



EPA's IRIS Assessment of Formaldehyde (Inhalation)

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Presentation to the NASEM external peer review panel

10/12/22

Outline of Presentation

- History in Brief
- Assessment Materials
- Assessment Methods and Organization (charge question 1; Preface)
- Toxicokinetics (charge question 2)
- Noncancer Health Effects (charge questions 3 [respiratory] and 4 [nonrespiratory])
- Noncancer Dose-Response and RfC (charge question 5)

[BREAK FOR QUESTIONS]

- Cancer Hazard Identification (charge question 6)
- Cancer Dose-Response and IUR (charge question 7)
- Summary of Main Messages

History in Brief

History in Brief

- **Current (2022) draft in development since 2012**
 - Completed draft was halted in late 2017 and suspended from 2018-2021 before development resumed.
- **Current draft built upon the NAS (2011) review and methods were subsequently used in the IRIS Handbook**
 - The methods and presentation of the 2022 draft reflect a direct response to comments from NAS (2011).
 - NAS (2011) identified problem formulation decisions for the current assessment and key science issues.
 - NAS (2011) recommended EPA not delay revision to implement a new systematic review (SR) approach.
 - Draft completion preceded adopting some SR methods within IRIS (e.g., protocol release began in 2018).
 - Methods developed in drafting this assessment were the basis for many SR methods in the IRIS Handbook.
- **Development of the current draft follows the IRIS 7-Step Process**

History in Brief

2012*	Complete restart of assessment using transparent systematic review approaches
2014	EPA Public Workshop: https://www.epa.gov/iris/formaldehyde-workshop
Fall 2017	Draft assessment complete & ready for Agency Review (Step 2 of IRIS 7-Step Process)
Spring 2018	IRIS assessment formally suspended at the request of EPA political leadership
March 2021	Announced that assessment is unsuspended and development within IRIS resumes
June–September 2021	IRIS Agency Review (Step 2), including a systematic evidence map on new literature
Dec. 2021–Jan. 2022	Interagency Review by federal partners (Step 3)
April 2022—June 2022	Public comment period (Step 4a): Docket # EPA-HQ-ORD-2010-0396
Ongoing	External peer review (Step 4b) managed by NASEM (accepting comments directly)

*After NAS (2011) review of prior draft IRIS assessment initiated in 1998; currently, final IRIS values are from 1990-1991

History in Brief

The comments and recommendations from NAS (2011) are addressed, including:

- ***“A Roadmap for Revision”***: Six ‘critical revisions’ (see later slides): “rigorous editing” [1], methods description [2], standardized evidence tables [3], evaluating critical studies using standardized approaches [4], rationales for study selection to derive toxicity values [5], and strengthened and integrated discussions of weight of evidence [6].
- **Toxicokinetics**: incorporate the latest literature quantifying exogenously-derived versus endogenous formaldehyde in respiratory and more distal tissues, examine the impact of endogenous formaldehyde on analyses.
- **Mode of action**: expand MOA discussions for health effects, explore mutagenicity and cytotoxicity in IUR derivation.
- **Hazard and dose-response transparency**: standardize and provide rationale for hazard conclusions, describe and justify decisions for study selection, assumptions and modeling decisions for RfC and IUR derivation.

EPA’s responses to the NAS (2011) recommendations are documented in Appendix E.

Assessment Materials

Assessment Materials

Assessment Materials for Peer Review	Other Materials Provided and Added to Docket
<ul style="list-style-type: none">• Toxicological Review<ul style="list-style-type: none">• Primary analyses of the evidence, assessment conclusions, and justifications• Appendices<ul style="list-style-type: none">• Supporting analyses and documentation• Charge Questions<ul style="list-style-type: none">• Details scope of review and ensures peer feedback on key areas of scientific complexity and controversy	<ul style="list-style-type: none">• Assessment Overview<ul style="list-style-type: none">• Abridged version of main messages that may be useful to some readers• Compilation of public comments submitted to EPA Docket # EPA-HQ-ORD-2010-0396 (collated by charge question)

Assessment Materials

Toxicological Review	Appendices
<ul style="list-style-type: none">• <u>Assessment methods (Preface)</u>• <u>Organization based on understanding of TK</u>• Evidence syntheses by health effect and discipline• Summaries of supporting analyses• Evidence integration judgments• Dose-response analyses and decision rationale• Interpretation of susceptibility• Toxicity values and discussion of uncertainties	<ul style="list-style-type: none">• Background information• Documentation (literature search; study evaluations)• Supporting analyses (genotoxicity; toxicokinetics, MOA; dose-response)• Summary of existing assessments• <u>Response to NAS (2011) comments</u>• <u>Systematic evidence map of literature: 2016-2021</u>• QA documentation

Charge Question #1: Assessment Development Methods and Organization.

(a) Please comment on whether the methods for assessment development (*Preface on Assessment Methods and Organization*) and the organization of the assessment are clear and transparent.

(b) Please comment on whether there is sufficient documentation on methods and criteria...

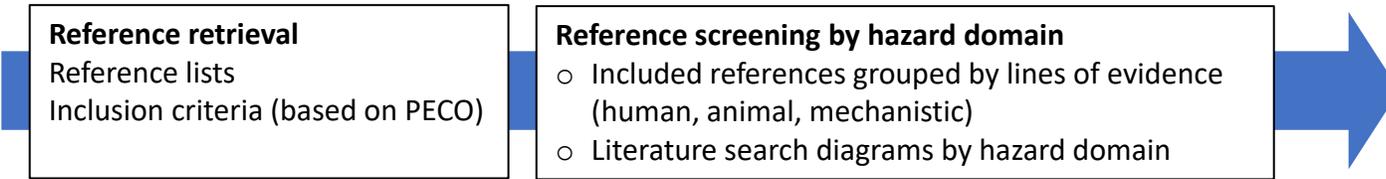
Assessment Methods: Systematic Review

Key Elements of Systematic Review Addressed in a Manner Consistent with the IRIS Handbook

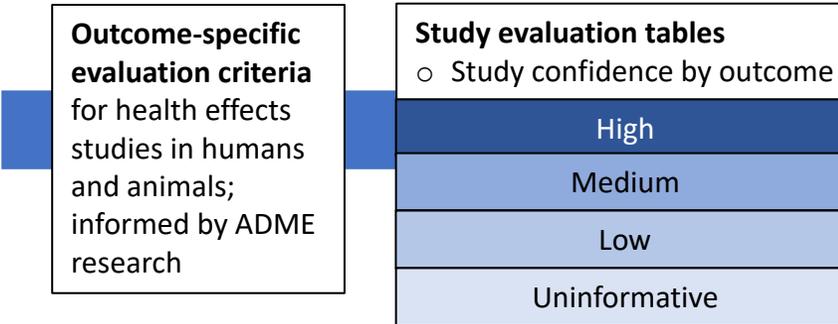
- *State a clearly defined objective:* PECO statements define the assessment-specific health questions.
- *Describe the criteria and approaches:* Detailed methods are described in the Preface and consistently applied.
- *Apply search strategy criteria in a literature search:* Details on search strings and databases in Appendices.
- *Select relevant studies using consistent criteria:* PECO criteria for health effect-specific searches in Appendices, with study-specific decisions on inclusion documented in HERO.
- *Evaluate individual studies using consistent criteria:* Criteria for study evaluations (risk of bias and sensitivity) are outlined in the Preface and documented in the Appendices with considerations by discipline and outcome.
- *Analyze and synthesize the evidence using consistent methodology:* Considerations for evaluating lines of evidence (human; animal; and mechanistic) are described in the Preface and applied within each synthesis section.
- *Interpret results and present a summary of findings:* A structured framework was used for evidence integration, with documentation of summary judgments by assessed health effect in evidence profile tables.

Assessment Methods: Overview of Approach

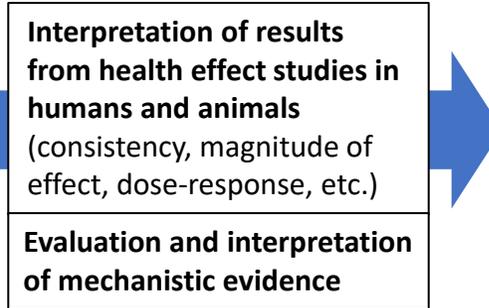
Literature Identification (hazard specific)



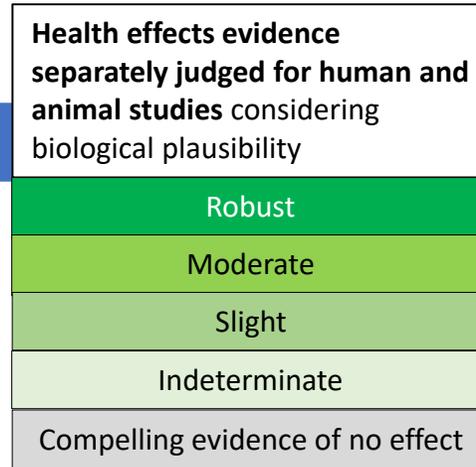
Evaluation of study methods (outcome-specific)



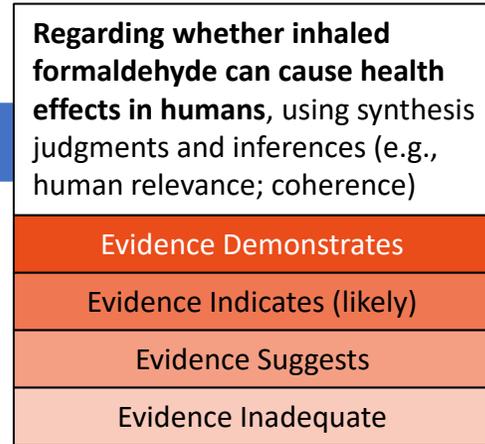
Syntheses of results



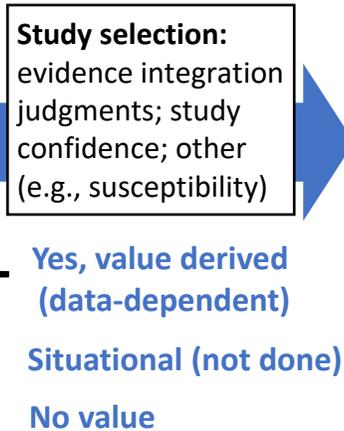
Synthesis judgments



Evidence integration judgments



Dose-response



Assessment Methods: Literature Searches

Databases	Health effect-specific literature searches
Web of Science ToxNet (now retired, contents moved) PubMed TSCATS2	[formaldehyde, formalin, paraformaldehyde, OR CASN 50-00-0] AND: <ul style="list-style-type: none"> • Sensory Irritation¹ • Pulmonary Function¹ • Immune-Mediated Conditions, focusing on Allergies and Asthma • Respiratory Tract Pathology • Developmental and Reproductive Toxicity • Nervous System Effects • Cancer • Inflammation and Immune Effects (mechanistic information²)

¹ No systematic consideration of animal studies on these outcomes.

