating to allergies and asthma.

Table 20. Summary of derivation of PODs for allergies and current asthma based on observational epidemiological studies

Endpoint and Reference	Population	Observed Effects by Exposure Level	POD_{ADJ} (mg/m^3)
Allergic conditions			
Rhinoconjunctivitis (prevalence); school-based exposure (5 d) Annesi-Maesano et al. (2012)	Children (M and F) *n* = 6,683	Prevalence 12.1%, OR (95% CI) (adjusted) ≤0.0191 mg/m^3 1.0 (referent) >0.0191–0.0284 1.11 (0.94, 1.37) >0.0284– ~0.055 1.19 (1.03, 1.39) NOAEL selection: 0.024 mg/m^3, midpoint of second exposure category LOAEL selection: 0.040 mg/m^3, midpoint of third exposure category	NOAEL: 0.024 LOAEL: 0.040
Atopic eczema (prevalence); personal monitor-based exposure (24 hrs) Matsunaga et al. (2008)	Adult women (pregnancy cohort) *n* = 998	Atopic eczema (5.7% prevalence) mg/m^3 | *n* | OR | (95% CI) <0.022 | 298 | 1.0 | (referent) 0.023–0.033 | 299 | 1.03 | (0.47, 2.29) 0.034–0.057 | 301 | 1.11 | (0.50, 2.42) 0.058–0.161 | 100 | 2.36 | (0.92, 6.09) (trend *p*-value) | | | (0.08) 0.058 to 0.161 vs. <0.058 | | 2.25 | (1.01, 5.01) per 0.0123 mg/m^3 | | 1.16 | (0.99, 1.35) [Stronger associations in women with no family history of atopy] For atopic eczema NOAEL selection: 0.046 mg/m^3, midpoint for third category; LOAEL selection: 0.062 mg/m^3, estimated median of fourth category (based on correspondence with Dr. Matsunaga) For rhinitis NOAEL selection: 0.062 mg/m^3, median of fourth category	Atopic eczema NOAEL: 0.046 LOAEL: 0.062

Endpoint and Reference	Population	Observed Effects by Exposure Level	POD_{ADJ} (mg/m^3)
Current asthma/degree of asthma control			
Current asthma (prevalence); school-based exposure (5 d) Annesi-Maesano et al. (2012)	Children (M and F) *n* = 6,683	Exposure (mg/m^3) / *n*[a] / OR / (95% CI) ≤0.0191 / 2,200 / 1.0 / (referent) >0.0191–0.0284 / 2,200 / 1.10 / (0.85, 1.39) >0.0284– ~0.055 / 2,200 / 0.90 / (0.78, 1.07) [a]approximation, based on tertiles, with total *n* = 6,590 NOAEL selection: 0.042 mg/m^3, midpoint of third exposure category	NOAEL: 0.042
Current asthma (prevalence); residence-based exposure (two 1-wk periods) Krzyzanowski et al. (1990)	Children (M and F) *n* = 298	Exposure (mg/m^3) / *N* / Proportion with asthma <0.049 / 248 / 0.12 0.049–0.074 / 24 / 0.04 0.075–0.172 / 21 / 0.24 (trend *p*-value) / / (0.03) Only a few values were reported to be above 0.11 mg/m^3. NOAEL selection: 0.062 mg/m^3, midpoint of second category LOAEL selection: 0.092 mg/m^3, estimated midpoint of third category	NOAEL: 0.062 LOAEL: 0.092
Asthma control among children with asthma, residence-based exposure (3 d) Venn et al. (2003)	Children (M and F) *n* = 194	Exposure (mg/m^3) / *N* / Proportion / OR / (95% CI) Frequent nighttime symptoms <0.016 / 39 / 0.41 / 1.0 / (referent) 0.016–0.022 / 35 / 0.49 / 1.40 / (0.54, 3.62) 0.022–0.032 / 36 / 0.53 / 1.61 / (0.62, 4.19) 0.032–0.083 / 33 / 0.67 / 3.33 / (1.23, 9.01) (trend *p*-value) / / / / (0.02) per quartile increase / / / 1.45 / (1.06, 1.98) Frequent daytime symptoms <0.016 / 37 / 0.62 / 1.0 / (referent) 0.020–0.022 / 34 / 0.47 / 0.47 / (0.47, 1.25) 0.022–0.032 / 37 / 0.73 / 2.00 / (0.71, 5.65) 0.032–0.083 / 32 / 0.73 / 2.08 / (0.71, 6.11) (trend *p*-value) / / / / (0.05) per quartile increase / / / 1.40 / (1.00, 1.94) NOAEL selection: 0.027 mg/m^3, median of third category LOAEL selection: 0.041 mg/m^3, median of fourth category (based on correspondence with Dr. Venn)	NOAEL: 0.027 LOAEL: 0.041 From regression results: $BMCL_5$: 0.0133
Asthma control among people with asthma, residence-based exposure (30 min) Dannemiller et al. (2013)	Children (M and F) *n* = 37	Geometric mean formaldehyde (mg/m^3) Very poor control (score <12, *n* = 6) 0.066 mg/m^3 All others (score ≥12, *n* = 31) 0.042 mg/m^3 *p* = 0.078	NOAEL: 0.042

Derivation of cRfCs

Table 21 describes the uncertainty factors used to adjust the PODs and the resulting cRfCs for allergy-related conditions and asthma. For rhinoconjunctivitis among children from Annesi-Maesano et al. (2012), a UF_H of 3 was used for the POD. Childhood is a susceptible lifestage for asthma and allergy, and the sample size of 6,600 children was large enough to have characterized an adequate spectrum of human variability. However, a UF_H of 1 was not used because susceptibility among subsets of the study population was not specifically assessed. For the cRfC for atopic eczema in women by Matsunaga et al. (2008), a UF_H of 3 was used. Matsunaga et al. (2008) was a study of pregnant women, a sensitive population for eczema prevalence, however no information was available for other sensitive lifestages, including children, a subgroup with a higher prevalence of eczema compared to adults.

A UF_H of 3 was used for the POD for current asthma prevalence among children from Annesi-Maesano et al. (2012) using the same rationale as described above for rhinoconjunctivitis. For current asthma prevalence among children with residential exposure (Krzyzanowski et al., 1990), a UF_H of 10 was used because susceptibility among subsets of the population was not specifically assessed, and the precision of the NOAEL was lower compared to that in Annesi-Maesano et al. (2012). For Venn et al. (2003), a UF_H of 3 was used because the POD was based on the degree of asthma control in children with asthma, a highly sensitive group. (A UF_H of 1 was considered but the number of individuals in the two higher exposure groups was relatively low [*n* = 31–35], and likely did not characterize a wide range of human variability).

The PODs for all studies were based on the NOAEL; therefore, a UF_L of 1 was applied. Further, a UF_S of 1 was used, based on the following rationale: (1) The definitions of prevalence of rhinoconjunctivitis, current asthma, or atopic eczema involved symptoms occurring during the past 12 months, while asthma control included symptoms during the past 4 weeks. These time frames are components of validated definitions for these conditions and are expected to capture the occurrence of symptoms that tend to be intermittent. (2) The evaluation of children using residential or school-based exposures is presumed to represent several years of exposure. This reflects a large portion of what is expected to be a vulnerable lifestage for these effects (particularly for asthma-related measures). Consistent with the rationale for developmental effects, this would not require the application of a UF_S. The study of the occurrence of atopic eczema during the past 12 months in a group of pregnant women was an exception where a subchronic UF of 3 was applied to the POD. In Matsunaga et al. (2008), the exposure assessment corresponded to the time during pregnancy, which is a less-than-lifetime window of vulnerability. However, this outcome may have been pre-existing in a portion of the study sample and the window of susceptibility may not have been sufficiently represented by the shorter exposure period (Cho et al., 2010). Therefore, a UF of 1 was not applied.

Table 21. Derivation of the cRfC for allergy-related conditions and asthma

Endpoint (*reference*; population)	POD	POD basis	UF_A	UF_H	UF_L	UF_S	UF_D	$UF_{COMPOSITE}$	cRfC (mg/m^3)
ALLERGY-RELATED CONDITIONS									
Rhinoconjunctivitis prevalence [Annesi-Maesano et al. (2012) children M+F, *n* = 2,200 at POD, school-based exposure]	0.024	NOAEL	1	3	1	1	1	3	**0.008**
Atopic eczema prevalence [Matsunaga et al. (2008) adult F (pregnant) *n* = 301 at POD, personal monitor-based exposure]	0.046	NOAEL	1	3	1	3	1	10	**0.005**
ASTHMA									
Current asthma prevalence [Annesi-Maesano et al. (2012) children M+F, *n* = 2200 at POD, school-based exposure]	0.042	NOAEL	1	3	1	1	1	3	**0.01**
Current asthma prevalence [Krzyzanowski et al. (1990) children M+F, *n* = 24 at POD, residential]	0.06	NOAEL	1	10	1	1	1	10	**0.006**
Degree of asthma control [Venn et al. (2003) with asthma M+F, *n* = 35 at POD, residential]	0.013	$BMCL_5$	1	3	1	1	1	3	**0.004**

Selection of osRfC

The osRfC for allergy-related conditions is based on one study in children (Annesi-Maesano et al., 2012) and one study in adults (Matsunaga et al., 2008). Both PODs were based on NOAELs and are interpreted with *high* confidence. In particular, the large study of children (*n* = 6,683) by Annesi-Maesano et al. (2012) was better able to address the variability in susceptibility that would be anticipated within a population. EPA selected an osRfC of 0.008 mg/m^3, based on the overall greater strength of Annesi-Maesano et al. (2012). The completeness of the database relating formaldehyde exposure to allergic sensitization is considered to be *high*, based on the variety of endpoints, populations, and exposure scenarios considered in these studies.

There were three cRfCs developed for asthma based on current asthma and degree of asthma control (Annesi-Maesano et al., 2012; Venn et al., 2003; Krzyzanowski et al., 1990). The POD based on Annesi-Maesano et al. (2012) was derived from a NOAEL using a large study with a relatively long exposure measurement period, supported by a collection of several other smaller studies. Although the effect estimates derived by Venn et al. (2003) were less precise because of relatively small group sizes, the POD derived from Venn et al. (2003) reflects the response among a susceptible population, asthmatic children. To account for the different uncertainties in the PODs from the three studies, the median of the three PODs, 0.006 mg/m^3, was selected for the osRfC. The confidence in the PODs was *medium*. As there was a relatively small number of limited studies (e.g., low statistical power,

incomplete reporting of study results and exposure measures) examining asthma risk in relation to exposures between 0.05 and 0.1 mg/m^3 and a scarcity of data pertaining to asthma control among people with asthma, the database for asthma was considered to be *medium*.

3.4. RESPIRATORY TRACT PATHOLOGY

This section describes research on formaldehyde inhalation and pathology endpoints in the respiratory system in experimental animal studies and observational studies in humans. Numerous well-conducted experimental animal studies, while testing relatively high formaldehyde concentrations, provide consistent support for concentration- and, to a lesser extent, duration-dependent upper respiratory tract hyperplasia and metaplasia after formaldehyde exposure. These data are supported by a set of four studies in formaldehyde-exposed workers that demonstrate consistent findings of an elevated prevalence of nasal lesions such as hyperplasia and metaplasia. The evidence for metaplasia, in particular, is considered to be the best representation of a potential health hazard.

In the URT, both hyperplasia and metaplasia often reflect adaptive tissue responses. These cellular responses help reduce the impact of stressors by changing the structure or function of the locally affected tissue (Harkema et al., 2013). Hyperplasia, generally a response to cell injury, involves an increase in the population of resident cells that results in additional cell layers noticeable by histology, whereas metaplasia, which typically occurs following prolonged or repeated insults, results in the replacement of one differentiated cell type with another, more resilient cell type (Harkema et al., 2013). Importantly, squamous metaplasia results in a hardened, drier, and non-ciliated skin-like layer (Tomashefski, 2008). Along with the acquisition of a protective, barrier-type phenotype, this metaplastic change causes a loss of normal tissue function, including reduced mucous secretion and ciliary clearance (Harkema et al., 2013). Thus, this loss of normal function is judged to be an adverse outcome in and of itself (i.e., independent from its potential role in progression to cancer). As an interpretation regarding adversity is less clear for hyperplasia, this discussion emphasizes the data on squamous metaplasia.

3.4.1. Literature Identification

This review focused on histopathological endpoints and signs of pathology in respiratory (including nasal) tissues. The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.5, as are the specific PECO criteria and the methods for identifying literature from 2016–2021 are described in Appendix F. The mechanistic studies related to pathology endpoints were considered in the overarching mechanistic evaluation informing all potential respiratory health effects (see Appendix A.5.6 for additional details and supporting analyses), the most relevant results of which are summarized herein.

3.4.2. Study Evaluation

Hyperplasia can be precipitated by damage to the nasal epithelium, which is evaluated histologically by measures of, for example, cell loss or necrosis, epithelial degeneration, and erosions. Relatedly, squamous metaplasia is an adaptive response to continued toxic insult that involves cellular substitution. Thus, it is useful to consider these cellular damage-related endpoints in the context of hyperplasia and metaplasia. While evaluations of necrosis- and cytotoxicity-related pathology can be informative, these endpoints were generally inconsistently measured or poorly reported across the available studies and are therefore only summarily discussed, whereas the potential development of hyperplasia and metaplasia was documented in nearly all the long-term histopathological studies. Studies that evaluated related outcomes, such as mucociliary flow rates, cellular proliferation counts based on DNA labeling, and mucosal swelling (which generally only investigated acute or short-term exposure), were included and summarized as part of the respiratory system MOA evaluation.

Given the large number of long-term exposure studies with information on URT pathology and the focus of the assessment on the effects of lifetime formaldehyde exposure, this section focuses on animal studies of subchronic or chronic exposure, and on human studies of occupational exposure where exposed employees were generally employed for longer than 5 years. Exceptions include discussion of shorter-term studies that might inform the potential for relationships between lesion types and studies specifically considering differences in exposure paradigm for lesion induction.

For human studies that evaluated histopathological lesions in nasal biopsies, the evaluation emphasized either a detailed explanation of how tissues were evaluated and scored, or a citation for a standard method. Cross-sectional studies among occupational cohorts likely were influenced by the selection of the workforce toward individuals less responsive to the irritant properties of formaldehyde, with a reduction in sensitivity. Confidence in these studies was downgraded because of this limitation. Age, gender, and smoking were considered to be important confounders to evaluate for effects on pathological endpoints. Confounding by other coexposures in the workplace specific to the occupational setting also was considered. Higher confidence was placed in studies with the ability to differentiate between exposed and unexposed, or between low and high formaldehyde exposure.

In addition to general factors considered for all toxicology studies of formaldehyde inhalation exposure (see Appendix A.5.1), factors specific to the interpretation of respiratory tract pathology were considered to give greater weight to results from the large database of well-conducted studies. These factors included: (1) the use of too few test subjects; (2) a failure to report lesion incidence or severity; (3) the lumping of multiple lesions (e.g., squamous metaplasia and hyperplasia); (4) a failure to report quantitative incidences or statistical analyses; (5) the use of insensitive sampling procedures (multiple sections across multiple levels of the respiratory tract were preferred); and (6) use of an exposure duration or follow-up that is likely insensitive for detecting slow-developing lesions (a duration of ≥1 year was preferred). Most studies of respiratory pathology used paraformaldehyde or freshly prepared formalin, which yield high purity formaldehyde gas. In studies that tested commercial formalin,

coexposure to methanol was less of a concern for investigations of URT respiratory pathology because most inhaled methanol bypasses the nose and is readily absorbed in the lungs for systemic distribution.

3.4.3. Synthesis of the Human Health Effect Studies

The epidemiological studies that evaluated pathological endpoints in the nasal epithelium indicated that formaldehyde exposure is associated with higher scores indicating a higher prevalence of cells with morphological changes including squamous metaplasia. There was no evidence of a time-dependent relationship with formaldehyde. Additionally, there was no indication that coexposure with wood-dust or smoking modifies the pathological effects of formaldehyde.

Cross-sectional studies among occupational cohorts likely were influenced by the selection of the workforce in favor of individuals less responsive to the irritant properties of formaldehyde, with resulting bias toward null results. Despite this methodological limitation and subsequent reduction in sensitivity, most of the studies observed increases in histopathological outcomes among exposed workers, which increased confidence in the reported exposure-related associations. Nasal biopsies were taken in four occupational studies, and tissues were subsequently stained and cell structure examined according to variations of the Torjussen et al. (1979) method. The original Torjussen method scored morphological characteristics of the nasal epithelium using a whole number between 0 and 8, with 0 indicating normal epithelium, 8 indicating carcinoma, and the midpoint of 4 signifying stratified squamous epithelium with a horny layer. Despite the variations of this scale, in each study the lowest numbers (0 or 1) always indicated normal cell structure while increasingly higher numbers indicated more disruptive cellular changes. Although the focus of this section is nonneoplastic histopathological lesions, the studies compared the means of the total score between exposed and referent groups.

Although more equivocal in one study (Boysen et al., 1990), the four studies examining histopathology found that participants exposed to average formaldehyde levels between 0.05 and 0.6 mg/m^3 had a higher average histopathology score than their respective comparison group (Ballarin et al., 1992; Holmstrom et al., 1989b; Edling et al., 1988). While the studies were limited by probable survival bias and, in some cases, other limitations resulting in a bias toward the null, a consistent association with histopathological endpoints, including squamous metaplasia, was observed. Therefore, the observational human data provide *moderate* evidence that inhaled formaldehyde induces histopathological lesions in the URT, including squamous metaplasia.

3.4.4. Synthesis of the Animal Health Effect Studies

A large database of well-designed studies has characterized formaldehyde-induced respiratory tract pathology in mice, hamsters, and monkeys, but primarily in rats. The durations of these studies ranged from a few hours to longer than 2 years, and several studies having included recovery periods that explored the reversibility of lesions. Because of the abundance of studies of respiratory pathology, this section focuses on longer duration (i.e., chronic and subchronic) studies interpreted with *high* or

medium confidence, primarily studies in rats (see Section 1.2.4 in the Toxicological Review for an expanded discussion of pathology in other species). Finally, although other nasal lesions have been observed to develop after formaldehyde exposure (e.g., necrosis), this summary focuses on the more reliably evaluated and more consistently reported information on hyperplasia and metaplasia.

Only a few studies evaluated sections of the respiratory tract distal to the nasal cavity, and these evaluations were generally less rigorous (e.g., examining only a single tissue section). Pathological findings in the lower respiratory tract were generally not identified in higher confidence studies, and are not discussed in detail in the assessment. However, the limited evidence for lesions beyond the nasal cavity in rats suggests that concentration is an important variable in long-term studies. Laryngeal or tracheal lesions, including hyperplasia and squamous metaplasia, were only observed at high concentrations, with no evidence for effects across multiple rat strains at levels <12 mg/m^3. Findings in a single study of rhesus monkeys observed changes in URT regions proximal to the nasal cavity (but not the lungs) at lower concentrations (i.e., exposure for ≤6 weeks to 7.4 mg/m^3 formaldehyde in Monticello et al. (1989), which might suggest that the monkey nose is less efficient than the rodent nose at scrubbing formaldehyde from inhaled air.

Hyperplasia and metaplasia have been consistently reported in multiple rodent species/strains, and in monkeys, with consistent and clear indications of concentration-dependence. These studies also identify a clear relationship between formaldehyde exposure duration and the development of squamous metaplasia, with somewhat weaker data indicating a duration-dependency for hyperplasia. Both squamous metaplasia and hyperplasia appear to be at least partially reversible after exposure ceases. Due to the high reactivity and water solubility of formaldehyde, nasal metaplasia and hyperplasia have primarily been assessed (and subsequently observed) in the epithelium lining the anterior regions of rodent nasal passages (typically levels I, II, and III: level I refers to the area posterior to the nostrils, with higher levels indicating more posterior sites) following formaldehyde inhalation exposure, mostly in regions containing respiratory epithelium.

Squamous metaplasia, in particular (which, as previously mentioned, is considered adverse), has been observed after chronic, subchronic, and short-term exposure to inhaled formaldehyde. Overall, the most robust responses (i.e., higher incidence or severity at lower formaldehyde concentrations) occur following chronic exposure, particularly in rats. As compared to rats, other laboratory rodents appear to require higher levels (i.e., mice) or exhibit a reduced response (i.e., hamsters), suggesting that there may be differences in species sensitivity to formaldehyde-induced squamous metaplasia. These differences in sensitivity are likely at least partially due to differences in the magnitude of reflex bradypnea across species. Multiple chronic rat studies have reported clear increases in squamous metaplasia following exposures of approximately 2.5–2.7 mg/m^3 (Kamata et al., 1997; Kerns et al., 1983; Battelle, 1982) or 11.3–11.6 mg/m^3 (Woutersen et al., 1989; Appelman et al., 1988), although some data suggest that slight increases might be present at lower levels (i.e., 0.4–1.2 mg/m^3; (Kamata et al., 1997; Woutersen et al., 1989). With subchronic exposure, squamous metaplasia is observed in rat noses at

higher concentrations (i.e., ≥11.3 mg/m^3) in *high confidence* studies by Appelman et al. (1988), Woutersen et al. (1987), and Feron et al. (1988), the results of which are supported by consistent observations in two *medium confidence* studies (Andersen et al., 2010; Zwart et al., 1988), although these latter studies observed increases at lower exposure levels (i.e., 2.5–3.7 mg/m^3). The rat data from *medium* or *high* confidence studies of chronic formaldehyde exposure are summarized in Figure 11.

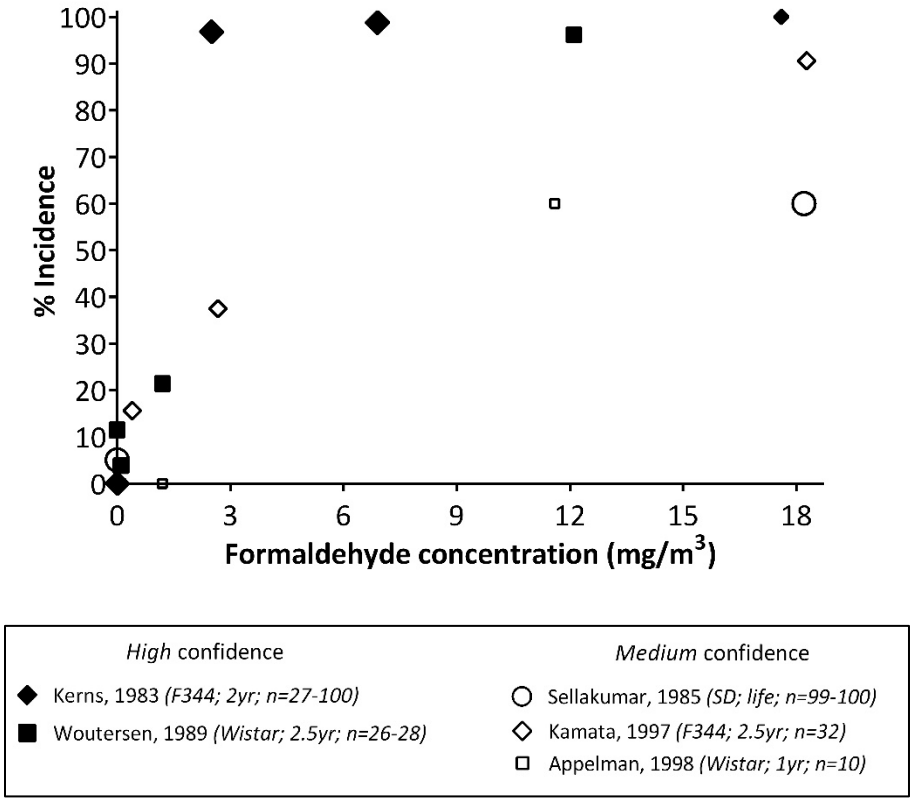


Figure 11. Squamous metaplasia incidence in chronic pathology studies of rats.

Smaller symbols reflect smaller sample sizes. *High* confidence studies are outlined in black.

The duration-dependency of these lesions in rat studies represents an important consideration. For squamous metaplasia, the duration of exposure affects the locations at which lesions develop, as well as their severity, probably in parallel with increases resulting from increasing formaldehyde concentration. The association with lesion location is demonstrated by the results of Kerns et al. in the supporting Battelle report (1983; 1982) who observed that, in anterior nasal regions (i.e., level I and II) of F344 rats exposed to ≥2.5 mg/m^3, the incidence of squamous metaplasia increased from ≤20% to 100% with increasing duration (i.e., 6–24 months); however, in posterior nasal regions (i.e., levels III–V), a duration-dependent increase in incidence was only observed at 17.6 mg/m^3. In some instances, noted by Kerns et al. (1983; 1982), more posterior lesions were entirely unique to longer exposure durations as compared to shorter exposures (e.g., level III at 6.9 mg/m^3 only with 24 months of exposure). Regarding

severity, squamous metaplasia was observed to increase (i.e., from slight focal lesions to metaplasia with keratinization) with exposure duration increases from 13 to 52 weeks of exposure to 11.6 mg/m^3 in Wistar rats (Appelman et al., 1988). Similarly, at ≥11.6 mg/m^3 in Wistar rats, an increase in the severity of squamous metaplasia in respiratory epithelium occurred as exposure duration increased from 4 to 8 to 13 weeks (Feron et al., 1988). Several studies in rats, which compared longer-term exposure to shorter-term exposure, confirm the important role for exposure duration in lesion development by demonstrating that the increases in lesions were not attributable to longer latencies after the formaldehyde exposures were begun (Woutersen et al., 1989; Feron et al., 1988). When animal ages at evaluation and formaldehyde exposure levels were matched, comparisons of subchronic exposure to chronic exposure (Woutersen et al., 1989) and of short-term exposure to subchronic exposure (Feron et al., 1988) revealed greater incidences or severity of these lesions with the longer exposure durations.

Comparisons of the formaldehyde concentrations at which significant increases in hyperplasia are observed across studies of differing exposure duration do not provide as clear a picture regarding the potential duration-dependence of formaldehyde-exposure induced hyperplasia. However, like the results for metaplasia, several rat studies comparing exposures of differing exposure duration (e.g., chronic versus subchronic) demonstrate that increasing exposure duration results in increases in the incidence or severity of hyperplasia in the respiratory epithelium when testing the same formaldehyde concentrations and anatomical levels (Woutersen et al., 1989; Appelman et al., 1988; Feron et al., 1988; Kerns et al., 1983; Battelle, 1982). Considering the notable influence of exposure duration on metaplasia at formaldehyde levels ranging from 2.5 to 2.7 mg/m^3 in rat studies (Kamata et al., 1997; Kerns et al., 1983; Battelle, 1982), the easier reversibility of hyperplasia, and the generally more robust effects of duration on the incidence of metaplasia as compared to hyperplasia across species, exposure duration appears to be more important to the development of metaplasia in laboratory animals than to the development of hyperplasia. Rat studies by Wilmer et al. (1989, 1987) indicate that formaldehyde, perhaps similar to mortality responses following acute exposure to some other local irritants (see below), does not appear to adhere strictly to Haber's rule for the induction of nasal pathology. Although duration of exposure has a clear and substantial role for the development of these nasal lesions (see discussion above), the experiments by Wilmer et al. (1989, 1987) suggest that a powers equation ($C^n \times t = K$) where n is >1 may better represent formaldehyde exposure-induced nasal lesions than $C \times t = K$, at least when interpreting short-term or subchronic exposure [the exposure scenarios examined by Wilmer et al. (1989, 1987)]. Although a value for n was not identified for formaldehyde, or specifically for exposure-induced nasal pathology, studies of acute exposure to other local irritants and the concentration-duration dependence for mortality suggest that the value for n, on average, is approximately 1.8–1.9 (ranging from 0.5 to 4.0)[4]. It is difficult to speculate where within this range a

[4]Values of n for 11 local irritants as estimated by Berge et al. (1986) averaged 1.9 (range: 1.0–3.5), while 21 local irritants relying on data in rats or mice, as summarized by California EPA (2008), averaged 1.8 (range: 0.5–4.0). Of potential interest to this assessment, the chemicals included ammonia (n = 2.0) and acrolein (n = 1.2).

value for n might be most applicable to formaldehyde, particularly within the context of respiratory pathology and long-term exposures (i.e., since these n values are for mortality after acute exposure); however, based on the data discussed in previous sections, it might be reasonable to expect that an n defined for associations with hyperplasia should be higher than one defined for metaplasia.

Overall, a number of well-conducted studies across multiple species (i.e., rats, mice, and monkeys) demonstrate a clear association between formaldehyde exposure and the development of respiratory tract pathology, primarily in the nasal cavity.

3.4.5. Mode-of-action Information

Histopathological lesions in the respiratory tract following formaldehyde exposure appears to result, at least in part, from a series of increasingly severe effects including altered mucociliary function, damage to the nasal epithelium (e.g., sustained cytotoxicity), and sustained reparative cell proliferation culminating in a hyperplastic epithelium, or transitioning to an adaptive, metaplastic tissue (see Figure 12; see Appendix A.5.6 for additional details, related analyses, and discussion). Consistent with observations of metaplasia without hyperplasia in some of the rodent health effect studies, this pathway illustrates that metaplasia can develop following damage (noting that damage does not need to be overt) to the epithelium in the absence of hyperplasia (i.e., hyperplasia may not be an essential precursor). All the mechanistic events and relationships between events in the proposed pathway are based on *robust* or *moderate* evidence, indicating that this is likely a mechanism by which formaldehyde exposure causes squamous metaplasia. Specifically regarding the well-established alterations to mucus flow and proliferation, mucociliary function appears to be affected at relatively low concentrations (e.g., 0.25–0.3 mg/m^3) in humans (Holmström and Wilhelmsson, 1988; Andersen and Molhave, 1983), whereas multiple *high* and *medium* confidence rodent studies do not see notable changes in either mucociliary function or proliferation below 1.23 mg/m^3 (increases generally occur above 2.5 or sometimes 3.5 mg/m^3) [e.g., (Monticello et al., 1996; Monticello et al., 1991; Morgan et al., 1986a; Morgan et al., 1986c)]. Overall, consistent with some of the animal health effect studies, these data suggest that concentration is likely to be more of a driver of these mechanistic effects than duration (noting that duration still contributes). Because modification of epithelial cell health and function in the URT can occur via multiple direct and indirect mechanisms following formaldehyde inhalation, which are expected to vary due to differences in both exposure duration and intensity, there are likely to be other plausible mechanisms by which formaldehyde exposure could cause this health effect. The current understanding provides strong biological support for an association between formaldehyde exposure and respiratory tract pathology. Additionally, as many of the mechanistic events in this pathway have been observed in both humans (sometimes indirectly) and experimental animals, including effects on mucociliary function and cell proliferation as well as evidence of elevated oxidative stress, findings from experimental animals are considered relevant to humans.

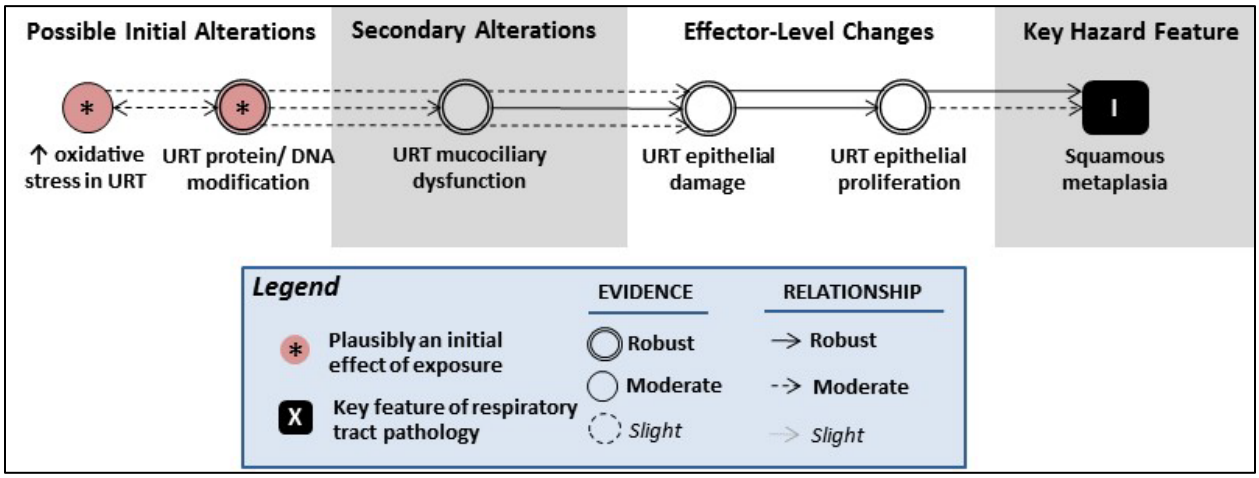


Figure 12. Possible mechanistic associations between formaldehyde exposure and respiratory tract pathology.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects identified this sequence of mechanistic events as likely to be a mechanism by which formaldehyde inhalation could cause respiratory tract pathology, specifically squamous metaplasia, although it is assumed that other plausible pathways explaining this association have yet to be defined.

3.4.6. Overall Evidence Integration Judgment and Susceptibility for Respiratory Tract Pathology

Overall, the strength of the evidence for hyperplasia and squamous metaplasia include *robust* evidence of an effect in animals and *moderate* human evidence from observational epidemiological studies, supported by more limited findings in mechanistic studies of exposed humans and strong support for a plausible MOA based largely on mechanistic evidence in animals (with coherent findings in human studies). Therefore, the **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans given appropriate exposure circumstances (see Table 22). The primary basis for this conclusion is based on rat bioassays of chronic exposure which consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3.

