Health Based Guidance for Air
Environmental Impacts Analysis Unit, Environmental Health Division
651-201-4899

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Air Toxicological Summary for: Formaldehyde

CAS: **50-00-0**

Synonyms: Formic aldehyde, methyl aldehyde, methylene oxide, oxymethylene, formalin, formol, methanal, oxomethane

Air Exposure Durations:

Acute = one hour averaged exposure concentration
Subchronic = 13-week averaged exposure concentration
Chronic = annual averaged exposure concentration

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = 50 µg/m³

$$= \frac{\text{(Point of Departure (POD), mg/m}^3\text{)}}{\text{(Uncertainty Factors (UF))}}$$

$$= \frac{\text{(0.53 mg/m}^3\text{)}}{\text{(10)}}$$

= 0.053 mg/m³ rounded to 50 µg/m³

Reference Concentration:	HEC/Total UF = 0.53/10 = 0.053 mg/m³-(human study)
Source of toxicity value:	Determined by MDH 2019; based on Kulle et al. 1987, Formaldehyde Dose-Response in Healthy Nonsmokers. *JAPCA*, 37:919-924
POD and Critical Effect:	$BMDL_{10}$ = 0.53 mg/m³; mild/moderate eye irritation
Human Equivalent Concentration (HEC):	No DAF needed, human study; the exposure duration was not adjusted as the critical effect was sensory irritation
Total uncertainty factor (UF):	10
Uncertainty factor allocation:	$UF_{H\text{-}d}$ was set at 10 because of the ability of formaldehyde to exacerbate the immune response to aeroallergens, which is of particular concern during lung development; $UF_{H\text{-}k}$ was set at 1 because critical effect is point of entry sensory irritation

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 9 µg/m³

$$= \frac{\text{(Point of Departure (POD), mg/m}^3\text{)}}{\text{(Uncertainty Factors (UF))}}$$

$$= \frac{\text{(0.09 mg/m}^3\text{)}}{}$$

(10)

= 0.009 mg/m^3 = 9 µg/m^3

Reference Concentration:	HEC/Total UF = 0.09/10 = 0.009 mg/m^3 (human study)
Source of toxicity value:	Cal OEHHA 2008; based on Wilhelmsson and Holmstrom, 1992. Possible mechanisms of formaldehyde-induced discomfort in the upper airways. *Scand J Work Environ Health* 18:403–407
POD and Critical Effect:	NOAEL = 0.09 mg/m^3; eye irritation, nasal obstruction and discomfort, and lower airway discomfort
Human Equivalent Concentration (HEC):	No dose-adjustment factor (DAF) needed, human study; OEHHA does not perform a time-adjustment on the POD (NOAEL or BMC) when the key endpoint is sensory irritation
Total uncertainty factor (UF):	10
Uncertainty factor allocation:	$UF_{H\text{-}d}$ was set at 10 because of the ability of formaldehyde to exacerbate the immune response to aeroallergens, which is of particular concern during lung development; $UF_{H\text{-}k}$ was set at 1 because critical effect is point of entry sensory irritation

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 9 µg/m^3

$$= \frac{\text{(Point of Departure (POD), mg/m}^3\text{)}}{\text{(Uncertainty Factors (UF))}}$$

$$= \frac{\text{(0.09 mg/m}^3\text{)}}{\text{(10)}}$$

= 0.009 mg/m^3 = 9 µg/m^3

Reference Concentration:	HEC/Total UF = 0.09/10 = 0.009 mg/m^3 (human study)
Source of toxicity value:	Cal OEHHA 2008; based on Wilhelmsson and Holmstrom 1992. Possible mechanisms of formaldehyde-induced discomfort in the upper airways. *Scand J Work Environ Health* 18:403–407
POD and Critical Effect:	NOAEL = 0.09 mg/m^3; eye irritation, nasal obstruction and discomfort, and lower airway discomfort
Human Equivalent Concentration (HEC):	No DAF needed, human study; OEHHA does not perform a time-adjustment on the POD (NOAEL or BMC) when the key endpoint is sensory irritation
Total uncertainty factor (UF):	10
Uncertainty factor allocation:	$UF_{H\text{-}d}$ was set at 10 because of the ability of formaldehyde to exacerbate the immune response to aeroallergens, which is of particular concern during lung development; $UF_{H\text{-}k}$ was set at 1 because critical effect is point of entry sensory irritation

Cancer Health Based Value/Risk Assessment Advice = Not Derived; Based on current carcinogenic mode of action information, MDH considers formaldehyde to be a nonlinear carcinogen. Use of a cancer slope value, based on a linear approach, to evaluate ambient levels of formaldehyde is considered inappropriate and not recommended by MDH.**

Cancer classification:	B1, probable human carcinogen, based on limited evidence in humans, and sufficient evidence in animals (EPA IRIS 1989); Group 2A probably carcinogenic to humans based on limited evidence in humans and sufficient evidence in animals (IARC 1987)
Inhalation Unit Risk (IUR):	Not Derived**
Source of IUR:	--
Tumor site(s):	--