² A separate, systematic literature search and evaluation was performed to augment the analyses of mechanisms.

Note: the draft cites a HERO project: https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/31; EPA is migrating this screening documentation to a new project to simplify the tagging structure: https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/4051.

Assessment Methods: Study Evaluation

All health effect studies considered in hazard identification were evaluated for strengths and limitations

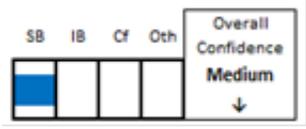
- Without regard to the direction or magnitude of the results
- Outcome-specific evaluations using criteria for several sources of bias or other limitations (including reduced sensitivity) that can affect the validity or interpretability of study results
- Confidence in results: *high, medium, low* and *uninformative* (*uninformative* not used in assessment judgments)

Domains evaluated in all health effect studies included in the assessment

Observational Epidemiology	Animal Toxicology	Controlled Human Exposure
<ul style="list-style-type: none">• Population selection• Exposure measurement and range• Outcome ascertainment• Potential confounding• Analytic approach, results reporting	<ul style="list-style-type: none">• Test animals• Exposure protocol• Endpoint evaluation• Experimental design• Data considerations and analysis	<ul style="list-style-type: none">• Randomization and blinding• Exposure generation• Outcome classification• Examination of confounding• Analytic approach, results reporting

Responsive to NAS (2011) Critical Revision 4: "All critical studies need to be thoroughly evaluated with standardized approaches... The findings of the reviews might be presented in tables to ensure transparency."

Assessment Methods: Documenting Study Evaluation

Human Studies	Exposure Measures and Range	Outcome Classification	Consideration of participant selection and comparability	Consideration of Likely Confounding	Analysis & Completeness of Results	Size/ Estimated Power	Study Confidence and Justification
<i>Ballarin et al., 1992 Prevalence study</i>	Personal sampling; 8-hr TWA (NIOSH, 1977): Warehouse (N=3), 0.39 ± 0.20 mg/m ³ , range 0.21 – 0.6 mg/m ³ ; Shearing-press (N=8), 0.1 ± 0.02 mg/m ³ , range 0.08 – 0.14 mg/m ³ ; Sawmill (N=1), 0.09 mg/m ³ Inspirable wood dust: 0.11 – 0.69 mg/m ³ , 0.73 in sawmill	Cytopathology analysis of nasal respiratory mucosa cells by two trained readers blinded to exposure status, scoring and classification analogous to Torjussen et al., 1979; Edling et al., 1988, most severe score present assigned.	Participant selection and recruitment not described. Non-smokers in plywood factory (N = 15) compared to non-smoking university or hospital clerks (N = 15) matched by age and sex. Excluded heavy drinkers. Use of referent group with different jobs results in less similar comparison groups	Addressed potential confounding by age and sex through matching and smoking and heavy alcohol use by exclusion.	Mean histological scores in exposed and referent compared using Mann-Whitney U test and frequency by classification using chi-square test	15 exposed/ unexposed pairs	 <p>Medium Confidence Inclusion only of current workers raises possibility of healthy worker survival effect due to irritation effects</p>

Animal Studies	Exposure Quality*	Test Subjects	Study Design	Endpoint Evaluation	Data Considerations & Statistical Analysis	Study Confidence and Justification
Animal studies: “Gray”= limitation expected to strongly influence results; “+” = limitation, but not expected to have a large impact on results interpretation; “++” = no notable limitations or any noted are not expected to impact results Horton et al. (1963) - Mouse	+ analytical concentrations not reported Note: extremely high formaldehyde levels examined (50-200 mg/m ³)	++ Note: n=15/ group; males only	+ Early mortality in high exposure group by 11th day of exposure	nose was not examined; lesion severity not reported	++	Low Confidence [nose was not examined; early mortality; failure to report lesion severity and analytical concentrations] Note: extremely high tested concentrations

*Exposure quality in the studies of controlled exposure was separately evaluated and documented in the appendices using a set of 7 criteria

Example on Respiratory Pathology (Documentation of study evaluations in Appendix A.5); responsive to NAS (2011) critical revision 4

Assessment Methods: Evidence Integration

To draw the strongest judgment for the available human evidence or the animal evidence requires:

Evidence from Human Studies

- *High or medium* confidence, independent studies;
- Results are largely consistent, and there are reasonable explanations when they differ;
- Reasonable confidence that alternative explanations are ruled out across studies;
- An exposure-response gradient is demonstrated; and
- The set of studies includes varied populations.

Supporting evidence may increase certainty: coherence (across endpoints; with mechanistic endpoints); large magnitude of effect.

Human		Animal
<i>Robust</i> ...human evidence		<i>Robust</i> ...animal evidence
<i>Moderate</i>		<i>Moderate</i>
<i>Slight</i>		<i>Slight</i>
<i>Indeterminate</i>		<i>Indeterminate</i>

Evidence from Animal Studies

- *High or medium* confidence, independent experiments;
- Results are largely consistent (inconsistent evidence is a set of weaker studies);
- Study designs address nonspecific effects (e.g., toxicity);
- Similar findings across laboratories or species; and
- Supporting evidence exists to increase certainty: coherence (across endpoints or mechanistic endpoints); a large or unusual magnitude of effect; a strong dose-response relationship; or consistency across exposure scenarios (e.g., duration), sexes, or strains.

An experimentally verified MOA can increase certainty to *robust* from *moderate* (not used in the current draft).

[Note: the Preface describes how these judgments are combined, considering human relevance and coherence across lines of evidence, etc.]

Responsive to NAS (2011) Critical Revision 6: “Strengthened, more integrative, and more transparent discussions of weight of evidence are needed... [including] the various determinants of weight of evidence, such as consistency.”