Table 22. Evidence Integration Summary for Effects of Formaldehyde Inhalation on Respiratory Pathology

Evidence	Evidence judgment	Hazard determination
Human	*Moderate* based on: *Human health effect studies:* Of the four occupational studies interpreted with *medium* confidence (less sensitive due to healthy survival bias), 3 observed a higher prevalence of abnormal nasal histopathology, including loss of ciliated cells, hyperplasia, and squamous metaplasia at concentrations ranging from 0.1–2 mg/m^3, while the remaining (1) study had more equivocal findings. *Biological plausibility:*	The **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans given appropriate exposure circumstances[a]

	Mechanistic changes in two studies (one interpreted with *medium* confidence) in humans provides evidence of changes in mucociliary clearance and mucus flow beginning at formaldehyde concentrations of 0.25–0.3 mg/m^3.	Primarily based on rat bioassays of chronic exposure which consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3. *Potential Susceptibilities:* Variation in sensitivity may depend on differences in URT immunity, allergen sensitivity, and nasal structure or past injury (e.g., studies support increased sensitivity of rodents with intentionally damaged nasal cavities), and males may be more sensitive than females.
Animal	*Robust,* based on: *Animal health effect studies:* • Consistent evidence of squamous metaplasia and hyperplasia in the nasal respiratory epithelium across numerous independent studies interpreted with *high or medium* confidence*,* with generally the most sensitive effects being metaplasia observed after chronic exposure to ≥2.5 mg/m^3 formaldehyde. • Evidence of both metaplasia and hyperplasia in monkeys, rats, mice, and hamsters; the data were more limited for monkeys; mice and hamsters exhibited less sensitivity. • Multiple studies provided clear evidence of a concentration dependence for lesion development, as demonstrated by increases in the incidence, severity, and anatomical location of the observed lesions with increasing exposure. *Biological plausibility:* Robust or moderate evidence for mechanistic events based predominantly on experimental animal studies supports a biological progression of changes that appears to include mucociliary dysfunction, epithelial damage, and often cellular proliferation, leading to the eventual development of nasal lesions, including squamous metaplasia.	
Other inferences	• *Relevance to humans:* Similarities in the function and properties of the nasal epithelium across species, as well as similar mechanistic and apical effects observed in both humans and animals, provide strong support for the relevance of the findings in experimental animals to humans. • *MOA*: Although it may be incomplete, a MOA involving effects on mucociliary function and epithelial cell health is well supported and considered to be a major contributor to these effects. • *Other:* Data from animal studies suggest that lesion development may be driven more by concentration than duration, particularly for hyperplasia. While estimates for formaldehyde were not identified, estimates for other irritants indicate that concentration is ~1.8- to 1.9-fold (on average) more influential than duration regarding exposure-induced mortality after acute exposure.	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis (see below)

3.4.7. Dose-response Analysis

Study selection

Of the *medium* and *high* confidence studies that exposed rodents to formaldehyde for at least one year, the chronic rat bioassays by Kerns et al. (1983; 1982) and Woutersen et al. (1989) were considered to be the most informative for dose-response analysis (see Table 23 for the rationale supporting this decision). As an interpretation regarding adversity was less clear for hyperplasia, dose-response analysis relied on the data on squamous metaplasia.

Table 23. Eligible studies for POD derivation and rationale for decisions to not select specific studies

Respiratory Pathology (Animal Exposure Duration ≥52 Weeks; Humans All Employed >5 Yrs)			
Reference	**Endpoint**	**POD derived?**	**Rationale for decisions to not select**
Kerns et al. (1983); Battelle (1982)	Squamous metaplasia: nasal turbinates, Fischer 344 rats	Yes	
Kerns et al. (1983); Battelle (1982)	Squamous metaplasia: nasal turbinates, B6C3F1 mice	No	Mice are less susceptible for this endpoint
Woutersen et al. (1989)	Squamous metaplasia: nasal turbinates, Wistar rats	Yes	
Appelman et al. (1988)	Squamous metaplasia: nasal turbinates, Wistar rats	No	Limited sample size (n = 10/group) and exposure duration (1 yr), as compared to Kerns et al. (1983; 1982) (n = up to ~100/group; 24 mos) and Woutersen et al. (1989) (*n* = 30/group; 28 mos)
Kamata et al. (1997)	Squamous metaplasia: nose and trachea, Fisher 344 rats	No	Some quantitative uncertainty associated with methanol coexposure; small sample size at 28 months; metaplasia results pooled across scheduled sacrifices

Derivation of PODs

There was *high* confidence in both studies selected for POD derivation, as both studies were well designed and executed with adequate reporting of data [notably, Kerns et al. (1983; 1982) was conducted under GLP conditions]. Table 24 summarizes the derivation of PODs using data from these studies. In determining the BMR level for the POD from Kerns et al. (1983; 1982), the average severity score was in the range of minimal-to-mild at the lowest dose for both the 18-month and 24-month durations for Level 1. This finding supports a BMR of 0.1 extra risk, representing a minimal level of adversity. Due to difficulties modeling the 24-month data, the 18-month data, for which incidence rises more gradually, were chosen even though these data would be less preferred (see Toxicological Review Section 2.2.1). Interspecies extrapolation of the rat BMCL level to humans was carried out in two steps. First, average flux values in the Level 1 region of the rat corresponding to the rat BMCL derived from the incidence of squamous metaplasia were estimated. Next, the exposure concentration at which any region in the human nose is exposed to this same level of formaldehyde flux at the inspiratory rate of 15 L/min was estimated.

For the POD from Woutersen et al. (1989) the same minimal adversity was assumed and a BMR of 0.10 extra risk was used; however, a dosimetry model for flux to the nasal lining of the Wistar rat was not available. U.S. EPA (2012) concluded that internal dose equivalency in the extrathoracic region for rats and humans is in general achieved through similar external exposure concentrations; that is, even for highly soluble and reactive gases ppm equivalence is a more appropriate default method for extrapolation than an approach based on adjustment by the ratio of surface area to minute volume.

Confidence in the POD calculation based on Woutersen et al. (1989) was *medium*, while confidence based on Battelle (1982) and Kerns et al. (1983) was *low*. Confidence is lower in the latter due to extrapolation well below the tested formaldehyde concentrations, a BMCL was based on the 18-month exposure although the response was greater in magnitude after 24 months, and modeling of the incidence at Level 1 in the nose, although concentrations in Level 2 were lower.

Table 24. Summary of derivation of PODs for squamous metaplasia

Endpoint and reference	Model	BMR	Rat BMC[a] (mg/m^3)	Rat BMCL[a] (mg/m^3)	Flux[a] ($pmol/mm^2$-hr)	Human Exposure (mg/m^3)	Human POD_{ADJ}[b] (mg/m^3)
Squamous metaplasia Kerns et al. (1983); Battelle (1982) F344 rat, M & F, 18 mos, Level 1	Log-probit	0.10	0.587	0.456	685	0.484	0.086[c]
Squamous metaplasia Woutersen et al. (1989) Wistar Rats, M, 28 mos, Level 1	Log-logistic	0.10[b]	1.00	0.526	N/A	N/A	0.094[d]

[a]Approximate average flux over nasal lining at this level corresponding to the BMCL.
[b]POD_{ADJ} is the human equivalent of the rat BMCL duration adjusted (6/24) × (5/7) for continuous daily exposure.
[c]Human extrapolation was based on modeled estimates of regional formaldehyde tissue flux. If extrapolation is based on ppm equivalence instead, value increases by 1.14-fold.
[d]Human extrapolation was based on ppm equivalence derived from pharmacokinetic principles.

Derivation of cRfC

Table 25 describes the uncertainty factors used to adjust the POD to the resulting cRfCs for each of the two selected studies. For both PODs, a UF_A of 3 was applied to address residual uncertainties in interspecies extrapolation after dosimetry modeling (Kerns et al., 1983; Battelle, 1982) or an assumption of ppm equivalence (Woutersen et al., 1989) was used to estimate a human equivalent concentration and account for toxicokinetic differences between animals and humans. A UF_H of 10 was applied to both PODs to address the limited variability in susceptibility factors encompassed by these typical studies of inbred laboratory animal populations. Finally, a UF_S of 3 was applied for the Battelle (1982) and Kerns et al. (1983) study because it was based on 18-month exposure data in lieu of the 24-month exposure data available in the same study. Specifically, the lesion incidence data were higher with longer exposure duration (i.e., 24 months versus 18 months), and thus a lower POD would be expected if the 24-month data could have been modeled. Although the 18-month exposure duration reduced the uncertainty associated with extrapolating to lifetime exposure compared with a shorter duration, this reduction was considered incomplete, and a factor of 3 was applied.

Table 25. Derivation of cRfCs for respiratory tract pathology

Endpoint (*reference*; population)	POD	POD basis	UF_A	UF_H	UF_L	UF_S	UF_D	$UF_{COMPOSITE}$	cRfC (mg/m^3)
RESPIRATORY TRACT PATHOLOGY									
Squamous metaplasia: [Kerns et al. (1983); Battelle (1982) F344 rat, M & F, 18 mos, Level 1]	0.088	$BMCL_{10}$	3	10	1	3	1	100	**0.0009**
Squamous metaplasia: [Woutersen et al. (1989) Wistar Rat, M, 28 months, Level 1]	0.094	$BMCL_{10}$	3	10	1	1	1	30	**0.003**

Selection of the osRfC

The osRfC for respiratory tract pathology is based on squamous metaplasia observed in anterior rodent nasal passages in two studies of long-term exposure. EPA could discern no particular basis to select either the Woutersen et al. (1989) study or the Battelle (1982) and Kerns et al. (1983) study over the other on grounds of confidence in the study methods, or known differences in sensitivity between Wistar and F344 rats. In addition, the PODs were nearly identical and the cRfCs were very similar for the two datasets (i.e., cRfCs of 0.0009 for Kerns et al. (Kerns et al., 1983; Battelle, 1982) and 0.003 for Woutersen et al. (1989) which are comparable given the limited precision of the calculations). However, there was lower confidence in the derivation of the POD from Battelle (1982) and Kerns et al. (1983), which involved an extrapolation well below the tested formaldehyde concentrations. In addition, the cRfC for Battelle (1982) and Kerns et al. (1983) involved the application of an uncertainty factor for exposure duration. While exposure duration is important to the development of this lesion, such effects appear to be more dependent on exposure concentration. Thus, if a factor describing the concentration-duration relationship[5] were available for formaldehyde (and interpretable in the context of metaplasia), a data-defined UFs could have been applied. Considering these uncertainties and the comparability of the cRfCs, to represent the results of both studies, the cRfC from Woutersen et al. (1989) was used to derive an osRfC of 0.003 mg/m^3 for the respiratory pathology endpoint. Since the POD basis for this value is from Woutersen et al. (1989) the confidence in the POD is considered *medium*. Completeness of the database for respiratory tract pathology is *high*, based primarily on numerous well-conducted long-term studies in experimental animals.

3.5. NERVOUS SYSTEM EFFECTS

Numerous studies reported data suggesting that formaldehyde inhalation might result in noncancer nervous system effects; however, few studies in humans were available and the animal data

[5]Studies of other irritants have, on average, identified a factor of ~1.8–1.9 for relationships between acute exposure and mortality (i.e., the observed mortality is more attributable to concentration, by 1.8- to 1.9-fold, than duration; see Toxicological Review Section 1.2.4). A value for formaldehyde was not identified, nor were values for long-term exposure.

were often compromised by significant methodological limitations. In addition, there was generally weak consistency in the evidence across well-conducted studies, a potential mode-of-action for nervous system effects without systemic distribution of inhaled formaldehyde has not been established, and the database is considered incomplete. Overall, conclusive evidence of a nervous system health hazard in humans exposed to formaldehyde was not identified (i.e., **suggestive evidence**). Thus, this Overview provides only a brief synopsis. However, given the potential for nervous system effects reported across a variety of study types, and the general lack of comprehensive and rigorous experiments, a need for additional studies, particularly well-conducted studies relevant to childhood exposure, was identified.

3.5.1. Literature Identification and Study Evaluation

Literature identification and study evaluations were conducted in a manner similar to the other noncancer health effect sections (see Appendix A.5.7 and Appendix F for details). The study evaluations emphasized an analysis of potential issues relating to exposure (e.g., for these systemic effects, known or presumed coexposure to methanol represented a serious study deficiency) and the irritant effects of formaldehyde.

3.5.2. Evidence Synthesis and Overall Evidence Integration Judgement for Nervous System Effects

Data were available and analyzed relating to the following outcomes:

- Amyotrophic lateral sclerosis (ALS): several *medium* and *high* confidence observational epidemiological studies were available, generally without quantified exposure levels and with outstanding questions of consistency.
- Developmental neurotoxicity: the evidence primarily consisted of a *medium* confidence animal study and some studies reporting potentially relevant mechanistic findings. Given the potential for effects in children exposed to formaldehyde, this represents a notable data gap.
- Neurobehavioral effects:
    - Neural sensitization (i.e., an exposure-induced increased responsiveness of the nervous system to other stimuli): several animal studies were available, with questions of human relevance.
    - Motor-related behaviors: numerous human and animal studies of *low* confidence and some studies reporting potentially relevant mechanistic findings were available.
    - Learning and memory: numerous human and animal studies of *low* confidence and some studies reporting potentially relevant mechanistic findings.

Among these outcomes, the studies of ALS are of particular note. An association between formaldehyde exposure and ALS was suggested across four studies in the United States, Sweden and Denmark by two separate groups of researchers (Peters et al., 2017; Seals et al., 2017; Roberts et al., 2016; Weisskopf et al., 2009). Positive associations observed in a large prospective study (Weisskopf et al., 2009) were somewhat corroborated by a few (but not most) comparisons in the other studies, noting that some associations were based on a very small number of cases or secondary analyses. However, two of the studies had uncertainties in the assignment of individual exposure to formaldehyde

(Roberts et al., 2016; Fang et al., 2009), and the third did not observe a dose-response relationship when the data were stratified by estimated formaldehyde levels (Peters et al., 2017). The observed association reported by the study in Denmark was not corroborated by a second study that examined joint effects by multiple health and chemical risk factors (Bellavia et al., 2021). In addition, the results were not verified in another study in a different population, which had greater certainty in individual exposure assessments (Pinkerton et al., 2013). Thus, the currently available human evidence was not considered sufficient to identify a clear hazard. However, the unexpected nature of the observed associations between formaldehyde exposure and this rare and fatal disease across a growing number of studies (the first association was reported in 2009, with corroborating evidence in 2015 and 2016) identifies an urgent need for additional research.

Overall, while a number of studies reporting evidence of potential neurotoxic effects were available, due to limitations identified in the database (e.g., poor methodology, lack of consistency), the integration of the evidence ultimately resulted in a determination (for each of the bulleted manifestations of potential neurotoxicity noted above) that the **evidence suggests,** but is not sufficient to infer, that formaldehyde inhalation might cause nervous system effects in humans given appropriate exposure circumstances.

The data were considered insufficient for developing quantitative estimates.

3.6. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Studies in humans, and a number of animal studies have analyzed effects of inhaled formaldehyde on pre- and post-natal development and on the female and male reproductive systems. The health effects studies of human exposure included studies of residential exposure during pregnancy and fetal and infant growth measures, as well as occupational epidemiological studies conducted in different industries and countries that evaluated decreased fecundity,[6] spontaneous abortion, and adverse birth outcomes associated with formaldehyde exposure among men and women. A few studies also analyzed sperm quality parameters. Exposure levels in the occupational settings were high (>0.1 mg/m^3) with intermittent peaks depending on specific uses. Animal studies investigated manifestations of developmental toxicity (i.e., decreased survival, decreased growth, or increased evidence of structural anomalies), female reproductive toxicity (ovarian and uterine pathology, ovarian weight, and hormonal changes), and effects on the male reproductive system. However, all of the available *medium* and *high* confidence studies exposed animals to high formaldehyde concentrations (>5 mg/m^3), and exposure protocols for the remaining studies were limited (i.e., the use of formalin, or an uncharacterized test substance). This review assesses health effects of exposure for females and males separately.

[6]The capacity to conceive and deliver a baby.

3.6.1. Literature Identification

The literature searches focused on reproductive and developmental outcomes in epidemiological studies and animal studies, as well as mechanistic studies. The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.8, as are the specific PECO criteria and the methods for identifying literature from 2016–2021 are described in Appendix F.

3.6.2. Study Evaluation

The epidemiological analyses that assigned individual-level exposures based on formaldehyde-specific quantitative information, such as formaldehyde measurements or reported frequency of product use, were considered to have greater accuracy than studies that defined participants as exposed or nonexposed. Several studies classified individuals based on work processes, an informed source, or occupation/industry codes from census data; there was less certainty about whether these exposure classifications successfully distinguished high exposure from low or no exposure. Exposure misclassification and the inclusion of individuals with probable low or infrequent exposure as exposed reduced the sensitivity of analyses; these analyses were considered to be of *low* confidence**.**

For studies in experimental animals, a key consideration for the interpretation of developmental and reproductive outcomes associated with inhalation exposures to formaldehyde was the potential for coexposure to methanol, a known developmental and reproductive toxicant, when the test article was an aqueous solution of formaldehyde. Studies that used formalin but did not control for methanol and studies that did not characterize the formaldehyde source were assigned a *low* confidence rating and contributed little to the synthesis of evidence regarding formaldehyde effects on development or the reproductive system.

3.6.3. Developmental and Female Reproductive Toxicity

Synthesis of human health effect studies

The observational studies of reproductive toxicity or pregnancy outcomes evaluated associations with exposure during pregnancy in three studies and with occupational exposure among cosmetologists, woodworkers, laboratory workers, and hospital staff. The evidence regarding fecundability[7] (e.g. time to pregnancy or TTP), spontaneous abortion, pre- and post-natal growth and other birth outcomes, and male reproductive toxicity was synthesized Time-to-pregnancy is a measure of fertility and has been characterized in terms of number of menstrual cycles that occurred prior to conception.[8] Increased TTP reflects potential effects on gametogenesis, transport, fertilization, migration, implantation, or survival of the embryo (Baird et al., 1986). Thus, the measure encompasses

[7]A couple's probability of conception in one menstrual cycle.

[8]Time-to-pregnancy of greater than 12 months of unprotected intercourse is indicative of reduced fertility. Time-to-pregnancy is not a measure of infertility, as these studies only include women who became pregnant and had a live birth.

both developmental and reproductive toxicity, reflects an impact on multiple biological processes in both partners, and is sensitive to the detection of early events before a pregnancy is clinically recognized. One *medium* confidence retrospective cohort study evaluated effects on TTP in relation to maternal occupational exposure to formaldehyde (Taskinen et al., 1999). The fecundability density ratio (FDR) for individuals in the highest formaldehyde exposure category (mean 8-hour TWA exposure of 0.27 mg/m^3) compared to nonexposed individuals was 0.57 (95% CI: 0.37, 0.85) in a model that adjusted for potential confounders and phenol exposure. Other coexposures in the workplace were ruled out as potential confounders. An ancillary analysis suggested that dermal exposure may have contributed to risk of increased TTP in this cohort; this is an uncertainty with regard to the TWA concentrations associated with this outcome.

Two *medium* confidence studies provided evidence that formaldehyde exposure to female workers is associated with an increased risk of spontaneous abortion (Taskinen et al., 1999; John et al., 1994). Of the six studies included in this review, three were determined to be *low* confidence, primarily because of concerns about exposure misclassification, with probable decreased study sensitivity (Steele and Wilkins, 1996; Hemminki et al., 1985; Hemminki et al., 1982). A fourth *low* confidence study evaluated dose-response patterns, an important consideration for the synthesis of formaldehyde associations, and, despite potential confounding by another exposure, found associations similar in magnitude to the *medium* confidence studies (Taskinen et al., 1994).

These studies examined diverse occupational groups exposed to different combinations of chemical exposures and products containing formaldehyde (wood working, cosmetology, research laboratories). Relatively high odds ratios were associated with formaldehyde exposure; odds ratios reported by the *medium* confidence studies were 2.1 (95% CI: 1.0, 4.3) and 3.2 (95% CI: 1.2, 8.3) (Taskinen et al., 1999; John et al., 1994). The studies addressed potential confounders, including other workplace exposures, and found that formaldehyde was independently associated with spontaneous abortion. Studies of hospital, nursing, or medical employees generally did not report an association, although these *low* confidence studies tended to use less precise exposure assessment methods, reducing their sensitivity.

The epidemiology literature is limited regarding formaldehyde exposure and birth outcomes. One *medium* confidence birth cohort study reported decreases in birth weight and head circumference, respectively, with each 1 µg/m^3 unit increase in formaldehyde concentration measured in the mother's homes at 34 weeks gestation (Franklin et al., 2019). Gestational age was not associated with exposure. The median concentration in the homes was 0.0028 mg/m^3 and 23.3% of samples were below the LOD in this relatively small study. Another *medium* confidence pregnancy cohort study in South Korea observed lower birth weights associated with increasing formaldehyde concentration measured at mid to late pregnancy (mean concentrations were 0.08 mg/m^3), although there was evidence of confounding in the positive direction by volatile organic compounds (Chang et al., 2017). An elevated association with congenital malformations and maternal exposure was reported by a set of *low* confidence studies

among female hospital or laboratory workers (Zhu et al., 2006; Saurel-Cubizolles et al., 1994; Stücker et al., 1990; Hemminki et al., 1985; Ericson et al., 1984), although the precision of the odds ratios was low (wide confidence intervals overlapping 1.0).

Synthesis of animal health effect studies

Several studies in experimental animals evaluated developmental toxicity (survival, growth, and morphological alterations), and a few evaluated reproductive toxicity in females, however they all were weak (*low* confidence) studies with methodological limitations. Notably, for most of the studies, lack of information about the test substance or the described use of formalin, with known or presumed methanol coexposures limited interpretation of their results. Effects on fetal survival, pre- or post-natal growth, or morphological alterations were observed in several studies and sometimes more than one rodent species, and maternal toxicity did not appear to be a confounding influence. However, inconsistencies in response were also observed, and clear dose-response relationships were not discernable. The studies tested concentrations ranging from 0.5 to 49 mg/mg^3.

Mode of action information

No experimentally established MOA exists, and any potential mechanisms have not been well-studied for any effects on development or the female reproductive system. However, evidence of elevated oxidative stress in the blood of occupationally exposed adults might provide a potential indirect linkage (Bono et al., 2010). Evidence of elevated oxidative stress and hormonal alterations in the blood and other tissues of adult rodents also might provide indirect evidence, as it is recognized that both oxidative stress and the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes have potential roles in developmental toxicity as well as female reproductive function (Sari et al., 2004; Sorg et al., 2001; Kitaev et al., 1984).

Overall evidence integration judgments and susceptibility for developmental or female reproductive toxicity

Overall, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans given appropriate exposure circumstances. This conclusion is based on *moderate* evidence in observational studies finding increases in TTP and spontaneous abortion risk among occupationally exposed women; the evidence in animals is *indeterminate*, and a plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde is lacking (see Table 26). The primary basis for this conclusion is from studies of women with occupational exposures involving periodic peaks.

Table 26. Evidence integration summary for effects of formaldehyde inhalation on developmental or female reproductive toxicity in humans

Evidence	Evidence judgment	Hazard determination
Human	*Moderate* for female reproductive or developmental toxicity, based on: *Human health effect studies*: • Two *medium* confidence studies in two independent populations (woodworkers, cosmetologists): decreased fecundability and increased spontaneous abortion risk. Supporting evidence of association with spontaneous abortion from one *low* confidence study among laboratory workers. All studies evaluated multiple exposure categories with highest risk at highest exposure level. • Two *low* confidence studies of maternal exposure among health workers with low precision: small increased risk of malformations (all combined). • Two medium confidence studies of pregnancy cohorts indicating decreased birth weight and head circumference. • Null evidence from five *low* confidence studies with low sensitivity: fecundability, spontaneous abortion. *Biological plausibility*: No direct evidence. However, evidence of elevated oxidative stress in the blood of exposed adults (see Section 1.2.3) might provide a potential indirect linkage (see explanation at right).	The **evidence indicates** that inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans, given the appropriate exposure circumstances[a] Primarily based on studies of women with occupational exposures to formaldehyde concentrations as high as 1.2 mg/m^3. *Potential susceptibilities*: no specific data were available to inform potential differences in susceptibility.
Animal	*Indeterminate* for developmental toxicity, based on: *Animal health effect studies*: • Mixed findings for evidence of decreased fetal survival (pre- or postimplantation loss) across multiple *low* confidence studies • Mixed findings for evidence of altered fetal or postnatal growth across multiple *low* confidence studies. Variations in study design and reporting deficiencies inhibit interpretation. • Mixed findings for evidence of structural anomalies across multiple *low* confidence studies. *Biological plausibility*: No direct evidence. However, evidence of elevated oxidative stress and hormonal alterations in the blood of adult rodents (see Section 1.2.3) might provide a potential indirect linkage, as it is recognized that both oxidative stress and the HPG axis have potential roles in developmental toxicity. *Indeterminate* for female reproductive toxicity, based on: *Animal health effect studies*: • Two *low* confidence studies in rats: decreased ovarian weight, ovarian histopathology, and hormonal alterations • One *low* confidence study in mice: Ovarian and uterine histopathology (hypoplasia) *Biological plausibility*: Neuroendocrine-mediated mechanisms, particularly involving disruption of the hypothalamic-pituitary-gonadal axis, are consistent with alterations of female reproductive hormones observed in *low* confidence rodent studies following formaldehyde exposures.	
Other inferences	• *Relevance to humans*: Relevant health effects observed in humans are the primary basis for the hazard determination.	

	• *MOA*: No experimentally established MOA exists, and any potential mechanisms have not been well studied.	

[a] The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis (see below).

3.6.4. Male Reproductive Toxicity

Synthesis of human health effect studies

Two *medium* confidence studies from one research group reported associations with lower sperm motility (total and progressive), delayed fertility, and spontaneous abortion (Wang et al., 2015; Wang et al., 2012). A quantitative, individual-level exposure assessment was conducted; average exposures in the workplace were 0.2–3 mg/m^3. Progressive motility and total motility were inversely associated with the formaldehyde exposure index, a cumulative measure of exposure based on a job exposure matrix, and a strong association was observed in logistic models of below-normal values of these motility measures (Wang et al., 2015). For example, odds ratios of 2.58 (95% CI: 1.11, 5.97) and 3.41 (95% CI: 1.45, 7.92) were found for progressive motility less than 32% in the low and high exposure groups, respectively, compared to the community-based referent group. TTP and spontaneous abortion also were associated with paternal exposure to formaldehyde in this cohort (Wang et al., 2012). Two *low* confidence studies with low sensitivity found no association (Lindbohm et al., 1991; Ward et al., 1984).

Synthesis of animal health effect studies

Fourteen studies in rodents assessed effects on the male reproductive system following inhalation formaldehyde exposure, although eight of the studies had substantial methodological limitations and were categorized as *low* confidence. The six remaining *medium* or *high* confidence studies (examining five cohorts of rats or mice) were conducted by three research teams and only tested high formaldehyde concentrations (>5 mg/m^3). In all of these studies paraformaldehyde was administered to the test animals and study methods provided adequate characterization of the exposure paradigm (Sapmaz et al., 2018; Vosoughi et al., 2013; Vosoughi et al., 2012; Ozen et al., 2005; Ozen et al., 2002; Sarsilmaz et al., 1999). Their studies reported that formaldehyde inhalation resulted in adverse testes and epididymides histopathological changes in mice (Vosoughi et al., 2013) and rats (Sapmaz et al., 2018; Ozen et al., 2005; Sarsilmaz et al., 1999), and decreased sperm count, motility, and morphology in mice (Vosoughi et al., 2013). The decreases in sperm count (44–49%), sperm motility (40–46%) and abnormal sperm morphology were observed at 35 days posttreatment involving concentrations ≥12.2 mg/m^3 to paraformaldehyde for 10 days (Vosoughi et al., 2013). The delayed response suggests that the effects may have resulted from a disruption of spermatogenesis. Decreases in serum testosterone in mice (32–49% at 24 hours postexposure) and rats (6–9% with 91 days exposure) also were observed with exposure levels ranging from 6–25 mg/m^3 (Vosoughi et al., 2013; Ozen et al., 2005), a response that is biologically consistent with the Leydig cell pathology also associated with these exposure levels (Vosoughi et al., 2013; Sarsilmaz et al., 1999). Results from the

low confidence studies were largely consistent (Han et al., 2015);(Zhou et al., 2011a);(Zhou et al., 2011b);(Zhou et al., 2006);(Golalipour et al., 2007);(Appelman et al., 1988);(Maronpot et al., 1986);(Xing Sy, 2007). Since the available studies only tested very high formaldehyde levels (i.e., the lowest levels tested were often >12 mg/m^3, with only a few studies testing 6.15 mg/m^3 as the lowest exposure level), significant uncertainties remain. Taken together, however, these studies provide coherent evidence of toxicity to the male reproductive system spanning biochemical, cellular, tissue, and functional levels.

Mode of action information

No experimentally established MOA exists, and any potential mechanisms have not been well-studied for any effects on the male reproductive system. However, mechanistic data provide some support for indirect effects, including multiple biomarkers of oxidative stress, as well as heat shock protein induction, that have been observed in the testes or epididymides of exposed rats in well conducted studies (Sapmaz et al., 2018; Zhou et al., 2011b; Ozen et al., 2008; Zhou et al., 2006; Ozen et al., 2005; Ozen et al., 2002). Heat shock protein (Hsp) immunoreactivity and oxidative stress resulting in hypomethylated sperm (no studies were identified that evaluated sperm methylation changes) have been linked to human male infertility (Werner et al., 1997).

Overall evidence integration judgments and susceptibility for male reproductive toxicity

Overall, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men given appropriate exposure circumstances, based on *robust* evidence in animals that presents a coherent array of adverse effects in two species, and *slight* evidence from observational studies of occupational exposure levels, and no plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde. However, some support for indirect effects in rodents is provided by relevant mechanistic changes in male reproductive organs (see Table 27). The primary basis for this conclusion is based on bioassays in rodents testing formaldehyde concentrations >6 mg/mg^3.

Table 27. Evidence integration summary for effects of formaldehyde inhalation on reproductive toxicity in males

Evidence	Evidence judgment	Hazard determination
Humans	*Slight* for male reproductive toxicity, based on: *Human health effect studies*: • One *medium* confidence study of exposure among male woodworkers: inverse association with sperm motility measures, increased prevalence of time to pregnancy, spontaneous abortion and birth defects. • Null evidence for effects on sperm counts and morphology in one *low* confidence study (because of low power). *Biological plausibility*: No directly relevant studies were identified.	The **evidence indicates** that inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men, given appropriate exposure circumstances[a] Primarily based on bioassays in rats and mice testing formaldehyde concentrations above 6 mg/mg^3 (no *medium* or
Animals	*Robust* for male reproductive toxicity, based on:	

	Animal health effect studies: • One *high* confidence study in mice, three *high* or *medium* confidence studies in rats, and five *low* confidence studies in rats: dose-related qualitative or quantitative histopathological lesions of the testes or epididymides. • Null evidence for testes histopathology in one *low* confidence study in mice. • One *high* confidence study in mice and *four* low confidence studies in rats: dose-related effects on epididymal sperm. • One *high* confidence study in mice, one *high* confidence study in rats, and one *low* confidence study in rats: dose-related decreased serum testosterone (and decreased serum luteinizing hormone in the *high* confidence study in mice). • Mixed results for organ weight changes (i.e., testes; epididymis) across multiple *high*, *medium*, and *low* confidence studies. • One *low* confidence study in mice with evidence of male-mediated decreases in fetal survival. • Note: No multigeneration study was conducted. *Biological plausibility*: Multiple biomarkers of oxidative stress, as well as heat shock protein induction, have been observed in the testes or epididymides of exposed rats in well-conducted studies. Heat shock protein immunoreactivity and oxidative stress resulting in hypomethylated sperm (no studies on this endpoint were identified) were linked to human male infertility.	*high* confidence studies tested lower exposure levels). *Potential susceptibilities*: No specific data were available to inform potential differences in susceptibility.
Other inferences	• *Relevance to humans*: Some uncertainty regarding the relevance of the animal evidence exists, as the studies only tested extremely high concentrations expected to cause strong irritant effects that may not occur in humans; however, in light of the concordant findings in a well-conducted study of humans and an absence of other evidence to the contrary, the relevance of animal male reproductive toxicity outcomes to humans is presumed. • *MOA*: No experimentally established MOA exists, and any potential mechanisms have not been well-studied; however, mechanistic data provide some support for indirect effects on the male reproductive system.	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis (see below).

3.6.5. Dose-response Analysis

Study selection

The dose-response analysis for developmental and female reproductive toxicity used data from one *medium* confidence epidemiological study that assessed dose-response relationships for the outcomes, TTP and spontaneous abortion, although the timing of exposure measurements had uncertain relevance to responses during the pregnancies that ended in spontaneous abortion. For male reproductive toxicity, two studies of rats exposed for 13 weeks, that assessed relatively sensitive endpoints, were considered appropriate for the derivation of toxicity values (see Table 28 for study selection rationales).

Table 28. Eligible studies for POD derivation and rationale for decisions to not select specific analyses

Reference	Endpoint	POD derived?	Rationale for decisions to not select
Taskinen et al. (1999)	Time-to-pregnancy	Yes	
Taskinen et al. (1999)	Spontaneous abortion	No	Uncertain temporal applicability of exposure data for evaluating 1st trimester effects
Franklin et al. (2019)	Birth weight, head circumference	No	Uncertainties in exposure distribution due to large % < LOD and impact on quantitative results
Chang et al. (2017)	Birth weight	No	Evidence of confounding by co-exposure; Log transformed formaldehyde concentration
Ozen et al. (2002)	Relative testes weight, 13-wk exposure	Yes	
Ozen et al. (2005)	Serum testosterone, Wistar rat, 13-wk exposure	Yes	
Ozen et al. (2005)	Seminiferous tubule diameter, Wistar rat, 13-wk exposure	No	Analysis of pooled tissues; interpretability to individual rats uncertain
(2013); Vosoughi et al. (2012)	Seminiferous tubule diameter, NMRI mice, 10-d exposure	No	Short exposure duration
(2013); Vosoughi et al. (2012)	Sperm abnormalities, NMRI mice, 10-d exposure	No	Short exposure duration
(2013); Vosoughi et al. (2012)	Serum testosterone, NMRI mice, 10-d exposure	No	Short exposure duration
Vosoughi et al. (2013)	Testes weight, NMRI mice, 10-d exposure	No	Short exposure duration
Sarsilmaz et al. (1999)	Leydig cell quantity or nuclear damage, Wistar rat, 4-wk exposure	No	Short exposure duration
Sarsilmaz et al. (1999)	Testes weight (relative), Wistar rats, 4-wk exposure	No	Short exposure duration; non-preferred metric (absolute testes weight preferred)
Sapmaz et al. (2018)	Seminiferous tubule measures, Sprague-Dawley rats, 4- and 13-wk exposure	No	Short exposure duration (for 4-wk experiment); single exposure level

Derivation of PODs

Developmental and female reproductive toxicity

Taskinen et al. (1999) presented fecundability density ratios (FDR) for increased time to pregnancy for index pregnancies of women in three exposure categories for jobs held beginning at least 6 months prior to the index pregnancy. TTP was elevated in the high exposure group relative to the unexposed group and the middle 8-hour TWA exposure level was selected as a NOAEL (see Table 29).

The mean 8-hour TWA concentrations reported for each exposure category were adjusted for likely background formaldehyde exposures experienced by the employees when they were not

conducting work tasks involving formaldehyde exposure. Normally, exposures from occupational studies are adjusted to account for the daily breathing volume appropriate to an environmental (versus occupational) setting and for exposure every day of the year (U.S. EPA, 1993). However, with formaldehyde, there is potential for exposure outside of work from in-home and environmental sources of formaldehyde. Therefore, the POD represents exposure during an 8-hour workday.

Table 29. Summary of derivation of PODs for developmental and reproductive toxicity in females

Endpoint and reference	Population	Observed effects by exposure level	POD (mg/m^3)
Time to pregnancy in females			
Occupational prevalence study Taskinen et al. (1999)	Adult women, *n* = 602	**Time to Pregnancy by Formaldehyde Category;** Fecundability density ratio (FDR)[a] Mean 8-hr TWA (mg/m^3) / # / FDR[b] / 95% CI Not exposed / 367 / 1.00 / - 0.042 / 119 / 1.09 / 0.86–1.37 0.106 / 77 / 0.96 / 0.72–1.26 0.278 / 39 / 0.64 / 0.43–0.92 Fecundability density ratio = ratio of average incidence densities of pregnancies in exposed compared to employed unexposed women Discrete proportional hazards regression; adjusted for employment, smoking, alcohol consumption, irregular menstrual cycles and # children Comparison: index pregnancies that occurred when participants were not employed in exposed workplace	NOAEL = 0.106 LOAEL = 0.278

[a]Concentrations converted to mg/m^3.
[b]8-hr TWA reported by authors were recalculated by EPA to account for background formaldehyde exposure while working in "nonexposed" work areas.