****Based on the current weight of evidence MDH will proceed with a nonlinear mechanism of action for formaldehyde carcinogenesis. MDH noncancer subchronic and chronic HBVs (9 µg/m^3 each) is based on nasal irritation in humans, which is more sensitive than the cancer precursor effects of cytotoxicity and regenerative cellular proliferation. Therefore, the noncancer subchronic and chronic HBV is protective of cancer effects.**

Volatile: Yes (average Henry's Law = 2.6E^{-6} atm-m^3/mol; EPA ChemDashboard, as of Aug 2019)

Summary of Guidance Value History:

MDH first derived a cancer HRV of 0.8 µg/m^3, based on USEPA IRIS (1989) in 1995. This cancer value was revised to 2.0 µg/m^3 in 2006, based on CalEPA 1992. In 2002 MDH also derived a noncancer acute HRV of 94 µg/m^3 based on CalEPA 1992. In 2019 MDH re-evaluated formaldehyde and derived new acute, subchronic and chronic HBV of 50, 9, and 9 µg/m^3, respectively. The 2019 re-evaluation also determined that formaldehyde was a nonlinear carcinogen and the subchronic/chronic HBV of 9 µg/m^3 is protective of cancer effects.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity	Respiratory
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes-limited[1]	Yes-limited[2]	Yes-limited[3]	Yes-limited[4]	Yes-limited[5]	Yes-limited[6]

Comments on extent of testing or effects:

[1] EPA IRIS Draft 2010 concluded that an endocrine-disrupting MOA is supported by some of the reproductive and developmental epidemiology and toxicology studies. Decreases in fetal body weight (6,000 – 49,000 μg/m^3), delayed ossifications, and delayed eruption of incisors noted in rats after gestational exposure to formaldehyde are consistent with developmental delays (concentrations ranging from 500 – 49,000 μg/m^3). Studies that directly tested for changes in hormones after formaldehyde exposure observed ovarian weight and serum LH and FSH increases after inhaled formaldehyde in adult female rats (490 – 1500 μg/m^3). In human studies, an endocrine MOA could also explain delayed time to pregnancy and increased incidence of spontaneous abortion (at a mean formaldehyde concentration of ~270 μg/m^3), consistent with some study findings from the toxicology literature. Alterations in hormone levels could lead to pregnancy maintenance problems. The NAS 2011 Review stated that the committee disagreed with EPA's overall conclusion regarding the totality of the epidemiologic evidence related to the reproductive and developmental effects of formaldehyde. Specifically, the draft IRIS assessment stated that "epidemiologic studies suggest a convincing relationship between occupational exposure to formaldehyde and adverse reproductive outcomes in women" (EPA 2010, p. 4-85). The committee, after assessing the literature, found a suggestive pattern of association among a small number of studies rather than a convincing relationship. The committee's assessment was based on the overall pattern of positive association among most of the studies, but the generally limited exposure assessment and concern about other biases lead to the more appropriate descriptor of suggestive rather than convincing.

[2] EPA IRIS Draft 2010 reported studies in four specific areas related to immunotoxicity after exposure to formaldehyde: increased upper respiratory tract infections, systemic immune dysfunction, sensitization and atopy, and production of formaldehyde-protein complexes (ranging from 390 to 25,000 μg/m^3. Some studies also evaluated immune system effects by investigating the role of reactive oxygen species from respiratory burst associated with immune cells and by assessing chromosomal damage in immune cells (range of 390 to 25,000 μg/m^3). The NAS 2011 Review provided the following recommendations: the systemic nature of the immune system and the interplay between the innate and adaptive arms of the immune system provide a plausible potential target of formaldehyde, despite its limited distribution beyond the point of entry. The committee agreed with EPA's decision not to calculate a candidate RfC for immunotoxicity.

[3] ATSDR 2010 addendum reported effects of maternal exposure to inhaled formaldehyde on embryonic and fetal toxicity in Sprague-Dawley rats. Groups of 25 dams were exposed to 0, 6,000, 12,000, 25,000, or 49,000 μg/m^3 formaldehyde in inhalation chambers on gestational days 6-20. Fetal body weights of male offspring from dams exposed to 25,000 μg/m^3 formaldehyde were 5% lower than controls ($p<0.05$). Furthermore, fetal body weights of male and female offspring from dams exposed to 49,000 μg/m^3 formaldehyde ($p<0.01$) were about 21% lower than those offspring of controls. Therefore, maternal exposure to formaldehyde at 49,000 μg/m^3 for 6 hours/day during gestational days 6– 20 was not teratogenic nor embryotoxic, but exposure at 25,000 μg/m^3 was slightly fetotoxic, as indicated by lower fetal body weights. Another study examined embryotoxics effect and fetal and juvenile offspring development from mongrel female white rat dams exposed to 0 or 490 μg/m^3 formaldehyde for 4 hours/day on gestational days 1-19. The results showed that prenatal exposure to formaldehyde does not affect the embryonic mortality and does not decrease the crown-tail (craniocaudal) lengths or the weights of embryos. However, examination of internal organs of the prenatal formaldehyde-exposed group revealed decreased fetal hyoid ossification and increased incidence of total anomalies, with absence of testes as the predominant anomaly.

