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IRIS Toxicological Review of Formaldehyde (Inhalation)

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EXECUTIVE SUMMARY

ES.1 OVERALL SUMMARY

This IRIS health assessment presents a systematic review of the publicly available evidence relevant to inhalation exposure to formaldehyde and potential adverse health outcomes. The assessment specifically focuses on the following health effects: sensory irritation; pulmonary function; immune system effects, focusing on allergic conditions and asthma; respiratory tract pathology; nervous system effects; reproductive and developmental toxicity; and cancer. For cancer, the assessment focuses on cancers of the upper respiratory tract (including nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx/hypopharynx, and laryngeal cancer in humans) and of the lymphohematopoietic system (including Hodgkin lymphoma, multiple myeloma, myeloid leukemia, and lymphatic leukemia in humans). The evidence identification, evaluation, synthesis, and integration framework used to conduct the assessment is schematically depicted in Figure 2-1, with detailed methods provided in Section 2.

The main conclusions of the assessment are summarized below, with additional details in Tables ES-1 and ES-2 and the following sections.

- Inhaled formaldehyde can cause health effects in humans, most notably respiratory effects. Children and those with respiratory disease appear to be most susceptible.
- Formaldehyde is ***carcinogenic to humans*** by the inhalation route of exposure.
- The noncancer reference concentration (RfC) is 0.007 mg/m^3. Confidence in the RfC is **high**.
- The cancer inhalation unit risk (IUR) is 1.1×10^{-5} per µg/m^3 (1.1×10^{-2} per mg/m^3). Confidence in the IUR is **medium.**

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

Noncancer health effect	Evidence integration judgment	POD basis	UFC	osRfC (mg/m^3)	Confidence in value [d]
Decreased pulmonary function	**evidence indicates [likely]** [c]	Human (children)	3	0.007	**High**
Allergic conditions	**evidence indicates [likely]**	Human (children)	3	0.008	**High-medium**
Prevalence of current asthma or degree of asthma control	**evidence indicates [likely]**	Human (children)	10 [c]	0.006 [c]	**Medium-high**
Sensory irritation	**evidence demonstrates**	Human (adults)	3	0.02	**Medium-low**
Female reproductive or developmental toxicity	**evidence indicates [likely]**	Human (adults)	10	0.01	**Low-medium**
Respiratory tract pathology	**evidence demonstrates**	Rat (adults)	30	0.003	**Medium-high**
Male reproductive toxicity	**evidence indicates [likely]**	Rat (adults)	1000	0.006	**Low**
Nervous system effects [a]	**evidence suggests**	Not Derived	-	-	
Reference Concentration (RfC) = 0.007 mg/m^3; confidence in the RfC is **high**					
Based on decreased pulmonary function, prevalence of current asthma or degree of asthma control, and allergic conditions [b]	**N/A**	Human	3 or 10	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]For each of the three potential manifestations of nervous system effects evaluated in this review (i.e., amyotrophic lateral sclerosis incidence or mortality, developmental neurotoxicity, or behavioral toxicity), it was concluded that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause these effects in humans.

[b]The RfC is supported by three osRfCs (shaded) from multiple *high* and *medium* confidence studies of residential or school-based formaldehyde exposure to children (Venn et al., 2003; Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012). The RfC value is selected as the midpoint of the three osRfCs (i.e., 0.006, 0.007, and 0.008 mg/m^3) with the highest confidence and the lowest UF_C values (see Section 5.1.5).

[c]This osRfC is based on multiple studies and candidate values, sometimes with different UF_Cs applied. The UF_C value shown in this table and Figure 5-3 reflects the candidate value selected to represent this osRfC [i.e., the UF_C applied to the POD from Krzyzanowski et al. (1990)].

[d]For hyphenated confidence classifications, the first term reflects the confidence category, and the second term indicates whether the judgment is closer to a higher or lower confidence category (e.g., **High-medium** is a **High** confidence judgment that is close to a judgment of **Medium** confidence). See Section 2.7 for the methods for drawing these confidence judgments, and Section 5.1.5 for the supporting rationale for each judgment.