Male reproductive toxicity

Both studies selected for candidate reference value derivation exposed the animals to paraformaldehyde via inhalation (Ozen et al., 2002) (Table 30). In Ozen et al. (2002), statistically significant duration- and dose-dependent decreases in testis weight (relative to body weight) were observed after 4 and 13 weeks of formaldehyde exposure. Although absolute organ weights are preferred for this measure, because testes weights are generally conserved when body weight is decreased, mean body weights were also significantly decreased with exposure; thus, this response pattern suggests that the organ weight decreases were likely due to a direct effect on the testis (note: in this case, decreased relative testis weight is likely an underestimate of the more appropriate decrease in absolute testis weight). For the decreased testis weight at week 13 (Ozen et al., 2002), a LOAEL of 12.3 mg/m^3 was adjusted for continuous exposure based upon the experimental paradigm to yield a POD_{ADJ} of 2.93 mg/m^3 (POD_{ADJ} = 12.3 mg/m^3 × 8 hr exposed per day/24 hours per day × 5 days exposed per week/7 days per week).

In Özen et al. (2005), statistically significant dose-dependent decreases in serum testosterone levels (6 to 9% decreases from control values) were observed following 91 days of inhalation exposure. At the same exposure levels, significant decreases of 23 to 26% from control were noted in mean seminiferous tubule diameters, an effect that could have been directly related to testosterone decreases. A $BMCL_{1SD}$ of 0.208 mg/m^3 was calculated. U.S. EPA (2012) indicates that for highly soluble and reactive gases that interact with tissue at the point of entry or for gases with systemic penetration ppm equivalence is an appropriate default method for extrapolation.

Table 30. Summary of derivation of PODs for reproductive toxicity in males

Endpoint and reference	Species/ sex	Model	BMR (mg/m^3)	BMC (mg/m^3)	BMCL (mg/m^3)	POD_{ADJ}[a] (mg/m^3)
Ozen et al. (2005) Decreased relative testes weight (13 wk)	Rat/M	LOAEL	N/A	N/A	N/A	2.93
Ozen et al. (2005) Decreased serum testosterone (13 wk)	Rat/M	Exponential (M2)	1 SD	0.284	0.208	0.050

[a]POD_{ADJ} is the human equivalent of the rat BMCL duration adjusted (6/24) × (5/7) for continuous daily exposure.

Derivation of cRfCs

A UF_H of 10 was applied to the developmental toxicity POD based on reduced fecundity in reproductive age women in an occupational cohort studied by Taskinen et al. (1999) to account for variation in the broader human population not represented by occupationally exposed groups. No other adjustments were made to this cRfC (see Table 31).

For interspecies uncertainty for results in the animal studies, an assumption of ppm equivalence (which is derived from pharmacokinetic principles) (Ozen et al., 2005; Ozen et al., 2002), male reproductive toxicity was used to estimate a human equivalent concentration. Then a UF_A of 3 was applied to account for residual uncertainties in interspecies extrapolation from the two cRfCs for reproductive toxicity in males derived from rat studies. A UF_S of 10 was applied to both PODs to approximate the potential effect of lifetime exposure, as these effects are not necessarily dependent on a specific exposure window and they are expected to worsen with continued exposure. In addition, a UF_L of 10 was applied to the POD for relative testis weight, which was based on a LOAEL (Ozen et al., 2002). Finally, a UF_H of 10 was applied to both PODs to account for the limited variability in susceptibility factors encompassed by these typical studies of inbred laboratory animal populations.

Table 31. Derivation of cRfCs for female reproductive or developmental toxicity and male reproductive toxicity

Endpoint (*reference*; population)	POD	POD basis	UF_A	UF_H	UF_L	UF_S	UF_D	$UF_{COMPOSITE}$	cRfC (mg/m^3)
FEMALE REPRODUCTIVE OR DEVELOPMENTAL TOXICITY									
Delayed pregnancy Taskinen et al. (1999); pregnant F, *n* = 77 at POD)	0.106	NOAEL	1	10	1	1	1	10	**0.01**
MALE REPRODUCTIVE TOXICITY									
Relative testes weight Ozen et al. (2005); adult rat M, 13-wk exposure)	2.93	LOAEL	3	10	10	10	1	3,000	**0.001**
Serum testosterone Ozen et al. (2005); adult rat M, 13-wk exposure)	0.05	$BMCL_{1SD}$	3	10	1	10	1	300	**0.0002**

Derivation of the osRfC

The cRfC for effects on delayed pregnancy (Taskinen et al., 1999) was chosen as the osRfC. Although TTP is a sensitive measure of effects on the reproductive system, confidence in the POD is judged to be *low* because the outcome was evaluated in a healthy working population with relatively high exposure, which raises uncertainty about its applicability to more diverse populations. More complete assessments of developmental endpoints by epidemiology or toxicology studies were not available. Thus, the completeness of the database is considered *low*. As a mechanistic understanding is lacking, the relevant time period for exposure effects on TTP through unrecognized fetal losses or factors controlling the ability to conceive could range from the weeks just prior and after conception, to the entire period of prior exposure during the life of the individual. Thus, the osRfC is **0.01 mg/m^3**.

The cRfC derived from Özen et al. (2002) was considered the stronger of the two candidates for male reproductive toxicity, and thus was chosen to represent the osRfC. The magnitude of the testes weight response in Özen et al. (2002) was greater than the testosterone decreases observed in Özen et al. (2005), and a number of other rodent studies in the formaldehyde database demonstrated similar testis (and epididymal) weight deficits, while specific evidence of treatment-related serum testosterone decreases was quite limited. The osRfC is **0.001 mg/m^3** using the cRFC from Özen et al. (2002). The confidence in the POD derived from its results is *low*, given that the lowest formaldehyde concentration tested in this study was 12 mg/m^3. Confidence in the database is also considered *low* because, while a number of published studies evaluated reproductive toxicity in males, the interpretation of study results is complicated by their methodological limitations and exclusive use of formaldehyde concentrations above 6 mg/m^3, and data are lacking regarding functional endpoints.

3.7. REFERENCE CONCENTRATION (Rfc) FOR NONCANCER HEALTH EFFECTS

3.7.1. Summary of cRfCs and osRfCs across Noncancer Health Effects

The RfC was chosen to reflect an estimate of continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC was determined from the group of osRfCs, which in turn were selected from the cRfCs in each health effect system. Figure 13 presents the cRfCs derived for each health effect system, the points of departure from each study, and the uncertainty factors that were applied to them. As summarized in Figure 13 and Table 32, the osRfCs for each health effect system were either selected from among the cRfCs or the values were combined. The rationales for osRfC selection were described previously in the hazard evaluations for each health effect system.

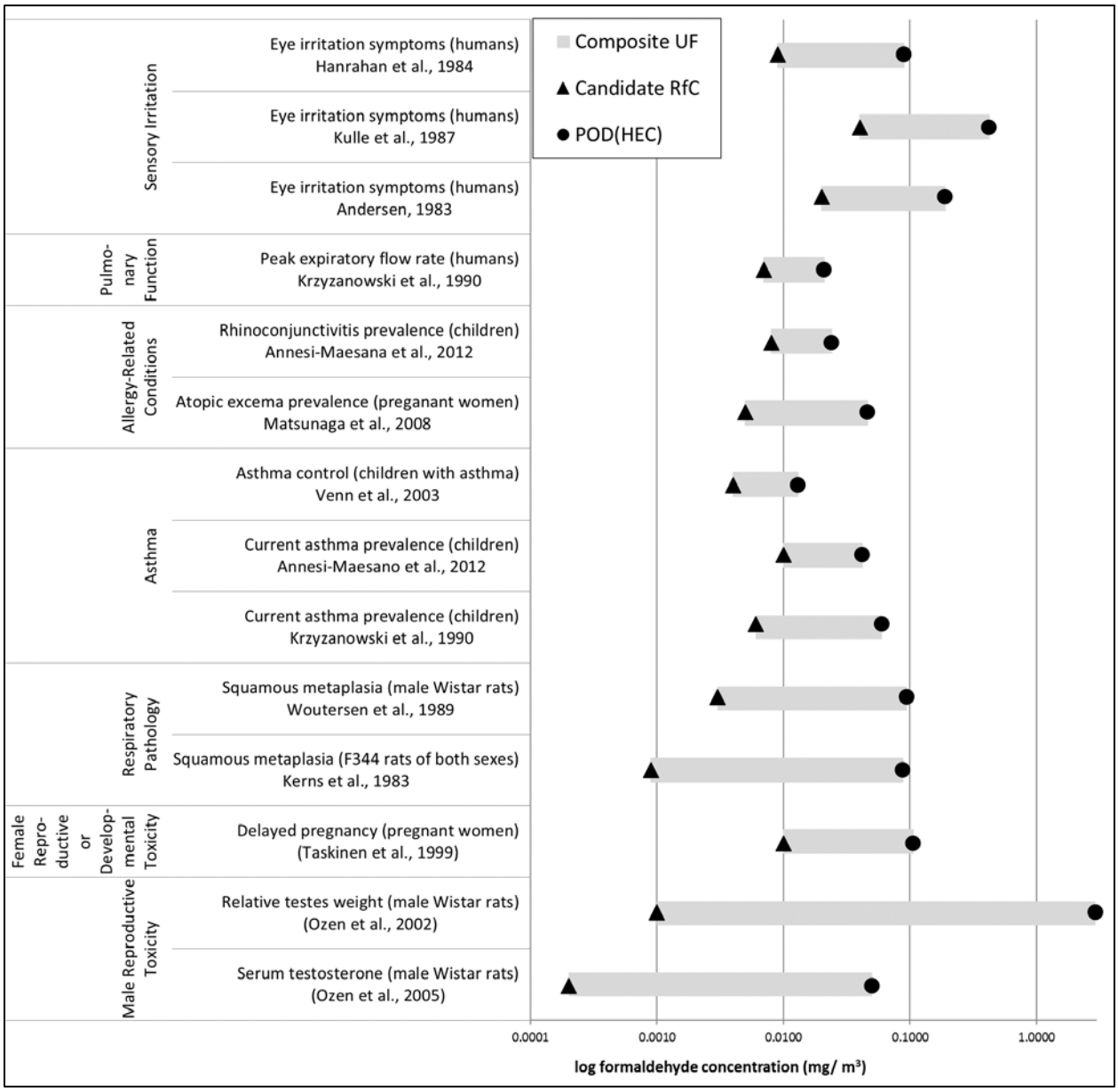


Figure 13. Candidate RfCs (cRfCs) with corresponding POD and composite UF.

Note: as PODs reflect exact values, and cRfCs are rounded to 1 significant figure, the extrapolation is not exact.

Table 32. Organ/System-specific RfCs (osRfCs) for formaldehyde inhalation

Health effect	Basis *reference(s)* [species]	UF_C	osRfC (mg/m^3)	Integrated hazard judgment	Confidence in POD estimate(s)[a]	Database completeness[b]
Sensory Irritation	Hanrahan et al. (1984) [human]	**10**	**0.009**	***Evidence demonstrates***	*medium*	*high*
Pulmonary Function	Krzyzanowski et al. (1990) [human]	**3**	**0.007**	***Evidence indicates (likely)***	*high*	*high*
Allergy-related Conditions	Annesi-Maesano et al. (2012) [human]	**3**	**0.008**	***Evidence indicates (likely)***	*high*	*high*
Asthma (prevalence of current asthma/degree of asthma control)	Annesi-Maesano et al. (2012); Venn et al. (2003); Krzyzanowski et al. (1990) [human]	**10**[c]	**0.006**	***Evidence indicates (likely)***	*medium*	*medium*
Respiratory Pathology	Kerns et al. (1983); Battelle (1982); Woutersen et al. (1989) [rat]	**30**[c]	**0.003**	***Evidence demonstrates***	*medium*	*high*
Female Developmental Toxicity	Taskinen et al. (1999) [human]	**10**	**0.01**	***Evidence indicates (likely)***	*low*	*low*
Male Reproductive Toxicity	Ozen et al. (2002) [rat]	**3,000**	**0.001**	***Evidence indicates (likely)***	*low*	*low*

This table presents the osRfCs, the studies and uncertainty factors used to derive them, and the level of confidence in the evidence integration, the PODs, and the completeness of the database.

[a]This reflects a judgment regarding how well the study-specific data are able to estimate a no-effect or minimal-effect level of response (e.g., a lower level of confidence would be applied to high concentration studies which required extrapolation far below the lowest tested concentration to estimate a POD). A *low* confidence level means that the POD derived is expected to be less accurate.

[b]Although no UF_D was applied to any cRfC, it is recognized that the evidence databases for the various health effects are not equal. This level of confidence was added to emphasize the health areas where additional research could reduce existing uncertainties. A *low* confidence level means the degree of certainty regarding the RfC is lower.

[c]These two osRFCs are based on multiple studies and candidate values, sometimes with different UF_Cs applied. The UF_C values shown in this table and Figure 13 reflect the candidate values selected to represent each osRfC [i.e., the UF_C applied to the POD from Krzyzanowski et al. (1990) for asthma and from Woutersen et al., (1989) for respiratory pathology].

3.7.2. Selection of the RfC and Discussion of Confidence

Choice of the RfC involved consideration of both the level of certainty in the estimated osRfCs, as well as the level of certainty in the evidence for the observed health effect(s). Thus, the collection of studies and results used to characterize the hazard(s) and derive the osRfCs, as well as the cRfC calculations themselves (including derivation of the PODs and the application of UFs), were considered when choosing the RfC. These considerations are illustrated separately in Table 32, and as a composite depiction of certainty in Figure 14 to support selection of the RfC (see Table 33). Based on this analysis, an RfC for formaldehyde of 0.007 mg/m^3 was selected. This value is within the narrow range (0.006–0.009 mg/m^3) of the group of respiratory system-related osRfCs derived from PODs that are the lowest

of those identified in human population studies for formaldehyde hazards (i.e., sensory irritation, pulmonary function, allergy-related conditions and current asthma prevalence or degree of control). These osRfCs are each interpreted with *high* or *medium* confidence in the hazard conclusion and in the POD estimate, and very low composite uncertainty factors were applied.

An overall confidence level of *high*, *medium*, or *low* is assigned to reflect the level of confidence in the study(ies) and hazard(s) used to derive the RfC, the completeness of the database, and the RfC itself, as described in EPA guidelines (U.S. EPA, 1994). Overall confidence in the RfC is **high**; the RfC is based on a spectrum of adverse effects reported in multiple well-conducted studies of exposed humans. Most of the study populations were exposed to formaldehyde levels in a residential or school setting, and some of the studies focused on sensitive individuals. Finally, the hazard conclusions are supported by an extensive literature database.

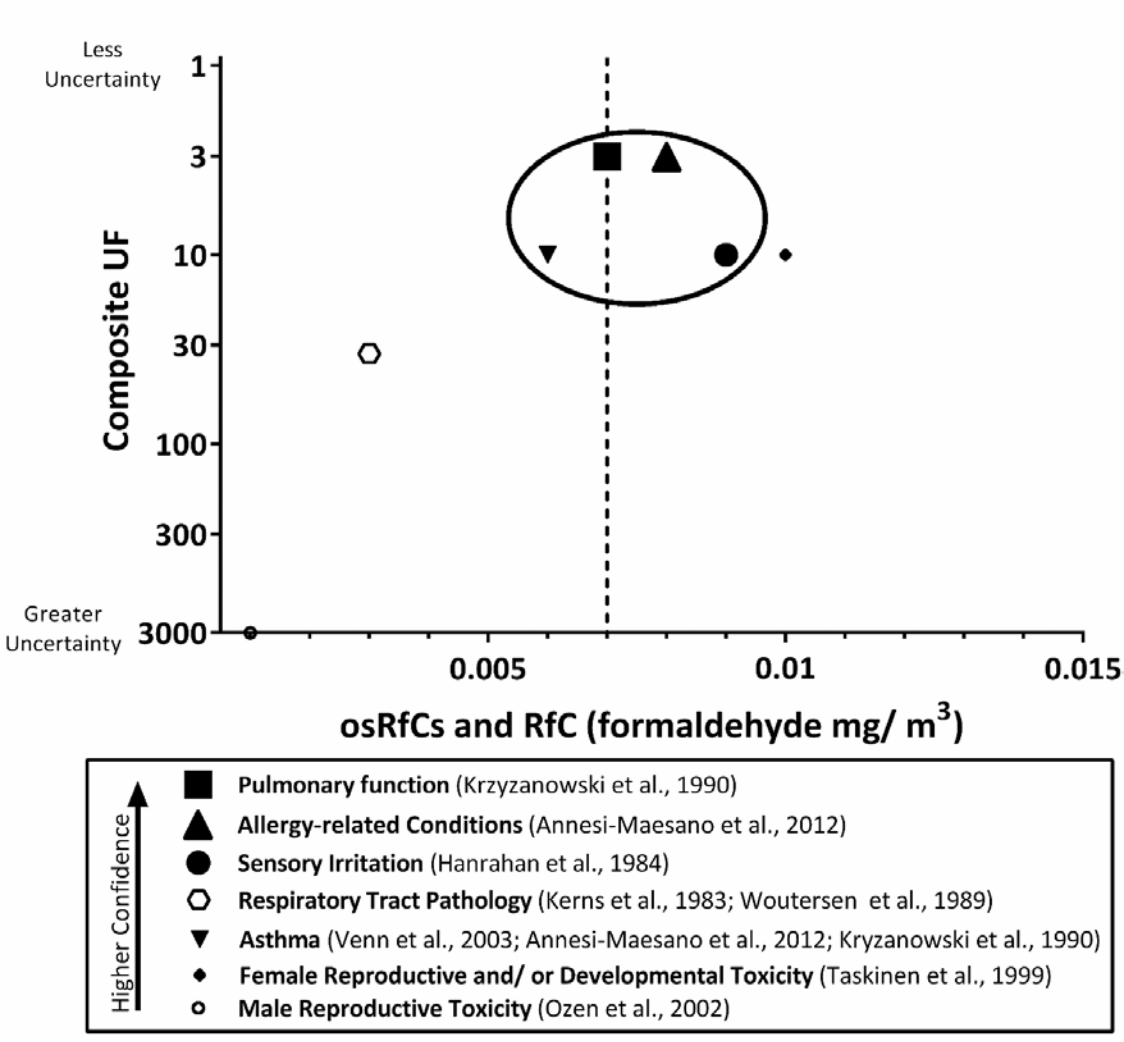


Figure 14. Organ or system-specific RfC (osRfC) scatterplot.

Organ/system RfCs (osRfCs) that are represented by larger shapes and that are closer to the top of the graph are interpreted with higher confidence regarding the basis from which the value was derived (see Table 32), and with less uncertainty (i.e., lower UFs were applied). Size of the shape represents confidence in the study(ies) and health hazard (i.e., hazards with **evidence demonstrates** judgments are larger than those with **evidence indicates [likely]** judgments), POD estimate(s) (for the purposes of this graphic, confidence in the POD was given slightly greater weight than the others), and completeness of the available evidence database for each health outcome: larger shapes indicate higher confidence; solid shapes indicate studies in humans; hollow shapes indicate animal studies. For composite UF, if multiple studies served as the basis for an osRfC, the composite UF associated with the candidate value selected to represent the osRfC was used (see Table 32). The dashed line represents the proposed overall RfC of 0.007 mg/m^3; the circled osRfCs indicate the cluster of effects selected as the basis for this value.

Table 33. Proposed RfC for formaldehyde-inhalation

Health effect(s) basis	RfC (mg/m^3)	Overall confidence
Sensory irritation, pulmonary function, allergy-related conditions, and degree of asthma control/prevalence of current asthma in humans[a]	0.007	**High**

[a]Based on the following studies: (Annesi-Maesano et al., 2012; Matsunaga et al., 2008; Venn et al., 2003; Krzyzanowski et al., 1990; Hanrahan et al., 1984)

3.7.3. Basis and Interpretation of the RfC

The RfC is an estimate of exposure that is likely to be without an appreciable risk of adverse health effects over a lifetime. As illustrated in Figure 15, the selected RfC is at the upper end of the range of outdoor formaldehyde levels recorded in some locations, and it would be expected that levels in indoor air would exceed this concentration in most situations. However, it is important to reiterate that this level is interpreted to be without appreciable risk. It is also important to note that the RfC does not provide information about the magnitude of the risk of respiratory-related effects that might occur at different concentrations above the RfC (e.g., at 0.02 or 0.03 mg/m^3). As illustrated in Figure 15, nearly all the study-specific findings of effects (e.g., LOAELs, BMCs) were not observed until formaldehyde levels were in the upper end of the range of average indoor air concentrations, with effects generally being observed at or above ~35–40 µg/m^3. As an example comparison, a fairly large study of 398 homes in Los Angeles, CA, Houston, TX, and Elizabeth, NJ, between 1999 and 2001 reported formaldehyde levels of 22 ± 7.1 µg/m^3 (Weisel et al., 2005). One study that contributed to the RfC derivation involved an analysis of the degree of asthma control in children with current asthma, and the RfC is expected to apply to this susceptible subgroup in the population. Although current asthma symptoms and allergic conditions were not observed in studies of children with exposures less than the range of 0.02–0.05 mg/m^3, at 0.021 mg/m^3, a 10.5% decrease in peak expiratory flow rate among asthmatic children could be estimated (the regression model included a term for asthma status), based on a model using results of Krzyzanowski et al. (1990). Thus, attributes that increase susceptibility in individuals are expected to play a role in increasing the advent of adverse responses to formaldehyde levels above the RfC (e.g., somewhere between 0.007 and 0.04 mg/m^3).

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 lifetime. Sensory irritation is an immediate response to reactive compounds such as formaldehyde. The relevant window of exposure for effects on asthma outcomes also is less than lifetime, although the time frame for the control of asthma symptoms (i.e., a few weeks) is expected to differ from that for the prevalence of current asthma symptoms or a decrease in pulmonary function (i.e., the past 12 months). In addition, the relevant window of exposure for the osRfC for female reproductive or developmental outcomes is from conception to the end of the pregnancy. Thus, while the RfC is a concentration associated with minimal risk over a lifetime of exposure, a few of the hazards or outcomes supporting the RfC could be relevant to a shorter exposure time frame. Such interpretations might be informed by the information presented in Figure 13 (POD to cRfC calculations) and Figure 15 (below).

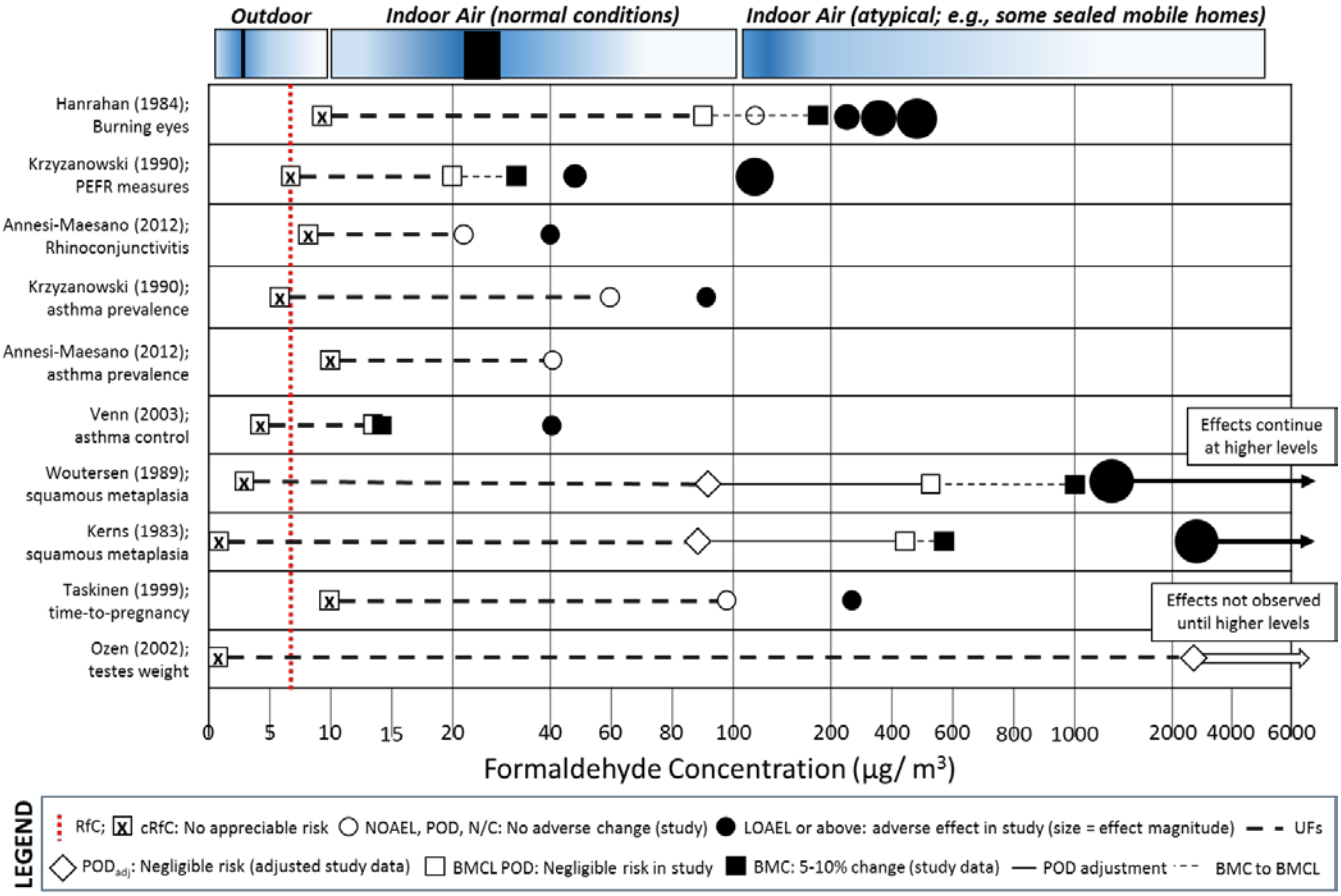


Figure 15. Illustration of noncancer toxicity value estimations.

This figure provides a representation of the estimates from studies supporting the osRfCs, including a summary of formaldehyde exposure data. Formaldehyde exposure estimates reflect approximates of the range (boxes), medians or means (black vertical bars), and more commonly reported estimates (gradations), based on the data discussed in Appendix A.1.2. Horizontal lines in the figure reflect the extrapolation process for arriving at points of departure (PODs) and toxicity values (unfilled symbols) in

the context of the study-specific evidence for effects (filled symbols; effect magnitude estimated based on study figures, tables, or reported regressions; see previous sections). Note: The x-axis is intentionally not on a linear or log scale so as not to convey a false level of precision. Abbreviations: cRfC (candidate RfC); N/LOAEL (no/lowest-observed-adverse-effect level); UFs (uncertainty factors); BMCL (benchmark concentration, lower confidence bound).

3.7.4. Previous IRIS Assessment: Reference value

An inhalation RfC for formaldehyde has not previously been derived. In 1990, an oral RfD of 0.2 mg/kg-day was developed. This value was based on reduced weight gain and histopathology (primarily of the gastrointestinal system) in Wistar rats during a 2-year bioassay in which formaldehyde was administered in the drinking water (Til et al., 1989). A UF_C of 100 was applied to the NOAEL to account for inter- and intraspecies differences. This RfD was interpreted with *medium* confidence, based on *high* confidence in the principal study and *medium* confidence in the database.

4. CARCINOGENICITY

Multiple review articles and meta-analyses have examined the epidemiological evidence informing potential associations between formaldehyde and cancer endpoints (e.g., Checkoway et al., 2012; Bachand et al., 2010; Zhang et al., 2009; Bosetti et al., 2008; Collins and Lineker, 2004; Collins et al., 2001; Ojajärvi et al., 2000; Collins et al., 1997; Blair et al., 1990). The vast majority of studies focused on cancers of the upper respiratory tract (URT) and lymphohematopoietic (LHP) system. Other cancer types studied include bladder, brain, colon, lung, pancreas, prostate, and skin. However, aside from lung and brain cancer, few studies showed evidence of increased risks; a cursory review of the studies of lung and brain cancer did not provide any indication of an association with formaldehyde exposure (see Appendix A.5.9). Given the large number of studies available on URT and LHP cancers, other cancer types were not systematically evaluated.

The occurrences of URT cancers in humans have been described and grouped according to the International Classification of Disease (ICD) codes. The specific cancers of the URT that are commonly reported are sinonasal cancers (nose and nasal sinuses), cancers of the pharynx (nasopharynx, oropharynx, and hypopharynx), and laryngeal cancer. Rarely, cancers of the buccal cavity are reported, but as this grouping includes lip, tongue, salivary glands, gums, and the floor of the mouth, which combine cancers of potentially different etiology and cell origin, cancers of the buccal cavity were not reviewed. Thus, the above groupings were used for literature identification and hazard analyses.

In human studies, the specific LHP cancers that were formally reviewed were Hodgkin lymphoma, multiple myeloma, myeloid leukemia, and lymphatic leukemia. Non-Hodgkin lymphoma is a non-specific grouping of dozens of different lymphomas and classification systems for specific subtypes

that have changed over time, complicating the evidence synthesis for this cancer type. As a cursory review of the available studies did not suggest an association between formaldehyde exposure and non-Hodgkin lymphoma, this endpoint was not formally reviewed.

4.1. METHODS FOR IDENTIFYING AND EVALUATING STUDIES

4.1.1. Literature Identification

The primary focus of this review was whether exposure to inhaled formaldehyde is associated with specific URT or LHP cancers in humans or, in separate searches (i.e., nasal and LHP cancer studies were searched separately), in animals. The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.9, as are the specific PECO criteria and the methods for identifying literature from 2016–2021 are described in Appendix F.

4.1.2. Study Evaluation

Human studies

The epidemiological studies generally examined occupational exposure to formaldehyde either in specific work settings (e.g., cohort studies) or in case-control studies. The overwhelming majority of information bias in epidemiological studies of formaldehyde stems from the use of occupational records to gauge exposures with some degree of exposure misclassification or exposure measurement error considered to be commonplace. Thus, a primary consideration in the evaluation of these studies was the ability of the exposure assessment to reliably distinguish between levels of exposure within the study population, or between the study population and the referent population. A large variety of occupations were included within the studies; some represent work settings with a high likelihood of exposure to high levels of formaldehyde, and some represent work settings with variable exposures and in which the proportion of people exposed is quite small. In the latter case, the potential effect of formaldehyde would be "diluted" within the larger study population, limiting the sensitivity of the study. EPA categorized the exposure assessment methods of the identified studies into four groups (A through D), reflecting greater or lesser degree of reliability and sensitivity of the measures. Outcome-specific associations based on Group A exposures were considered without appreciable information bias due to exposure measurement error, while other groups were considered increasingly biased towards the null.

Studies with small case counts may have little statistical power to detect divergences from the null but are not necessarily expected to be biased, and no study was excluded solely on the basis of case counts as this methodology would exclude any study which saw no effect of exposure. Therefore, cohort studies with extensive follow-up that reported outcome-specific results on a number of different cancers, including very rare cancers such as nasopharyngeal cancer (NPC) and sinonasal cancer, were evaluated even when few or even no cases were observed, if information on the expected number of

cases in the study population was provided so that confidence intervals could be presented for the effect estimate. Studies with five or fewer exposed cases were considered to have *low* confidence.

Other considerations included an evaluation of limitations in effect estimates that may have been confounded by exposure to other substances in the workplace that were known risk factors for URT or LHP cancers and were likely to have been highly correlated with formaldehyde, as well as strong healthy worker effects, and other selection biases.

Animal studies

Studies of cancer development in experimental animals exposed for at least subchronic duration (shorter exposure durations were not prioritized for review, given the robust database), and which performed histopathological evaluations of respiratory tract or hematopoietic tissues, were evaluated (with preference given to studies that included a reasonable latency for cancers to develop, such as conducting histopathological evaluations at ≥1 year of age). As these evaluations consider many of the same studies previously evaluated for inclusion in the noncancer respiratory tract pathology section, many parallels exist between both sets of evaluations, although several notable differences exist. For example, duration of exposure was more important for evaluations of dysplasia and neoplasms, as compared with evaluations of noncancer respiratory tract lesions. In addition, whereas a substantial emphasis was placed on the characterization of the severity of the lesion for noncancer respiratory tract changes, severity was not considered integral to the identification of cancers and dysplasia. Generally, the study authors did not provide statistical comparisons for reported respiratory tract tumors; given the rarity of these neoplasms in unexposed animals, any observations of malignant tumors were considered to be biologically relevant, abnormal changes. Finally, although most studies used paraformaldehyde or freshly prepared formalin as the test article, some studies tested commercial formalin. Coexposure to methanol was considered to be a major concern for LHP cancers; it was considered to be less of a concern when identifying effects of inhaled formaldehyde on respiratory cancers. A final minor difference involved the preference for microscopic examination of several tissues applicable to assessing potential LHP cancers, and a preference for blinded assessment of the slides.

4.2. UPPER RESPIRATORY TRACT CANCERS

This section examines the evidence pertaining to the carcinogenic effect of formaldehyde exposure on the URT of humans and animals. The specific endpoints considered included diagnoses of nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx and hypopharynx, and laryngeal cancer; however, as it was ultimately judged that there was **inadequate evidence** on laryngeal cancer, these data are not discussed in this Overview (see Section 1.2.5 in the Toxicological Review). This section describes experimental animal studies examining the potential for cancers of the nasal cavity and proximal regions of the URT, and mechanistic studies relevant to interpreting potential carcinogenic effects on the URT.

4.2.1. Synthesis of Human Health Effect Studies

Nasopharyngeal Cancer

The evidence for formaldehyde exposure and the risk of nasopharyngeal cancer presents consistent findings of increased risk in exposed groups across several studies, including results classified with *high*, *medium*, and *low* confidence. These studies examined different populations, in different geographical locations, under different exposure settings and employing different study designs. Fourteen of 17 studies reported increased risks of nasopharyngeal cancer with at least one metric of formaldehyde exposure—often with both clear statistical significance and dose-response relationships (see Figure 16). These included the results of a large cohort study of 25,619 U.S. workers (Beane Freeman et al., 2013) classified with *high* confidence, and all four sets of results classified with *medium* confidence. Nine studies in eight independent populations reported relative effect estimates greater than three-fold. The study results exhibited a biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from nasopharyngeal cancer, allowing time for cancer induction, latency, and mortality.