Assessment Methods: Evidence Integration Summary Table

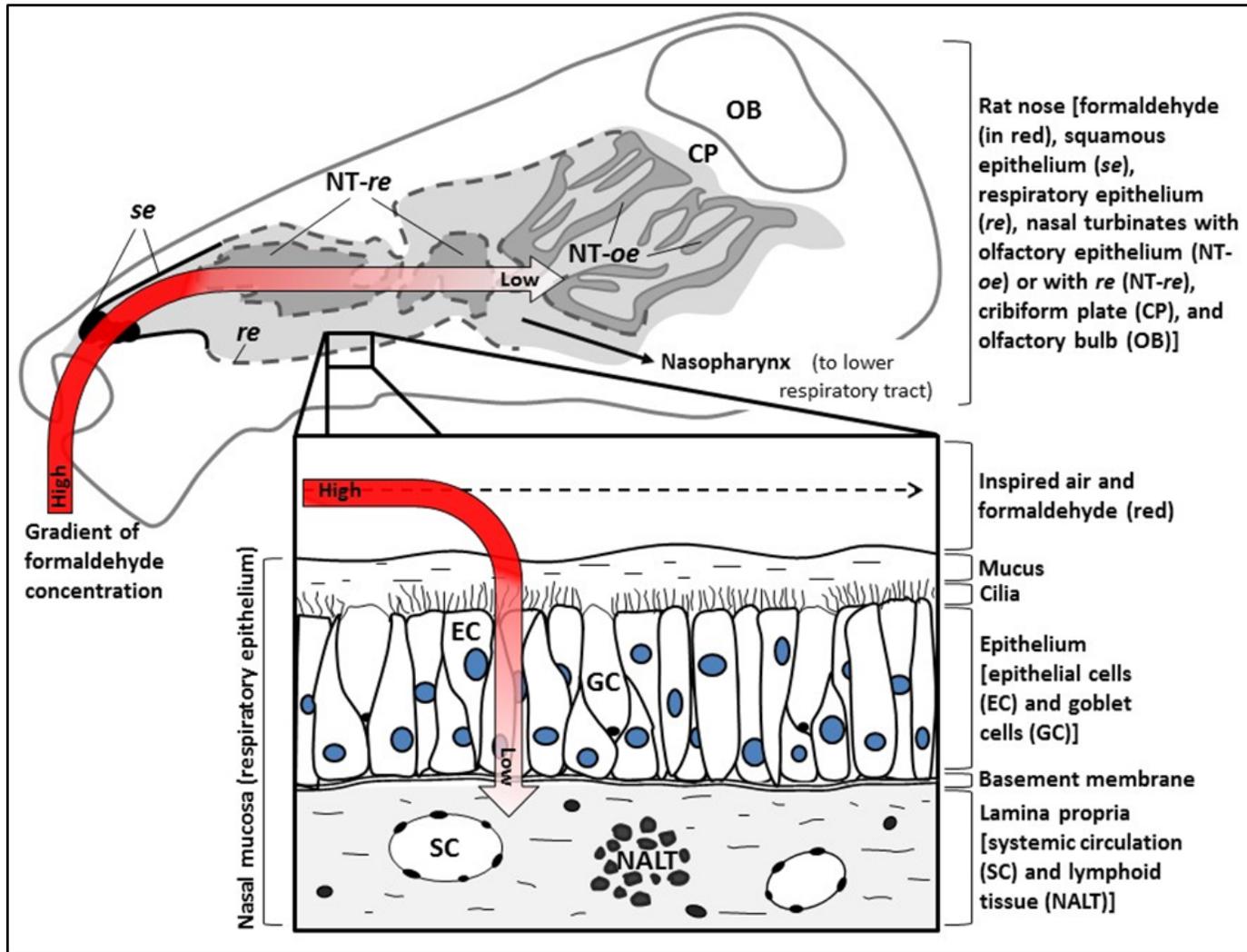
Evidence	Evidence Judgment	Hazard Determination
Human	<p>Moderate, based on: <i>Human health effect studies:</i></p> <ul style="list-style-type: none"> Of the 4 occupational studies, which were all interpreted with <i>medium</i> confidence (less sensitive due to health survival bias), 3 observed a higher prevalence of abnormal nasal histopathology, including loss of ciliated cells, hyperplasia, and squamous metaplasia at concentrations ranging from 0.1–2 mg/m³, while the remaining (1) study had more equivocal findings. <p><i>Biological plausibility:</i> Mechanistic changes in 2 studies (1 <i>medium</i> confidence) in humans provides evidence of changes in mucociliary clearance and mucus flow beginning at formaldehyde concentrations of 0.25–0.3 mg/m³.</p>	<p>The evidence demonstrates that inhalation of formaldehyde causes respiratory tract pathology in humans given appropriate exposure circumstances</p>
Animal	<p>Robust, based on: <i>Animal health effect studies:</i></p> <ul style="list-style-type: none"> <u>Consistent</u> evidence of squamous metaplasia and hyperplasia in the nasal respiratory epithelium across numerous, <u>independent high or medium confidence studies</u>, with generally the most sensitive effect being metaplasia after chronic exposure to ≥ 2.5 mg/m³. Evidence of both metaplasia and hyperplasia <u>across species</u>, in monkeys, rats, mice, and hamsters; the data were more limited for monkeys; mice and hamsters exhibited less sensitivity. Multiple studies provided <u>clear dose-dependence</u>, as demonstrated by increases in the incidence, severity, and anatomical location of the observed lesions with increasing exposure. <p><i>Biological plausibility:</i> Robust or moderate evidence for mechanistic events based predominantly on experimental animal studies supports a biological progression of changes including mucociliary dysfunction, epithelial damage, and often cellular proliferation, leading to the eventual development of nasal lesions, including squamous metaplasia.</p>	<p>Primarily based on rat bioassays of chronic exposure which consistently observed squamous metaplasia at formaldehyde levels ≥ 2.5 mg/m³.</p> <p><i>Potential Susceptibilities:</i> Variation in sensitivity may depend on differences in URT immunity, allergen sensitivity, and nasal structure or past nasal injury (e.g., studies support increased sensitivity of rodents with intentionally damaged nasal cavities), and males may be more sensitive than females.</p>
Other inferences	<p><i>Relevance to humans:</i> Similarities in the function and properties of the nasal epithelium across species, as well as similar mechanistic and apical effects in both humans and animals, provide strong support for the relevance of the findings in experimental animals to humans.</p> <p><i>Mode-of-action:</i> Although it may be incomplete, a MOA involving effects on mucociliary function and epithelial cell health is well supported and likely a major contributor to effects.</p> <p><i>Other:</i> 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 ~1.8–1.9-fold (on average) more influential than duration regarding exposure-induced mortality after acute exposure.</p>	

Example Evidence Profile Table on Respiratory Pathology (complements the evidence integration narrative text summary in the draft Toxicological Review); responsive to NAS (2011) critical revision 6

Charge Question #2: Toxicokinetics.

- (a) Please comment on the Toxicological Review conclusion that inhaled formaldehyde is not likely to be distributed in appreciable amounts beyond the respiratory tract to distal tissues.
- (b) Please comment on the Toxicological Review [toxicokinetic] assumptions drawn based on (a)...
- (c) Please comment on the Toxicological Review evaluation of considerations regarding endogenous formaldehyde in assessing the health risk due to inhaled formaldehyde.

Toxicokinetics: Distribution



Draft assessment conclusions and implications

There is no evidence that inhaled formaldehyde is distributed in measurable quantities beyond the respiratory tract to tissues such as bone marrow and blood. This judgment was reinforced by the research of Dr. Swenberg and colleagues examining inhaled vs. endogenous formaldehyde in various tissues at low exposure levels. Thus:

- 1) The organizational framework of the assessment follows this assumption, with the draft divided into effects in the respiratory system vs. at systemic (nonrespiratory) sites.
- 2) Particular attention is given to the quality of the exposure, especially in experimental studies.
- 3) Mechanistic discussions assume inhaled formaldehyde is not systemically distributed, and that it does not affect normal formaldehyde metabolic processes at those sites.

NAS (2011) Comment: "... high reactivity and extensive nasal absorption of formaldehyde restrict systemic delivery of inhaled formaldehyde beyond the upper respiratory tract and major conducting airways of the lung, so systemic responses are unlikely to arise from the direct delivery of formaldehyde (or its hydrated form, methanediol) to a distant site in the body."

Toxicokinetics: Endogenous Formaldehyde

- Formaldehyde is an essential metabolic intermediate generated in the body during normal cellular metabolic processes.
- The draft assessment computes extra risk over background
- Studies show that, at low exposures, inhaled formaldehyde may be less than endogenous tissue levels and endogenous formaldehyde may impact inhaled internal dose (e.g., in respiratory tissues). The current draft investigates this, finding:
 - the extent of this impact on inhaled dose is highly uncertain (see expanded discussion in the Toxicological Review)
 - endogenous levels are highly variable (see expanded discussion in Toxicological Review)

Separately, some have compared the draft RfC or IUR against formaldehyde in exhaled breath. These are not appropriate comparisons.



www.americanchemistry.com (2018)

Charge Question #3: Respiratory System Health Effects (Noncancer).

Charge Question #4: Systemic (i.e., nonrespiratory) Health Effects (Noncancer).

Please comment on whether the evidence integration decisions for hazard identification are clearly described and scientifically justified ... please separately comment on whether the dose-response decisions [POD(s) for each effect] are transparent and scientifically justified.

Charge Question #5: Noncancer Dose-Response and Reference Concentration.

Please comment on whether the approach and selection of the proposed RfC was clear and scientifically justified, including consideration of other potentially sensitive health effects.

Noncancer – Respiratory Health Effects: Summary

Health Effect	Human (primary basis)	Animal (primary basis)	Other	Judgment (susceptibility)
Sensory Irritation	Robust (many consistent observational and acute controlled exposure studies)	Robust (established effect with robust support for biological plausibility)	Dominant MOA identified; Duration not a clear driver	Evidence Demonstrates (nasal health may affect sensitivity)
Pulmonary Function	Moderate (several long-term residential and worker studies)	Slight (mechanistic changes in airways support biological plausibility)	MOA incomplete, but a few likely key events identified	Evidence Indicates [for long-term exposure only] (respiratory health and age may affect sensitivity)
Respiratory Pathology	Moderate (several worker studies and slight support for biological plausibility)	Robust (many consistent findings of metaplasia and hyperplasia across species with robust support for biological plausibility)	MOA incomplete, but several key events identified; levels more important than duration	Evidence Demonstrates (nasal and immune health and sex may affect sensitivity)
Allergic Conditions	Moderate (consistent but small increases across residential studies)	Slight (mechanistic changes in airways and allergen response support biological plausibility)	Several incomplete, potentially contributory MOAs with slight support	Evidence Indicates [for both] (respiratory and immune health, pregnancy status, and age may affect sensitivity)
Prevalence of Current Asthma	Moderate (residential and, more strongly, worker studies)			

Noncancer – Nonrespiratory Health Effects: Summary

	Health Effect	Human (primary basis)	Animal (primary basis)	Other	Judgment (susceptibility)
	Female Reproductive/ Developmental	Moderate (a few medium confidence occupational studies)	Indeterminate (low confidence studies with some mixed results)	Unknown MOA	Evidence Indicates (no information on susceptibility)
	Male Reproductive	Slight (one medium confidence occupational study)	Robust (several consistent rat studies with coherent effects on testes and sperm at high formaldehyde levels)	Uncertainty regarding human relevance; Unknown MOA, but a few mechanistic changes of interest identified	Evidence Indicates (no information on susceptibility)
Nervous System	Amyotrophic Lateral Sclerosis	Slight (mixed across studies but some strong signals in occupational settings)	Indeterminate (no relevant studies or mechanistic evidence)	Unknown MOA	Evidence Suggests [for all three] (for ALS, which disproportionately affects males, sex may influence sensitivity; age could be influential for all three effects)
	Developmental neurotoxicity	Indeterminate (no relevant studies or mechanistic evidence)	Slight (one medium confidence study suggesting effects with no contrary evidence)	Unknown MOA	
	Neurobehavior	Slight for some behaviors (some associations in low confidence studies)	Slight for some behaviors (findings from low confidence studies)	Unknown MOA; No long-term studies	