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

Cancer type investigated	Evidence integration judgment for cancer type risk	Unit risk estimate basis	Unadjusted unit risk estimate (per µg/m³)	Inhalation unit risk estimate (per µg/m³)[a] [ADAF-adjusted]	Confidence in the inhalation unit risk estimate
Nasopharyngeal cancer (or nasal cancer in animals)	**evidence demonstrates**[b]	Human	7.4×10^{-6}	**1.1×10^{-5}**	**Medium**
		Animal[c]	8.9×10^{-6} to 1.8×10^{-5}	NA[d]	NA[d]
Myeloid leukemia	**evidence demonstrates**[e]	Too uncertain[f]	-	-	
Sinonasal cancer	**evidence demonstrates**[g]	No usable data	-	-	
Oropharyngeal/Hypo-pharyngeal 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	-	-	
Carcinogenicity Descriptor:	***Carcinogenic* to Humans**				
Total cancer risk (IUR)[h]:	**1.1×10^{-5} per µg/m³** (1.1×10^{-2} per mg/m³); Confidence in the IUR is **Medium**				

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

[a]ADAF adjustments are recommended for cancers for which there is sufficient evidence that formaldehyde has, at least in part, a mutagenic MOA (see Section 5.2.4).

[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 selected unit risk estimate for NPC is based on a cancer mortality study in humans, several estimates in general agreement with this value and each other were also derived based on animal nasal tumor incidence. The points of departure for these estimates were based on multiple mechanistic and statistical models, including biologically based dose-response (BBDR) modeling. Results for human extrapolation were based on internal dose metrics and BMRs ≤ 0.01 extra risk (see Section 5.2.1). In addition, an RfC for cytotoxicity-induced regenerative cell proliferation, one of the mechanisms contributing to nasal cancer development, was estimated to be between 0.006 and 0.018 mg/m³ (see Section 5.2.1).

[d]NA = not applicable; an ADAF-adjusted value was not calculated and a level of confidence was not assigned for the unit risk estimates based on the animal data on nasal cancer, as the human unit risk estimate for NPC was the selected 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 *indeterminate* 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 lymphohematopoietic (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]Although several attempts were made to derive a unit risk estimate for myeloid leukemia, it was ultimately concluded that these estimates were too uncertain. Thus, while the best estimate currently available (see Appendix D.2.3) may provide some perspective on the extent to which the IUR underestimates cancer risk (i.e., because estimates for myeloid leukemia and sinonasal cancer are not included), this estimate was not selected to represent a unit risk for myeloid leukemia or included in the IUR.

[g]The judgment of **evidence demonstrates** for sinonasal cancer is based primarily 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; see Section 3.2.5).

[h]The full lifetime IUR estimate is based on the ADAF-adjusted estimate for nasopharyngeal cancer (which includes a mutagenic MOA; Section 3.2.5). 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 7.4×10^{-6} per $\mu g/m^3$ or the adult-based estimate of 6.4×10^{-6} per $\mu g/m^3$. Otherwise, see Section 5.2.4 for how to apply the ADAFs to obtain total cancer risk estimates for less-than-lifetime exposure scenarios.

ES.2 NONCANCER HEALTH EFFECTS CONCLUSIONS AND QUANTITATIVE ESTIMATE

Overall, the integrated **evidence demonstrates** that inhalation of formaldehyde causes increased sensory irritation and respiratory tract pathology in humans (see Section 2.6 for a description of the bolded evidence integration judgments and their definitions), given sufficient exposure conditions[1]. Well-conducted studies in humans and animals support these hazard conclusions, and strong mechanistic evidence in animals provides plausible modes of action (MOAs) for the identified endpoints.

The available **evidence indicates** that formaldehyde inhalation likely causes decreased pulmonary function, an increased frequency of current asthma symptoms or difficulty controlling asthma, and increased allergic responses in humans, given sufficient exposure conditions. These conclusions were supported primarily by evidence in exposed humans, with supportive mechanistic evidence indicating that formaldehyde inhalation results in biological changes related to these outcomes in exposed animals. In addition, the **evidence indicates** that inhalation of formaldehyde likely causes female reproductive or developmental toxicity and reproductive toxicity in men, given sufficient exposure conditions. The conclusion for female reproductive or developmental toxicity is supported by evidence in humans, specifically increases in time-to-pregnancy (TTP) and spontaneous abortion risk; mechanistic evidence explaining such effects without systemic distribution of formaldehyde is lacking. The conclusion for male reproductive toxicity is supported primarily by coherent evidence of several alterations to the male reproductive

[1] Use of this phrase, "given sufficient exposure conditions", throughout the assessment highlights that, for those assessment-specific health effects identified as potential hazards, the exposure conditions associated with those health effects are defined (as are the uncertainties in the ability to define those conditions) during dose-response analysis.

system in animals exposed to very high levels of formaldehyde (> 6 mg/m^3), with some corroborative changes in an occupational epidemiological study; although no MOA is available, some relevant mechanistic changes have been observed in well-conducted studies of the male reproductive organs of exposed rodents.