The reported dose-response relationships showing that multiple measures of increased exposure to formaldehyde were repeatedly associated with increased risk of mortality from nasopharyngeal cancer were especially strong among studies primarily focused on squamous cell carcinomas. Excluding nasopharyngeal cancer cases with undifferentiated or nonkeratinizing histology, Vaughan et al. (2000) reported a clear dose-response with increased probability of exposure. Among those subjects considered to be "definitely exposed," there were increasing risks of nasopharyngeal cancer with increasing duration of formaldehyde exposure ($p < 0.001$) and with increased cumulative formaldehyde exposure ($p < 0.001$). Further evidence of dose-response relationships was reported by Beane Freeman et al. (2009) for peak formaldehyde exposures ($p = 0.005$, model including exposed and unexposed person-years), and, to a lesser degree, for cumulative exposures ($p = 0.06$, model including exposed and unexposed person-years) and with average intensity of formaldehyde exposure ($p = 0.09$, model including exposed and unexposed person-years).

The evaluation of potential biases resulted in reasonable confidence that alternative explanations have been ruled out, including chance, bias, and confounding within individual studies or across studies. There are reasonable explanations for the lack of findings in the three studies with very low background rates of nasopharyngeal cancer. The NPC results from the Coggon et al. (2014), Meyers et al. (2013), and Siew et al. (2012) studies were all considered to lack sensitivity to detect any true effect because there was a very low number of expected cases in study populations, which contributed to their classifications of *low* confidence.

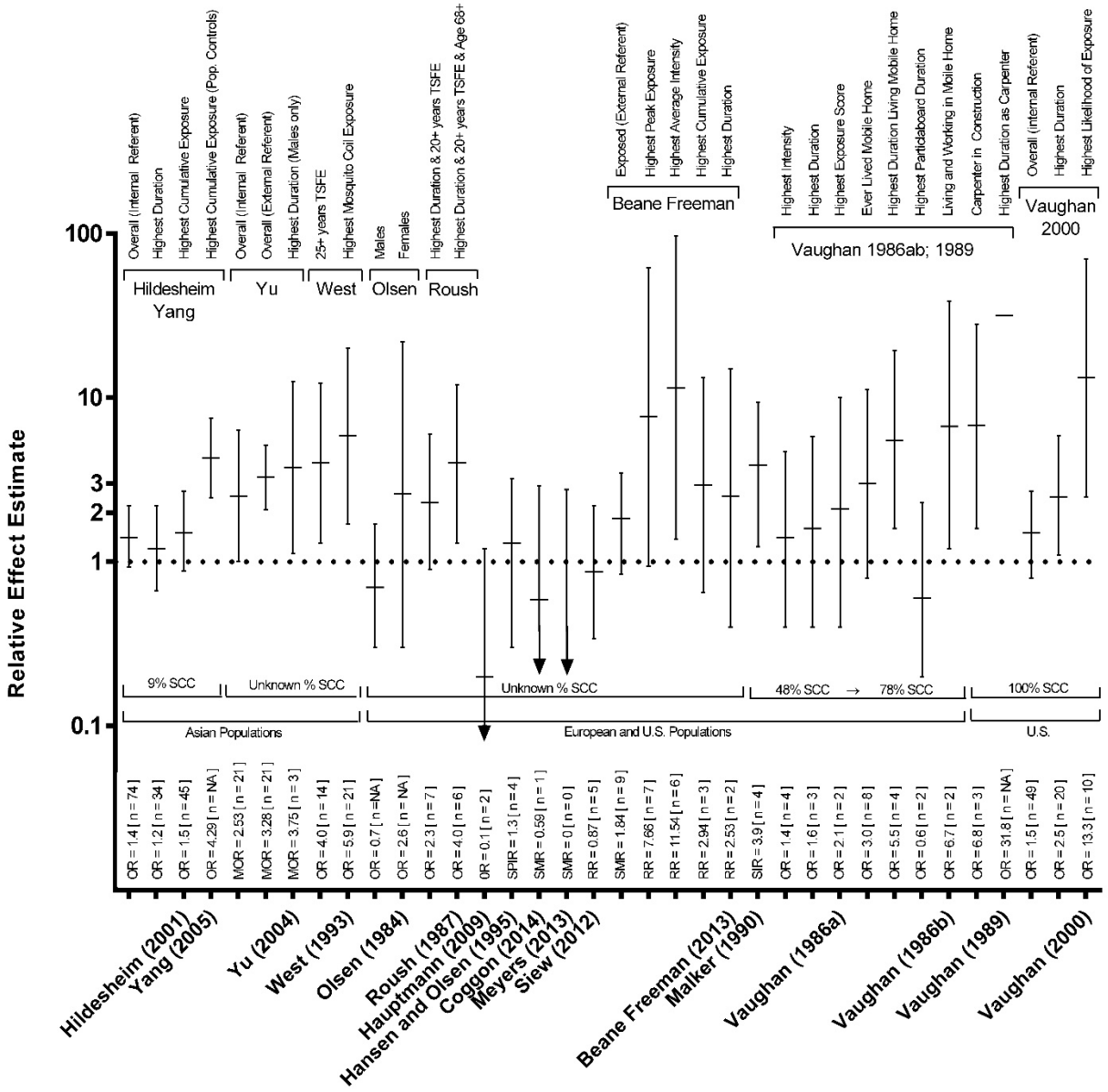


Figure 16. All epidemiological studies reporting nasopharyngeal cancer risk estimates.

Results are grouped by population background risk and arrayed from lowest to highest by the percentage of cases in each study's results, which were considered likely to be squamous cell carcinomas (SCC). SMR: standardized mortality ratio. PMR: proportionate mortality ratio. SPIR: Standardized Proportional Incidence Ratio. RR: relative risk. OR: odds ratio. MOR: mortality odds ratio. TSFE: time since first exposure. For each measure of association, the number of exposed cases is provided in brackets. For studies reporting results on multiple metrics of exposure, only the highest category of each exposure metric is presented in the figure.

Sinonasal Cancer

The evidence for formaldehyde exposure and the risk of sinonasal cancer presents consistent findings of increased risk in exposed groups across several studies, including results classified with

medium and *low* confidence. Seventeen informative studies evaluated sinonasal cancer among study subjects with formaldehyde exposure based on occupational history, including 4 sets of results classified with *medium* confidence—one of which represents a large, pooled analysis of 12 case-control studies (see Figure 17). These studies examined different populations, in different locations, under different exposure settings, and used different study designs.

For sinonasal cancer, it is important to consider the histological subtype or types in each report (squamous cell carcinoma, adenocarcinoma, or mixed). Sinonasal cancer is exceedingly rare; eight cohort studies reported zero cases in their study populations. With expected rates for sinonasal cancer as low as 0.6 cases per 100,000 people each year, these studies lacked the statistical sensitivity to detect an association with formaldehyde and were classified with *low* confidence. Of the nine studies that did observe cases of sinonasal cancer, results from six reported increased risks of sinonasal cancer that appeared to be associated with exposure to formaldehyde—four of six sets of results had been classified with *medium* confidence (Beane Freeman et al., 2013; Luce et al., 2002; Roush et al., 1987; Olsen and Asnaes, 1986) and two with *low* confidence (Teschke et al., 1997; Hansen and Olsen, 1995). Associations were stronger for adenocarcinomas than for squamous cell carcinomas. However, both histological cell type groupings, and a mixed type group, yielded results that were consistently elevated—with a clear demonstration of statistical significance for the adenocarcinomas. Two *medium* confidence studies reported at least a 3-fold increase in risk for adenocarcinoma. Potential confounding by wood dust was addressed and ruled out by the authors. Each of the other three sets of results that did not report some increase in risk associated with formaldehyde exposure had been in the group classified with *low* confidence, in part due to their lack of sensitivity to detect a true effect (Coggon et al., 2014; Siew et al., 2012; Pesch et al., 2008).

A dose-response relationship was observed in a large, pooled analysis of 12 case-control studies. Luce et al. (2002)[9] pooled 196 cases of sinonasal adenocarcinoma and 432 cases of squamous cell carcinoma and were able to contrast risks in three levels of exposure probability with the risk in the unexposed. An exposure-response relationship for adenocarcinoma, controlling for coexposure to wood dust, was observed for both men and women with the highest risks among those with the highest probability of exposure. The odds ratio (OR) among men with the highest cumulative exposure was 3.0 (95% CI: 1.5, 5.7), while it was 5.8 (95% CI: 1.7, 19.4) among women. No dose-response pattern was observed for squamous cell carcinoma. Analyses by Luce et al. (2002) allowing for a 20-year induction period showed only minimal impacts on the magnitude of relative risk; longer latency periods were not evaluated, which leaves some uncertainty.

The evaluation of chance, bias, and confounding within individual studies or across studies resulted in the conclusion that these alternative explanations for the observed associations could be reasonably ruled out. While smoking and alcohol may be independent risk factors for sinonasal cancer

[9]Note the pooled study by Luce et al. (2002) includes data from 12 publications and thus represents substantially more information than a single result (see Toxicological Review for additional details).

they are unlikely to be related to formaldehyde exposure and therefore unlikely to be across-the-board confounders. Wood dust, however, is a potential confounder as many wood-related jobs also have exposures to formaldehyde and the association between wood dust exposure and sinonasal cancer is extremely strong, with relative risks greater than 30-fold (Olsen and Asnaes, 1986). Wood dust may be an independent risk factor for sinonasal cancer; however, the majority of investigators presented analytic results for formaldehyde among workers who were either not exposed to wood dust (Hansen and Olsen, 1995; Olsen and Asnaes, 1986), or else controlled for the potential confounding of the effects of wood dust on the risk of sinonasal cancer and did not find wood dust to be a confounder (Luce et al., 2002). Although many of the analyses lacked precision due to the rarity of sinonasal cancer, the observations of multiple instances of very strong associations in different settings reduces the likelihood that chance, confounding, or other biases can explain the observed associations.

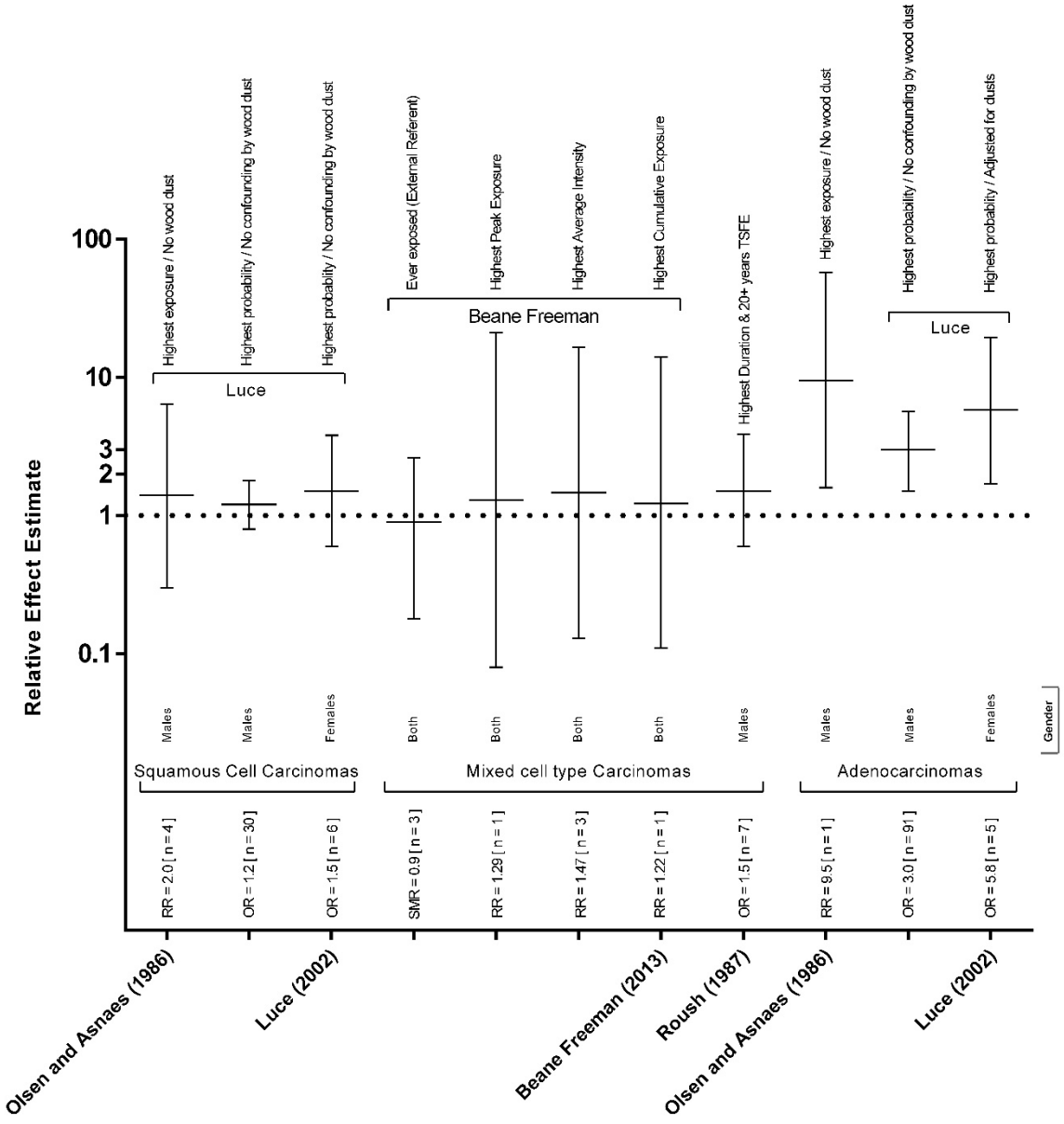


Figure 17. Highest (medium) confidence epidemiological studies reporting sinonasal cancer risk estimates.

Results are grouped by histological type as squamous cell carcinomas, mixed cell types, or adenocarcinoma. SMR: standardized mortality ratio. SPIR: Standardized Proportional Incidence Ratio. RR: relative risk. OR: odds ratio. TSFE: time since first exposure. For each measure of association, the number of exposed cases is provided in brackets. For studies with multiple metrics of exposure, only the highest category of each exposure metric is presented. Note that two studies (Luce et al., 2002; Olsen and Asnaes, 1986) reported separate results for squamous cell carcinoma and adenocarcinoma and appear twice in the figure. Also note that the pooled analysis by Luce et al. (2002) includes data from 12 publications and thus represents substantially more information than a single set of results.

Oropharyngeal/Hypopharyngeal cancer

Evidence describing an association between formaldehyde exposure and the risk of oropharyngeal/hypopharyngeal cancer was available from nine reports on six distinct study populations—four reports on three cohort studies (Coggon et al., 2014; Meyers et al., 2013; Marsh et al., 2007; Marsh et al., 2002) and five reports on three case-control studies (Laforest et al., 2000; Gustavsson et al., 1998; Vaughan, 1989; Vaughan et al., 1986a, b).

Overall, the findings were heterogeneous. Increased risks of oropharyngeal/hypopharyngeal cancer were reported by two *medium* confidence studies associated with multiple metrics of formaldehyde exposure, but little other evidence of increases in risk across one other *medium* and two *low* confidence was observed (see Figure 18). The strength of the association was variable with several studies reporting results near the null, and two *medium* confidence studies reporting 3- to 5-fold increases in risk among groups with the highest exposure probability or duration. One study observed dose-response relationships using multiple metrics of exposure.

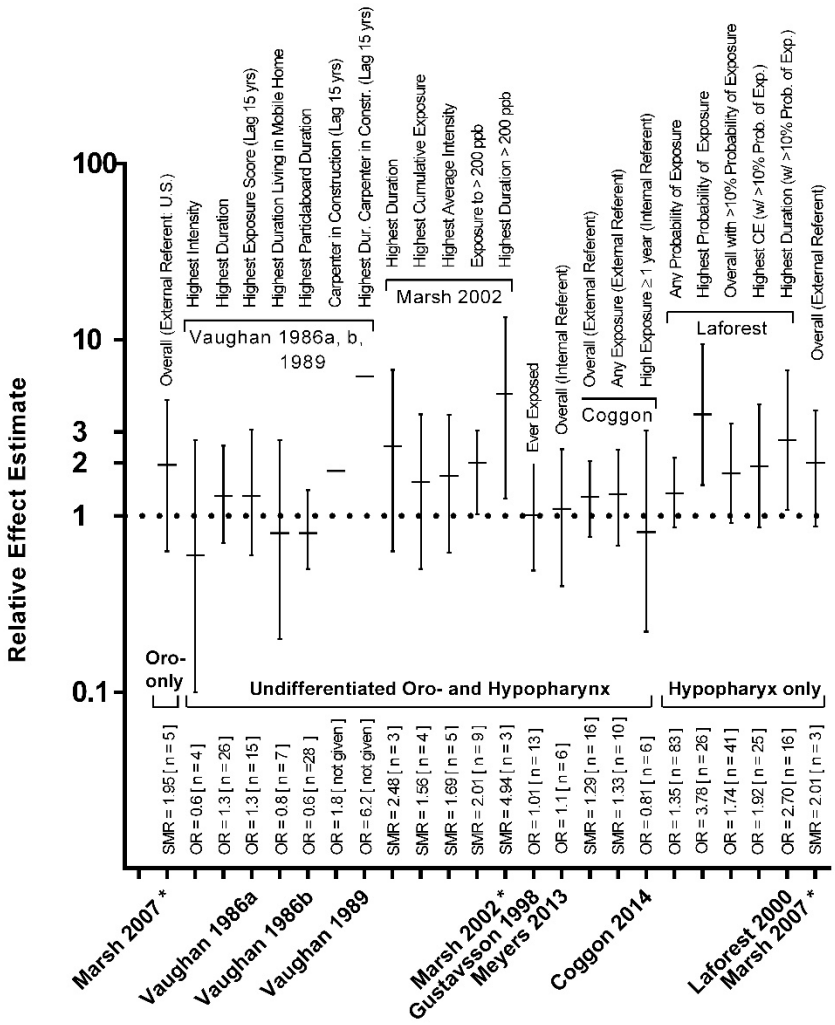


Figure 18. All epidemiological studies reporting oropharyngeal/hypopharyngeal cancer risk estimates.

Results are grouped by cancer site as oropharyngeal only, oropharyngeal grouped with hypopharyngeal and unspecified pharyngeal, or hypopharyngeal only. SMR: standardized mortality ratio. RR: relative risk. OR: odds ratio. CE: cumulative exposure. For each measure of association, the number of exposed cases is provided in brackets. For studies with multiple metrics of exposure, only the highest category of each exposure metric is presented. Data from Marsh et al. (2007; 2002) are based on the same study subjects; however, dose-response data were only included in the 2002 study, and the 2007 study had more recent comparisons with external referents.

4.2.2. Synthesis of Animal Health Effect Studies

Overall, tumors of the respiratory tract were consistently observed in mice and in several strains of rats, but not in hamsters, exposed to formaldehyde (Kamata et al., 1997; Monticello et al., 1996; Holmstrom et al., 1989a; Woutersen et al., 1989; Sellakumar et al., 1985; Kerns et al., 1983; Dalbey, 1982). The most consistent animal evidence of formaldehyde-induced respiratory cancers was the development of squamous cell carcinomas (SCCs), with the most useful data from studies of exposed

rats (see Figure 19). Following exposure of rats to formaldehyde for 2 years, an increase in SCCs was observed in five of six studies interpreted with *medium* or *high* confidence. SCCs were not reproducibly detected below 6 mg/m^3 formaldehyde; however, none of the available rat studies tested exposure between 3 and 6 mg/m^3, introducing some uncertainty.

Specifically regarding SCCs, these exposure-induced tumors were restricted to the nasal cavity, were not observed in other respiratory tract regions, such as the larynx and lung, and generally developed in animals that were observed for longer than 12 months. The locations of the induced SCCs were consistent with both the distribution of inhaled formaldehyde and locations of other formaldehyde-induced nasal pathologies. There were clear species differences in the severity of SCCs, with hamsters displaying little evidence of toxicity and rats exhibiting amplified responses as compared to mice (likely attributable to a lower inhaled dose of formaldehyde). While these tumors were detected in exposed male and female Fischer 344 (F344) and Sprague Dawley (SD) rats, findings in Wistar rats were less clear. The rat studies are summarized in Figure 19.

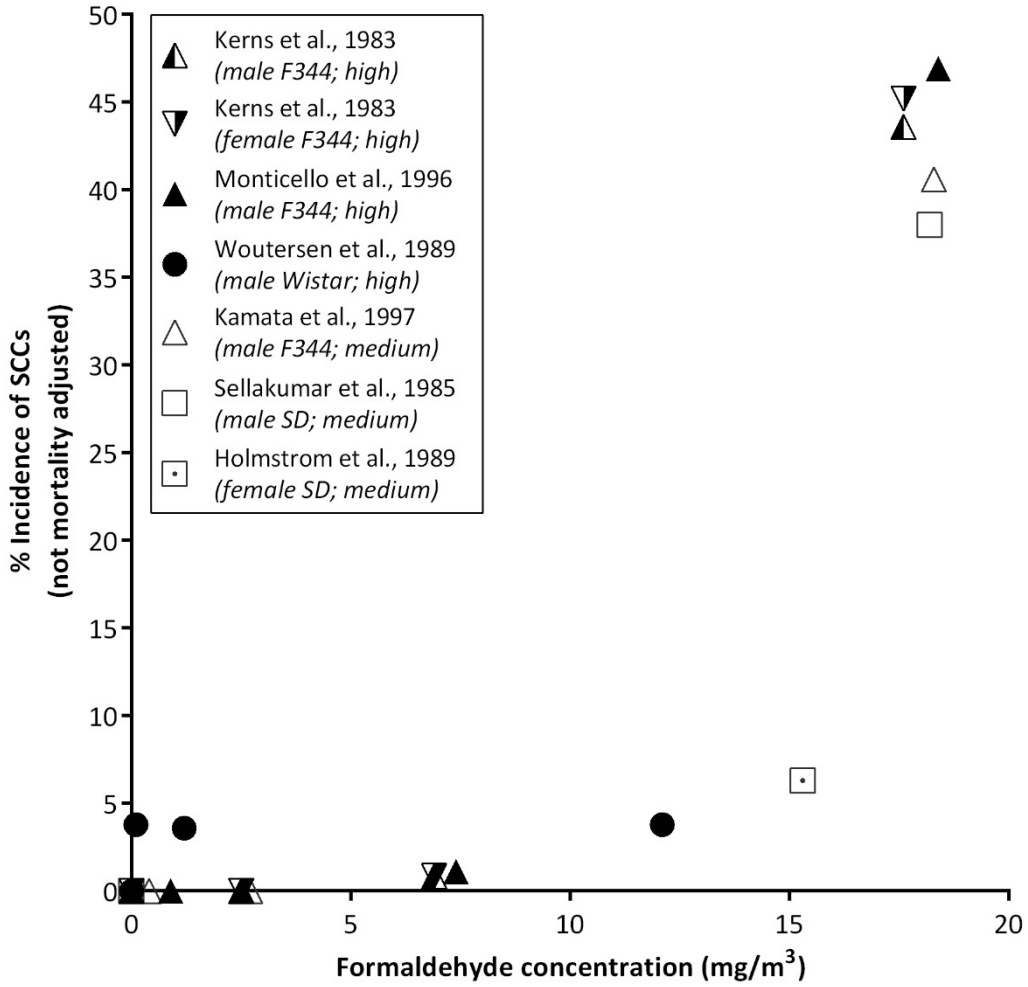


Figure 19. Incidence of nasal squamous cell carcinomas in rats exposed to formaldehyde for at least 2 years.

% incidence data from the *high* (black outline and fill) and *medium* (gray outline and no fill) confidence studies are arrayed. Different shapes represent different rat strains.

In addition to SCCs, precancerous dysplastic lesions were induced in rats and mice (Holmstrom et al., 1989a; Morgan et al., 1986b; Kerns et al., 1983), sometimes at lower formaldehyde concentrations than those at which malignant tumors were observed. The dysplasia and neoplasms were predominantly localized to anterior regions of the nasal respiratory epithelium, although the lesions progressed to more posterior locations with increasing duration and concentration of formaldehyde exposure, with one study reporting that dysplasia can develop in portions of the proximal trachea in rats.

SCC development depended on the duration of observation and, based on an increasing incidence and severity of lesions in animals exposed for longer periods of time, the formaldehyde exposure duration. Most notably, the lesion incidence, as well as the tumor invasiveness and latency, was reproducibly shown, across two species, to worsen with increasing exposure concentration.

4.2.3. Mode-of-action Information

In F344 rats chronically exposed to formaldehyde, there is a clear temporal, dose-responsive and biological relationship in the appearance of exposure-related genotoxicity, sustained epithelial damage, cellular proliferation, and eventual development of SCC or polypoid adenoma (PA; a benign lesion independent from, and not a precursor to, SCC), consistent with similar relationships evident in analogous URT tissues from both the monkey and human databases. Furthermore, the chronic formaldehyde exposure concentrations reported to elicit nasal cytotoxic pathology appear to be higher in the rats and monkeys evaluated experimentally, compared with the results from human epidemiological cohorts, whereas formaldehyde-associated genotoxicity has been induced in analogous portal-of-entry tissues from rats, monkeys, and humans exposed to similar formaldehyde concentrations (see Toxicological Review for details). Together, genotoxicity, cellular proliferation, and cytotoxicity-induced tissue regenerative proliferation exhibit multiple layers of coherence as a function of species and anatomy, temporality, concentration, and duration of exposure. When integrated, this evidence forms a biologically relevant MOA for formaldehyde-induced URT carcinogenesis (U.S. EPA, 2005a). A summary and evaluation of the mechanistic evidence is presented in Table 34.

Strong, consistent evidence from rodents and monkeys supports the role for both direct (i.e., potentially DNA-protein crosslinks, DPX, or hmDNA adduct associated) mutagenicity as well as indirect genotoxicity, mutagenicity, and regenerative proliferation resulting from respiratory tissue pathology, in rodent URT carcinogenesis (see Toxicological Review Section 1.2.5 Upper Respiratory Tract Cancer Mode-of-Action Analysis for details). DNA labeling studies in rodent nasal epithelium suggest that cell division may also accelerate in response to marginally cytotoxic tissue concentrations resulting from short-term, lower level, or discontinuous exposure scenarios, although this evidence was neither strong nor consistent across similar studies and model systems. Observations of mutagenicity, cytotoxic epithelial pathology, and proliferation correspond histologically, anatomically, temporally, and dose-responsively with subsequent SCC and PA formation, consistent with contribution of both mutagenesis and regenerative proliferation to rodent URT carcinogenesis following formaldehyde exposure.

Mutagenicity is presumed to be a relevant component of URT carcinogenesis in humans, supported by strong evidence of direct genotoxicity in both rodents and monkeys and consistent observations of direct genotoxicity and mutagenicity from human epidemiological studies. Increased nasal epithelial cell proliferation (in rats and monkeys) coincides anatomically with dysplastic lesions found in tissues from similar species as well as with progressive, proliferative lesions in the nasal/buccal epithelium and nasopharynx of chronically exposed humans. This cross-species concordance, combined with the observation that cellular proliferation may be induced at lower exposures or following shorter durations of exposure than those eliciting tissue metaplasia, suggests that cellular proliferation in the presence of marginal tissue toxicity may also be potentially relevant to human URT carcinogenesis, as this episodic exposure scenario may be more frequently encountered in human populations than the continuous, chronic high-level exposures traditionally employed in rodent cancer bioassays. Increasing

incidence or severity of nasal dysfunction and progressive pathology is associated with escalating formaldehyde exposure concentration or duration in humans, monkeys, and rats. While POE tissue sensitivity to formaldehyde toxicity may quantitatively differ from humans to rats and other rodents, qualitatively similar nasal dysfunction and pathology consistent with pre-neoplastic stages of cancer progression are observed across analogous tissues from all affected species, and therefore conclusions derived from these model systems are presumed relevant to human URT carcinogenesis. Given this presumed relevance, the potential for an increased susceptibility of specific human populations to developing URT cancers can be informed by both the human data and relevant mechanistic evidence from experimental model systems.

Table 34. Summary considerations for upper respiratory tract (URT) carcinogenesis (the primary support for genotoxicity or mutagenicity is noted; see Toxicological Review for additional details)

Hypothesized mechanistic event	Experimental evidence pertinent to mechanistic event	Human relevance	Weight-of-evidence and biological plausibility
Direct, or presumed direct, genotoxicity and mutagenicity (and indirectly supporting information)	• ↑ MN in URT tissue from human students and workers at average concentrations as low as 0.1 mg/m^3 (subchronic-to-chronic exposure) (Aglan and Mansour, 2018); (Ballarin et al., 1992); (Burgaz et al., 2001); (Burgaz et al., 2002); (Costa et al., 2019); (Costa et al., 2008); (Ladeira et al., 2013); (Peteffi et al., 2015); (Viegas et al., 2013); (Viegas et al., 2010); (Ye et al., 2005) • ↑ DNA monoadducts in nasal tissues of exposed rats and monkeys using highly sensitive methods (short-term or subchronic exposure) (Yu et al., 2015; Lu et al., 2011; Moeller et al., 2011; Lu et al., 2010) • ↑ DPX in URT tissues of monkeys (acute exposure) and F344 rats (acute-to-subchronic exposure) (e.g., (Lai et al., 2016; Georgieva et al., 1999; Casanova et al., 1994)) [note: not observed in 2 short- term controlled exposure studies] • No effect on MN incidence nasal tissue (Speit et al., 2011) or in BAL cells (Neuss et al., 2010) in single studies in rats (28d exposure)	Yes. Markers of direct genotoxicity correspond anatomically and temporally with subsequent URT neoplasia in experimental animal models, are consistent with increased MN induction following exposure in humans and are presumed relevant to human carcinogenesis.	Strong and consistent evidence for formaldehyde-induced direct genotoxicity and mutagenicity exists from both experimental animal models and human molecular epidemiology to support a significant role for mutagenicity in URT carcinogenesis.

Hypothesized mechanistic event	Experimental evidence pertinent to mechanistic event	Human relevance	Weight-of-evidence and biological plausibility
	• While several studies suggest a role for exposure-induced modifications to the tumor suppressor, p53, in SCC development (see Appendix A.4.5), a short-term study in mice deficient for Trp53 (encodes p53) failed to observe increases in tumors (Morgan et al., 2017) • Indirect support: strong and consistent evidence of mutagenicity (increased incidence of MN, CA, and chromosome aneuploidies) in PBLs of human workers (see Section 4.3) • Indirect support: strong and consistent evidence of genotoxicity and mutagenicity in numerous *in vitro* mammalian and non-mammalian systems (see Appendix A.4)		
Cytotoxicity-induced regenerative proliferation	• ↓ Nasal mucociliary function, ↑ nasal hyperplasia, keratinization or squamous metaplasia, URT rhinitis, irritation, and inflammation in humans (acute-to-chronic exposure) • ↓ Nasal cilia content, ↑ hyperplasia and squamous metaplasia in URT tissues from monkeys (acute-to-subchronic exposure) • Associated with ↑ URT cell proliferation in rhesus monkeys • ↓ Nasal mucociliary function, ↑ nasal rhinitis, hyperplasia and squamous metaplasia dysplasia in various rat strains and B6C3F1 mice (acute-to-chronic exposure) • Associated with ↑ URT proliferation (rats; mice)	Yes. Increasing incidence or severity of URT dysfunction or pathology is positively associated with formaldehyde exposure in humans, monkeys, and rats. A continuum of similar epithelial pathology is observed across affected species at POE tissues, and therefore the resulting increased cellular turnover observed in experimental models is presumed relevant to human carcinogenesis.	Strong and consistent evidence exists which associates the nasal epithelial pathology-driven proliferation with SCC abundance following formaldehyde exposure in rodent experimental models to support a significant role for regenerative proliferation in URT carcinogenesis.
Cellular mitogenesis in the absence of cytotoxic tissue pathology	• Clear evidence of ↑ URT cell proliferation under conditions also resulting in tissue pathology in rhesus monkeys • Exposure to subcytotoxic concentrations not evaluated • Clear evidence of ↑ URT cell proliferation under conditions also resulting in tissue pathology in Wistar and F344 rats (≥4 mg/m^3) • Suggestive evidence of ↑ URT cell proliferation under conditions not clearly causing tissue pathology (<4 mg/m^3)	Yes. Cellular proliferation may be increased at lower exposures or following shorter durations of exposure than that eliciting tissue pathology, which suggests that mitogenesis may be directly stimulated by formaldehyde exposure. Proliferation is expected to accelerate and enhance carcinogenesis in both humans and animals and is presumed relevant to human carcinogenesis.	Limited and inconsistent evidence associates cellular proliferation with formaldehyde exposures below those eliciting cytotoxic pathology in the rat nasal epithelium, which precludes a determination as to the importance of this phenomenon in URT carcinogenesis.

Hypothesized mechanistic event	Experimental evidence pertinent to mechanistic event	Human relevance	Weight-of-evidence and biological plausibility
Oxidative stress, immune disease and dysfunction in the URT	• ↑ LRT infection frequency, inflammation, allergic outcomes in children; ↑ leukocyte activation, allergy symptoms, chronic URT inflammation and ↓ infection resistance in adult workers (subchronic-to-chronic exposure) • ↑ LRT oxidative stress, markers of inflammation and leukocyte recruitment in rats and mice; ↑ airway wall thickening or remodeling in mice and rats following ovalbumin sensitization • ↑ Malignancy and neutrophil involvement of lung metastases, ↓ lung natural killer (NK) cell numbers and activity in C57BL/6 mice	Yes. Nasal infection, markers of persistent inflammation or immune dysfunction are positively associated with a range of formaldehyde exposure in both humans and rodents. Oxidative stress and chronic inflammatory diseases (immunosuppression) are presumed relevant to human carcinogenesis. The relevance of other immune system dysfunctions to human carcinogenesis, such as allergy, is less clear.	While evidence exists supporting oxidative stress, chronic inflammation and various immune dysfunctions following formaldehyde exposure in humans and experimental animal models, the evidence supporting associations between these effects and URT carcinogenesis is insufficient to evaluate the contribution of these effects independently in either humans or experimental animals.

4.2.4. Overall Evidence Integration Judgments and Susceptibility for Upper Respiratory Tract Cancers

Table 35 summarizes the evidence integration judgments and supporting rationale for the individual URT cancers.

Epidemiological findings provide *robust* evidence for nasopharyngeal cancers (NPCs), based on groups with occupational exposure. Consistent increases in NPC risk were reported by numerous *high* and *medium* confidence studies involving occupational exposure to formaldehyde among diverse populations in different geographic locations and exposure settings that accounted for expected temporal relationships for cancer induction and progression, with several reporting a large magnitude of relative risk (RR ≥3). A dose-response gradient was reported for various measures of exposure, including cumulative exposure, duration of exposure, and peak exposure. *Robust* evidence for nasal cancers is provided from studies in experimental animals (rats and mice). In animals, the incidence of lesions, as well as the tumor invasiveness and latency, was reproducibly shown to worsen with increasing formaldehyde exposure level. The distribution of tumors was dependent on duration of exposure as well as formaldehyde concentration. Mechanistic changes associated with the development of cancer in the nasal cavity were consistently observed in humans and experimental systems, including genotoxicity, epithelial damage and proliferation, and eventual cancer development in relevant URT tissues. The mechanistic changes and URT lesions exhibited a temporal and dose-response relationship coherent with carcinogenesis and supportive of a mutagenic MOA. The observed formaldehyde exposure-induced nasal tumors and mechanistic changes in animals are considered directly relevant to changes in the human nasopharynx (the nasopharynx is part of the nasal cavity and a recognized target of inhaled nasal toxicants). Thus, based on *robust* human evidence, *robust* animal evidence, and mechanistic evidence supporting a mutagenic MOA for NPC, the **evidence demonstrates** that

formaldehyde inhalation causes nasopharyngeal cancer in humans, given appropriate exposure circumstances. This conclusion is primarily based on studies of groups exposed to occupational formaldehyde levels and coherent findings in animals, with tumors in rodents generally only observed at formaldehyde concentrations above 6 mg/m^3.