Noncancer Dose-Response and RfC: Bottom Line

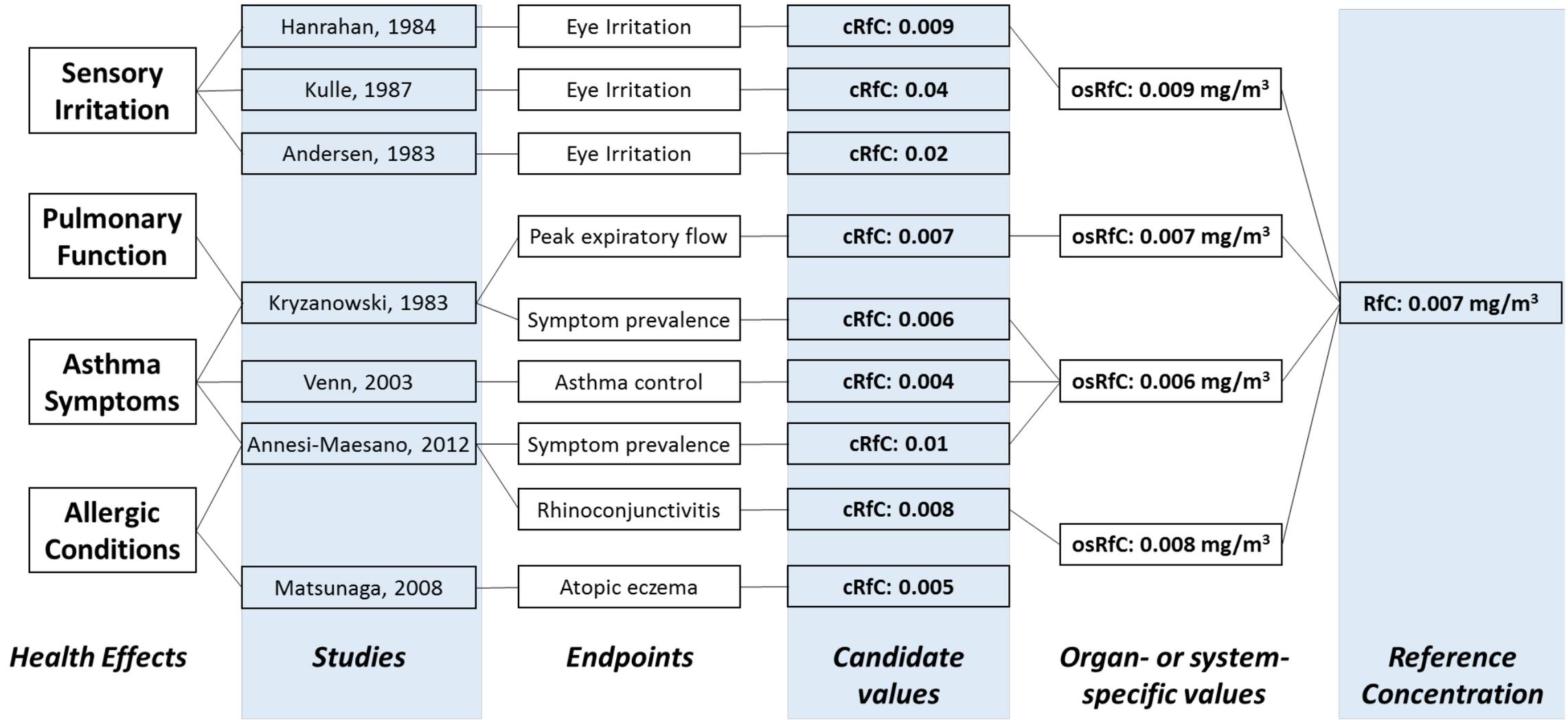
Noncancer health effect	E.I. judgment for health effect	Point of Departure (POD) basis	Confidence in POD	Composite Uncertainty Factor (UF _c)	osRfC (mg/m ³)
Decreased pulmonary function	Evidence indicates (likely)	Human (residential)	High	3	0.007
Allergic conditions	Evidence indicates (likely)	Human (residential)	High	3	0.008
Current asthma symptoms or degree of asthma control	Evidence indicates (likely)	Human (residential)	Medium	10 *	0.006 *
Sensory irritation	Evidence demonstrates	Human (residential)	Medium	10	0.009
Female reproductive and/or developmental toxicity	Evidence indicates (likely)	Human (occupational)	Low	10	0.01
Respiratory tract pathology	Evidence demonstrates	Rat (chronic)	Medium	30 *	0.003 *
Male reproductive toxicity	Evidence indicates (likely)	Rat (subchronic)	Low	3000	0.001
Nervous system effects	Suggestive evidence	Not Derived	-	-	-

	E.I. judgment for health effects	PODs basis	Confidence in PODs	Confidence in database	RfC (mg/m ³)	Overall Confidence
RfC:	Evidence indicates or demonstrates	Human (residential)	Medium or High	High	0.007	High

* osRfCs based on multiple studies/PODs

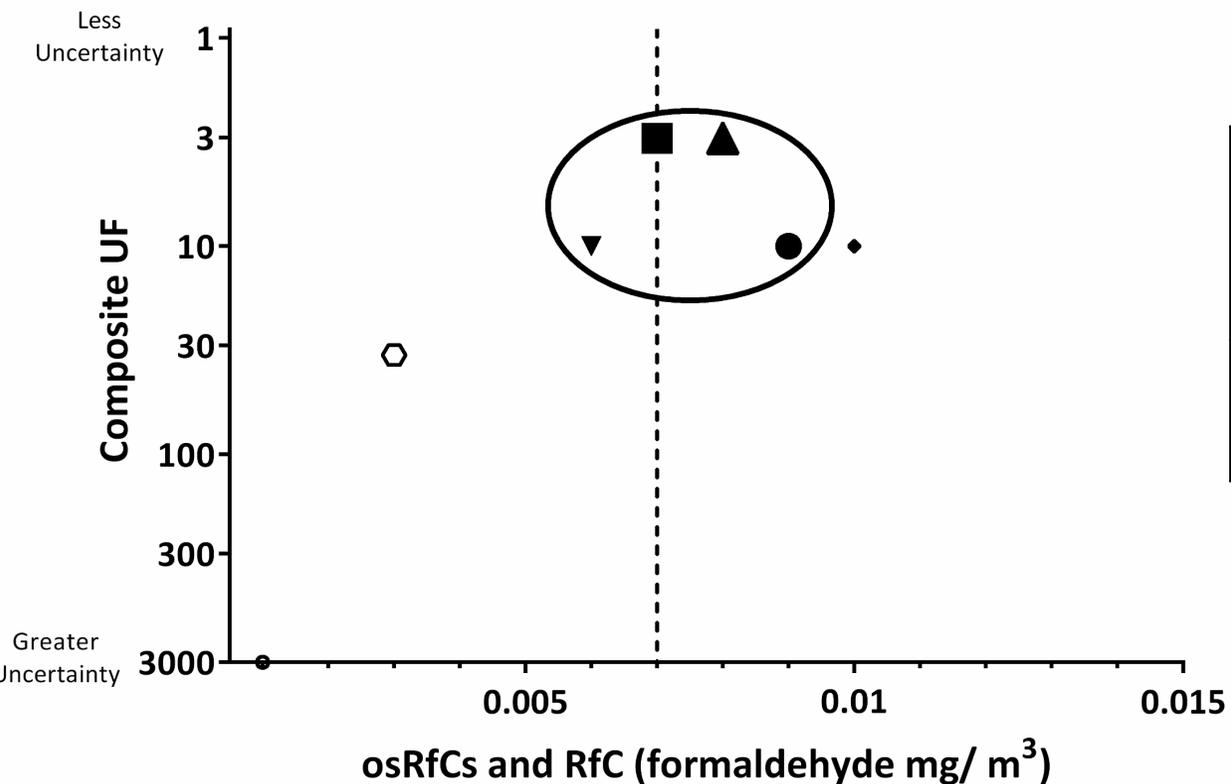
- RfC, Reference concentration: an estimated concentration of a continuous daily exposure of formaldehyde to a human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime
- osRfC, organ- or system-specific RfC: values that may be useful for some purposes (e.g., assessing cumulative effects)

Noncancer Dose-Response and RfC: RfC support



NAS (2011) Critical Revision #5: “The rationales for the selection of studies that are advanced for consideration in calculating the [toxicity values] need to be expanded... RfCs should be evaluated together with the aid of graphical displays...”

Noncancer Dose-Response and RfC: Selection of the RfC



RfC (mg/m ³)	Overall Confidence	Justification and Certainty			
		E.I. judgment for health effects	PODs basis	Confidence in PODs*	Confidence in database
0.007	High	Evidence indicates or demonstrates	Human	Medium or High	High

Note: *evidence demonstrates* is the strongest hazard ID judgment, *indicates* is second

*UF_Cs applied to the osRfCs supporting the RfC were no higher than 10

Higher Confidence ↑	Symbol	Endpoint (Source)
	■	Pulmonary function (Krzyzanowski et al., 1990)
	▲	Allergy-related Conditions (Annesi-Maesano et al., 2012)
	●	Sensory Irritation (Hanrahan et al., 1984)
	◻	Respiratory Tract Pathology (Kerns et al., 1983; Woutersen et al., 1989)
	▼	Asthma (Venn et al., 2003; Annesi-Maesano et al., 2012; Krzyzanowski et al., 1990)
	◆	Female Reproductive and/ or Developmental Toxicity (Taskinen et al., 1999)
	○	Male Reproductive Toxicity (Ozen et al., 2002)

*Confidence here combines confidence in the: study(ies), hazard judgment, POD (given more weight), and completeness of the hazard-specific evidence base.

Questions on the Methods or Noncancer Conclusions?

Charge Question #6: Cancer Hazard [Respiratory cancers].

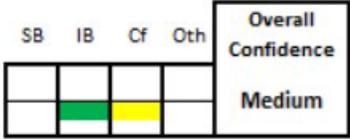
The assessment concludes that formaldehyde is ***Carcinogenic to Humans by the Inhalation Route of Exposure***. Please comment on whether the judgments below are clearly described and scientifically justified. Note that each of the three judgments in (a), (b), and (c, see myeloid leukemia]) would independently substantiate the carcinogenicity conclusion.

(a) Nasopharyngeal cancer, including support for a mutagenic MOA (see also question 6e)

(b) Sinonasal cancer, including support for a mutagenic MOA (see also question 6e)

(d) The carcinogenicity conclusion was not influenced by the judgments for several other cancer types ... including oropharyngeal/hypopharyngeal cancer and laryngeal cancer.