Lastly, while a number of studies reported evidence of potential neurotoxic effects, including developmental neurotoxicity, behavioral toxicity, and an increased incidence of, or mortality from, the motor neuron disease amyotrophic lateral sclerosis (ALS), due to limitations in the database (e.g., poor methodology, lack of consistency), the integration of the evidence for each of these manifestations of potential neurotoxicity ultimately resulted in the determination that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation may pose a human health hazard, and additional study is warranted. The available data on potential nervous system effects were considered insufficient for developing quantitative toxicity estimates.

ES.2.1. Inhalation Reference Concentration (RfC)

The reference concentration (the RfC) of 0.007 mg/m^3 formaldehyde is level of a 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.

In this assessment, the RfC is based on several organ- or system-specific RfCs based on the evidence for effects on that particular organ or system (osRfCs), which are themselves based on candidate reference concentrations (cRfCs). The cRfCs are estimates for a specific endpoint based on a single, specific study within an organ- or system-specific hazard domain. The osRfCs differ from the associated cRfCs only when there are multiple cRfCs for the same organ system. The osRfCs were selected from those cRfCs that best represented the general population, including sensitive subgroups and which had a greater degree of certainty with regard to both reliability of study results and cRfC derivation (including POD selection). In addition, cRfCs with lower composite (total) uncertainty factors (UF_Cs) were preferred.

The osRfCs that were used to calculate the overall RfC in this assessment were all based on epidemiological studies of residential or school-based formaldehyde exposure to children that were interpreted with either **High** or **Medium** confidence and had the lowest composite uncertainty factor (UF_Cs) (see Table ES-1).

The selected RfC is the midpoint of three osRfCs (0.006, 0.007 0.008 mg/m^3) representing a group of respiratory system-related effects (i.e., pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control) that were interpreted with the highest confidence and had the lowest UF_Cs. These health effects were observed in the range of typical formaldehyde exposures in population studies (effects were observed in the underlying studies at approximately ≥ 33 μg/m^3). The selected RfC is likely to be above outdoor formaldehyde levels in most locations, and levels in indoor air would be expected to exceed this concentration in many situations. However, as the RfC is interpreted to be without appreciable risk, even in sensitive subgroups, it is

important to note that the potential for health effects in individuals at concentrations between the RfC (0.007 mg/m^3) and levels at which health effects have been observed in the available population studies (~ ≥ 0.033 mg/m^3) is unknown.

Although the RfC is designed to apply to exposures over a lifetime, the relevant window of exposure for some of the effects observed in the contributing studies may be less than a lifetime. For example, the relevant window of exposure for effects on asthma outcomes is also less than lifetime, although the time frame for the control of asthma symptoms (i.e., a few weeks) is different than that for the prevalence of current asthma symptoms or a decrease in pulmonary function (i.e., the past 12 months).

Overall confidence in the RfC is **High.** There is **high** confidence in the composite set of studies used to derive the RfC, **high** or **medium** confidence in the derivation of the underlying cRfC numerical values, and **high** confidence in the completeness of the literature database supporting the judgment that formaldehyde causes the adverse noncancer health effects identified.

ES.3 HUMAN CARCINOGENICITY CONCLUSION AND QUANTITATIVE ESTIMATE

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), formaldehyde is ***Carcinogenic to Humans by the Inhalation Route of Exposure***. This 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. 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 (i.e., *robust* human evidence). 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 lymphohematopoietic (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., *indeterminate* animal evidence). The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.

ES 3.1. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK: INHALATION EXPOSURE

The inhalation unit risk (IUR) is 1.1×10^{-5} per $\mu g/m^3$, which is an upper-bound estimate of the increased lifetime risk of cancer from inhaling 1 $\mu g/m^3$ of formaldehyde for 70 years (see Table ES-2). The estimate is based on an estimate of increased risk for NPC, for which **evidence demonstrates** that formaldehyde inhalation causes this type of cancer in humans. The IUR does not incorporate a unit risk estimate for myeloid leukemia (also for which the **evidence demonstrates** that formaldehyde inhalation causes this type of cancer in humans) because the interpretation of the published exposure-response modelling results was deemed too uncertain (see Section 5.2.2). This estimate also does not incorporate risk from sinonasal cancer for which the **evidence demonstrates** that formaldehyde inhalation exposure causes this type of cancer in humans, as amenable data were unavailable. Thus, the IUR may underestimate actual cancer risk, to an unknown extent.