Epidemiological findings also provide *robust* evidence for sinonasal cancer (SNC), based on groups with occupational exposure. The *robust* judgment for SNC is supported by a smaller set of epidemiological studies than for NPC, although a large, pooled analysis of 12 casecontrol studies included a large number of cases and greater detail on formaldehyde exposures, which increased confidence. This study observed an increasing trend in risk for adenocarcinoma with higher cumulative exposure among men and women in analyses that controlled for key confounders including exposure to wood dust. The studies were conducted in different geographic locations and exposure settings that accounted for expected temporal relationships for cancer induction and progression. Rodent nasal cancers and related mechanistic changes in the nasal cavity are considered relevant to human SNC, although some uncertainty in their applicability to SNC, as compared to NPC remains, and thus judgments of both *robust* and *moderate* animal evidence were considered. Ultimately, given this uncertainty in applicability, while the animal and mechanistic evidence cited for NPC is judged as informative and supportive for interpreting SNC, including providing sufficient support for a mutagenic MOA for this cancer type, the animal evidence overall is interpreted as *moderate* rather than *robust*. Based on *robust* human evidence, *moderate* animal evidence, and mechanistic evidence supporting a mutagenic MOA for SNC, the **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer in humans, given appropriate exposure circumstances. This conclusion is primarily based on studies of groups exposed to occupational formaldehyde levels.

For oropharyngeal/hypopharyngeal cancers, the human evidence is *slight*, based on data from highly exposed workers, and s*light* animal evidence is provided from relevant observations of preneoplastic lesions and mechanistic changes. Taken together, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause oropharyngeal/hypopharyngeal cancers given appropriate exposure circumstances.

Table 35. Evidence integration summary for effects of formaldehyde inhalation on URT cancers

Evidence	Evidence judgment	Hazard determination
Nasopharyngeal cancer (NPC)		
Human evidence	*Robust*, based on: *Human health effect studies:* •Consistent increases in risk across numerous *high*, *medium* and *low* confidence studies •Very strong associations (eight studies reported at least a threefold increase in risk for some exposure categories, three of the eight were of *high* or	The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer in humans, given appropriate exposure circumstances[a]

	medium confidence, direction of potential bias toward the null) •Evidence of exposure-response relationships across multiple measures of increased exposure • A temporal relationship consistent with causality (i.e., allowing for cancer induction, latency and mortality) *Biological Plausibility:* Although not as strong as the animal database of mechanistic studies, mechanistic evidence from human studies indicates a clear biological relationship with genotoxicity, epithelial damage and proliferation, and eventual cancer development in relevant URT tissues	Primarily based on studies of groups of workers exposed to occupational formaldehyde levels, coherent findings in animals (with tumors in rodents generally only at formaldehyde levels above 6 mg/m^3), and a well-supported MOA for nasal tumor development *Potential Susceptibilities*: There is very little evidence to evaluate the potential risk to sensitive populations and/or lifestages. However, several animal studies suggest that prior damage to the nasal epithelium might increase the development of cancer in these damaged regions.
Animal evidence	*Robust*, based on: *Animal health effect studies:* • Tumors of the respiratory tract (predominantly nasal squamous cell carcinomas, SCCs, but including other epithelial and nonepithelial tumors) were consistently observed in mice and in several strains of rats in numerous *high* and *medium* confidence studies, but not in hamsters, generally at formaldehyde levels above 6 mg/m^3. • The lesions progressed to more posterior locations with increasing duration and concentration of formaldehyde exposure • The development of these lesions, particularly the SCCs, depended on the duration of observation and, based on an increasing incidence and severity of lesions in animals exposed for longer periods of time, the formaldehyde exposure duration. Most notably, the lesion incidence, as well as the tumor invasiveness and latency, was reproducibly shown to worsen with increasing formaldehyde exposure level. *Biological Plausibility:* Mechanistic changes consistent with cancer development in nasal tissues were observed across species, including rats, mice, and monkeys. In rats chronically exposed to formaldehyde, a clear temporal, dose-responsive, and biological relationship was observed in the appearance of genotoxicity, sustained epithelial damage, cellular proliferation, and eventual tumor development.	
Other Inferences	• *Relevance of the animal evidence to human NPC*: The types of findings were consistent and coherent across species (including humans). Although site concordance is not essential (U.S. EPA, 2005a), considering the anatomy of the rodent and human URT and the importance of the distribution of inhaled formaldehyde, the observed formaldehyde exposure-induced nasal tumors and mechanistic changes in animals are considered directly relevant to changes in the human nasopharynx. • *MOA*: Together, genotoxicity, cellular proliferation, and cytotoxicity-induced regenerative proliferation exhibit multiple layers of coherence as a function of species, anatomy, temporality, concentration, and duration of exposure, and when integrated, form a biologically relevant MOA for formaldehyde-induced URT carcinogenesis (U.S. EPA, 2005a). While the chronic formaldehyde exposure concentrations reported to elicit nasal cytotoxic pathology appear to be higher in the rats and nonhuman primates evaluated experimentally (≥4 mg/m^3), compared with the results from human epidemiological cohorts (≥0.3 mg/m^3), formaldehyde-associated genotoxicity has been induced in analogous POE tissues from rats, nonhuman primates and humans exposed similarly (≤0.9 mg/m^3).	
Sinonasal cancer (SNC)		
Human evidence	*Robust*, based primarily on: *Human health effect studies:*	The **evidence demonstrates** that formaldehyde inhalation

	• Consistent increases in risk across a set of *medium* and *low* confidence studies; four (2 *medium* and *2 low* confidence) studies reporting at least a threefold increase in risk, primarily for adenocarcinoma, including the largest study, a pooled analysis of 12 case-control studies, demonstrating a clear exposure-response relationship. • Increased risk of lower magnitude reported by two other medium confidence studies. • Null results in 3 insensitive low confidence studies. *Biological Plausibility:* The human mechanistic evidence cited for NPC is informative and supportive for interpreting the biological plausibility of SNC.	causes sinonasal cancer in humans, given appropriate exposure circumstances[a] Primarily based on studies of groups of workers exposed to occupational formaldehyde levels. Although less certain than the support provided for NPCs, animal and MOA evidence provide support for the human evidence. *Potential Susceptibilities*: There is very little evidence to evaluate the potential risk to sensitive populations and/or lifestages. However, several animal studies suggest that prior damage to the nasal epithelium might increase the development of cancer in these damaged regions.
Animal evidence	*Moderate*, based on: *Animal health effect studies:* (Same evidence base as for NPC above) • Note: tumors were not reported in the maxillary sinus of exposed animals *Biological Plausibility:* (Same mechanistic evidence base as for NPC above) • Although infrequently examined, studies that measured noncancer lesions in the maxillary sinus did not detect treatment-related respiratory tract pathology, although cell proliferation was observed (see Section 1.2.4). • Although also poorly studied, some mechanistic changes consistent with the MOA for nasal cancers, including increased DPX in the monkey maxillary sinus, have been observed.	
Other Inferences	• *Relevance of the animal evidence to human SNC*: The types of findings were consistent and coherent across species (including humans). The strong animal and mechanistic evidence for nasal cancers across species is interpreted to provide *moderate* evidence supportive of sinonasal cancer (a judgment of *moderate* rather than *robust* reflects some uncertainty in interpreting the nasal cavity findings in animals as fully applicable to human sinonasal cancer specifically). • *MOA*: Similar to the inference above, although there is uncertainty in the application of the identified MOA to SNC, the evidence overall is interpreted to provide reasonable support for the mutagenic MOA asapplicable to SNC.	
Oropharyngeal/ Hypopharyngeal cancer (OHPC)		
Human evidence	*Slight*, based on: *Human health effect studies:* • Increased risks in two of three *medium confidence* studies that evaluated multiple metrics of exposure and reported three- to fivefold increases in those highly exposed, including one which demonstrated clear exposure-response relationships across several metrics • However, little evidence of increases in risk (near the null) across one *medium* and two *low* confidence results *Biological Plausibility:* Although cells from exposed humans in tissues closely apposed to the oropharynx and, more indirectly, the hypopharynx (e.g., buccal cells) demonstrate mechanistic changes consistent with the development of cancer, including genotoxicity, these data were not interpreted as sufficient to further strengthen the human evidence judgment beyond *slight*.	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause oropharyngeal /hypopharyngeal cancer, given appropriate exposure circumstances[b]
Animal evidence	*Slight*, based on: *Animal health effect studies:* • While most findings in animals were localized to the nasal cavity, some data	

	suggest that changes in more caudal (e.g., in the trachea) regions, including evidence of dysplasia (a dedicated pre-neoplastic lesion) in one study, can occur with very high formaldehyde exposures and/or different breathing patterns (e.g., oronasal breathing in monkeys). • Changes in the more caudal URT tissues most relevant to OHPC were generally less direct indicators of cancer development, were less severe, or occurred only at very high exposure levels. *Biological Plausibility:* Mechanistic changes within caudal portions of the rodent and monkey URT have been observed, and oronasal breathing in humans (contrasting nasal-only breathing in rodents) infers an increased potential relevance of mechanistic changes in rostral (anterior) regions of the rodent to human OHPC. However, this was not interpreted as sufficient to further strengthen the evidence judgment beyond *slight*.	
Other inferences	• *Relevance of the animal evidence to human OHPC*: While cancer site concordance is not required for hazard determination (U.S. EPA, 2005a), given the known reactivity and distribution of inhaled formaldehyde, a lesser level of confidence in the applicability of the animal nasal findings is inferred for OHPC as compared to NPC or SNC. • *MOA*: While aspects of the MOA for nasal cancers, including NPC and SNC, may be operant for OHPC, the evidence overall is not interpreted to provide reasonable support for a MOA that is relevant to OHPC.	

Note: Laryngeal cancer evidence is not presented in this Overview (see Section 1.2.5 of the Toxicological Review).
[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis (Section 4.5).
[b]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define what might be the "appropriate exposure circumstances" for developing this outcome.

4.3. LYMPHOHEMATOPOIETIC (LHP) CANCERS

This section examines the evidence pertaining to the carcinogenic effect of formaldehyde exposure on lymphohematopoietic (LHP) cancer in humans and animals. The specific endpoints included: Hodgkin lymphoma, multiple myeloma, myeloid leukemia, and lymphatic leukemia; however, as it was ultimately judged that there was **inadequate evidence** on lymphatic leukemia, these data are not discussed in this Overview (see Section 1.3.3 of the Toxicological Review). This section discusses experimental animal studies examining histopathological lesions associated with leukemia or lymphoma, and mechanistic studies relevant to interpreting potential carcinogenic effects on these tissues.

4.3.1. Synthesis of Human Health Effect Studies

Myeloid Leukemia

Evidence describing the association between formaldehyde exposure and the risk of myeloid leukemia was available from 13 epidemiological papers reporting on 10 different study populations: three case-control studies (Talibov et al., 2014; Hauptmann et al., 2009; Blair et al., 2001) and nine cohort studies (Coggon et al., 2014; Pira et al., 2014; Meyers et al., 2013; Saberi Hosnijeh et al., 2013; Beane Freeman et al., 2009; Hayes et al., 1990; Ott et al., 1989; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983). Hauptmann et al. (2009) combined the study populations from Hayes et al.

(1990) with those from Walrath and Fraumeni (1984, 1983) and reconstructed individual exposure estimates. Checkoway et al. (2015) reanalyzed Beane Freeman et al. (2009) with different definition of the exposure categories and presented results for specific sub-types of myeloid leukemia. For the purposes of this evaluation, cancer cases reported as monocytic leukemia or nonlymphocytic leukemia were included as myeloid leukemia.

The majority of the studies of the 10 populations reported increased risks of myeloid leukemia associated with exposure to formaldehyde for at least one metric of exposure, although four *low* confidence studies reported results based on fewer than 10 cases and two other *low* confidence studies reported relative effect estimates of RR = 1.02 and OR = 1.17. These studies examined different populations in different locations and exposure settings and using different study designs. Consistent reports of elevated risks were provided by the five studies with population-level exposure assignments (Pira et al., 2014; Hayes et al., 1990; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983). The results from Walrath and Fraumeni (1984, 1983) and Hayes et al. (1990) were classified with *medium* confidence, while the results from the other two studies were classified with *low* confidence. Although the exposure settings in studies of anatomists and embalmers involved coexposure to methanol, whether there is an association of methanol exposure with leukemia is not known, and elevations in leukemia risk also were observed in studies involving other exposure settings. Four *high* and *medium* confidence studies with individual-level exposure assignments (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009) also showed elevated risks; three of the studies allowed for the evaluation of dose-response relationships with increased formaldehyde exposures using multiple metrics of exposure (see Figures 20 and 21 for all myeloid leukemia studies and *high* or *medium* confidence studies only, respectively). A pattern of increasing dose-response was indicated in analyses of exposure duration (Meyers et al., 2013; Hauptmann et al., 2009), cumulative exposure (Meyers et al., 2013), and with peak exposure metrics (Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009). These three studies with *high* confidence results also observed some indication of an increase in mortality risk at about 15–20 years since the initial exposure consistent with a biologically relevant induction/latency period; Hauptmann et al. (2009) showed a clear increase in risk at 20+ years since first exposure.

Studies with higher quality exposure data based on individual-level exposure assessment generally reported stronger associations. The results at the highest levels of formaldehyde showed an approximately 2- to 3-fold relative increase in risk of mortality (Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009; Blair et al., 2001). One study's results that were classified with *medium* confidence due to exposure measurement error (Coggon et al., 2014) showed no increase in risk among those who had ever had a job in the highest category of exposure. However, this high exposure category included workers with a broad range of duration, resulting in low sensitivity to detect an association. Alternative explanations for the associations observed by the *high* and *medium* confidence studies can be reasonably ruled out, reinforced across studies by the consistency in results

and dose-response patterns. Four other studies with results classified as *low* confidence were less consistent, possibly because these studies were limited by low case numbers and missing or imprecise exposure information (Talibov et al., 2014; Saberi Hosnijeh et al., 2013; Blair et al., 2001; Ott et al., 1989).

Different measures of exposure reflected different risks both within and among studies, although most provided some evidence of increased mortality from myeloid leukemia associated with formaldehyde exposure. One study showed the strongest relationship of myeloid leukemia mortality with duration of formaldehyde exposure (Hauptmann et al., 2009). Another showed increased risks for peak exposure and average exposure but not for cumulative exposure or "any" exposure (Beane Freeman et al., 2009). A third study showed increased risk in the study population as a whole that was stronger among workers with the longest duration of exposure and workers with the greatest length of time since first exposure to formaldehyde (Meyers et al., 2013). As the different measures of exposure are likely to be correlated, it may not be possible to single out one exposure metric as most biologically meaningful.

The pattern of increased risk of myeloid leukemia reflects the associations seen within two subtypes, acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). However, among the studies with separate estimates by subtype, risks were elevated for both AML and CML, with the associations for CML appearing to be as strong as or stronger than the associations with AML (Checkoway et al., 2015; Saberi Hosnijeh et al., 2013; Blair et al., 2001; Stroup et al., 1986). Six studies reported specific results for AML; two were classified with *high* confidence (Meyers et al., 2013; Hauptmann et al., 2009), and four with *low* confidence (Checkoway et al., 2015; Talibov et al., 2014; Saberi Hosnijeh et al., 2013; Blair et al., 2001). Both of the *high* confidence results showed non-significantly elevated risks of AML associated with formaldehyde, as did three out of four of the *low* confidence results—although substantially higher risks were reported in the *high* confidence results. The precision of these more specific analyses was very low (a total of 0 to 6 exposed cases were observed in these studies). The Checkoway et al. (2015) reanalysis of Beane Freeman et al. (2009) reported non-significant increased risks of AML and CML with a redefinition of peak exposure that shifted nine cases of myeloid leukemia from the highest category of peak exposure in Beane Freeman et al. (2009) to the lowest category (referent group) in Checkoway et al. (2015).[10] Checkoway et al. (2015) also reported stronger effects of peak exposure with CML compared to AML but the number of cases in each exposure category was small. Results specific to AML are plotted in Figure 22.

[10]In Beane Freeman et al. (2009), for peak exposure there were 4 cases of ML who were unexposed, 14 cases with peak exposure from >0 to <2 ppm, 11 cases with peak exposure from 2 to <4 ppm and 19 cases with peak exposure ≥4 ppm. In Checkoway et al. (2015) the new definition of peak exposure and the recategorization results in 27 cases of ML with peak exposures from 0 to <2 ppm, 11 cases with peak exposure from 2 to <4 ppm, and 10 cases with peak exposure ≥4 ppm. The Checkoway et al. (2015) results were classified with *low* confidence due to information bias and low sensitivity.

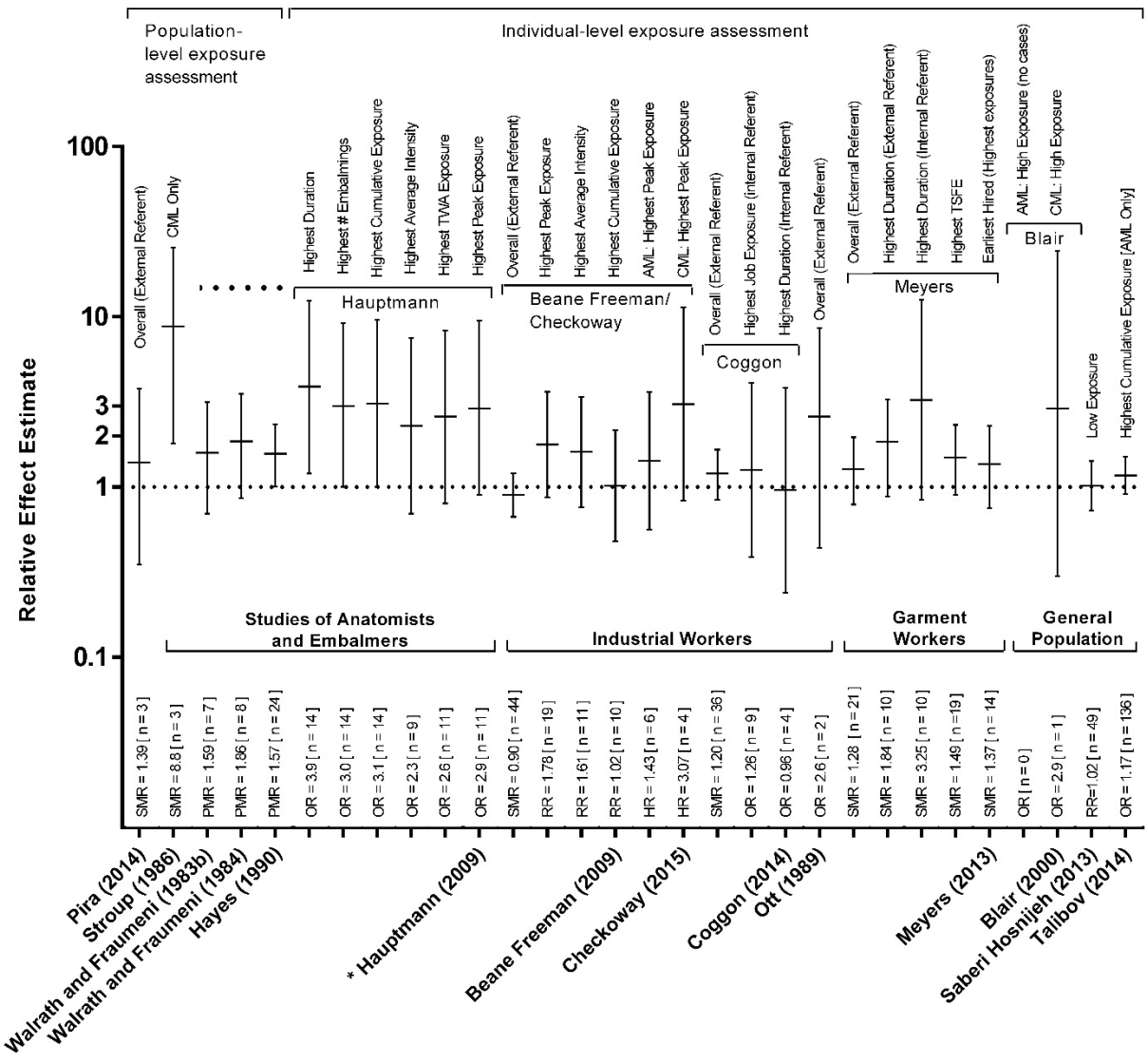


Figure 20. All epidemiological studies reporting myeloid leukemia risk estimates.

Results specifically for acute or chronic myeloid leukemia (AML or CML) are noted by these abbreviations. SMR: standardized mortality ratio. PMR: proportionate mortality ratio. RR: relative risk. OR: odds ratio. For each measure of association, the number of exposed cases is provided in brackets. For studies with multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented. *The dotted line extending from Hauptmann et al. (2009) reflects that study's inclusion of the original cohorts from Walrath and Fraumeni (1984, 1983) and Hayes et al. (1990), which were combined with extended follow-up in Hauptmann et al. (2009) in a nested case-control study with internal referents.

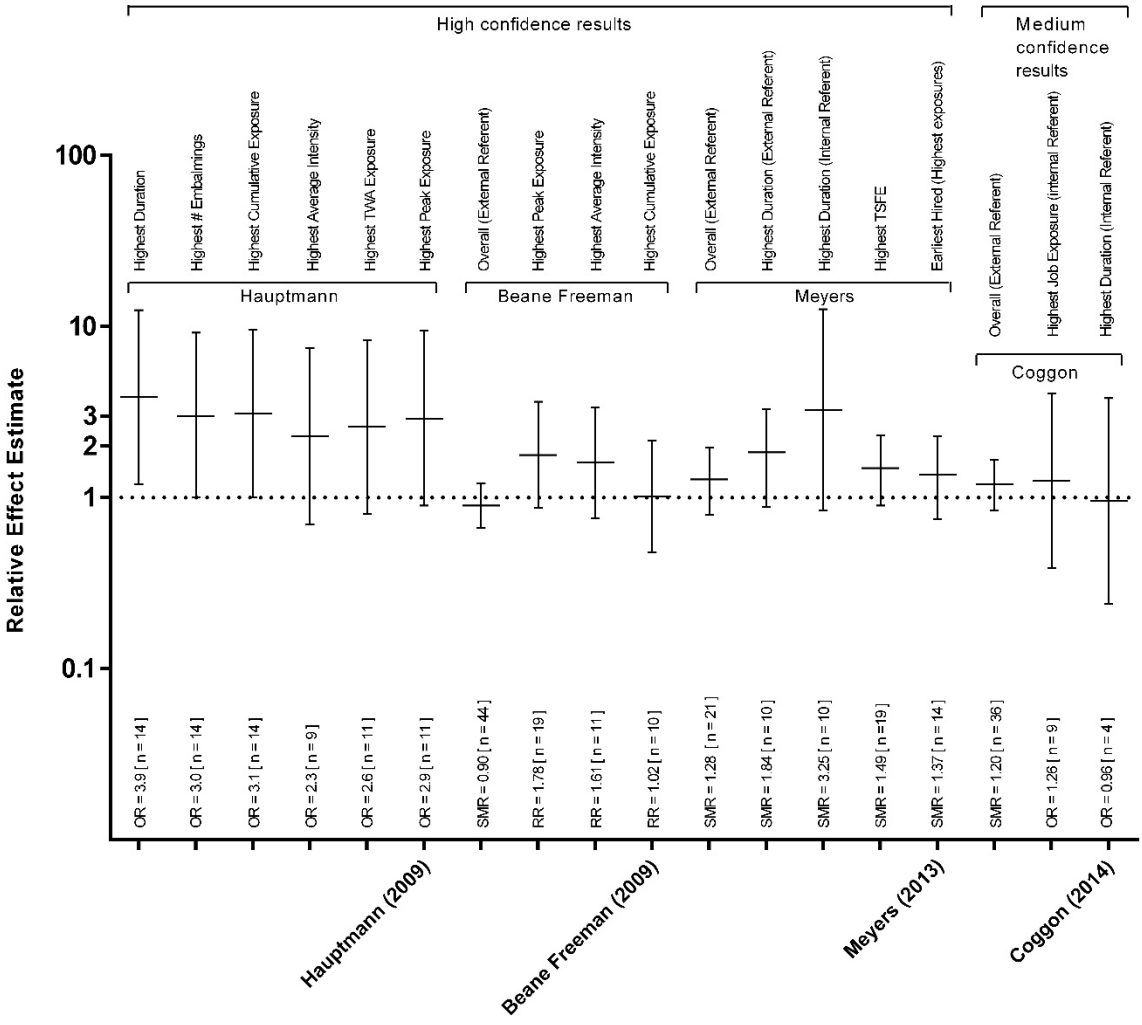


Figure 21. High and medium confidence epidemiological studies reporting myeloid leukemia risk estimates.

OR: odds ratio. RR: relative risk. SMR: standardized mortality ratio. HR: hazard ratio. For each measure of association, the number of exposed cases is provided in brackets (i.e., [*n* = 14]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure.

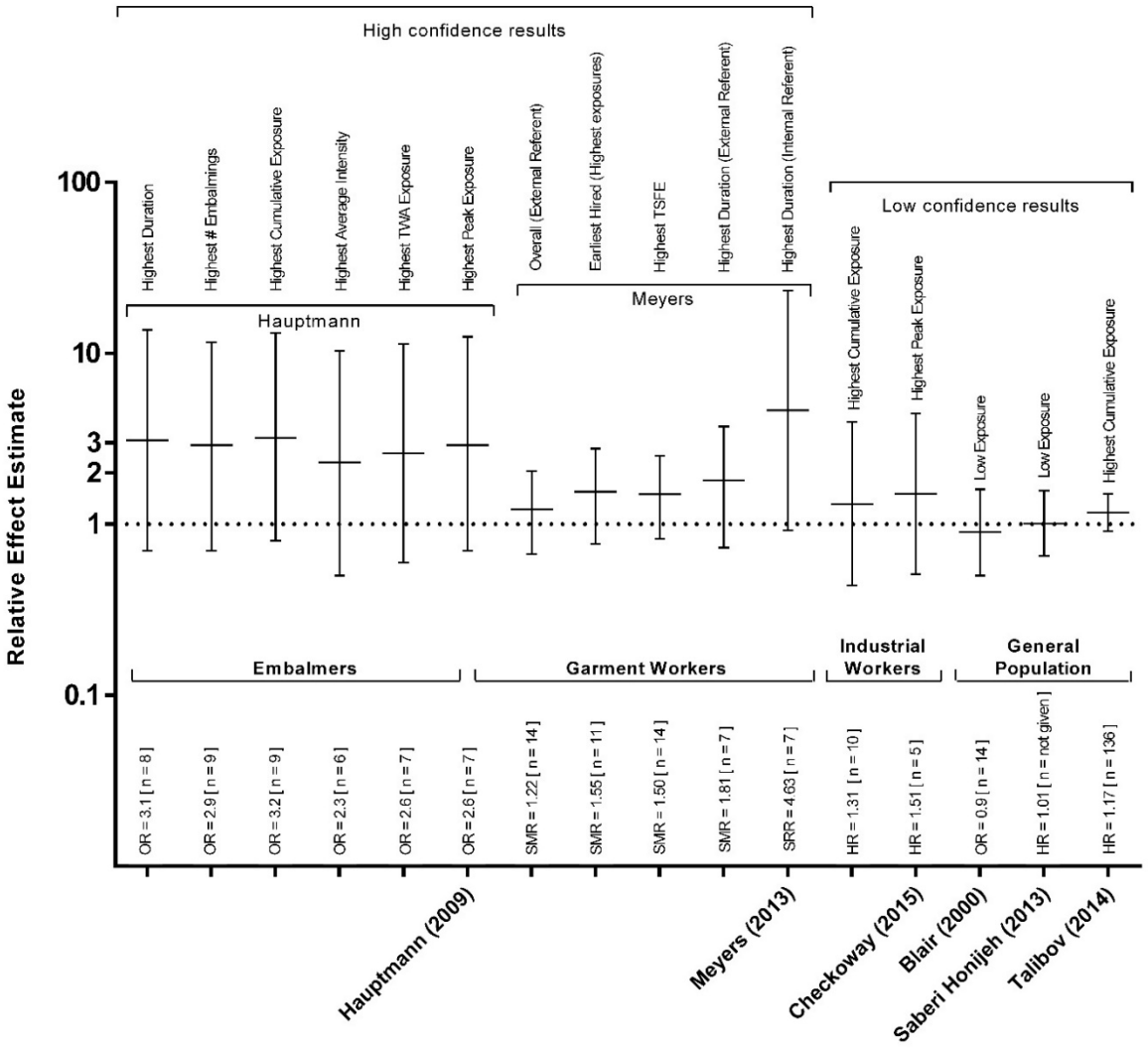


Figure 22. Epidemiological studies reporting acute myeloid leukemia risk estimates.

For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 8]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. Abbreviations: OR = odds ratio; RR = relative risk; SMR = standardized mortality ratio; HR = hazard ratio.

Multiple Myeloma

Evidence describing the association between formaldehyde exposure and the risk of multiple myeloma was available from 14 epidemiological studies: 5 case-control studies (Hauptmann et al., 2009; Heineman et al., 1992; Pottern et al., 1992; Boffetta et al., 1989; Ott et al., 1989) and 9 cohort studies (Coggon et al., 2014; Pira et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009; Stellman et al., 1998; Band et al., 1997; Dell and Teta, 1995; Hayes et al., 1990; Edling et al., 1987).

The results of these studies appear to be mixed with some showing non-significant increases in risk and other showing non-significant decreases in risk. Nine of the 14 studies were low confidence

(Pira et al., 2014; Stellman et al., 1998; Dell and Teta, 1995; Pottern et al., 1992; Boffetta et al., 1989; Ott et al., 1989; Edling et al., 1987) with many results based on fewer than five cases. (see Figure 23). Among all the studies that used individual-level exposure assessment, the study with the highest quality exposure assessment methodology was the National Cancer Institute study (Beane Freeman et al., 2009) among industrial workers. The most pronounced effects in this *high* confidence study showed a two-fold increased risk of mortality from multiple myeloma associated with the highest level of peak exposure to formaldehyde (RR = 2.04; 95% CI: 1.01, 4.12). The evaluation of the study for this review produced reasonable confidence that alternative explanations were ruled out, including chance, bias, and confounding.

The findings by Beane Freeman et al. (2009) are supported by the results of one *medium* confidence study (Hayes et al., 1990) and two *low* confidence studies (Dell and Teta, 1995; Edling et al., 1987), all with population-level exposure assessments. The occupational exposures in the three studies involved very high peaks and were consistent with Beane Freeman et al. (2009) in showing an elevated risk, although none was able to rule out chance. Hauptmann et al. (2009) and Ott et al. (1989) assessed individual-level exposure but only presented results specific to formaldehyde exposures for the study population as a whole. Similarly, the study of garment workers, a *medium* confidence study, Meyers et al. (2013) relied on individual measures of the timing of exposure but did not have formaldehyde concentration data beyond the industrial hygiene data used to plan the study (Stayner et al., 1988). Continuous area monitoring showed that formaldehyde levels were relatively constant with no substantial peak levels over the work shift (Stayner et al., 1988), a possible explanation for differences in results. A set of four studies that assessed individual-level exposure gathered minimal information (e.g., questionnaire data on "ever" exposure to formaldehyde) on formaldehyde exposure and were considered to be *low* confidence (Stellman et al., 1998; Heineman et al., 1992; Pottern et al., 1992; Boffetta et al., 1989). The weaknesses of their relatively imprecise exposure assessment may have precluded their ability to detect an association, thus explaining their generally null results. Overall, the collection of studies with analyses of multiple myeloma found an association with formaldehyde exposure limited to groups of people who experienced high peak exposures.

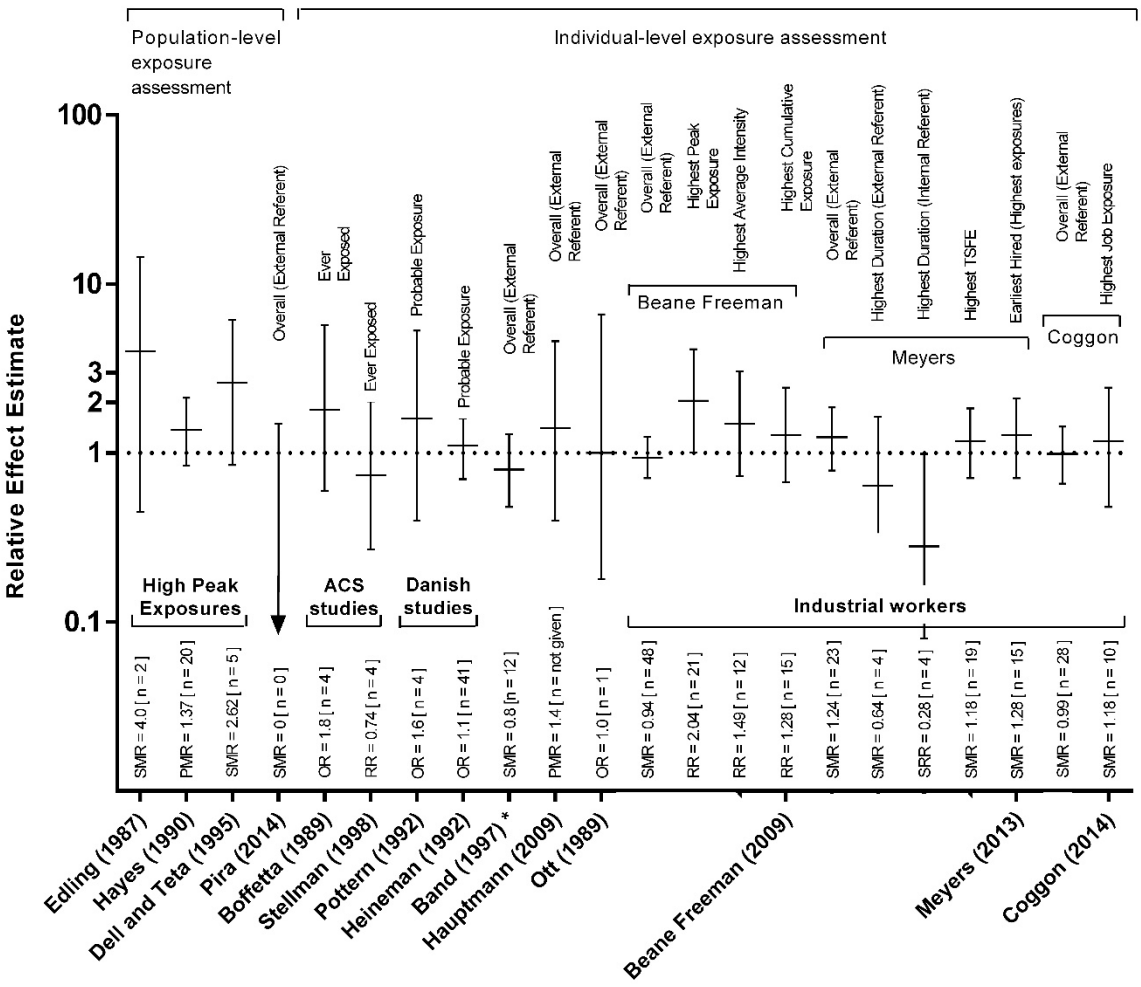


Figure 23. All epidemiological studies reporting multiple myeloma risk estimates.