The NAS committee disagreed with EPA's overall conclusion regarding the totality of the epidemiologic evidence related to the reproductive and developmental effects of formaldehyde. Specifically, the draft IRIS assessment stated that "epidemiologic studies suggest a convincing relationship between occupational exposure to formaldehyde and adverse reproductive outcomes in women" (EPA 2010, p. 4-85). The committee, after assessing the literature, found a suggestive pattern of association among a small number of studies rather than a convincing relationship. The committee's assessment was based on the overall pattern of positive association among most of the studies, but the generally limited exposure assessment and concern about other biases lead to the more appropriate descriptor of suggestive rather than convincing.

[4] ATSDR 2010 addendum, several comprehensive reviews concluded that formaldehyde does not produce significant reproductive and developmental toxicity. In a review of available reproductive and developmental toxicity data for humans and laboratory animals, the World Health Organization concluded, "There is no convincing evidence that formaldehyde is a teratogen in either animals or human beings. Formaldehyde has not produced any adverse effects on reproduction in test animals or human beings". EPA IRIS Draft 2010 stated that several epidemiologic studies report a relationship between occupational exposure to formaldehyde and increases in risk of spontaneous abortion following maternal occupational formaldehyde exposure (at a mean formaldehyde concentration of ~270 $\mu g/m^3$). However, other studies found no association between occupational formaldehyde exposure and spontaneous abortion. Paternal occupational exposure to formaldehyde was not related to spontaneous abortion.

[5] EPA IRIS Draft 2010 stated one study reported elevations in the mRNA for NMDA receptor subunits in brain homogenates following exposure to 2,900 $\mu g/m^3$. Another study reported a significant increase in NMDA receptor subunit transcripts, along with other neuropeptide genes, in nasal tissue of rats instilled into nostril with 400 mM formaldehyde (Described in EPA IRIS Draft 2010 Section 4.2.1.2.2.1). Together, these changes may be related to formaldehyde-induced sensory irritation and, perhaps, changes throughout the brain. In general, behavioral effects in animals and humans appear to occur at similar exposure levels. Animal studies demonstrated LOAELs as low as 123 $\mu g/m^3$ following acute or repeated exposures; human controlled exposure studies have found effects in that same range, with LOAELs of approximately 370 $\mu g/m^3$ following acute exposures. In a controlled exposure study, it was reported that, when workers with chronic formaldehyde exposure were challenged with an acute formaldehyde exposure, they exhibited poorer performance on some neurocognitive tests compared with workers without chronic exposure undergoing the same acute challenge conditions. Per NAS 2011 Formaldehyde review, the committee found that EPA overstated the evidence in concluding that formaldehyde is neurotoxic; the human data are insufficient, and the candidate animal studies deviate substantially from neurotoxicity-testing guidelines and common practice… There was concern that the selected studies were not sufficiently robust in design to be considered "well executed" for the purpose of neurotoxicity hazard identification.

[6] EPA IRIS Draft 2010 stated exposure to formaldehyde in early life can cause damage to the lungs and permanently influence airway function, resulting in increased vulnerability to toxicants later in life. Thus, young children may demonstrate increased susceptibility to formaldehyde-related health effects. One study reported an association between physician-diagnosed asthma and chronic bronchitis in children who lived in homes with formaldehyde levels that were higher than 74 $\mu g/m^3$, after controlling for socioeconomic status and ethnicity. Another study reported a statistically significant increased risk of asthma with increased residential concentrations (30 $\mu g/m^3$ - lower limit of NOAEL range) of formaldehyde.

Another study reported an increased association between bedroom concentration (ranging from 16 – 139 $\mu g/m^3$) of formaldehyde and increased risk of atopy in children. These studies suggested that formaldehyde exposure may exacerbate responses in sensitive airways, particularly in children. Animal studies have shown evidence and confirmed that the upper respiratory tract is a critical target for inhaled formaldehyde and that exposure-response relationships for upper respiratory tract irritation and epithelial damage exist in several species. Acute animal studies have also shown that inhaled formaldehyde at certain exposure concentrations damages epithelial tissue in specific regions of the upper respiratory tract in rats, mice, and monkeys.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Toxicological Profile for Formaldehyde.

Agency for Toxic Substances and Disease Registry (ATSDR). 2010. Addendum to the Toxicological Profile for Formaldehyde.

California OEHHA. December 2008 (Updated July 2014). Appendix D. Individual Acute, 8-Hour, and Chronic Reference Exposure Level Summaries. https://oehha.ca.gov/media/downloads/crnr/appendixd1final.pdf

National Academy of Sciences. 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. The National Academies Press. Washington DC. https://www.nap.edu/catalog/13142/review-of-the-environmental-protection-agencys-draft-iris-assessment-of-formaldehyde

US EPA IRIS. 2010. Toxicological Review of Formaldehyde – Inhalation Assessment DRAFT. EPA/635/R-10/002A