The IUR is based on the modeling results of the association of cumulative formaldehyde exposure with NPC mortality in an occupational cohort followed by the National Cancer Institute (Beane Freeman et al., 2013). The regression coefficient from the dose-response model (log-linear models) was applied to age-specific cancer incidence rates from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) database using life-table methods to estimate the upper bound on the extra risk[2] expected at a formaldehyde concentration of 0.1 ppm. The IUR is expressed as the upper-bound extra cancer risk estimated for a lifetime inhalation exposure to 1 $\mu g/m^3$. This estimate, based on a human study, was similar to what would be estimated using any of a tight range of values derived using experimental animal data. The analyses of the experimental data were based on multiple dose-metrics and included estimates derived using BBDR modeling approaches incorporating available mechanistic evidence (see Section 5.2.1). The unit risk estimate for NPC cancer prior to any age adjustments is 7.4×10^{-6} per $\mu g/m^3$ (see Table ES-2). EPA guidelines recommend that ADAFs be used when estimating the risk of NPC from childhood inhalation exposures to formaldehyde because the NPCs are judged to be due, at least in

[2] Extra risk is defined as $(R_x - R_o)/(1 - R_o)$, where R_x is the lifetime risk in the exposed population and Ro is the lifetime risk in an unexposed population; it is the added risk applied to the portion of the population that did not show background tumors.

part, to a mutagenic MOA. In the absence of information to support a chemical-specific age adjustment factor, EPA's default ADAFs are applied. Thus, the unit risk estimate was adjusted using age-dependent adjustment factors (ADAFs) to address expected increased susceptibility from early-life exposures (see Table ES-2).

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

There are several uncertainties that, when considered together, are expected to result in an underestimation of the IUR. First, an important uncertainty is the inability to derive a unit risk estimate that incorporates risk for all three cancer types with conclusions of "**evidence demonstrates"** that formaldehyde inhalation exposure causes the cancer. Second, since industrial workers are healthier than the general population overall, the unit risk estimates derived from the NCI worker cohort data could underestimate the cancer risk for the general population to an unknown, but likely small, extent. Third, given the high survival rates for NPC, cancer incidence risk estimates were calculated using the dose-response relationships from the NCI mortality study to reduce the potential for underestimating the unit risk. However, the calculation required certain assumptions, thus, the estimates may under- or overpredict the true risk by an amount expected to be relatively small.

Because a mutagenic MOA was established for NPC (see Section 3.2.5 for details), the IUR was calculated using linear low-dose extrapolation from the 95% lower bound on the exposure level associated with the extra risk level serving as the benchmark response, which is considered to be a plausible upper bound on the risk at lower exposure levels. Use of the upper bound is a health-protective practice recommended in EPA guidelines (U.S. EPA, 2005a).

ES.4 SUSCEPTIBLE POPULATIONS AND LIFESTAGES

Overall, the most extensive research on the health effects of inhaled formaldehyde and susceptible groups indicates a greater susceptibility among children to formaldehyde's respiratory effects, manifested as reduced pulmonary function, increased prevalence of current asthma, and greater asthma severity (reduced asthma control). More research is needed to investigate the role of sex, race, nutrition, exercise, and coexposures that may modulate susceptibility to formaldehyde toxicity. Increased early-life susceptibility for cancer is assumed because of the mutagenic MOA for NPC carcinogenicity. Health status and disease, particularly related to the respiratory system, are likely to be modifying factors of formaldehyde toxicity. Studies suggest that asthmatics are more susceptible than nonasthmatics to declines in respiratory function following formaldehyde exposure. Based on multiple mechanistic studies of respiratory hypersensitivity, it also appears

likely that persons with preexisting respiratory allergies would be more sensitive to the respiratory health effects of formaldehyde exposure, although the data informing potential associations between more generalized atopy and respiratory effects in the available human studies were inconsistent. Experimental animal studies and occupational studies indicate that formaldehyde exposure-induced nasal lesions are more severe among individuals with prior nasal damage, which could result in heightened susceptibility to the development of nasal cancer following formaldehyde exposure.

In addition, epidemiological and toxicological studies identify female reproductive or developmental toxicity as a hazard of formaldehyde exposure. At this time, it is not clear whether increased time to pregnancy and spontaneous abortion rates seen in occupationally exposed women are due to reproductive system toxicity or to toxicity to the developing fetus. Finally, reproductive toxicity in males has been associated with formaldehyde inhalation, although this association has only been tested in well-conducted studies of rodents at very high formaldehyde concentrations.