SMR = standardized mortality ratio; PMR = proportionate mortality ratio; RR = relative risk; OR = odds ratio. For each measure of association, the number of exposed cases is provided in brackets. For studies with multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. *Note that the confidence intervals for Band et al. (1997) are 90% rather than 95%.

Hodgkin lymphoma

Evidence describing the association between formaldehyde exposure and the specific risk of Hodgkin lymphoma was available from 15 epidemiological studies: 1 case-control study (Gérin et al., 1989) and 14 cohort studies (Meyers et al., 2013; Beane Freeman et al., 2009; Coggon et al., 2003; Band et al., 1997; Andjelkovich et al., 1995; Hansen and Olsen, 1995; Hall et al., 1991; Hayes et al., 1990; Matanoski, 1989; Solet et al., 1989; Robinson et al., 1987; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983).

The results of the 12 studies considered to be informative and included in the review were not consistent. The study of the largest cohort of formaldehyde-exposed workers (Beane Freeman et al.,

2009) reported an elevated mortality risk from Hodgkin lymphoma for the cohort as a whole (SMR = 1.42; 95% CI: 0.96, 2.1; 27 cases) and a pronounced increase in risk among those workers with the highest peak formaldehyde exposures (RR = 3.96; 95% CI: 1.31, 12.02; 11 cases)—results that were classified with *medium* confidence. However, the other *medium* confidence result from Gérin et al. (1989) was an OR = 0.5 (95% CI: 0.2, 1.2; 8 cases). The results of the other 10 studies (all *low* confidence) were largely null, based on small numbers of cases and wide confidence intervals. The high survival rate for Hodgkin lymphomas (86%) indicates that mortality data may not be a good proxy for incidence data for this LHP cancer subtype. Given the relatively weak evidence, these data are not illustrated in this Overview.

4.3.2. Synthesis of Animal Health Effect Studies

This section considers incidence data for histopathological lesions associated with leukemia or lymphoma; other evidence supportive of the development of these cancers (e.g., hematological changes) is discussed in the mode-of-action section. Two *medium* or *high* confidence animal bioassays (in addition, two *low* confidence studies are briefly discussed in the Toxicological Review) evaluated the carcinogenic potential of inhaled formaldehyde with respect to lymphohematopoietic (LHP) malignancies (Kamata et al., 1997; Kerns et al., 1983; Battelle, 1982). The majority of formaldehyde exposure studies in animals focused primarily on the respiratory tract and did not provide routine examination of other tissues, preventing their ability to inform leukemia and lymphoma.

The largest and most comprehensive cancer bioassay evaluating formaldehyde inhalation exposure in animals is the chronic study in B6C3F1 mice and F344 rats conducted by Kerns et al., with documentation in the supporting Battelle report (1983; 1982). The cumulative incidence of lymphoma (in B6C3F1 mice) and leukemia (in F344 rats) as indicated in the summary tables of this report are shown in Table 36. The *p*-values reported by the authors were based on a Cox-Tarone test for the comparison that adjusts for reduced survival (Battelle, 1982). There was a suggestion of a possible slightly increased incidence in lymphoma (*p*-value, 0.06) in female mice, and a slightly decreased incidence in leukemia in female rats (*p*-value, 0.006) at the high dose. Taken together with the exposure-induced increases in bone marrow hyperplasia in rats, this represents an area of uncertainty warranting additional study. A separate study in male F344 rats also did not report any significant intergroup differences in non-nasal neoplasms using histopathological evaluations that included tissues relevant to leukemia or lymphoma (Kamata et al., 1997), although specific incidence data were not provided to compare with the results of the more comprehensive bioassay. In addition, high mortality at 18.5 mg/m^3 (the next lower group was 2.43 mg/m^3) limited this study's ability to detect long-term effects (e.g., surviving rats: 0/32 at 28 months; ~3/32 at 24 months). Given the findings in the well-reported bioassay by Kerns et al. (1983; 1982), there is a need for additional animal studies specifically designed to target LHP cancers as the main endpoint.

Table 36. Incidence of hematopoietic cancers in B6C3F1 mice and F344 rats [source: (Kerns et al., 1983; Battelle, 1982)]

Endpoint, species	Sex	Incidence (% incidence)		*p*-values[a]
		0 ppm	18.5 mg/m^3	
Lymphoma, B6C3F1 Mice	Male	0/119 (0%)	0/115 (0%)	
	Female	19/121 (16%)	27/121 (22%)	0.062
Leukemia, F344 Rats	Male	11/120 (9%)	5/120 (4%)	0.690
	Female	11/120 (9%)	7/120 (6%)	0.006

[a]The authors' *p*-values were based on a Cox-Tarone test that adjusts for reduced survival.

While the results of both Kerns et al. (1983; 1982) and Kamata et al. (1997) suggest that LHP cancers do not appear to develop in F344 rats, given the identified limitations of the available studies and the few suggestive changes that were reported (i.e., bone marrow hyperplasia in rats and slight but uncertain increases in lymphomas in mice), it is difficult to draw definitive conclusions (i.e., *indeterminate* evidence) as to whether formaldehyde exposure might be capable of causing leukemia or lymphoma in animals based on the currently available evidence.

4.3.3. Mode-of-action Information

The mechanistic database pertinent to leukemogenesis was evaluated based upon the fundamental assumption that exogenous formaldehyde is not distributed appreciably beyond the portal-of-entry. The available evidence supports some events that could contribute to plausible mechanistic pathways relating formaldehyde exposure to LHP carcinogenesis (summarized in Table 37). However, the database was insufficient to support the evaluation or development of any specific MOA. There is largely consistent and strong evidence linking genotoxicity and mutagenicity in circulating blood cells with formaldehyde exposure in studies of humans. Both temporal and dose-response relationships have been demonstrated in these studies, and mechanistic pathways exist that support a biologically plausible relationship between formaldehyde exposure and cancer, even though the mechanistic pathways explaining such systemic effects are unclear (NRC, 2014b). In addition, the evidence supporting noncancer systemic effects following formaldehyde exposure (e.g., reproductive or developmental toxicity) provides additional plausibility for cancers at systemic sites. It is important to note that systemic delivery of formaldehyde is not a prerequisite for the observed mechanistic changes, as some of the reported systemic effects might result from direct interactions with formaldehyde in the URT, while others could plausibly result indirectly from events such as URT irritation, cytotoxicity, oxidative stress, and inflammation locally initiated at the POE.

Table 37. Summary conclusions regarding plausible mechanistic events associated with formaldehyde induction of lymphohematopoietic cancers

Hypothesized mechanistic event	Experimental support for mechanistic event	Human relevance	Evidence integration considering biological plausibility
Formaldehyde-induced DNA damage to peripheral blood leukocytes	• HSPC aneuploidy and structural chromosome damage in myeloid progenitors (CFU-GMs) from one population of human workers occupationally-exposed to median levels of 1.6 mg/m^3 (Lan et al., 2015; Zhang et al., 2010): ↑ Monosomy and polysomy in multiple chromosomes (especially monosomy 1, 5, 7) consistent with damage observed in patients with MDS or AML (Bassig et al., 2016; Lan et al., 2015); and ↑ breaks, deletions, and translocations in chromosome #5. Assay methodology could not distinguish whether formaldehyde exposure is associated with a potential tendency toward cytotoxicity in CFU-GM cells either in vivo or during the in vitro cell culture period. Inconsistencies in assay protocol reported by Gentry et al. (2013), which were addressed by Rothman et al. (2017). • Deficiencies in progenitor cells (CFU-GM and BFU-E) in exposed mice (Zhao et al., 2020), although results may be confounded by methanol coexposure (*low* confidence) • ↑ genotoxicity or mutagenicity in circulating PBLs from exposed humans, including increases in strand breaks, MN, CA (Costa et al., 2019; Wang et al., 2019; Aglan and Mansour, 2018; Zendehdel et al., 2018; Costa et al., 2015; Peteffi et al., 2015; Kirsch-Volders et al., 2014), NBUDs, or SCE induction at ≥0.14 mg/m^3 (Jiang et al., 2010), and DPX at higher exposures (Lin et al., 2013; Shaham et al., 2003) • ↑ DPX in PBLs from mice (Ye et al., 2013), although results may be confounded by methanol coexposure (*low* confidence) • ↑ MN in human PBLs and buccal cells from exposed humans, and associations with years of exposure, in studies evaluating both tissues (Ladeira et al., 2011; Viegas et al., 2010)	Yes. Evidence comes primarily from exposed humans.	Strong and consistent human data exist associating formaldehyde exposure with various genotoxic outcomes in myeloid progenitors and PBLs, and dose-response relationships demonstrated. Genotoxicity in circulating leukocytes shows concordance with similar endpoints in POE tissues. Aneugenic damage observed in CFU-GMs from formaldehyde-exposed human workers is associated with MDS or AML in humans. Together this evidence constitutes the strongest support for the biological plausibility for LHP cancer induction by formaldehyde.
Evidence of formaldehyde-induced impacts other than genotoxicity on circulating blood cell populations, including inflammatory changes or immune system dysfunction	• ↓ CFU-GM colony formation in human workers occupationally-exposed to median levels of 1.6 mg/m^3 (Zhang et al., 2010), which may reflect not only altered bone marrow progenitor cell viability, but also immune dysfunction or altered activation • Numerous published studies reporting divergent changes in various peripheral blood cell populations from formaldehyde exposed humans, including: ↑ pancytopenia in a few studies and reasonably consistent decreases in total WBCs; ↓ or ↑ in some lymphocyte populations, with decreased CD8 T cells likely at	Yes. Most of the available data come from human studies.	The evidence supporting changes in populations or function of circulating blood leukocytes following human exposure to formaldehyde is strong in terms of a frequency of alterations, but different patterns in changes are reported (e.g., specific direction of changes in various lymphocyte subpopulations, or in blood

Hypothesized mechanistic event	Experimental support for mechanistic event	Human relevance	Evidence integration considering biological plausibility
	concentration >0.5 mg/m^3; and fluctuations in immune cell numbers and immune/inflammation markers show a complex pattern with concentration, with decreases in blood cell number and decreased cytotoxic response generally at higher concentrations, some of which are consistent with observations in AML patients (Kim et al., 2015). Other studies indicate immune cell activation generally observed at lower concentrations ≤0.36 mg/m^3.		levels of soluble signaling mediators). LHP cancer risk increases with loss of normal immune function.
Formaldehyde-induced systemic oxidative stress	• ↑ Malondialdehyde-dG adducts in whole blood DNA from pathologists, compared to workers and students in other science labs (Bono et al., 2010), elevated plasma malondialdehyde (MDA) and plasma p53 associated with each other and with urinary formate concentrations (imprecise marker of formaldehyde exposure) among cosmetics workers (Attia et al., 2014), and ↑ 15-F2t isoprostane levels in the urine of formaldehyde-exposed workers (Romanazzi et al., 2013) • Inconclusive evidence for and against involvement by genes that regulate oxidative stress in formaldehyde associations with DNA damage risk in PBL in humans • ↓ GSH, ↑ ROS, ↑ MDA in bone marrow, peripheral blood mononuclear cells, liver, spleen and testes (Ye et al., 2013), although markers of oxidative stress were not correlated with changes in DPX	Yes. Some human data available, and results from experimental models are presumed relevant to humans without evidence to the contrary.	Limited human and rodent evidence supports the association between formaldehyde exposure and induction of oxidative stress beyond the POE. While biologically plausible, the available evidence is inadequate to determine what role such oxidative stress may play in LHP carcinogenesis.
Formaldehyde-induced changes in the bone marrow niche	• DNA adducts linked to inhaled (exogenous) formaldehyde were not found in the bone marrow of monkeys or rats in studies using highly sensitive detection methods • ↑ Bone marrow hyperplasia in rats from one study (Kerns et al., 1983; Battelle, 1982), unclear if other results were negative or null (Sellakumar et al., 1985); (Kamata et al., 1997) due to imprecise reporting • Dose-related ↑ DPX in the bone marrow of formalin-exposed mice (Ye et al., 2013), although results may be confounded by methanol coexposure • HSPC mobilization and the BM-MSC niche is regulated by cytokines, hormones and signals, which may be distributed through circulation as a result of inflammation; however, these effects have not been directly evaluated following formaldehyde exposure	Yes. Available data are from experimental models presumed relevant to humans.	The limited evidence available is currently inadequate to evaluate any effect on bone marrow or stromal cells following formaldehyde exposure, although such an effect appears consistent with current understanding of hematopoiesis.
Evidence of formaldehyde-induced changes in gene expression or post-transcriptional regulation in peripheral blood	• Limited study reported some statistically significant differences in mRNA expression in either nasal or whole blood samples from human volunteers associated with 5 day exposures up to 1 mg/m^3 formaldehyde, however study limitations prevent interpretation that results were related to formaldehyde exposure (Zeller et al.,	Yes. Available data are from experimental models presumed	Limited rodent evidence supports the association between formaldehyde exposure and epigenetic effects in circulating leukocytes; the available human evidence is

Hypothesized mechanistic event	Experimental support for mechanistic event	Human relevance	Evidence integration considering biological plausibility
leukocytes or bone marrow	2011) In F344 rats, significant changes in both miRNA and mRNA expression were reported in the nasal epithelium and circulating white blood cells following inhalation exposure to 2.5 mg/m^3 formaldehyde for 1 or 4 wks; no changes were observed in miRNA expression in the bone marrow, and mRNA was not evaluated (Rager et al., 2014): "Immune system/inflammation" markers were enriched in both nasal tissue and WBCs at both time points; and ↑ WBC miR-326 expression, associated with bone marrow metastasis in other models (Valencia et al., 2013)	relevant to humans.	inadequate. Insufficient evidence is available to determine what role epigenetics may play in LHP carcinogenesis.

4.3.4. Overall Evidence Integration Judgments and Susceptibility for LHP Cancers

Table 38 summarizes the evidence integration judgments and supporting rationale for the individual LHP cancers.

The strength of the evidence from human studies is *robust* for myeloid leukemia. The assessment of LHP cancers was based on epidemiological studies of groups with occupational formaldehyde levels either in specific work settings (e.g., cohort studies) or in case-control studies. Aneuploidy in chromosomes 1, 5, and 7 in circulating myeloid progenitor cells, considered a potential primary target for LHP carcinogenesis, was associated with occupational formaldehyde exposure. The type of aneuploidies observed in the formaldehyde-exposed asymptomatic human workers are also found in patients with leukemia, specifically MDS and AML, as well as other worker cohorts at increased risk of developing leukemias, which provides support for the plausibility of an association between chronic formaldehyde exposure and leukemogenesis. Moreover, the strong and consistent evidence from a large set of studies that observed mutagenicity in circulating leukocytes of formaldehyde-exposed humans, specifically chromosomal aberrations (CA) and micronucleus (MN) formation, provides additional evidence of biological plausibility for these cancer types. Further support is provided by studies that observed perturbations to immune cell populations in peripheral blood associated with formaldehyde exposure. In particular, decreases in RBCs, WBCs, and platelets, along with a 20% decrease in CFU-GM colony formation in vitro were observed in the same exposed group (Zhang et al., 2010), suggesting both a decrease in the circulating numbers of mature RBCs and WBCs as well as possible decreases in the replicative capacity of myeloblasts.

Increased LHP cancers have not been observed in a well-reported chronic rodent bioassay involving inhalation exposure of both rats and mice to formaldehyde, nor in another rat bioassay that failed to report the incidence of non-nasal neoplastic lesions. Further, positive associations with leukemia have not been reported in rodent studies, although there are notable uncertainties in the available data (i.e., increased bone marrow hyperplasia in rats; slight but uncertain increases in lymphoma in mice; and a general lack of rigorous evaluation of non-respiratory tissues). Thus, there

appears to be a lack of support for the human epidemiological evidence from rodent bioassays, although concordance across species is not necessarily expected (U.S. EPA, 2005a). The apparent lack of consistency in results raises uncertainties about the currently available research results on these diseases, including both how formaldehyde-induced LHP cancers might arise without substantial distribution to target sites. Notably, the available animal evidence was judged as *indeterminate* and not *compelling evidence of no effect* (see assessment Preface), as there are important uncertainties that prevent such an interpretation. Thus, the animal evidence does not detract from the strength of the association between formaldehyde exposure and myeloid leukemia (and related mechanistic changes) in epidemiological studies (NRC, 2014b). Differences in physiology between humans and rodents, as well as the relative insensitivity of rodent models to reflect the human pathogenesis of myeloid leukemia, in particular, may together contribute to the potential lack of concordance between the abundant human epidemiological data and the limited results available from rodent bioassay data.

Taken together, based on the *robust* human evidence , the **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans given appropriate exposure circumstances. Separately, based on a limited number of epidemiological studies and potentially relevant mechanistic evidence in exposed humans, the evidence integration results in a judgment that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause Hodgkin lymphoma and multiple myeloma, given appropriate exposure circumstances. While mechanisms for the induction of myeloid leukemia are yet to be elucidated, they do not appear to require direct interactions between formaldehyde and bone marrow constituents, and either are different in animals or the existing animal models tested thus far do not characterize the complex process leading to cancers in exposed humans. These conclusions were primarily based on epidemiological studies of groups with occupational formaldehyde exposure. Notably, evidence exists to suggest a lack of concordance between chronic rodent bioassays and human epidemiological evidence.

Table 38. Evidence integration summary for effects of formaldehyde inhalation on LHP cancers

Evidence	Evidence judgment	Hazard determination
Myeloid Leukemia		
Human evidence	*Robust* for myeloid leukemia based on: *Human health effect studies:* • Consistent increases in risk across a set of *high* and *medium* confidence, independent studies with varied study designs and populations • Several of these studies demonstrated strong associations (1.5- to 3-fold increase in risk) and clear exposure-response relationships across multiple measures of increasing exposure • The studies possessed a temporal relationship consistent with causality (e.g., allowing time for induction, latency, mortality) *Biological plausibility* (also of potential relevance to LHP cancer types below): Evidence from *high* and *medium* confidence studies of exposed humans	The **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans, given appropriate exposure circumstances[a] This conclusion was primarily based on epidemiology studies of groups with occupational formaldehyde exposure. While evidence exists to

	identifies relevant mechanistic changes for cancers of the blood such as myeloid leukemia, including impacts on peripheral immune cell populations (which seem to be affected in a complex manner), and elevated levels or severity of DNA or chromosomal damage in circulating myeloblasts and mature lymphocyte populations. The DNA damage exhibits aneugenic characteristics similar to that found in humans with, or at increased risk for, AML.	suggest a lack of concordance between chronic rodent bioassays and human epidemiological evidence, notable uncertainties prevent an animal evidence judgment of compelling evidence of no effect *Potential susceptibilities:* There is no evidence to evaluate the potential risk to sensitive populations or lifestages
Animal evidence	*Indeterminate* for *any LHP cancer type*, based on: *Animal health effect studies:* Overall, the available data do not provide evidence supporting the development of LHP cancers in a *high* confidence chronic bioassay of rats and mice, a second *medium* confidence rat bioassay, and two other *low* confidence, long-term exposure studies. *Biological plausibility:* Although some potentially relevant changes have been observed in mechanistic studies of exposed animals (e.g., inflammatory and immune changes in systemic tissues and bone marrow hyperplasia in rats), the evidence related to genotoxicity (i.e., in systemic tissues) or other more directly relevant changes were weak (e.g., only in *low* confidence studies) or not observed and, overall, the mechanistic data do not suggest a judgment other than *indeterminate* for LHP cancers in animals.	
Other Inferences	• *Relevance to humans:* The evidence is from studies in humans. • *MOA:* No MOA exists to explain how formaldehyde might cause LHP cancers without systemic distribution (i.e., without direct interactions of inhaled formaldehyde with constituents in bone marrow tissue); however, given the mechanistic changes in exposed humans, it is reasonable to infer that an undefined MOA is likely to involve modulatory effects on circulating immune cells.	
Multiple myeloma		
Human evidence	*Slight* for multiple myeloma, based on: *Human health effect studies:* • Increases in risk associated with peak exposure metrics across one *high*, one *medium*, and two *low* confidence studies; no associations with other exposure metrics • Increases spanned an approximate 1.2- to 4-fold increase in risk, with the highest confidence evidence showing a 2-fold increase • Very limited evidence of an exposure-response relationship in one *high* confidence study • However, risks may have been driven by peak exposures as increases were limited to groups of people who experienced high peak exposures, and two *low* confidence studies reported inverse relationships with duration of exposure	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma given appropriate exposure circumstances[b]
Animal evidence	*Indeterminate* (for any LHP cancer type): See explanation for myeloid leukemia	
Other Inferences	• *Relevance to humans:* The evidence is from studies in humans. • *MOA:* No MOA exists to explain how formaldehyde might cause LHP cancers without systemic distribution	
Hodgkin lymphoma		
Human evidence	*Slight* for Hodgkin lymphoma, based on: *Human health effect studies:*	The **evidence suggests**, but is not sufficient to infer, that

	• Significantly increased risk in the highest peak exposure group alongside an exposure-response relationship in one *medium* confidence study of industrial workers • An inconsistent pattern of risks across 1 *medium* and the *low* confidence studies, many with <5 exposed cases • The high survival rate for Hodgkin lymphoma may indicate that mortality data are not a good proxy for incidence.	formaldehyde inhalation might cause Hodgkin lymphoma given appropriate exposure circumstances[b]
Animal evidence	*Indeterminate* (for any LHP cancer type): See explanation for myeloid leukemia	
Other inferences	• *Relevance to humans:* The evidence is from studies in humans. • *MOA:* No MOA exists to explain how formaldehyde might cause LHP cancers without systemic distribution	

Note: Lymphatic leukemia evidence is not presented in this Overview (see Section 1.3.3 of the Toxicological Review).
[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis (Section 4.5).
[b]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define what might be the "appropriate exposure circumstances" for developing this outcome.

4.4. WEIGHT-OF-EVIDENCE SUMMARY FOR CARCINOGENICITY

"Formaldehyde is <u>Carcinogenic</u> to Humans by the Inhalation Route of Exposure"

This conclusion is independently supported by three evidence integration judgments, namely that the **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia in exposed humans given appropriate exposure circumstances.

These overall evidence integration judgments, as well as the strength of the human and animal evidence (i.e., *robust, moderate, slight, indeterminate*), were based on the currently available evidence using the approaches presented in the description of methods in the Introduction to this Overview (Section 1), which included a consideration of mechanistic evidence when drawing each conclusion.

4.4.1. Weight-of-evidence Narrative Summary

The carcinogenicity conclusion is independently supported by three evidence integration judgments:

- The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer (NPC) in humans. This is based primarily on observations of increased risk of NPC in groups exposed to occupational formaldehyde levels and nasal cancers in mice and several strains of rats, 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 the animal data). The nasopharynx, although not typically specified in animal studies, is the region adjacent to the nasal cavity, where the animal evidence was predominantly observed (thus, the animal evidence is judged as *robust*). In addition, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity.

- The **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer (SNC) in humans. This is based primarily on observations of increased risk of SNC in groups exposed to occupational formaldehyde levels (i.e., *robust* human evidence) and supported by apical and

mechanistic evidence for nasal cancers across multiple animal species. Some uncertainties remain in the interpretation of the animal nasal cavity data as wholly applicable to interpreting human sinonasal cancer (thus, the animal evidence is judged as *moderate*). In addition, while uncertainties remain, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced sinonasal carcinogenicity.

- The **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans. This is based primarily 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**). The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.

Other information

The remaining evidence relevant to evaluating the potential for formaldehyde inhalation to cause cancer (see Sections 4.2 and 4.3) did not contribute to the carcinogenicity conclusion above, including evaluations of oropharyngeal/hypopharyngeal cancer, Hodgkin lymphoma, and multiple myeloma (the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause these types of cancers given appropriate exposure circumstances), and of laryngeal cancer and lymphatic leukemia (there is **inadequate evidence** to determine whether formaldehyde inhalation may be capable of causing these types of cancers in humans; evidence not presented in this Overview).

4.5. INHALATION UNIT RISK (IUR) FOR CARCINOGENICITY

Unit risk estimates for cancer were derived from different data sets available from both epidemiological and experimental animal studies. In addition, an approach to bound low-dose cancer risks from formaldehyde exposure using DNA adduct concentrations in nasal epithelium and bone marrow from animal experiments and U.S. cancer incidence statistics (a "bottom-up" approach) is summarized to provide some perspective on the uncertainty in extrapolating from high-dose animal toxicology or human occupational data (Starr and Swenberg, 2016, 2013). Unit risk estimates could be derived for two cancer types for which the evidence supporting a human health hazard was sufficiently strong: nasal cancers (i.e., nasopharyngeal cancer in human studies; nasal squamous cell carcinoma in experimental animal studies) and myeloid leukemia.

Specifically, unit risk estimates were derived based on dose-response modeling of mortality and cumulative formaldehyde exposure for nasopharyngeal cancer (NPC) and myeloid leukemia in a human

occupational cohort. Cumulative exposure, which incorporates both average concentration and the duration of time over which exposure occurred, is generally the preferred metric for quantitative estimates of lifetime risk from environmental exposure to carcinogens, and thus cumulative exposure was chosen as the exposure metric for calculations in this assessment. The "true" exposure metric best describing the biologically relevant delivered dose of formaldehyde is unknown. Few epidemiological studies presented dose-response analyses based on cumulative measures of formaldehyde concentration that could support the derivation of unit risk estimates; estimates were derived only for NPC and myeloid leukemia.

In experimental animals, multiple approaches, including biologically based dose-response (BBDR) modeling, and statistical time-to-tumor modeling, were used to derive unit risk estimates based on data in rats. Results from the different approaches were evaluated and compared. In addition, other approaches based on mechanistic hypotheses, including derivation of cRfCs based solely on cell proliferation (one mechanism that contributes to cancer risk) and assessing the potential impacts of endogenous formaldehyde concentration on dosimetric estimates, were explored quantitatively and compared.

The unit risk estimates from the well-conducted human occupational study were preferred. However, while the estimates for nasopharyngeal cancer and myeloid leukemia could be combined to derive an IUR for formaldehyde, there is considerable scientific uncertainty in the data used to estimate a unit risk for myeloid leukemia. Therefore, the unit risk estimate for myeloid leukemia is not included in the IUR calculation in this draft assessment. The following sections outline the best supported approaches for each cancer subtype based on the data currently available. The strengths and weaknesses of the statistical approaches, as well as the rationale supporting each estimate, are presented, including scientific judgments of confidence in the estimates for each cancer type.

4.5.1. Derivation of Cancer Unit Risk Estimates for Nasal Cancers

Derivation of a nasal cancer unit risk estimate based on human data

The quantitative analysis of nasal cancer from epidemiological studies is based on the NPC results from the latest follow-up of the NCI cohort of industrial workers exposed to formaldehyde (Beane Freeman et al., 2013). While the evidence supporting a human health hazard from sinonasal cancer from studies in occupational cohorts and experimental animals also was sufficiently strong, it was not possible to derive a unit risk estimate for this cancer types. Out of almost 14,000 deaths observed in the NCI cohort, there were 10 deaths from NPC and 5 deaths from cancers of the nose and nasal sinus. Only the data for NPC could be modeled with adequate precision. The NCI cohort study is the largest of the three independent industrial worker cohort studies [the other two being Meyers et al. (2013) and Coggon et al. (2014)] and, more importantly, it is the only one with sufficient individual exposure data for dose-response modeling. In addition, the NCI study is the only one that used internal comparisons

rather than standardized mortality ratios (SMRs), thus minimizing the potential impact of the healthy worker effect by addressing unmeasured confounding, which can bias effect estimates.

The NCI cohort consists of 25,619 workers (88% male) employed prior to 1966 in any of the 10 plants in the study. The most recent follow-up, based on 998,239 person-years of observation (through 2004) reported a total of 13,951 deaths (Beane Freeman et al., 2013). Beane Freeman et al. (2013) analyzed 10 deaths from NPC as well as deaths from other solid tumors. A detailed exposure assessment was conducted for each worker in the NCI cohort, based on exposure estimates for different jobs held and tasks performed (Stewart et al., 1986). Exposure estimates were made using several different metrics—peak exposure,[11] average intensity, cumulative exposure, and duration of exposure. Respirator use and exposures to formaldehyde-containing particulates and other chemicals were also considered.

Dose-response modeling of data from the NCI cohort

The results of the internal analyses (i.e., comparing exposed workers to an internal referent group of other workers in the cohort) of Beane Freeman et al. (2013) for NPC using the cumulative exposure metric are presented in Table 39. The relative risks (RRs) were estimated using log-linear Poisson regression models stratified by calendar year, age, sex, and race and adjusted for pay category. Beane Freeman et al. (2013) used a 15-year lag interval in estimating exposures to account for a latency period for the development of solid cancers, including NPCs. Models with alternative lag intervals (2–20 years) produced similar results. The NCI investigators used the low-exposure category as the reference category to "minimize the impact of any unmeasured confounding variables since nonexposed workers may differ from exposed workers with respect to socioeconomic characteristics" (Hauptmann et al., 2004). In this review, the nonexposed person-years were included in the primary cancer risk analyses to be more inclusive of all the dose-response data. The analyses adjusted for pay category, a measure of socioeconomic status, thus possible SES differences between exposed and nonexposed were at least partially addressed. Final results for the exposed person-years only are also presented for comparison.

Cumulative exposure was included as a continuous variable in the log-linear models analyzed by Beane Freeman et al. (2013) (general model form: $RR = e^{\beta X}$, where β represents the regression coefficient and X is exposure). The regression coefficients are presented in Table 39.

[11]Some of the strongest exposure-response relationships in the NCI cohort (Beane Freeman et al., 2013) (e.g., for NPC) were observed for the peak exposure metric. It is not clear how to extrapolate RR estimates based on peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from continuous exposure to low environmental levels. If a short-term (<15 minute) excursion above the 8-hour TWA concentration for a job was observed, or expected based on industrial hygiene expertise, then that job was assigned to a peak exposure category, namely none, >0 to <0.5 ppm, 0.5 to <2.0 ppm, 2.0 to <4.0 ppm, or ≥4.0 ppm. Individual workers may have experienced these peak concentrations rarely, intermittently, or routinely, and in jobs they held for a long time or only briefly. At a given time point, a worker's peak exposure estimate is the highest peak exposure category ever attained by the worker. As such, this exposure metric is not interpretable in terms of a lifetime exposure risk.

Table 39. Relative risk estimates for mortality from NPC (based on ICD code) and regression coefficients from NCI log-linear trend test models[a] by level of cumulative formaldehyde exposure (ppm × years). Source: Beane Freeman et al. (2013)

Relative risk estimates for nasopharyngeal cancer	**Rate ratio (number of deaths)**				***p*-trend, all person-years[b]**	***p*-trend, exposed person-years[c]**
	0	**>0 to <1.5[d]**	**1.5 to <5.5**	**>5.5**		
	1.87 (2)	1.0 (4)	0.86 (1)	2.94 (3)	0.07	0.06
Regression coefficients for nasopharyngeal cancer	**Person-years**	**β (per ppm × year)[e]**		**Standard error (per ppm × year)[e]**		
	All	0.04311		0.01865		
	Exposed only	0.0439		0.01852		

[a]Models stratified by calendar year, age, sex, and race and adjusted for pay category; cumulative exposures calculated using a 15-year lag interval for NPC and a 2-year lag interval for LHP cancer types.
[b]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (as a continuous variable) among all (nonexposed and exposed) person-years.
[c]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (as a continuous variable) among exposed person-years only.
[d]Reference category for all categories.
[e]Source: Personal communications from Laura Beane Freeman to Jennifer Jinot (February 22, 2013 and February 21, 2014) and to John Whalan (August 26, 2009).

Prediction of lifetime extra risk of nasopharyngeal cancer mortality

To predict the extra risk of NPC mortality from environmental exposure to formaldehyde:

$$\text{Extra risk} = (Rx - Ro) \div (1 - Ro)$$

where Rx is the lifetime risk in the exposed population and Ro is the lifetime risk in an unexposed population (i.e., the background risk). Extra risk estimates were calculated using the β regression coefficients and a life table program that accounts for competing causes of death.[12] U.S. age-specific 2010 all-cause mortality rates and 2000–2010[13] NPC mortality rates for all race and sex groups combined were used to specify the all-cause and cause-specific background mortality rates in the life table program. Risks were computed up to age 85 years because cause-specific mortality (and incidence) rates for ages above that are less reliable. Conversions between occupational formaldehyde exposures and continuous environmental exposures were made to account for differences in the number of days exposed per year (240 versus 365) and in the amount of air inhaled per day (10 versus 20 m^3). An adjustment was also made for the 15-year lag period. The reported standard errors for the regression coefficients were used to compute the one-sided 95% upper confidence limits (UCLs) for the extra risks based on a normal approximation.

[12]This program is an adaptation of the approach that was previously used in BEIR IV, "Health Risks of Radon and Other Internally Deposited Alpha Emitters." National Academy Press, Washington, DC, 1988, pp. 131–134.
[13]Typically, 5-year ranges are used as the basis for population cause-specific disease and mortality rates; a larger range is used here to get better stability in the rates because NPC is a rare cancer.

Consistent with EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), the life table program was used to estimate the exposure level (effective concentration [EC_x]) and the associated (one-sided) 95% lower confidence limit (LEC_x) corresponding to an extra risk of 0.05% (x = 0.0005). Although EPA guidelines emphasize the use of exposure levels associated with a 10% extra risk level for the POD for low-dose extrapolation, for epidemiological studies, this can result in the need to extrapolate upward to risks well above those that were observed in the study populations. Thus, a 1% extra risk level is typically used for epidemiological data. However, NPC has a very low background mortality rate (e.g., lifetime background risk is about 0.00019); therefore, even a 1% extra risk (i.e., 0.01) would be a large increase relative to the background risk. This is consistent with the fact that, even with a large cohort followed for a long time, only 10 NPC deaths were observed in the NCI follow-up through 2004.[14] Based on the life table program, the 1% level of risk for NPC mortality is associated with an RR estimate of 53, a level substantially higher than was observed in the epidemiological study. A 0.05% extra risk level yields an RR estimate of 3.6, which better reflects the RRs in the range of the data. Thus, 0.05% extra risk was selected for determination of the POD, and the LEC value corresponding to that risk level was used as the POD.