Cancer Hazard: NPC Evidence Table

<p>Reference: {West, 1993, 626646@@author-year}</p> <p>Population: Male and female Filipinos between the ages of 11 and 83 years recruited from the Philippine General Hospital and diagnosed prior to 1992. Among 234 suspicious cases, 9% refused biopsy and were excluded and 104 were pathologically confirmed as cases {Hildesheim, 1992, 4183293}, of which 100% agreed to participate. All 104 hospital controls agreed to participate while only 77% of community controls agreed to participate {Hildesheim, 1992, 4183293}.</p> <p>Outcome definition: Diagnosis of nasopharyngeal was confirmed by histological review for all cases. Histological typing not reported.</p> <p>Design: Hospital-based case-control study of 104 predominantly non-Chinese cases of nasopharyngeal cancer. 205 controls (104 hospital and 101 community cases) matched on gender, age, and hospital or neighborhood.</p> <p>Analysis: RRs estimated by ORs were calculated by conditional logistic regression and adjusted for education, years since first exposure to dust and exhaust fumes, smoking, antimosquito coils, herbal medicines, and diet including processed meats and fresh fish.</p> <p>Related studies: {Hildesheim, 1992, 4183293}</p>  <p>Confidence in effect estimates: MEDIUM ↓ (Potential bias toward the null)</p> <p>IB: Exposure Group C</p> <p>Cf: Controlling for other sources of formaldehyde may have underestimated effect of main formaldehyde exposures.</p>	<p>Exposure assessment: Occupational history obtained by interview for all participants. Occupational exposure to formaldehyde classified by industrial hygienist as likely or unlikely. Multiple exposure metrics including analysis by length of exposure, length of exposure lagged 10 years, TSFE, and age at first exposure were evaluated.</p> <p>Duration and timing: Duration of exposure was evaluated.</p> <p>Variation in exposure:</p> <p>Time since first exposure:</p> <ul style="list-style-type: none"> Level 1 (never) Level 2 (<25 years) Level 3 (≥25 years) <p>Antimosquito coil exposure:</p> <ul style="list-style-type: none"> Level 1 (never) Level 2 (<daily) Level 3 (≥ daily) <p>Length of exposure:</p> <ul style="list-style-type: none"> Level 1 (never) Level 2 (<15 years) Level 3 (≥15 years) <p>Length of exposure lagged 10 years:</p> <ul style="list-style-type: none"> Level 1 (no) Level 2 (<15 years) Level 3 (≥15 years) <p>Time since first exposure:</p> <ul style="list-style-type: none"> Level 1 (never) Level 2 (<25 years) Level 3 (≥25 years) Level 4 (≥35 years) <p>Age at first exposure:</p> <ul style="list-style-type: none"> Level 1 (never) Level 2 (<25 years) Level 3 (≥25 years) <p>Other exposures: dust and exhaust exposure, fresh or salted fish consumption, smoking, antimosquito coils, and herbal medicines.</p> <p>Note [truncated]...formaldehyde concentrations from 0.87 µg/m³ (0.7 ppb) to 25 µg/m³ (20 ppb).</p>	<p>Internal comparisons (Multivariate results from Table 4)</p> <p><u>Time since first exposure:</u></p> <ul style="list-style-type: none"> Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 1.2 (0.41–3.6) [12] Level 3 OR = 4.0 (1.3–12.3) [14] <p><u>Antimosquito coil exposure:</u></p> <ul style="list-style-type: none"> Level 1 OR = 1.0 (Ref. value) [59] Level 2 OR = 1.4 (0.64–2.8) [24] Level 3 OR = 5.9 (1.7–20.1) [21] <p>Additional: Bivariate results adjusted only for dust/exhaust from Table 1</p> <p><u>Length of exposure (bivariate):</u></p> <ul style="list-style-type: none"> Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 2.7 (1.1–6.6) [19] Level 3 OR = 1.2 (0.48–3.2) [8] <p><u>Length of exposure lagged 10 years (bivariate):</u> (Reference value included eight cases and three controls exposed only in the 10 years before diagnosis)</p> <ul style="list-style-type: none"> Level 1 OR = 1.0 (Ref. value) [83] Level 2 OR = 1.6 (0.65–3.8) [11] Level 3 OR = 2.1 (0.70–6.2) [8] <p><u>Age at first exposure (bivariate):</u></p> <ul style="list-style-type: none"> Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 2.7 (1.1–6.6) [16] Level 3 OR = 1.2 (0.47–3.3) [11] <p><u>Time since first exposure (bivariate):</u></p> <ul style="list-style-type: none"> Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 1.3 (0.65–3.8) [12] Level 3 OR = 2.9 (1.1–7.6) [14] <p><u>Time since first exposure (bivariate):</u></p> <ul style="list-style-type: none"> Level 4 OR = 5.6 (0.58–52.9) [5] <p>Authors note [truncated]: stronger effects were not evident among those considered most likely [or more highly] exposed...</p>
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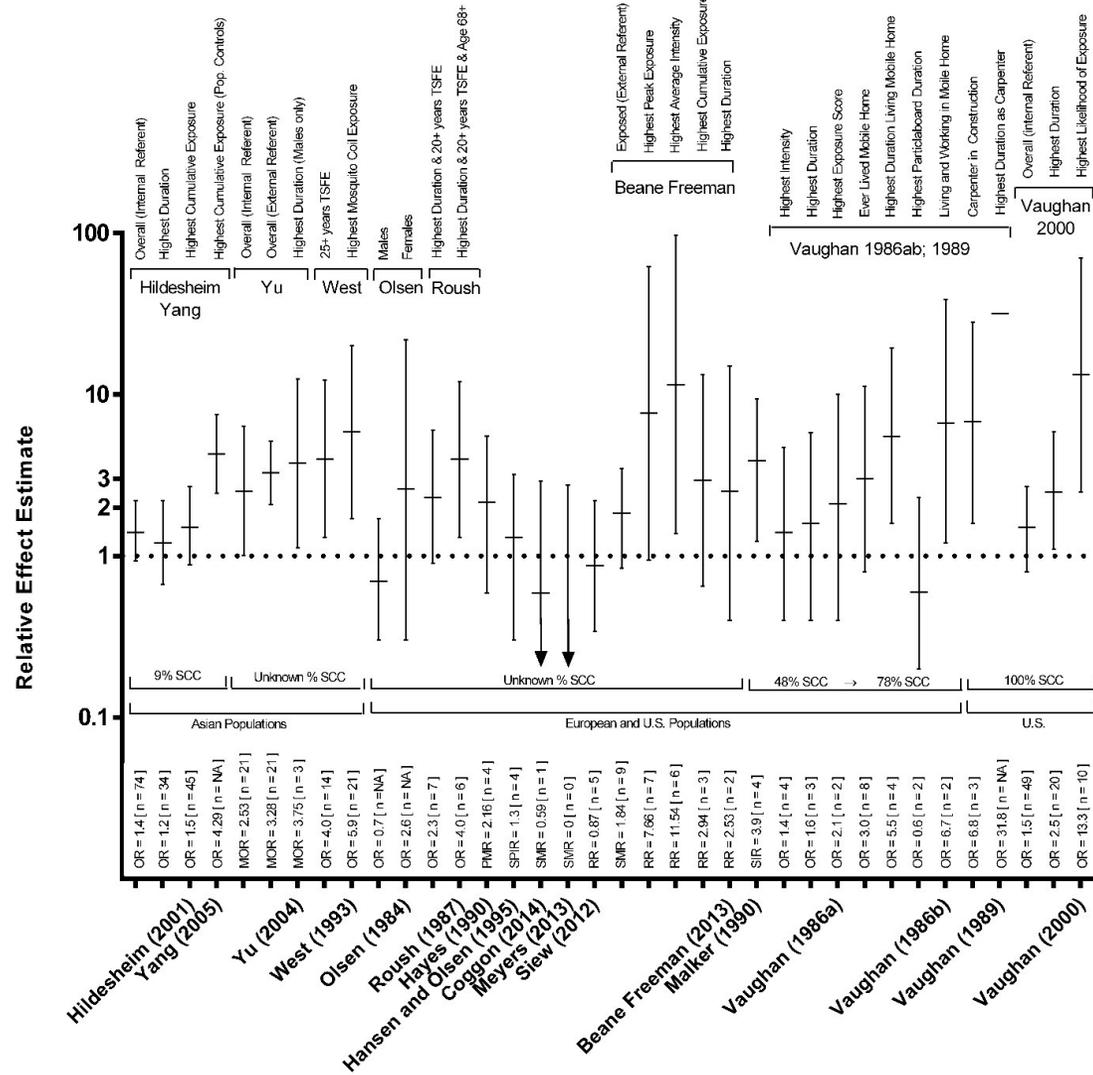
NAS (2011) Critical Revision #3: “Standardized evidence tables for all health outcomes need to be developed. If there were appropriate tables, long text descriptions of studies could be moved to an appendix or deleted.”