Because formaldehyde is a mutagenic carcinogen and the weight of evidence supports the conclusion that formaldehyde carcinogenicity for URT cancers can be attributed, at least in part, to a mutagenic MOA, a linear low-dose extrapolation was performed in accordance with EPA's cancer guidelines (U.S. EPA, 2005a). The EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for NPC mortality are presented in Table 40.

Table 40. EC_{0005}, LEC_{0005}, and unit risk estimates for nasopharyngeal cancer mortality based on the Beane Freeman et al. (2013) log-linear trend analyses for cumulative formaldehyde exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.191	0.112	4.5×10^{-3}	3.7×10^{-3}
Exposed only	0.187	0.111	4.5×10^{-3}	3.7×10^{-3}

[a]Unit risk = $0.0005/LEC_{0005}$.

Prediction of lifetime extra risk of nasopharyngeal cancer incidence

EPA cancer risk estimates are typically derived to represent a plausible upper bound on increased risk of cancer incidence, as from experimental animal incidence data. Cancer data from epidemiological studies are more often mortality data, as is the case in the NCI study. For cancers with low survival rates, mortality-based estimates are reasonable approximations of cancer incidence risk.

[14]Eleven NPCs were reported on death certificates and included in NCI's SMR analyses, but one of these cases was apparently misclassified on the death certificate, so only 10 cases were used to estimate the RRs in the internal comparison analyses (Beane Freeman et al., 2013).

However, for NPC, the survival rate is substantial [51% at 5 years in the 1990s in the United States, according to Lee and Ko (2005)], and incidence-based risks are preferred because EPA is concerned with cancer occurrence, not just cancer mortality.

Therefore, an additional calculation was done using the same regression coefficients provided by Dr. Beane Freeman but with age-specific NPC incidence rates for 2000–2010 from NCI's Surveillance, Epidemiology, and End Results (SEER) Program in place of the NPC mortality rates in the life table program (www.seer.cancer.gov). The incidence-based calculation relies on the reasonable assumptions that NPC incidence and mortality have the same dose-response relationship for formaldehyde exposure and that the incidence data are for first occurrences of NPC or that relapses provide a negligible contribution. The calculation also takes advantage of the fact that NPC incidence rates are negligible compared with the all-cause mortality rates and thus no special adjustment to the population at risk to account for live individuals who have been diagnosed with NPC is necessary.

The resulting EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for NPC incidence are presented in Table 41. The unit risk estimate for cancer incidence is two-fold higher than the corresponding mortality-based estimate, for all person-years, reflecting the high survival rates for NPC.

Table 41. EC_{0005}, LEC_{0005}, and unit risk estimates for nasopharyngeal cancer incidence based on the Beane Freeman et al. (2013) log-linear trend analyses for cumulative formaldehyde exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.0942	0.0550	9.1×10^{-3}	7.4×10^{-3}
Exposed only	0.0925	0.0546	9.2×10^{-3}	7.5×10^{-3}

[a]Unit risk = $0.0005/LEC_{0005}$.

The preferred estimate for the inhalation cancer unit risk for NPC is the estimate of 9.1×10^{-3} per ppm derived using incidence rates for the cause-specific background rates, for all person-years. The results from the exposed person-years are essentially identical.

Because NPC is a rare cancer in the United States, with a relatively low number of cases occurring per year, a rough calculation was done to ensure that the unit risk estimate derived for NPC incidence is not implausible in comparison to actual case numbers. For example, assuming an average constant lifetime formaldehyde exposure level of 5 ppb for the U.S. population (probably at the very low end of potential lifetime averages) the inhalation unit risk estimate for NPC equates to a lifetime extra risk estimate of 4.6×10^{-5}. Assuming an average lifetime of 75 years (this is not EPA's default average lifetime of 70 years but rather a value more representative of actual demographic data) and a U.S. population of 300,000,000, this lifetime extra risk estimate suggests a crude upper-bound estimate of 180 incident cases of NPC attributable to formaldehyde exposure per year. Alternatively, for 20 ppb (probably toward the upper end of potential lifetime averages), the calculation suggests a crude upper-

bound estimate of 730 incident cases of NPC per year. Both upper-bound estimates, using different assumed lifetime exposure levels, are well below the estimated 2,300 total incident NPC cases per year calculated from the SEER NPC incidence rate of 0.75/100,000.[15,16]

Dose-response modeling of nasal SCC tumor incidence in the F344 rat

Dose-response analyses of cancer risk were calculated using conventional multistage-Weibull time-to-tumor modeling and a biologically based clonal expansion model of cancer, both based on nasal squamous cell carcinoma (SCC) incidence data from laboratory bioassays using F344 rats. The biologically based modeling was informed by a large body of mechanistic data on cell replication, DNA protein cross-link (DPX) and DNA monoadduct formation, and dosimetry modeling of formaldehyde flux to local tissue, and was therefore considered useful to provide potential information on the shape of the dose-response curve as well as the interpretation and extrapolation of results from the rat bioassays to humans.

These models were employed to derive multiple PODs and corresponding human equivalent concentrations. Unit risks derived by straight line extrapolation from a point of departure as well as a candidate RfC (cRfC) derived from these human equivalent concentrations were presented, with the cRfC interpreted as the concentration below which nasal cancers arising from increased cell proliferation due to cytotoxicity are unlikely to occur (some researchers have argued that protection against this putative precursor event is sufficient to prevent a cancer response). cRfCs for this mechanism contributing to cancer were also derived from modeling of data on cell proliferation and basal hyperplasia in F344 rats and Wistar rats, respectively.

Approaches to modeling the animal nasal tumor incidence

An increased incidence of nasal SCCs was seen in two long-term bioassays using F344 rats (Monticello et al., 1996; Kerns et al., 1983; Battelle, 1982), with similar incidences between the two studies even though they were conducted 13 years apart (and similar incidences between males and females in Kerns et al. (1983; 1982), which tested both sexes). Therefore, for greater power in dose-response analysis, these data were combined (see Table 42).

[15]This crude NPC incidence rate is similar to a published NPC incidence rate for the United States of 0.7/100,000 person-years (Lee and Ko, 2005). The age-adjusted NPC incidence rate from SEER was also 0.75/100,000.

[16]With the application of age-dependent adjustment factors, the lifetime unit risk estimate for NPC would increase by a factor of 1.42, and the crude upper-bound estimates of the incident cases per year attributable to formaldehyde exposure would similarly increase by a factor of 1.42. The resulting adjusted upper-bound estimates of 260 and 1,030 for 5- and 20-ppb exposure levels, respectively, are still well below the estimated total number of 2,300 incident cases per year in the United States.

Table 42. F344 rat nasal cancer data

Formaldehyde exposure levels	Incidence of SCC tumors	References
0, 0.7, 2.0, 6.01, 9.93, and 14.96 ppm (0, 0.86, 2.5, 7.4, 12.2, and 18.4 mg/m^3)	0/341, 0/107, 0/353, 3/343, 22/103, 162/386	(Kerns et al., 1983; Battelle, 1982) & (Monticello et al., 1996) (combined bioassays)

Several models (described below) were used to calculate BMCs and the corresponding BMCLs (95% lower confidence bounds on dose) at a benchmark response (BMR) level at the lowest end of the range of the observed data [(U.S. EPA, 2012); see Table 43]. Benchmark concentrations at the 0.005 as well as 0.01 extra risk levels were determined with the BBDR models. The BMCs and corresponding BMCLs were then converted to their human equivalent concentrations (HECs) based on formaldehyde flux to the nasal tissue obtained using computational fluid dynamic (CFD) modeling in the rat and human (Kimbell et al., 2001b). The HEC corresponding to a particular benchmark level in the rat was then calculated by assuming that continuous lifetime exposure to a given steady-state flux of formaldehyde leads to equivalent risk of nasal cancer across species. This extrapolation included an adjustment to the laboratory exposure regimen for continuous exposure (multiplication by 6/24 × 5/7).

Table 43. Benchmark concentrations and human equivalents using formaldehyde flux to nasal tissue as a dose-metric

	Rat benchmark conc. (ppm)						Human equivalent conc. (ppm)[a]				
		Extra risk[b]						Extra risk[b]			
Models		0.005	0.01	0.05	0.1	Dose metric[a]		0.005	0.01	0.05	0.1
Multistage Weibull time-to-tumor	EC LEC		4.28 3.57	5.93 5.52	6.84 6.41	Flux	EC LEC		0.35 0.30	0.49 0.46	0.57 0.53
Weibull with threshold Schlosser et al. (2003)	EC LEC		5.91 5.58	6.12 5.94	6.40 6.22	Flux	EC LEC		0.75 0.71	0.78 0.76	0.82 0.79
Rat BBDR "model 1"[c]	EC LEC	4.99[d] 4.95	5.37[d] 5.19			Flux	EC LEC	0.42 0.41	0.45 0.43		
Rat BBDR "model 2"[c]	EC LEC	5.41 5.25	5.75 5.59			Flux	EC LEC	0.45 0.44	0.48 0.46		

EC=BMC and LEC=BMCL at the specified extra risk; these abbreviations are used here to facilitate comparisons to the modeling of the human data.

[a]The human equivalent benchmark concentrations decrease by a factor of 1.4 if flux estimates based on Schroeter et al. (2014) are used instead of Kimbell et al. (2001b).

[b]The BMR of 0.005 is lower than the value of 0.0085 corresponding to the lowest observed tumor response, corrected for survival, and was used only with the BBDR modeling because these models incorporate precursor response data related to cellular proliferation. Because benchmark concentrations at 0.005 and 0.010 extra risk levels were reported, they were not calculated at the higher levels when BBDR modeling was used.

[c]See text for a description of models 1 and 2.
[d]Benchmark concentrations corresponding to the hockey-stick model in Conolly et al. (2003) as discerned from Figure 5 of their paper were EC_{005} = 4.84 ppm and EC_{01} = 5.48 ppm. LEC levels could not be estimated since confidence bounds were not reported by these authors.

Weibull time-to-tumor modeling

Because higher exposures were associated with both earlier tumor occurrence and increased mortality in the rats, methods that can reflect the influence of competing risks and intercurrent mortality on site-specific tumor incidence rates were preferred. For this reason, EPA used the multistage Weibull time-to-tumor model (Portier and Bailer, 1989; Krewski et al., 1983), which (a) modeled the replicate animal data, (b) included the exact time of observation of the tumors and therefore gave appropriate weight to the amount of time each animal was on study without a tumor, and (c) acknowledged earlier tumor incidence with increasing dose level.

Weibull modeling of the grouped incidence data assuming a threshold in dose

This assessment also presents results from statistical modeling of the same data by Schlosser et al. (2003) in Table 43. These authors did not carry out a time-to-tumor analysis of the individual animal data but applied a Kaplan-Meier survival adjustment of the grouped incidence data. The best fit in Schlosser et al. (2003) was obtained with the polynomial and Weibull (shown) models for the tumor incidence data with a nonzero intercept (threshold) on the dose axis.

Biologically based dose-response modeling

A biologically based dose-response (BBDR) time-to-tumor model for the formaldehyde-induced rat nasal tumors was available (Conolly et al., 2003; CIIT, 1999). This model consisted of interfacing dosimetry models for formaldehyde and formaldehyde-induced DPX in the rat nasal passages (Kimbell et al., 2001a; Kimbell et al., 2001b; Conolly et al., 2000) with two-stage clonal expansion (TSCE) models for predicting the probability of occurrence of nasal SCC (Conolly et al., 2003). Formaldehyde-induced changes in cell replication and DPX concentrations were considered a function of local formaldehyde flux to each region of nasal tissue as predicted by computational fluid dynamics (CFD) modeling on anatomically accurate representations of the nasal passages of a single F344 rat. DPX tissue concentrations were calculated in Conolly et al. (2003) using a physiologically based pharmacokinetic model developed in Conolly et al. (2000). In addition to the data from the two tumor bioassays, these authors included all historical control data on 7,684 animals obtained from National Toxicology Program F344 rat inhalation and oral bioassays. Conolly et al. (2003) characterized the dose-response for cell replication rates as a J-shaped curve, indicating that at low exposure concentrations cell division rates decreased below that determined for the unexposed case. In addition, these authors used a hockey stick shaped curve such that the dose-response for cell division rates remained changed from the baseline only at 6 ppm and higher exposure concentrations. This resulted in more conservative estimates of risk when used in the clonal expansion model for cancer. The BBDR models for the rat used

here for the purpose of calculating benchmark concentrations were based on Conolly et al. (2003) with the following modifications.

"Model 1" presented in Table 43 was based on the more conservative, "hockey stick", model in Conolly et al. (2003), with one critical modification. Conolly et al. (2003) added historical control data from *all* NTP studies to the concurrent controls, whereas the model used here included historical data from only the inhalation route of exposure.[17]

"Model 2" presented in Table 43 made major modifications to Conolly et al. (2003) in regard to model structure as well as values for input parameters: (1) the shape of the dose-response for the division rates of normal cells as a function of formaldehyde flux, α_N(flux), was monotone increasing without a threshold in dose, and obtained by fitting the cell replication data for 13-week exposure duration in Monticello et al. (1996); (2) the dose-response for the division rates of initiated cells was assumed to be a sigmoid-shaped curve, increasing monotonically with flux; (3) the death rate of an initiated cell was assumed to be proportional to its division rate at all formaldehyde flux values and given by β_I(flux) = $\kappa \cdot \alpha_I$(flux), where κ is an unknown estimated constant of proportionality; and (4) as in model 1, only historical controls from NTP inhalation studies were added to the concurrent controls.

Estimated impact of a revised dosimetry model incorporating endogenous formaldehyde

Schroeter et al. (2014) revised the dosimetry model of Kimbell et al., used for the flux estimates in the table above, to include endogenous formaldehyde production and to explicitly model formaldehyde pharmacokinetics in the respiratory mucosa. EPA estimated the extent to which the results in the above table change if flux estimates from Schroeter et al. (2014) were used. The average flux over non-squamous regions of the rat nose was roughly one-third[18] of that in the human based on the dosimetry in Schroeter et al. (2014) in which endogenous formaldehyde was taken into account, compared to a ratio of roughly one-half based on the dosimetry in Kimbell et al. (2001b). As a result, the benchmark concentrations calculated in the above table were not appreciably altered (decreasing by roughly a factor of 1.4[19]) if the revised dosimetry model by Schroeter et al. (2014) was applied.

Threshold-based RfC approach for precursor lesion data in the rat: cell proliferation and hyperplasia

The highly curvilinear and steeply increasing dose-responses for DPX formation and cell proliferation, concomitant with the highly nonlinear observed tumor incidence in the F344 rat, have led to mechanistic arguments that formaldehyde's nasal carcinogenicity arises only in response to significant cytotoxicity-induced regenerative cell proliferation (Conolly et al., 2002; Morgan, 1997). In particular, Conolly et al. (2003) and Conolly et al. (2004) inferred from BBDR modeling results that the

[17]In accordance with generally accepted practice when using historical controls (Peddada et al., 2007; Haseman, 1995).
[18]0.33 at 0.1 ppm, 0.32 at 1 ppm.
[19]This is only approximate because the various components of the BBDR modeling were not recalibrated or rerun in light of the revised flux estimates for both species. Furthermore, the above estimate is for resting inspiration, whereas the human flux values in this assessment pertain to an equal apportionment of sleeping, sitting, and light activity levels.

direct mutagenicity of formaldehyde is not an important contributor compared to the importance of cytotoxicity-induced cell proliferation in explaining the rat tumor response. Thus, candidate RfCs (cRfCs) derived from available experimental data relevant to this mechanism were presented and discussed.

The interpretation of these cRfCs was that they may help identify formaldehyde concentrations below which it is unlikely that hyperplastic lesions develop or that cancers arising from cytotoxicity-induced regenerative cell proliferation occur. Cytotoxicity-induced regenerative cell proliferation and the subsequent development of hyperplastic lesions were considered precursor events that, if protected against, would prevent these mechanisms from contributing to the cancer response. Below these cRfCs, formaldehyde may still increase the risk of nasal or upper-respiratory cancer through direct mutagenicity or other mechanisms, but the magnitude of cancer risk may be significantly lower due to the absence of increased cellular proliferation or hyperplasia.

Significantly increased cell proliferation and hyperplasia (increased cellular proliferation that is identified to be pathologically "abnormal" in tissues) have been observed in response to exposure to formaldehyde, and these data were used to estimate benchmark PODs to calculate cRfCs. Schlosser et al. (2003) modeled the dose-response for cellular proliferation using labeling index data reported by Monticello et al. (1996) and calculated a value of 0.44 ppm for the HEC corresponding to the $BMCL_{01}$ (rat BMC and BMCL of 4.79 and 3.57 ppm, respectively) using dose-response functions that allowed for a threshold in dose.[20]

Although Monticello et al. (1996) represented the longest duration cell proliferation study available that included a range of exposure durations and nasal regions, five other *medium* or *high* confidence cellular proliferation studies testing formaldehyde exposure durations of 12–13 weeks were also available. Based on the findings from these studies, reasonable alternatives or adjustments to the Schlosser et al. (2003) estimate were presented in the assessment. The range of results from the various cell labeling data attempt to represent some key uncertainties; these include the single-day time frame (the last day of exposure) over which cell labeling was carried out (a methodological constraint intrinsic to all available cellular labeling studies) and the specific averaging approach employed in Schlosser et al. (2003), where the labeling index was weighted by exposure durations and averaged over several locations on the F344 rat nose. Such a time-weighted averaging underweights early exposures that may have contributed significantly to carcinogenesis (note: the few studies that investigated latent effects in rats did observe an increased tumor incidence at 1–2+ years following high-level formaldehyde exposure lasting only ~13 weeks (Woutersen et al., 1989; Feron et al., 1988). It was estimated that the data from these additional studies would result in benchmark levels that were roughly 2- to 3-fold lower.

Separately, EPA developed a benchmark POD based on modeling the incidence of basal hyperplasia reported by Woutersen et al. (1989) in a 28-month bioassay using Wistar rats. The BMC and

[20]They also modeled with functions that were constrained to pass through the origin, but BMCL values are not reported.

BMCL at the benchmark response of 0.1 extra risk[21] were 1.68 and 1.108 ppm, respectively. The HEC corresponding to the BMCL was 0.1609 ppm when adjusted for continuous human lifetime exposure, which was roughly three times lower than the HEC derived from the time-weighted averaged labeling index by Schlosser et al. (2003). As a point of comparison, this value is roughly similar to the LEC_{0005} derived from EPA's modeling of the NPC risk from the NCI epidemiology data.

Based on these estimates, proliferation-based cRfCs were estimated as follows:

1) The HEC derived from Schlosser et al. (2003) was 0.44 ppm (0.54 mg/m^3); the other cell-labeling studies indicated a 2-fold or 3-fold lower adjustment to this value, i.e., values of 0.27 and 0.18 mg/m^3, respectively. Applying a UF = 3 to reflect other uncertainties in extrapolating from animals to humans and a UF = 10 to account for human variability (total UF = 30) resulted in cRfCs based on cell proliferation data that ranged from **0.006 mg/m^3 to 0.018 mg/m^3**.

2) The hyperplasia data from Woutersen et al. (1989) resulted in an HEC of 0.1609 ppm (0.1979 mg/m^3); applying the UFs described above (total UF=30), the cRfC = **0.007 mg/m^3**.

As noted earlier, it has been argued that the rat nasal tumors can be quantitatively explained based solely on formaldehyde's cytotoxic potential. In accordance with this point of view, a cRfC estimated from benchmark concentrations derived using the two rat BBDR models in Table 43 may be a reasonable approximation for the dose at which there is no regenerative cell proliferative contribution to the nasal or upper-respiratory cancer response. A cRfC of **0.017 mg/m^3** may be obtained in this manner corresponding to the average HEC estimated using the two models at a benchmark response of 0.005 extra risk and reduced by an uncertainty factor of 30. This value is encompassed by the range of **0.006–0.018 mg/m^3** obtained for the proliferation-based cRfCs above.

However, the direct mutagenicity of formaldehyde plays a key role in its carcinogenicity. Cytogenetic effects in occupational studies and the formation of DPX in experimental animals have been reported at exposures well below those considered to be cytotoxic (e.g., approximately 0.7–2 ppm in rats). In addition, genotoxicity is itself thought to be one of the mechanisms by which formaldehyde exerts its cytotoxic action, arguing against a demarcation of one MOA over the other along the concentration axis. Overall, because formaldehyde-induced tumors are not fully explained only by indirect mutagenicity (i.e., due to regenerative cell proliferation) at any exposure, and since other modes of action also contribute to the tumor response, the use of an RfC approach was not preferred.

Human Extrapolation of Rat BBDR Model

Subsequent to their model for predicting the risk of rat nasal cancer, Conolly et al. (2004) developed a corresponding model for humans for the purpose of extrapolating the observed risk in the rat to human exposures. This human extrapolation model was conceptually very similar to the rat two-stage clonal expansion model in Conolly et al. (2003) but did not incorporate any data on human

[21]A 10% BMR was chosen to reflect "minimal adversity," consistent with the noncancer respiratory pathology modeling.

responses to formaldehyde exposure. Specifically, it used DPX concentrations and values of local formaldehyde flux to the tissue obtained from the PBPK and CFD models and incorporated a more detailed biological hypothesis and mechanistic data than are normally employed in modeling cancer risk.

For perspective, Table 44 presents continuous human lifetime extra risk estimates from the Conolly et al. (2004) model following inhalation exposure to formaldehyde concentrations of 1.0 ppb–1.0 ppm, in comparison to human risk estimates derived from EPA's modeling of the NPC mortality in the NCI occupational data. Conolly et al. (2004) developed two models: the "optimal model" in Table 44 refers to derivations using the best fit, a J-shaped curve, to the dose-response for the time-weighted averaged cell-labeling data in rats such that values at 0.7 ppm and 2.0 ppm were below the control value; the "conservative model" was derived using a hockey stick-, rather than J-, shape in the low dose portion (i.e., values at 0.7 and 2.0 ppm were the same as the control). In calculating risk estimates, Conolly et al. (2004) used a statistical upper bound of the model parameter (kmu)[22] (which related DPX to the probability of mutation per cell generation) and used maximum likelihood (MLE) values for all other model parameters. Since there is uncertainty inherent to using any statistical model to extrapolate outside the range of observed data, the relevant question in the context of using the BBDR modeling for such extrapolation is whether it decreased uncertainty in extrapolating risk (i.e., as compared to default approaches) or if, by explicitly identifying the sources of uncertainty, the BBDR modeling pointed to approaches and data needs that may have helped reduce the uncertainty.

Table 44. BBDR model estimated extra risk of SCC in human respiratory tract compared with EPA's modeling of extra risk of NPC from the human occupational data

Formaldehyde levels:	0.001 ppm	0.01 ppm	0.10 ppm[a]	1.0 ppm
Conolly et al. (2004) "J-shape optimal model"	-1.0×10^{-5}	-1.0×10^{-4}	-9.1×10^{-4}	-5.0×10^{-3}
Conolly et al. (2004) "hockey stick conservative model"	$+3.1 \times 10^{-8}$	$+3.2 \times 10^{-7}$	$+3.5 \times 10^{-6}$	$+2.7 \times 10^{-4}$
EPA analysis of NCI NPC, MLE (UCL)[b]	$+1.2 \times 10^{-6}$ ($+2.1 \times 10^{-6}$)	$+1.3 \times 10^{-5}$ ($+2.3 \times 10^{-5}$)	$+1.8 \times 10^{-4}$ ($+4.1 \times 10^{-4}$)	$+2.7 \times 10^{-1}$ ($+8.7 \times 10^{-1}$)

[a]The mortality-based EC_{0005} (LEC_{0005}) from the NCI epidemiology data correspond roughly to 0.2 (0.1) ppm.
[b]MLE = maximum likelihood estimate; UCL=95% upper confidence limit.

[22]The model estimated MLE value for kmu was found to be zero, leading to the inference by the authors that formaldehyde's direct mutagenic action is not relevant to carcinogenicity in the rat or human, and that the observed tumor response in the rat can be explained on the basis of regenerative cellular proliferation to cell injury.

The assessment included a careful evaluation of the level of confidence and sources of uncertainties in different components of the rat BBDR and the corresponding human extrapolation models. Of the potential issues identified, those related to replication rates of normal and initiated cells, and the use of historical control animals were found to have major impacts on qualitative and quantitative conclusions from the modeling. In particular, modeling results were unstable in response to slight perturbations in the assumed values for the division rates for initiated cells, and there are currently no data of any kind even in rats to inform the effect of formaldehyde on the kinetics of initiated cells. The model was also extremely sensitive to the inclusion of historical control animals. Because SCC in the nose is a rare tumor, Conolly et al. (2004, 2003) included in their model control rats from all NTP cancer bioassays. When the NTP control data were restricted to those animals from NTP inhalation studies, the upper bound human risk estimate obtained by Conolly et al. (2004) (i.e., with everything else in their modeling retained unchanged) was increased by 50-fold (Crump et al., 2008). If only concurrent controls were used, the model for extrapolation of risk to humans became numerically unstable (i.e., the MLE and upper-bound estimates of risk became infinite). Subramaniam et al. (2007) and Crump et al. (2008) provide details. The human extrapolation model exhibited extreme uncertainty at all exposure concentrations, above as well as below the human equivalent concentrations that were calculated in Table 43 [see (2009; Crump et al., 2008)].

Unit risk estimates based on animal data, considering confidence in the available models

Overall, use of biologically based modeling allowed utilization of various data, including mechanistic information, in an integrated manner for modeling the incidence of nasal SCCs in F344 rats and for deriving benchmark levels for extrapolation. In this way, the rat BBDR modeling improved the dose-response modeling of the observed nasal cancers in the F344 rat, and multiple BBDR model implementations provided similar estimates of risk and confidence bounds in the general range of the observed rat tumor incidence data. Therefore, the rat BBDR models were used to calculate benchmark concentrations for points of departure (PODs). In addition, given the reasonable confidence in flux estimates derived from the rat and human CFD models, model-derived formaldehyde flux values were used in deriving human equivalent concentrations corresponding to these PODs and candidate unit risk estimates using these values were calculated.

However, it was determined that the human extrapolation modeling in Conolly et al. (2004) was extremely uncertain and did not provide robust measures of human nasal SCC risk at any exposure concentration. Therefore, this human extrapolation model was not used to directly calculate risk at human exposure scenarios.

The assessment presents strong arguments in support of a low dose linear extrapolation from the POD. Given formaldehyde's direct mutagenic potential, following the procedures in EPA's cancer guidelines (U.S. EPA, 2005a) for when the knowledge of the MOA does not support an alternative approach, a low dose linear approach was used to predict low-dose formaldehyde cancer risk from the

rat data. Extrapolation was carried out as a straight line drawn to the origin from the HEC corresponding to the BMDL. Unit risks were calculated using several modeling approaches, including modifications to the rat BBDR model, as shown in Table 45 below. The unit risks corresponding to BMRs at the 0.005 or 0.01 extra risk levels spanned a remarkably tight range of 0.01–0.03 per ppm.

Table 45. Unit risk estimates derived from benchmark estimates using animal data and formaldehyde flux as dose-metric

Models	Unit risk estimates (1/ppm)			
	LEC_{005}	LEC_{01}	LEC_{05}	LEC_{10}
Weibull with threshold[a] Schlosser et al. (2003)		0.014	0.066	0.127
Multistage Weibull time-to-tumor		0.033	0.109	0.189
Rat BBDR "model 1"	0.012	0.023		
Rat BBDR "model 2"	0.011	0.022		

[a]Estimates using steady-state DPX as a dose metric were identical.
Note = values were not estimated for vacant cells.

Selection of a unit risk estimate for nasal cancers

The unit risk estimates derived using the available human and animal data on nasal cancers are similar (see Table 46), with the human estimate being only slightly lower than those values estimated using rat bioassay and mechanistic data.

Table 46. Comparison and basis of unit risk estimates for NPC in humans and nasal SCCs in rats

	Human NPC estimate	Animal nasal cancer estimate
Study/Endpoint	Beane Freeman et al. (2013) (NCI industrial cohort): NPC mortality	Kerns et al. (1983); Monticello et al. (1996): Incidence of nasal squamous cell carcinoma in rats
Model features	Estimation of inhalation unit risk using Poisson regression model and life table analysis: • U.S national incidence data • Regression coefficients from log-linear models of nasopharyngeal (NPC) mortality (exposed and unexposed workers) • Linear low-dose extrapolation from LEC	Multiple mechanistic and statistical models, including BBDR modeling, used for modeling tumor incidence. Mechanistic information included: • Dosimetric (CFD) modelling of formaldehyde flux to rat, monkey and human airway lining • PBPK model for rats incorporating dose-response data on DNA-protein crosslinks • Site-specific cell labeling measurements in nose Linear low-dose extrapolation was carried out from human equivalent dose at BMCL

	Human NPC estimate	Animal nasal cancer estimate
POD	95% lower bound on concentration at 0.05% incidence (approx. 0.05 ppm)	95% lower bound on concentration at 0.5% incidence (approx. 0.2 ppm)
Unit risk estimate[a]	7.4×10^{-3} per mg/m^3 (9.1×10^{-3} per ppm)	8.9×10^{-3} to 1.8×10^{-2} per mg/m^3 (1.1×10^{-2} to 2.2×10^{-2} per ppm)

[a]Note that these estimates are provided for comparison purposes and do not represent ADAF-adjusted values.

Ultimately, it was determined that the human data provided a more appropriate basis for estimating human nasal cancer risk than did the rodent data, given that a well-conducted epidemiological study was available with appropriate quantitative analyses. However, candidate unit risks in Table 46 at 0.005 extra risk were comparable to that derived using the occupational data on nasopharyngeal cancers (see Section 2.2.1 in the Toxicological Review). Because the unit risk estimates from the human data were preferred, the rodent-based estimates were not adjusted for the assumed increased early-life susceptibility arising from the determination of a mutagenic MOA for URT cancers; however, if the rodent-based estimates were to be used, ADAFs should be applied (U.S. EPA, 2005b).

As previously described, using the human NPC data, a plausible upper bound lifetime extra cancer mortality unit risk of 4.5×10^{-3} per ppm (3.6×10^{-6} per µg/m^3) of continuous formaldehyde exposure was estimated using a life table program and linear low-dose extrapolation of the excess NPC mortality and log-linear modeling results (for cumulative exposure) reported in a *high* confidence occupational epidemiological study (based on 10 NPC deaths). Applying the same regression coefficient and life table program to background NPC incidence rates yielded a lifetime extra cancer (incidence) unit risk estimate of 9.1×10^{-3} per ppm (7.4×10^{-6} per µg/m^3).

The weight of evidence supports the conclusion that formaldehyde carcinogenicity for URT cancers such as NPC can be attributed, at least in part, to a mutagenic MOA. Therefore, because there were no chemical-specific data to evaluate susceptibility of different lifestages, increased early-life susceptibility was assumed for NPC and age-dependent adjustment factors (ADAFs) were applied, consistent with EPA guidelines (U.S. EPA, 2005b).

The application of ADAFs resulted in a lifetime unit risk estimate of 1.1×10^{-5} per µg/m^3 (1.3×10^{-2} per ppm) for NPC incidence, adjusted for postulated increased early-life susceptibility, assuming a 70-year lifetime and constant exposure across age groups.

Uncertainties and confidence in the selected unit risk estimate for nasal cancers

The strengths and uncertainties in the unit risk estimate for NPC incidence are summarized in Table 47. One of the largest sources of uncertainty in the NPC estimate has to do with the rarity of the cancer and, thus, the small number of exposed cases (n = 8) that informed the dose-response analysis. It is important to note that, although a unit risk estimate could only be calculated for NPC (for which an evidence integration judgment of **evidence demonstrates** was drawn), the systematic evaluation of evidence on URT cancers also resulted in a judgment that the **evidence demonstrates** (based on studies

in occupational cohorts and animals) that inhalation of formaldehyde causes sinonasal cancer, given appropriate exposure circumstances.

Table 47. Strengths and uncertainties in the cancer type-specific unit risk estimate for NPC

Strengths	Uncertainties
• IUR estimated from data that are directly relevant to humans. • Based on the results of a large, *high* confidence epidemiological study involving multiple industries with detailed, individual cumulative exposure estimates and allowance for cancer latency. • Low-dose linear extrapolation is supported by a mutagenic MOA (i.e., not a default). • Similar unit risk estimates derived using rat bioassay and mechanistic data on nasal cancers.	• NPC is a very rare cancer. This study followed more than 25,000 workers for over 40 years and observed a statistically significant increase in relative risk associated with the highest category of average exposure intensity, however, only 10 cases occurred. The small number of deaths creates uncertainties for the dose-response modeling (borderline model fit for cumulative exposure including exposed and unexposed person-years, $p = 0.07$). • Uncertainty about optimal exposure metric(s). Cumulative exposure is the standard metric used for unit risk estimates. Use of cumulative exposure assumes equal importance of concentration and duration on cancer incidence; yet, associations with peak exposure in epidemiological studies and the nonlinear shape of the dose-response from animal bioassays suggest greater influence of concentration. • Although statistically significant increases in risk for NPC were reported by multiple studies for several metrics of exposure (duration, cumulative, time since first exposure, peak), the relationship with cumulative exposure in the study used for IUR derivation was less precise (p-trend = 0.07 based on the regression coefficient for the continuous model). • Some uncertainty in the low-dose extrapolation is introduced based on the potential for endogenous formaldehyde to reduce the uptake of the inhaled gas at low doses, as demonstrated in modeling efforts by Schroeter et al. (2014) and Campbell et al. (2020).

Based on the attendant strengths and uncertainties outlined above, there is *medium* confidence in the unit risk estimate for NPC incidence. The greatest uncertainty was related to the small number of cases that contributed to the statistical analysis and resulting imprecision in modeling the shape of the dose-response curve.

4.5.2. Derivation of Cancer Unit Risk Estimates for Myeloid Leukemia

The quantitative analyses of myeloid leukemia are based on results from the latest follow-up of the NCI cohort of industrial workers exposed to formaldehyde (Beane Freeman et al., 2009). Although no association was indicated for cumulative exposure and myeloid leukemia in this study, the combination of myeloid leukemia and other/unspecified leukemia was marginally associated ($p = 0.1$) with cumulative formaldehyde exposure. The evaluation of this combined group is supported by analyses by NCI during the 1980s and 90s that compared diagnoses on death certificates to original

hospital diagnoses and found that as many as 50% of deaths classified as other or unspecified leukemia were originally diagnosed as myeloid leukemia (Percy et al., 1990; Percy et al., 1981).[23]

Derivation of a myeloid leukemia unit risk estimate based on human data

Choice of epidemiology study

Similar to the unit risk estimate for NPC, the estimate for myeloid leukemia is based on results from the latest follow-up of the NCI cohort of industrial workers exposed to formaldehyde (Beane Freeman et al., 2009), the largest (25,619 workers) of the three independent industrial worker cohort studies and the only one with sufficient individual exposure data for dose-response modeling. Beane Freeman et al. (2009) conducted dose-response analyses of 123 deaths attributed to leukemia and leukemia subtypes, as well as deaths from other LHP malignancies. As previously described, this well-conducted study is the only one that used internal comparisons rather than standardized mortality ratios (reducing the impact of potential unmeasured confounding), and it included a detailed exposure assessment conducted for each worker based on exposure estimates for different jobs held and tasks performed (Stewart et al., 1986), and exposure estimates were made using several different metrics—peak exposure, average intensity, cumulative exposure, and duration of exposure.