Cancer Hazard: Bottom Line

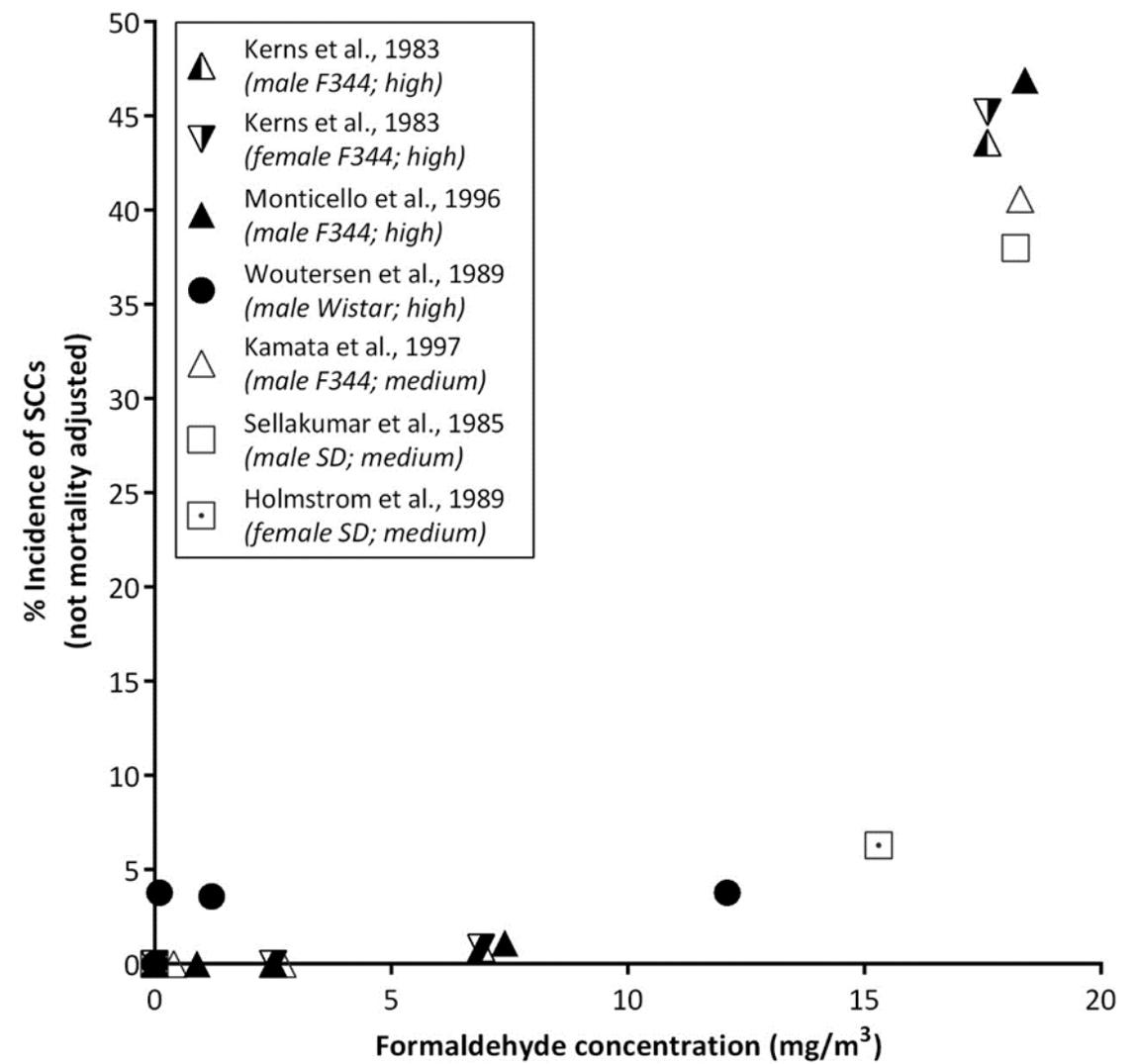
	Cancer Type	Human (primary basis)	Animal (primary basis)	Other	Judgment (susceptibility)
Respiratory	Nasopharynx (NPC)	Robust (many consistent studies with mechanistic support for biological plausibility)	Robust (nasal tumors in multiple species were exposure level- and duration-dependent; primarily observed at higher formaldehyde levels)	Mutagenic MOA	Evidence Demonstrates (prior nasal injury and smoking status might influence susceptibility)
	Sinonasal (SNC)	Robust (consistent studies for adenocarcinoma with mechanistic support for biological plausibility)	Moderate (evidence base same as above)	Mutagenic MOA	Evidence Demonstrates (see above)
	Oropharyngeal/ Hypopharyngeal	Slight (mixed across studies)	Slight (see draft)	Unclear MOA	Evidence Suggests
	Laryngeal	Indeterminate (see draft)	Indeterminate (see draft)	Not evaluated	Evidence Inadequate
Nonrespiratory	Myeloid leukemia	Robust (several consistent studies with mechanistic support for biological plausibility)	Indeterminate (predominantly null but overall inconclusive)	Unknown MOA	Evidence Demonstrates
	Multiple myeloma	Slight (see draft)	Indeterminate (see draft)	Unknown MOA	Evidence Suggests
	Hodgkin lymphoma	Slight (see draft)	Indeterminate (see draft)	Unknown MOA	Evidence Suggests
	Lymphatic leukemia	Indeterminate (see draft)	Indeterminate (see draft)	Not evaluated	Evidence Inadequate

Cancer Hazard: Nasal Cancers*

Epidemiology studies of nasopharyngeal cancer (mortality)



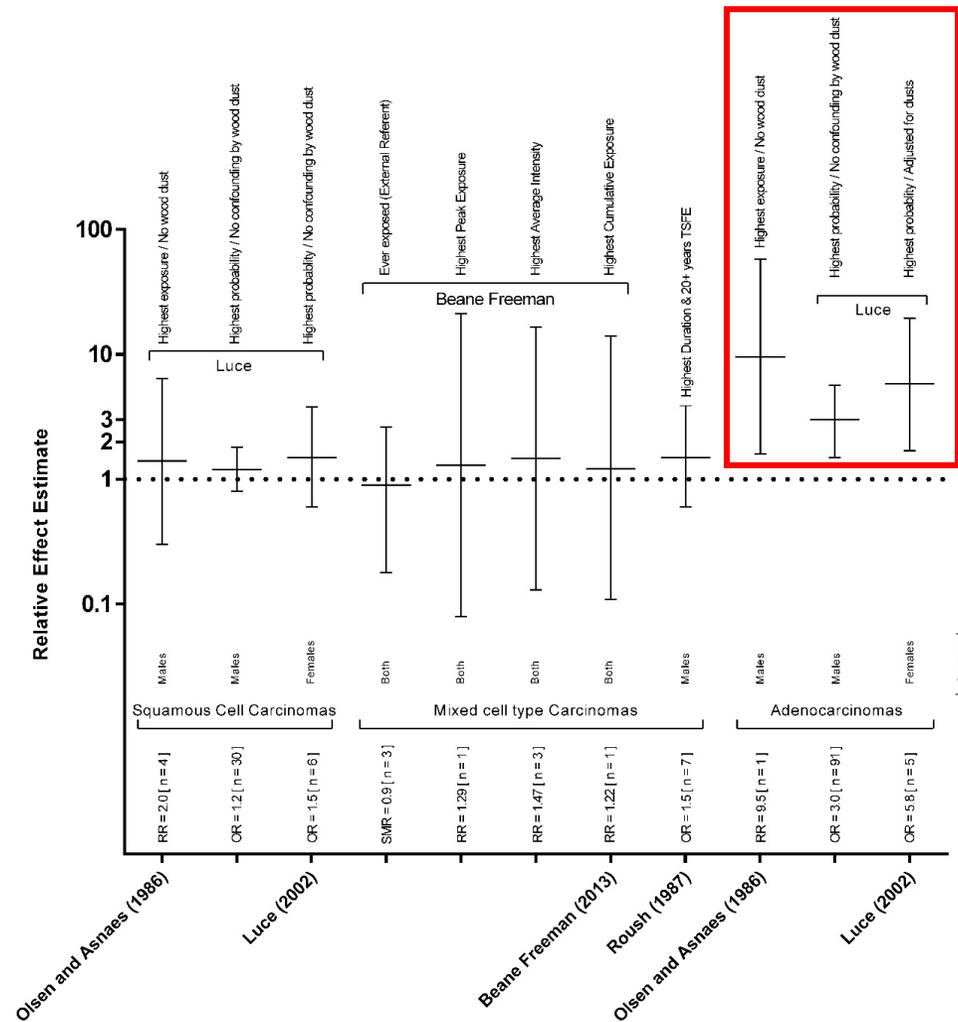
Nasal squamous cell carcinoma in rats exposed ≥ 2 yrs



* The assessment also considers (and derives estimates) based on mechanistic data, including BBDR modeling

Cancer Hazard: Nasal Cancers

Epidemiology studies of sinonasal cancer (mortality)



Sinonasal Cancer

- Sinonasal cancer is rare and some of the effect estimates have wide confidence intervals
- Evidence for adenocarcinoma was stronger than for squamous cell carcinoma
- Effects plotted here for Luce et al. (2002) represent a pooled case-control study of 12 independent case-control studies
 - Represents substantially more information than a single study result
 - Exposure-response relationship with categories of cumulative exposure while controlling for wood dusts
 - No quantitative estimate of the exposure-response function available
- An animal evidence judgment of *moderate* reflects some uncertainty in interpreting the strong animal and mechanistic evidence for nasal cavity cancers as fully applicable to human sinonasal cancer specifically

Charge Question #6: Cancer Hazard [Nonrespiratory cancers].

The assessment concludes that formaldehyde is ***Carcinogenic to Humans by the Inhalation Route of Exposure***. Please comment on whether the judgments below are clearly described and scientifically justified. Note that each of the three judgments in (a, see NPC), (b, see SNC), and (c) would independently substantiate the carcinogenicity conclusion.

(c) Myeloid leukemia, with no known MOA (see also question 6f)

(d) The carcinogenicity conclusion was not influenced by the judgments for several other cancer types ... including Hodgkin lymphoma, multiple myeloma, and lymphatic leukemia

Cancer Hazard: Nonrespiratory Cancers

- Focuses on the specific diagnoses of myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma
- No hazard conclusions for the broad categories of “all leukemias”, grouping of non-specific lymphomas, or “all LHP cancers.”
- However, the majority of the epidemiology studies that assessed lymphohematopoietic cancers did not report analyses at the level of granularity suggested by the NAS. If a study did report analyses for a more specific diagnosis, such as acute myeloid leukemia, it was provided in the evidence tables, but EPA conclusions were not drawn at that level.

NAS (2011) Comment: “The committee does not support the grouping of “all LHP cancers” because it combines many diverse cancers that are not closely related in etiology and cell of origin. The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas.”

Cancer Hazard: Myeloid Leukemia

Epidemiology study evaluations

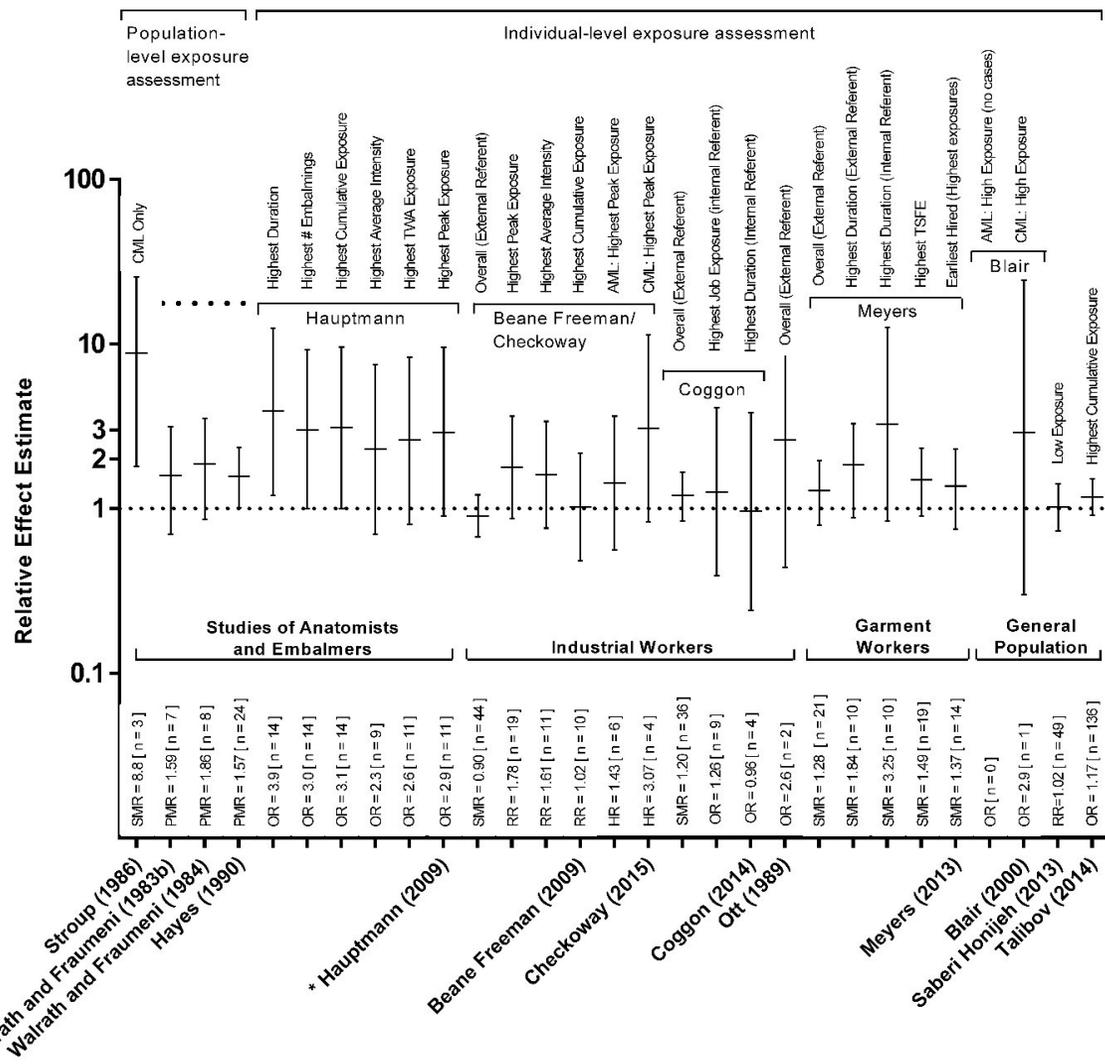
- 12 publications on 10 different study populations.
- *High* confidence studies: individual level exposure assessment, internal comparison groups, and evaluated cancer latency.
- *Low* confidence studies: limited by low sensitivity due to exposure misclassification, low precision.

Synthesis of evidence for myeloid leukemia

- Increased RR in studies of varied populations and designs.
- Strong associations in higher confidence studies (RR = 1.5 – 3)
- Associations with multiple exposure metrics (cumulative, duration, average, high peak).
- Exposure-response for some metrics in 3 higher confidence studies.
- Support for biological plausibility from immune cell changes and genotoxicity and mutagenicity in peripheral blood cells of exposed workers.
- Animal LHP data, including 2 chronic bioassays, were generally null, and animal mechanistic evidence relevant to potential carcinogenicity at systemic sites was weak.

Cancer Hazard: Myeloid Leukemia

Epidemiology studies of myeloid leukemia (mortality)



Summary of high confidence studies of reported exposure-response trends describing the effect estimates of association between formaldehyde exposure and risk of myeloid leukemia

High confidence studies reporting exposure-response trend assessments						
	Hauptmann, 2009 ^a		{Beane Freeman, 2009, 627726@@author-year} ^a		{Meyers, 2013, 1998382@@author-year} ^a	
Exposure metric	Continuous	Categorical	Continuous 2004 follow-up	Continuous 1994 follow-up	Continuous	Categorical
Duration	p = 0.020	NR	NR	NR	p = 0.30	NR
# of Embalming	p = 0.314	p = 0.012	NR	NR	NR	NR
Cumulative	p = 0.192	p = 0.023	p = 0.44	p = 0.171	NR	NR
Average	p = 0.058	NR	p = 0.40	p = 0.110	NR	NR
TWA8	p = 0.396	p = 0.021	NR	NR	NR	NR
Peak	p = 0.036	NR	p = 0.07	p = 0.0087	NR	NR

Abbreviations: TWA8 = 8-hour time-weighted average; NR = not reported.

^aFormaldehyde exposure measured as a continuous variable among unexposed and exposed persons.

Cancer Hazard: Myeloid Leukemia

The current EPA draft conclusion is based on:

- **Robust** human evidence of increased risk in workers exposed to high formaldehyde levels.
 - Supporting mechanistic evidence consistent with leukemia development across numerous studies of peripheral blood isolated from exposed workers, including mutagenicity and other genotoxic damage in lymphocytes and myeloid progenitors, and perturbations to immune cell populations.
- The assessment acknowledges that there appears to be a lack of concordance across species for leukemia (**Indeterminate** animal evidence) and no MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution.

Based on the **Robust** human evidence, the draft concludes that the **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans.

Charge Question #7: IUR [estimates for Respiratory cancers]

Please comment on the clarity and scientific justification for each specific decision in the draft cancer dose-response analyses, including study selection, POD estimates, and confidence in the calculated values.

(a) NPC IUR estimate from human data, including application of ADAFs for mutagenic MOA

(b) Nasal cancer IUR estimates from rat bioassays, including use of BBDR modeling, with presentation of both linear and nonlinear extrapolation approaches

(c) Given no quantifiable data, the IUR does not incorporate risk for SNC. Please comment on this decision and, if not supported, include a recommended method to account for this risk.

Cancer Dose-Response and IUR: NPC Estimate

Given the hazard conclusion for nasopharyngeal cancer in humans, the assessment derived an inhalation unit risk (IUR) estimate

- Selection of study for derivation of the IUR for nasopharyngeal cancer
 - Beane Freeman et al. (2013) presented results of the follow-up of the large National Cancer Institute (NCI) retrospective cohort mortality study [originally described by Blair et al. (1986) of 25,619 workers at 10 U.S. plants producing or using formaldehyde
 - Marsh et al. (2005) re-evaluated the association with NPC in the NCI cohort and reported that the majority of NPC cases arose in one of the 10 plants (Wallingford, CT) and thought there might be something specific about this plant – perhaps confounding. Marsh et al. (2007) speculated potential confounding by silversmithing.
 - Beane Freeman (2013) noted that the association did not change when analyses adjusted for silversmithing or 10 other co-exposures that were assessed.
 - Marsh et al. (2005) reported that two plants with the highest average intensity of formaldehyde exposure had the two highest SMR estimates for NPC (including Wallingford, CT).
 - The overall evidence does not indicate confounding of the formaldehyde association with increased risk of NPC.

Cancer Dose-Response and IUR: Bottom Line

Cancer type investigated	E.I. judgment for cancer type	Unit risk estimate basis	Unadjusted Unit risk estimate (per $\mu\text{g}/\text{m}^3$)	Age-Dependent Adjustment Factor-adjusted unit risk (per $\mu\text{g}/\text{m}^3$) *
Nasopharyngeal cancer	Evidence demonstrates	Human (occupational)	6.4×10^{-6}	1.1×10^{-5}
Myeloid leukemia	Evidence demonstrates	Human (occupational)	3.4×10^{-5}	NA
Sinonasal cancer	Evidence demonstrates	No usable data	-	-
Oro-/Hypo-pharyngeal cancer	Evidence suggests	No usable data	-	-
Multiple myeloma	Evidence suggests	No usable data	-	-
Hodgkin lymphoma	Evidence suggests	Not Derived	-	-
Laryngeal cancer	Inadequate evidence	Not Derived	-	-
Lymphatic leukemia	Inadequate evidence	Not Derived	-	-
Cancer Descriptor:	<u>Carcinogenic to humans</u> (strongest conclusion available in EPA guidelines)			
Total cancer risk (IUR) *:	1.1×10^{-5} per $\mu\text{g}/\text{m}^3$ (1.1×10^{-2} per mg/m^3) ; Confidence in the IUR based on NPC is Medium			

Note: 1991 IUR based on nasal cancers in rats = 1.3×10^{-5} per $\mu\text{g}/\text{m}^3$

* The draft IUR is based on NPC alone and the application of ADAFs based on an operant mutagenic MOA. A charge question has been posed to the peer review panel on potential inclusion of the myeloid leukemia estimate in the draft IUR.