Dose-response modeling of data from the NCI cohort

The results of the internal analyses (i.e., comparing exposed workers to an internal referent group of other workers in the cohort) of Beane Freeman et al. (2009) for LHP cancer types using the cumulative exposure metric are presented in Table 48. The relative risks (RRs) were estimated using log-linear Poisson regression models stratified by calendar year, age, sex, and race and adjusted for pay category. A two-year lag interval was used to determine exposures to account for a latency period for LHP cancers. For all cancer types, the NCI investigators used the low-exposure category as the reference category to "minimize the impact of any unmeasured confounding variables since nonexposed workers may differ from exposed workers with respect to socioeconomic characteristics" (Hauptmann et al., 2004). In this review, the nonexposed person-years were included in the primary cancer risk analyses to be more inclusive of all the dose-response data. The analyses adjusted for pay category, a measure of socioeconomic status, thus possible SES differences between exposed and nonexposed were at least partially addressed. Final results for the exposed person-years only are also presented for comparison.

[23]In the Percy et al. (1990; 1981) studies, only about 10% of leukemia deaths were classified as "other or unspecified" based on hospital diagnoses (versus 29% from death certificates in the Beane Freeman et al. (2009) study), and 51% (Percy et al., 1981) and 53% (Percy et al., 1990) of leukemia deaths were myeloid leukemias based on hospital diagnoses (versus 39% from death certificates in the Beane Freeman et al. (2009) study), suggesting that about a third or more of the "other or unspecified" leukemia deaths in the Beane Freeman et al. (2009) study were probably myeloid leukemias. Percy et al. (1990) reported in their study that "Of the nearly 600 deaths from leukemia NOS [other or unspecified] nearly 50% were originally diagnosed as myeloid... Obviously myeloid leukemia is grossly underreported on death certificates."

Cumulative exposure was included as a continuous variable in the log-linear models (general model form: RR = eβX, where β represents the regression coefficient and X is exposure). The regression coefficients are presented in Table 48.

Table 48. Relative risk estimates for mortality from leukemia (based on ICD codes) and regression coefficients from NCI log-linear trend test models[a] by level of cumulative formaldehyde exposure (ppm × years). Source: Beane Freeman et al. (2009)

Relative risk estimates cancer type	Rate ratio (number of deaths)				*p*-trend, all person-years[b]	*p*-trend, exposed person-years[c]
	0	>0 to <1.5[d]	1.5 to <5.5	>5.5		
Leukemia	0.53 (7)	1.0 (63)	0.96 (24)	1.11 (29)	0.08	0.12
Myeloid leukemia	0.61 (4)	1.0 (26)	0.82 (8)	1.02 (10)	0.44	>0.50
Other/unspecified leukemia	0.77 (2)	1.0 (15)	1.65 (10)	1.44 (9)	0.13	0.15

Regression coefficients cancer type	Person-years	β (per ppm × year)[f]	Standard error (per ppm × year)[f]
Leukemia	All	0.01246	0.006421
	Exposed only	0.01131	0.00661
Myeloid leukemia	All	0.009908	0.01191
	Exposed only	0.008182	0.01249
Myeloid leukemia plus other/unspecified leukemia[e]	All	0.01408	0.007706
	Exposed only	0.01315	0.007914

[a]Models stratified by calendar year, age, sex, and race and adjusted for pay category; cumulative exposures calculated using a 15-year lag interval for NPC and a 2-year lag interval for LHP cancer types.
[b]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (as a continuous variable) among all (nonexposed and exposed) person-years.
[c]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (as a continuous variable) among exposed person-years only.
[d]Reference category for all categories.
[e]*p*-trend values for the myeloid and other/unspecified leukemia categories combined are 0.10 for all person-years and 0.13 for exposed person-years only.
[f]Source: Personal communications from Laura Beane Freeman to Jennifer Jinot (February 22, 2013 and February 21, 2014) and to John Whalan (August 26, 2009).

Approaches used for quantitative risk assessment of myeloid leukemia

EPA explored several approaches for deriving a unit risk estimate for myeloid leukemia based on cumulative exposure. A standard approach for deriving the unit risk estimate was considered using the regression coefficient for myeloid leukemia and cumulative exposure; however, the *p*-value (0.44) for that regression coefficient was far from 0.05, indicating a poor model fit. The poor model fit could be due, at least in part, to inadequate statistical power, likely exacerbated by the underreporting of

myeloid leukemia deaths. The regression coefficient for all person-years for myeloid leukemia is only slightly lower than that for all leukemia (0.0099 and 0.0125 per ppm-years, respectively). The association with all leukemia cancer had a lower *p*-value of 0.08 and should include all the myeloid leukemia deaths, both specified and unspecified. The "other/unspecified" leukemias comprise a sizeable portion of all leukemia deaths (almost 30%) in the cohort and presumably include a good proportion of unclassified myeloid leukemias (Percy et al., 1990; Percy et al., 1981). To address this underreporting, two additional approaches for deriving a unit risk estimate for myeloid leukemia were considered.

One approach involved using the all leukemia grouping.[24] Use of the all leukemia background rates in the life table calculations (described in more detail below) might inflate the unit risk estimate for myeloid leukemia by increasing the background risk relative to which the formaldehyde-related risks are calculated. However, the inclusion of any leukemia subtypes not related to formaldehyde exposure should theoretically dampen the dose-response relationship (lowering the regression coefficient) relative to that for all the myeloid leukemias alone; thus, this should mitigate at least some of the effect of using the all leukemia background rates.

The preferred approach involved using a combined grouping of the myeloid leukemia and other/unspecified leukemias subcategories. The myeloid and other/unspecified leukemias grouping had a stronger association with cumulative exposure (*p*-trend = 0.10 for all person-years) in the Beane Freeman et al. (2009) study than did myeloid leukemia alone and it captures the unclassified myeloid leukemias with the least inclusion of nonmyeloid leukemias. There is likely more uncertainty associated with the background rates for the other/unspecified leukemias than for the specified myeloid and lymphocytic leukemia subtypes; however, the benefits of focusing on the myeloid plus other/unspecified leukemias rather than the broader "all leukemias" grouping in attempting to be more inclusive of all the myeloid leukemias were deemed to outweigh any additional uncertainty associated with the background rates. Although the unit risk estimate based on the preferred approach of using myeloid plus other/unspecified leukemias inevitably includes some nonmyeloid leukemias, it is considered the best approach for deriving a unit risk estimate for myeloid leukemia specifically.[25]

[24]The all leukemia category includes all 123 leukemias observed in the cohort. Of these, 48 (39.0%) were myeloid, 37 (30.1%) were lymphoid, and 36 (29.3%) were other/unspecified; the remaining 2 (1.6%) were monocytic leukemias (ICD-8 code 206).

[25]Although the inclusion of cancer subtypes not necessarily causally associated with the chemical exposure in the grouping of cancers represented in the regression coefficient and the corresponding background rates for the life table analysis is overt here, it is not uncommon that, due to data limitations, unit risk estimates based on human data reflect cancer groupings broader than what might be strictly causally associated with the chemical exposure (e.g., all leukemias or all lung cancers). As noted in the text, any inclusion of unassociated cancer subtypes in the derivation of the regression coefficient should theoretically attenuate the coefficient in a manner that would offset the use of the unassociated subtypes in the background rates in the life table analysis.

Prediction of lifetime extra risk of myeloid leukemia mortality and incidence

Unit risk estimates for myeloid leukemia mortality (and incidence) were calculated from the regression results using the different approaches discussed above and the same general methodology described for the NPC mortality estimates with the exception of the use of a 2-year lag period, as selected by Beane Freeman et al. (2009). Mortality (and incidence) rates from the time frame 2006–2010 were used in the life table program. Although the background mortality rates of leukemia are higher (lifetime risk of 0.0062 according to the life table analysis) than those of NPC, the 1% extra risk level typically used as the basis for the POD for epidemiological data still corresponds to an RR estimate (2.5) that would be above the highest categorical result reported, even after adjusting the RR estimates upward relative to the 0-exposure group (because our primary analyses include the nonexposed workers). A 0.5% extra risk level yields an RR estimate of 1.8, which better corresponds to the RRs in the range of the data. Thus, the LEC value corresponding to 0.5% extra risk (LEC_{005}) was selected for the POD for all leukemia and for myeloid leukemia and myeloid plus other/unspecified leukemias, which have lower background rates than all leukemia (lifetime risks of 0.0031 and 0.0046, respectively).

There are insufficient data to establish the MOA for formaldehyde-induced myeloid leukemia; thus, linear low-dose extrapolation was performed as the default approach, in accordance with EPA's cancer guidelines (U.S. EPA, 2005a). The EC_{005}, LEC_{005}, and inhalation unit risk estimates for myeloid plus other/unspecified leukemia mortality are presented in Table 49.

Table 49. EC_{005}, LEC_{005}, and unit risk estimates for myeloid plus other/unspecified leukemia mortality based on log-linear trend analyses of cumulative formaldehyde exposure data from the Beane Freeman et al (2009) study

Person-years	EC_{005} (ppm)	LEC_{005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.253	0.133	3.8×10^{-2}	3.1×10^{-2}
Exposed only	0.269	0.135	3.7×10^{-2}	3.0×10^{-2}

[a]Unit risk = $0.005/LEC_{005}$.

All leukemia and myeloid leukemia have substantial survival rates;[26] thus, it is preferable to derive incidence estimates. Unit risk estimates for leukemia incidences were calculated as described above for the NPC incidence estimates. The incidence-based calculation relies on the assumptions that incidence and mortality for these leukemia subtype groupings have the same dose-response relationship for formaldehyde exposure and that the incidence data are for first occurrences of the cancers or that relapses provide a negligible contribution. The first assumption is more uncertain for all leukemia, myeloid leukemia, and myeloid plus other/unspecified leukemias than it was for NPC because these are

[26]Survival rates were 55.0% at 5 years for all leukemia [http://seer.cancer.gov/statfacts/html/leuks.html], 23.4% at 5 years for acute myeloid leukemia [http://seer.cancer.gov/statfacts/html/amyl.html], and 59.1% at 5 years for chronic myeloid leukemia [http://seer.cancer.gov/statfacts/html/cmyl.html] based on 2002–2009 SEER data.

groupings of subtypes with quite different survival rates (e.g., see footnote 26). The incidence-based calculation also takes advantage of the fact that incidence rates for these cancer types are negligible compared with the all-cause mortality rates and thus no special adjustment to the population at risk to account for live individuals who have been diagnosed with these cancers is necessary.

The EC_{005}, LEC_{005}, and inhalation unit risk estimates for myeloid plus other/unspecified leukemia incidence are presented in Table 50. The incidence unit risk estimate is about 10% higher than the mortality estimate. This difference is lower than the ~24% increase that would have been seen for specified myeloid leukemias alone (see the LEC_{005}s in Table 51). This is because the difference between age-specific mortality and incidence rates for the other/unspecified leukemias is not very large, and for some age groups the mortality rates are actually larger than the incidence rates. This irregularity is to be expected for "other/unspecified" classifications because greater attention is given to diagnosing incident leukemia cases than to accounting for causes of death, so one would anticipate less underreporting of myeloid leukemias as incident cases than as causes of death on death certificates.

Table 50. EC_{005}, LEC_{005}, and unit risk estimates for myeloid plus other/unspecified leukemia incidence based on Beane Freeman et al. (2009) log-linear trend analyses for cumulative formaldehyde exposure

Person-years	EC_{005} (ppm)	LEC_{005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.224	0.118	4.2×10^{-2}	3.4×10^{-2}
Exposed only	0.239	0.120	4.2×10^{-2}	3.4×10^{-2}

[a]Unit risk = $0.005/LEC_{005}$.

The EC_{005} and LEC_{005} estimates for mortality and incidence and incidence unit risk estimates for all leukemia and for myeloid leukemia using the alternate approaches discussed above are presented in Table 51. The same underlying life table methodology was used for each approach—only the regression coefficients and background cancer rates differed. As discussed above, and consistent with the results just presented, the preferred approach (shaded in Table 51) is the life table analysis using the regression coefficient and background rates for myeloid plus other/unspecified leukemias because this grouping captures the unclassified myeloid leukemias with the least inclusion of non-myeloid leukemias.

Table 51. EC_{005} and LEC_{005} estimates for mortality and incidence and unit risk estimates for all leukemia and myeloid leukemia using alternate approaches (all person-years) – shaded estimate is preferred

Approach (by cancer type used as basis for regression coefficient and cause-specific background rates)	EC_{005} (ppm) LEC_{005} (ppm)		Unit risk estimate (per ppm)[a]	Unit risk estimate (per mg/m^3)
	Incidence	Mortality	(Incidence)	(Incidence)
Myeloid leukemia	0.378 0.127	0.468 0.157	3.9×10^{-2}	3.2×10^{-2}
All leukemia	0.156	0.229	5.9×10^{-2}	4.8×10^{-2}

	0.0846	0.124		
Myeloid + Other/Unspecified	**0.224** **0.118**	**0.253** **0.133**	**4.2×10^{-2}**	**3.4×10^{-2}**

[a]Unit risk estimate = 0.005/(LEC_{005} for incidence).
[b]Incidence background rates also include monocytic leukemia, but that contribution is negligible.

Thus, the preferred unit risk estimate for myeloid leukemia is the estimate of 4.2×10^{-2} per ppm.[27] The unit risk estimate calculated using the exposed person-years only is essentially indistinguishable from the preferred estimate using all person-years (see Table 50). The unit risk estimates from the other approaches considered are fairly close, with the unit risk estimate based on the myeloid leukemia category's being virtually identical to the preferred estimate based on myeloid plus other/unspecified leukemias, and the estimate based on all leukemia being somewhat greater (see Table 52).

Table 52 summarizes some of the key information comparing the different approaches considered for the derivation of the unit risk estimate for myeloid leukemia.

Table 52. Dose-response modeling (all person-years) and (incidence) unit risk estimate derivation results for different leukemia groupings – shaded estimate is preferred

Cancer grouping	Deaths in NCI cohort	Regression coefficient (per ppm × year)	SE (per ppm × year)	*p*-value	Unit risk estimate (per ppm)	Unit risk estimate (per mg/m^3)
Myeloid leukemia	48	0.009908	0.01191	0.44	3.9×10^{-2}	3.2×10^{-2}
All leukemia	123	0.01246	0.006421	0.08	5.9×10^{-2}	4.8×10^{-2}
Myeloid + Other/Unspecified leukemias	**84[a]**	**0.01408**	**0.007706**	**0.10**	**4.2×10^{-2}**	**3.4×10^{-2}**

[a]This is the sum of the leukemias classified as myeloid and those classified as "other/unspecified." At least 70–80% of this number are expected to be myeloid leukemias, assuming that a third to a half of leukemias not otherwise specified on death certificates are myeloid leukemias, as discussed above.

Selection of a unit risk estimate for myeloid leukemia

The best estimate that can be derived for myeloid leukemia was calculated using human occupational data from the NCI industrial cohort (Beane Freeman et al., 2009). As previously described, a plausible upper bound lifetime extra cancer mortality unit risk of 3.8×10^{-2} per ppm (3.1×10^{-5} per µg/m^3) of continuous formaldehyde exposure was estimated using a life table program and linear low-

[27]Comparable to calculations done for NPC, a rough calculation was done to ensure that the unit risk estimate derived for myeloid leukemia incidence is not implausible in comparison to actual case numbers. For example, assuming an average constant lifetime formaldehyde exposure level of 20 ppb for the U.S. population, the inhalation unit risk estimate for myeloid (and other/unspecified) leukemia equates to a lifetime extra risk estimate of 8.4×10^{-4}. Assuming an average lifetime of 75 years (this is not EPA's default average lifetime of 70 years but rather a value more representative of actual demographic data) and a U.S. population of 300,000,000, this lifetime extra risk estimate suggests a crude upper-bound estimate of 3,400 incident cases of myeloid leukemia attributable to formaldehyde exposure per year. This upper-bound estimate is well below the estimated 17,100 total incident myeloid leukemia (not including other/unspecified leukemias) cases per year.

dose extrapolation of the excess myeloid plus other/unspecified leukemia mortality and log-linear modeling results (for cumulative exposure) reported in a well-conducted occupational epidemiological study (based on 84 deaths). Applying the same regression coefficient and life table program to background myeloid leukemia incidence rates yielded a lifetime extra cancer (incidence) unit risk estimate of 4.2×10^{-2} per ppm (3.4×10^{-5} per µg/m^3).

Since there is no knowledge as to whether a mutagenic MOA might be operative for formaldehyde-induced myeloid leukemia, no adjustments for increased early-life susceptibility (i.e., application of age-dependent adjustment factors) were made for myeloid leukemia, consistent with EPA guidelines (U.S. EPA, 2005b).

Uncertainties and confidence in the selected unit risk estimate for myeloid leukemia

The strengths and uncertainties in the unit risk estimate for myeloid leukemia incidence are summarized in Table 53. The primary uncertainty in this estimate relates to the complexities in the study-specific data for cumulative formaldehyde exposure and mortality from myeloid leukemia.

Table 53. Strengths and uncertainties in the cancer type-specific unit risk estimate for myeloid leukemia

Strengths	Uncertainties
• IUR estimated from data that are directly relevant to humans. • Based on the results of a large, *high* confidence epidemiological study involving multiple industries with detailed, individual cumulative exposure estimates and allowance for cancer latency. • Moderate number of deaths to model *(n* = 84).	Uncertainties with a potentially greater impact: • Although the dose-response relationship with peak exposure was marginally significant (*p* = 0.07), and statistically significant associations were reported for several metrics of exposure in other studies, the reported relationship with cumulative exposure showed a non-significant, small increase in risk for myeloid leukemia (based on the regression coefficient for the continuous model), potentially due in part to misclassification of myeloid leukemia cases. • The association with cumulative exposure was stronger for the other/unspecified grouping of leukemia diagnoses *(n* = 36) than for myeloid leukemia alone (*n* = 48). Although a sizable proportion of this category is assumed to include myeloid leukemia cases, the stronger association is surprising given the more heterogeneous set of leukemia cases in this category, some presumably not associated with formaldehyde exposure. Hence, the association would be expected to be attenuated. • Uncertainty about optimal exposure metric(s). Use of cumulative exposure assumes equal importance of concentration and duration on cancer incidence. The specific metrics analyzed differed across studies, and the results of the NCI study were not completely consistent with those of other studies (associated only with peak exposure). Uncertainties likely to have a minor impact: • Grouping of myeloid leukemias used for exposure-response modeling includes non-myeloid leukemias.

Strengths	Uncertainties
	• Borderline model fit for myeloid plus other/unspecified leukemias (p = 0.1) and uncertain shape of exposure-response function.

Based on the attendant strengths and uncertainties outlined above, there is *low* confidence in the unit risk estimate for myeloid leukemia incidence. This uncertainty is discussed further in the summary section below. However, given the judgment that the available **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans given appropriate exposure circumstances, and the associated public health burden that it poses (e.g., myeloid leukemia is far more prevalent than NPC), EPA thoroughly considered the complexity in the data and used an innovative approach to derive and present potential unit risk estimates for myeloid leukemia. A charge question will be provided for the peer-review panel regarding the development of a unit risk estimate for myeloid leukemia and asking for advice about how, if at all, the unit risk estimate might inform the quantification of risk for cancer.

4.5.3. Estimates of Cancer Risk based on "Bottom-up" Approach

Swenberg et al. (2011) and (Starr and Swenberg, 2013), followed by an update of results in Starr and Swenberg (2016), developed an approach to bound low-dose human cancer dose-response from formaldehyde exposure in a manner that only uses information regarding: (1) background incidence of the target tumors (nasopharyngeal cancers, leukemia, and Hodgkin lymphoma) in the U.S. population, (2) assumptions as to the target tissue for a key event interaction with formaldehyde for each type of tumor, and (3) measures of internal formaldehyde tissue dose in laboratory animals derived from either endogenously produced formaldehyde or from exogenous exposure to formaldehyde. The tissue dose measures are based on highly sensitive measurements in rats and monkeys of formaldehyde-induced DNA adducts (Yu et al., 2015; Lu et al., 2011; Moeller et al., 2011; Lu et al., 2010).

To develop these bounding estimates, the authors attributed the background tumor incidences to endogenous formaldehyde in the presumed target tissues (as measured by endogenous adducts). The approach assumed extra cancer incidence to be linearly related to exogenous adduct levels, with a slope equal to the ratio of background tumor incidence to background tissue dose of endogenous formaldehyde.

Risk estimates from this approach are claimed by the authors to produce conservative upper bounds, primarily because (a) the method attributes all the background risks of specific cancers to endogenous formaldehyde although other environmental factors might also contribute to these cancers, (b) lower confidence bounds on measured adduct levels are used, and (c) the above linear relationship is assumed.

Swenberg et al. (2011) and Starr and Swenberg (2016) then compared these values with the risk estimates in EPA's 2010 draft Toxicological Review, which were obtained by linearly extrapolating to

lower doses from a point of departure (a lower bound on the concentration associated with the benchmark response) derived by dose-response modeling of the epidemiological data. When adduct data from rats were used, the estimates Swenberg and Starr derived at 1 ppm exposure concentration were 2.67×10^{-4} for nasal cancer (based on Yu et al., 2015) and were at most 12.6×10^{-4} for leukemia (based on the limit of detection, LOD, from Lu et al. (2010), since no exogenous adducts were detected in bone marrow). In monkeys (Yu et al., 2015), the Swenberg and Starr bottom-up estimates were 2.69×10^{-4} for NPC and were less than 1.24×10^{-6} for leukemia. In comparison, the EPA upper-bound risk estimates were higher than the adduct-based upper-bound estimates by 40-fold for NPC and at least 45-fold (rat adduct data) or over 45,000-fold (monkey adduct data) for leukemia.

EPA concludes that the bottom-up approach does not necessarily provide an upper bound on the slope of the dose-response at low exogenous exposures, primarily because the ratio of background tumor incidence to internal endogenous concentration at the true target tissue may underpredict the slope of the dose-response above that endogenous concentration. This is further discussed in Crump et al. (2014). Furthermore, the approach assumes direct interaction of inhaled formaldehyde with a particular target tissue; if other sites of interaction and mechanisms are involved, the measures of DNA adducts in a specific tissue could lead to underestimates of the cancer potency when utilizing the "bottom-up" approach. Nonetheless, the bottom-up approach, which uses cancer incidence in the general population and is independent of the tumor dose-response data, can potentially provide some perspective on the likely contribution of a specific mode-of-action and the uncertainty in risk estimates derived from occupational exposures or derived by extrapolating downward from higher dose animal data where other phenomena may be occurring.

4.5.4. Summary of Unit Risk Estimates and the Preferred Estimate for Inhalation Unit Risk

As discussed previously, the NPC unit risk estimate based on data from the human occupational epidemiology study of the NCI updated by Beane Freeman et al. (2013) was preferred over estimates based on rodent cancer bioassay data. The best estimate for myeloid leukemia was also derived from the human occupational epidemiology study of the NCI updated by Beane Freeman et al. (2009). These estimates are presented in Table 54.

Table 54. Summary of inhalation unit risk estimates from occupational epidemiological studies[a,b]

Cancer type	Preferred unit risk estimate (ppm^{-1})	ADAF-adjusted unit risk estimate (ppm^{-1})	Preferred unit risk estimate ($(\mu g/m^3)^{-1}$)	ADAF-adjusted unit risk estimate ($(\mu g/m^3)^{-1}$)
Nasopharyngeal	0.0079[c]	0.013	6.4×10^{-6}[c]	1.1×10^{-5}
Myeloid leukemia	0.042	NA[d]	3.4×10^{-5}	NA[d]

[a]The inhalation unit risk estimate is typically expressed as the (upper-bound) increase in cancer risk estimated for an exposure increase of 1 µg/m^3.
[b]The unit risk estimates are all for cancer incidence.
[c]Adult-based (rescaled) unit risk estimate for NPC intended for the application of ADAFs.
[d]NA = not applicable; no ADAF adjustment is recommended for myeloid leukemia.

However, the data reported for myeloid leukemia (Beane Freeman et al., 2009) are complex and there are reasons for and against the use of these data in the derivation of the inhalation unit risk (IUR). Given the judgment that the available **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans given appropriate exposure circumstances, and the associated public health burden that it poses (e.g., myeloid leukemia is far more prevalent than NPC), EPA thoroughly considered the complexity in the data and used an innovative approach to derive and present potential unit risk estimates for myeloid leukemia. Some important uncertainties are discussed in greater detail below.

- Despite the quality of the literature base for the formaldehyde assessment and the judgment that the available **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans given appropriate exposure circumstances, the only study suitable for dose-response quantification for myeloid leukemia may be viewed as insufficient for developing a quantitative estimate of risk with an acceptable level of confidence.
  - The Beane Freeman study failed to observe an association between cumulative formaldehyde exposure and myeloid leukemia (p = 0.44), despite a reasonable number of cases (n = 48) and adequate follow up. The peak exposure metric was marginally associated (p = 0.07). This result raises questions about the relative importance of the intensity of exposure and duration in the association of myeloid leukemia mortality. On the other hand, myeloid leukemia mortality increased with time since first exposure, cumulative exposure, and exposure duration in two other occupational cohorts (garment workers and embalmers).
  - The available animal studies do not provide any compelling evidence for an association between formaldehyde inhalation and myeloid leukemia. Thus, there are no other data that can be used to support the POD estimate that can be derived from the only suitable human study.
- Analyses from NCI comparing causes of death recorded on death certificates with original diagnoses in hospital records suggest a misclassification of myeloid leukemia cases (n = 48), with a significant proportion reported as "other/unspecified" (n = 36).
  - In the Percy et al. (1990; 1981) studies, only about 10% of leukemia deaths were classified as "other or unspecified" based on hospital diagnoses (versus 29% from death certificates in the Beane Freeman et al. (2009) study), and 51% (Percy et al., 1981) and 53% (Percy et al., 1990) of leukemia deaths were myeloid leukemias based on hospital diagnoses (versus 39% from death certificates in the Beane Freeman et al. (2009) study), suggesting that about a third or more of the "other or unspecified" leukemia deaths in the Beane Freeman et al. (2009) study were probably myeloid leukemias. Percy et al. (1990) reported in their study that "Of the nearly 600 deaths from leukemia NOS [other or unspecified] nearly 50% were originally diagnosed as myeloid... Obviously myeloid leukemia is grossly underreported on death certificates."
  - Because it is likely that a proportion of myeloid leukemia cases were reported as "other/unspecified," a more complete estimate of the association of cumulative formaldehyde

exposure with myeloid leukemia might be obtained using the regression results for a combination of myeloid leukemia and other/unspecified leukemia.
  - Although a unit risk estimate that combines myeloid leukemia and other/unspecified leukemia overtly includes cancer subtypes not necessarily causally associated with the chemical exposure, it is sometimes the case that, due to data limitations, unit risk estimates are based on human data that reflect cancer groupings broader than what might be strictly causally associated with the chemical exposure (e.g., all leukemias or all lung cancers). The inclusion of unassociated cancer subtypes in the derivation of the regression coefficient should theoretically attenuate the association.
  - A comparison of the unit risk estimates for all leukemia, myeloid leukemia plus other unspecified leukemia, and myeloid leukemia (ICD-8/9: 205) indicates that all of the estimates are within a factor of 1.5. Unit risk estimates were 3.9×10^{-2}, 4.2×10^{-2}, and 5.9×10^{-2} for all leukemia, myeloid leukemia plus other unspecified leukemia, and myeloid leukemia (ICD-8/9: 205), respectively.
- The approach for combining myeloid leukemia and other/unspecified leukemia to estimate risk, while arguably consistent with the identified misclassification of myeloid leukemia on death certificates (Percy et al., 1990; Percy et al., 1981) is uncommon, and retains significant quantitative uncertainties, including some inconsistencies in statistical results. To a limited extent, it might also be viewed as combining cancer types that differ in terms of the cell of origin and other characteristics of cancer development (e.g., latency; MOA).
  - The combination of myeloid leukemia and other/unspecified leukemia in the regression model yields a *p*-value of 0.1. While the number of cases is increased by $n = 36$, cancers in this category, with the exception of the myeloid leukemia cases, were not identified to be causally associated with formaldehyde exposure during the hazard evaluation. The inclusion of cancers not causally associated with formaldehyde exposure would be expected to attenuate the association, but in contrast to this expectation, there was a stronger association for the regression model of other/unspecified leukemia alone ($p = 0.13$) compared to the model of myeloid leukemia alone ($p = 0.44$). There is not a clear explanation for why the association would be stronger for the more heterogeneous leukemia category.
  - There is likely more uncertainty associated with the background cancer rates in the U.S. population for the other/unspecified leukemias than for the specified myeloid and lymphocytic leukemia subtypes. The survival rates of the other/unspecified cancers had to be estimated by subtracting myeloid and lymphocytic leukemia rates from the rates for all leukemia.
  - As the Beane Freeman et al. (2009) study did evaluate myeloid leukemia, the use of either myeloid leukemia plus other/unspecified leukemias or the even broader category of all leukemias would represent deviations from using the most specific diagnoses possible. Depending on the extent to which the combined cancer types differ (e.g., in terms of cancer development), this could introduce significant quantitative uncertainties. However, such a decision to group or focus on individual cancer types must also consider the number and power of the available studies to be capable of detecting changes with reasonable confidence.
- Given the completely unknown MOA for myeloid leukemia, it is possible and perhaps likely that there are dose and duration effects for the development of myeloid leukemia following formaldehyde inhalation that are not fully understood.

- Acknowledging the complexity of the different dose metrics available in the observational studies, as well as the lack of an association between cumulative exposure and myeloid leukemia in the Beane Freeman et al. (2009) study, it is possible that the specific, individual exposure metrics in this study failed to fully capture the patterns of exposure most relevant to the development of myeloid leukemia. Importantly, this concern is independent of the identified hazard for myeloid leukemia, as myeloid leukemia mortality was increased in association with the peak exposure metric in this study (industrial workers) and others, as well as with duration-dependent metrics including time since first exposure, cumulative exposure, and exposure duration in two other occupational cohorts (garment workers and embalmers).
- As information supporting a nonlinear extrapolation from the identified POD is not available for myeloid leukemia, the current approach uses a default linear extrapolation. It is possible that additional study on the development of this cancer after formaldehyde exposure could provide support for the linear extrapolation or, alternatively, support a nonlinear approach.

Considering these uncertainties in the myeloid leukemia unit risk estimate, the selected IUR, summarized in Table 55, reflects the estimate for NPC incidence alone. For benefits analyses and certain other situations, "central" estimates of risk per unit dose may be preferred over (upper bound) unit risk estimates. Therefore, the assessment also provides estimates of risk per unit dose resulting from linear extrapolations of risk from the central estimate (here, the EC, or effective concentration associated with the benchmark response level of risk).

Table 55. Inhalation unit risk[a,b]

Cancer type	Preferred unit risk estimate (ppm^{-1})	ADAF-adjusted unit risk estimate (ppm^{-1})	Selected unit risk estimate $((\mu g/m^3)^{-1})$	ADAF-adjusted unit risk estimate $((\mu g/m^3)^{-1})$
Nasopharyngeal	0.0079[c]	0.013	6.4×10^{-6} [c]	1.1×10^{-5}

[a]The inhalation unit risk estimate is typically expressed as the (upper-bound) increase in cancer risk estimated for an exposure increase of 1 $\mu g/m^3$.
[b]The unit risk estimate is for cancer incidence.
[c]Adult-based (rescaled) unit risk estimate for NPC intended for the application of ADAFs.

Sources of uncertainty associated with the selected inhalation unit risk

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 study used as the basis for the selected unit risk estimate was considered a high-quality study for the purposes of deriving unit risk estimates. The NCI study is a large longitudinal cohort study that developed individual-worker exposure estimates using detailed employment histories and formaldehyde concentration measurements. In addition to the detailed exposure assessment, the study used internal analyses and gave careful consideration to potential confounding or modifying variables. Moreover, the NCI study comprises a large cohort that has been followed for a long time. Nonetheless, uncertainties in the derived unit risk estimates are inevitable.

The primary uncertainty in the selected inhalation unit risk is the lack of inclusion of an estimate for the prevalent cancer, myeloid leukemia, due to complexities in the quantitative data, the strengths and limitations of which are outlined above. Other important sources of uncertainty in the selected unit risk estimate are the retrospective estimation of individual worker exposures, the dose-response modeling of the NCI data, the exposure metric, and the high-to-low exposure extrapolation. These factors, particularly the latter two, could have a large impact on the unit risk estimate. The former two factors could result in either overprediction or underprediction of the true risk, although regarding the retrospective estimation of exposures, comparisons with the Marsh et al. (1996) exposure estimates suggest that the NCI exposure estimates might be overestimates, which would tend to underpredict the true risk. The latter two factors, the use of cumulative exposure as the exposure metric and the use of linear high-to-low exposure extrapolation, which are related, would tend to overpredict the true risk.

Additional sources of uncertainty include the use of a single study for the derivation of the unit risk estimate and the derivation of unit risk estimates for the general population from an occupational study. The first factor could result in either overprediction or underprediction of the true risk. The second factor would tend to underpredict the true risks.

While the proven genotoxicity and mutagenicity of formaldehyde and the observation of human cytogenetic effects in human occupational exposures provide strong support for preferring the linear extrapolation, an uncertainty in the low dose-response comes from the potential for endogenous formaldehyde levels in respiratory tissue to reduce the uptake of the inhaled gas at low doses, as demonstrated in modeling efforts by Schroeter et al. (2014) and Campbell et al. (2020). This would be expected to result in an overprediction of the true risk.

Sources of uncertainty expected to have minimal quantitative impact include the inability to derive unit risk estimates for potential cancer sites other than NPC and myeloid leukemia, the derivation of incidence estimates from mortality data, the influence of confounding and modifying factors (with the possible exception of particulates, where a modifying effect cannot be ruled out; if particulates are modifying the NPC risk, the NCI data would tend to overestimate the risk from formaldehyde alone, possibly to a more considerable extent), and the application of the ADAFs used to address assumed increased early life susceptibility.

Although substantial uncertainty exists with respect to the low-exposure extrapolation, the estimate is based on human data from a large, high-quality epidemiological study and mutagenic and cytogenic modes-of-action are well documented. Furthermore, the estimate is similar to estimates derived from rodent data. Based on these considerations, overall confidence in the selected inhalation unit risk is ***medium***.

4.5.5. Previous IRIS Assessment: Inhalation Unit Risk

In the previous assessment (last updated in 1991), an inhalation unit risk of 1.3×10^{-5} per $\mu g/m^3$ was developed based on nasal SCCs in F344 rats from Kerns et al. (1983). The data were modeled from

the estimates of the probability of death with tumor and its variance using a linearized multistage procedure.

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