Cancer Dose-Response and IUR: Nasal Unit Risk Comparison

	<i>Human</i> – selected approach	<i>Animal</i>
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	Regression model and lifetable analysis of U.S national incidence data of NPC mortality <ul style="list-style-type: none"> • Linear low-dose extrapolation because of mutagenic MOA 	Statistical modeling of the time-to-tumor incidence data and models incorporating multiple lines of mechanistic information (formaldehyde flux, DNA-protein crosslinks and site-specific cell labeling measurements) <ul style="list-style-type: none"> • Linear low-dose extrapolation because of mutagenic MOA
POD	BMDL = 0.068 mg/m ³	BMDL = 0.25 mg/m ³
Unit risk estimate *	7.4 x 10⁻³ per mg/m³	8.9 x 10⁻³ to 1.8 x 10⁻² per mg/m³

* Note that these estimates are provided for comparison purposes and do not represent the ADAF-adjusted values

Cancer Dose-Response: Nasal Cancer Modeling

The draft also presents results based on non-linear approaches

- CIIT's (Conolly et al) non-linear BBDR modeling of the rat tumor data and corresponding human extrapolation model are evaluated.
 - Results from the human BBDR modeling are compared with EPA's modeling of the NCI epidemiology data. At 0.15ppm where the epidemiology data indicate an extra risk of 0.0055, the predicted extra risk from CIIT models are: a) -0.0011 (i.e., lower than baseline) for the optimal model, and b) 5.7×10^{-6} for a conservative case.
 - The human BBDR extrapolation model was not robust at any exposure concentration.
 - PODs at the LEC005 were calculated from multiple implementations of the rat BBDR modeling resulting in similar unit risk $\sim 0.012 \text{ ppm}^{-1}$.
- cRfCs representing contribution from a MOA based on cytotoxicity-induced regenerative cell proliferation are calculated, including a cRfC based on the rat BBDR model. The cRfCs fall between 0.006 to 0.018 mg/m³. While provided for comparison, the use of an RfC approach was not preferred since a mutagenic MOA also contributes to the tumor response.

Charge Question #7: IUR [estimate for Myeloid leukemia]

Please comment on the clarity and scientific justification for each decision in the draft cancer dose-response analyses, including study selection, POD estimates, and confidence in the calculated values.

(d) For myeloid leukemia, a unit risk estimate is presented ... The derivation of a unit risk estimate for myeloid leukemia is not straightforward, and several approaches were considered. The selected data set used to derive the myeloid leukemia unit risk estimate combined the results from myeloid leukemia with results for other/unspecified leukemias ... ADAFs were not applied.

(e) Although the draft concludes that formaldehyde inhalation causes myeloid leukemia, the only data available to develop a unit risk estimate for myeloid leukemia are uncertain. The draft discusses the strengths and limitations of the myeloid leukemia estimate in detail. Please comment specifically on how the unit risk estimate for myeloid leukemia should inform the IUR, if at all.

Cancer Dose-Response and IUR: Myeloid Leukemia Estimate

Relative risk estimates for mortality from different cancers (ICD-based) by level of formaldehyde exposure

Cancer type	Relative risk (number of deaths)				<i>p</i> -trend, all person-years
	0	> 0 to < 1.5	1.5 to < 5.5	≥ 5.5	
	Cumulative formaldehyde exposure (ppm × years)				
	0	> 0 to < 1.5	1.5 to < 5.5	≥ 5.5	
Leukemia	0.53 (7)	1.0 (63)	0.96 (24)	1.11 (29)	0.08
Myeloid leukemia	0.61 (4)	1.0 (26)	0.82 (8)	1.02 (10)	0.44
Other/unspecified leukemia	0.77 (2)	1.0 (15)	1.65 (10)	1.44 (9)	0.13

Exposure-response modeling (all person-years) and (incidence) unit risk estimate derivations; shaded estimate preferred

Cancer grouping	Deaths in NCI cohort	Regression coefficient- β (per ppm × year)	SE (per ppm × year)	<i>p</i> -value	Unit risk estimate (per ppm)*
All leukemia	123	0.01246	0.006421	0.08	5.9×10^{-2}
Myeloid leukemia	48	0.009908	0.01191	0.44	3.9×10^{-2}
Other/unspecified leukemia	36	0.01754	0.01011	0.13	Not calculated
Myeloid + Other/ Unspecified leukemias **	84^a	0.01408	0.007706	0.10	4.2×10^{-2}

* The estimates are based on PODs reflecting the 95% lower confidence limit on the concentration estimated to result in a 0.5% increase in cancer incidence risk

** 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.

Cancer Dose-Response and IUR: Myeloid Leukemia Estimate

Given the strong hazard conclusion and the prevalence of (and mortality from) myeloid leukemia in humans, the assessment develops a unit risk estimate for myeloid leukemia; however, the assessment:

- Includes a frank discussion of the strengths and limitations/ uncertainties of the data available for quantification.
- Acknowledges that the approach presented is uncommon and not-straightforward because of complications in the data in the only study with suitable dose-response information.
- Given the uncertainties in the estimate, the myeloid leukemia estimate is NOT included in the draft IUR sent to peer review.
- A specific charge question is included requesting that peer reviewers comment on the utility (if any) of the estimate for myeloid leukemia, and how (if at all) the estimate should be used in the final assessment.

Cancer Dose-Response and IUR: Summary

EPA concludes: *“Formaldehyde Is Carcinogenic to Humans by the Inhalation Route of Exposure”*

Three separate evidence integration judgments independently substantiate this conclusion:

- Nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia
- An IUR for nasopharyngeal cancer was derived
- An IUR for sinonasal cancer could not be estimated
- An IUR for myeloid leukemia was estimated with uncertainty
- If the NASEM panel supports the draft cancer hazard judgments, the draft IUR underestimates the total cancer risk
- EPA is seeking the panel’s input on providing the best IUR estimate of total cancer risk

Summary of Main Messages

Summary of Main Messages: Draft Conclusions

Noncancer

- Formaldehyde inhalation can cause a spectrum of noncancer respiratory effects in humans (including in children) and is also likely to affect reproduction and development.
- The **draft RfC = 7 µg/m³** based on respiratory effects in human residential studies.
- There is currently no RfC for formaldehyde in IRIS.

Cancer

- Formaldehyde inhalation is *carcinogenic to humans* based on nasopharyngeal cancer, sinonasal cancers, and myeloid leukemia evidence (Note: this draft conclusion is stronger than the EPA 1991 conclusion).
- The **draft IUR = 1.1 x 10⁻⁵ per µg/m³** based on nasopharyngeal cancers in workers.
- This draft IUR is close to EPA's 1991 value.
- If the NASEM panel supports the draft IUR estimate for nasopharyngeal cancers and recommends the myeloid leukemia estimate be included, the combined IUR would be approximately 4-fold higher.

Summary of Main Messages: Comparison to Current IRIS Values

Current Draft (2022)				EPA 1990/1991
Noncancer Health Effect	Noncancer Hazard Identification	osRfC (mg/m ³) ^a	Overall RfC	Overall RfC
Sensory Irritation	Evidence demonstrates	0.009	0.007 mg/m ³ (6 ppb)	[inhalation noncancer effects not characterized]
Pulmonary Function	Evidence indicates [likely]	0.007		
Allergy-related Conditions	Evidence indicates [likely]	0.008		
Current asthma symptoms or degree of asthma control	Evidence indicates [likely]	0.006		
Respiratory Tract Pathology	Evidence demonstrates	0.003		
Female and/or Developmental Toxicity	Evidence indicates [likely]	0.01		
Male Reproductive Toxicity	Evidence indicates [likely]	0.001		
Neurotoxicity	Suggestive evidence	Not advanced		
Cancer type	Carcinogenicity Descriptor	Unit risk (per ppm) ^b	Total unit risk ^b	Total unit risk
Nasopharyngeal cancer	“Carcinogenic to Humans” (independently substantiated by evidence demonstrating that inhaled formaldehyde can cause each of these 3 cancer types)	1.3 x 10 ⁻²	1.1 x 10 ⁻² per mg/m ³ (1.3 x 10 ⁻² per ppm)	1.3 x 10 ⁻² per mg/m ³ (1.6 x 10 ⁻² per ppm)
Myeloid leukemia		4.2 x 10 ⁻²	Charge Question to NASEM	No hazard identified
Sinonasal cancer		No data available to quantify		No hazard identified

^a osRfC (organ/ system-specific RfC); these values may be useful for some purposes (e.g., consideration of cumulative risk by EPA risk assessors)

^b based on incidence estimates (includes ADAFs where applicable; note: the value in the 2022 draft without ADAF adjustments is 6.4 x 10⁻³ per mg/m³)



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And “Thank You!” to many other contributors

Questions on the Cancer Conclusions?

Takeaway Points from this presentation on the draft IRIS formaldehyde (inhalation) assessment:

- In addressing NAS (2011) comments, the application of key tenets of systematic review was operationalized.
- Methods used to develop this draft served as a platform for, and are consistent with, methods in the IRIS Handbook.
- All relevant evidence is considered, and multiple opportunities are provided to identify missed studies.
- Draft development and review follows the IRIS 7-step process.
- Standardized methods, structured frameworks, and graphical aids promote transparency of complex hazard analyses.
- Understanding of toxicokinetics and MOA are incorporated in multiple ways, including in quantitative estimates.
- Strengths and uncertainties of different options for deriving toxicity values are discussed and all decisions justified.
- *The draft identifies several noncancer and cancer hazards of potential concern for exposed persons, provides a new RfC, and derives an IUR close to what is on IRIS; a key peer review charge question focuses on the IUR.*