CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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Via Electronic Filing

EPA-HQ-OPPT-2018-0438

Administrator Lee Zeldin
U.S. Environmental Protection Agency
Office of Chemical Safety and Pollution Prevention
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001

Re: *Formaldehyde; Updated Draft Risk Calculation Memorandum; Notice of Availability and Request for Comment*, 90 Fed. Reg. 55,726 (Dec. 3, 2025)

Dear Administrator Zeldin:

The California Office of Environmental Health Hazard Assessment (OEHHA) appreciates the opportunity to provide comments on the Updated Draft Risk Calculation Memorandum (Draft Memo) for a revised Risk Evaluation for Formaldehyde under the Toxic Substances Control Act (TSCA) [EPA-HQ-OPPT-2018-0438; FRL-11608-05-OCSPP]. OEHHA comments cover the US EPA document titled "Revised Draft Human Health Risk Assessment for Formaldehyde" (Draft Assessment; US EPA 2025a), as it presents the detailed methodology relied on in the Draft Memo.

As detailed below, several of the key conclusions and considerations in US EPA's revised health risk assessment are not scientifically supported and go against long-standing risk assessment guidelines used by US EPA (US EPA 2005), as well as OEHHA (OEHHA 2008, 2009). The updated draft TSCA risk evaluation does not reflect the current state of science on formaldehyde and is inconsistent with the determinations of other authoritative bodies (e.g., IARC, 2006, IARC, 2012; NTP, 2021) and US EPA's own Integrated Risk Information System (IRIS) Program (US EPA 2024a, 2024b), which was conducted in accordance with US EPA risk assessment guidelines. The 2024 IRIS Formaldehyde Toxicological Review underwent a rigorous 7-step review process that included external public peer-review by the National Academies of Science, Engineering

and Medicine (NASEM, 2023). Moreover, the revised TSCA human health risk assessment is not based on new science, which creates further confusion for businesses and the public, including at the state level. Finally, OEHHA is concerned about the precedent being set by this apparent movement away from US EPA guidelines for carcinogens in the absence of a rigorous process that includes meaningful public input and independent external peer review.

Specifically, OEHHA is concerned that the lack of a quantitative, linear extrapolation based cancer risk evaluation, the selection of a subjective end point (sensory irritation) as the critical non-cancer effect, and the elimination of the interindividual variability factor while using limited human data are not scientifically supported or health protective, as presented below. OEHHA strongly recommends addressing these deficiencies with the formaldehyde assessment in the final draft to ensure that sound scientific methods are followed and the public health impacts of formaldehyde are properly addressed.

1. **Ignoring quantitative cancer risk evaluation and using a threshold approach for formaldehyde are not health protective and inconsistent with the current state of knowledge on formaldehyde and US EPA's own cancer risk assessment guidelines.**

US EPA's Draft Memo incorrectly concludes that the acute hazard value for formaldehyde (0.3 ppm) is protective across all exposure durations, including chronic exposure and cancer outcomes. The stated rationale that formaldehyde induced carcinogenicity occurs only at sustained exposure levels well above those that induce sensory irritation is scientifically flawed. For carcinogens, irrespective of systemic or portal-of-entry modes of action (MOAs), both concentration and exposure duration are relevant, and acute thresholds alone do not characterize long-term risk. Rather than assuming that the acute sensory irritation-based safety level is sufficient to protect against cancer risk, TSCA should assess formaldehyde as a carcinogen, and include a non-threshold based quantitative cancer risk assessment consistent with EPA cancer guidelines (US EPA, 2005).

The US EPA identified formaldehyde as a carcinogen over 30 years ago,[1] and since has concluded that the epidemiologic evidence in humans demonstrates that formaldehyde inhalation causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia (US EPA 2024a). Formaldehyde is also recognized as a carcinogen by additional authoritative bodies, including the US National Toxicology Program Report on Carcinogens[1] (NTP 2021), which classifies it as "known to be a human carcinogen" and

[1] US EPA (1989). IRIS Summary of Formaldehyde (Cancer), https://iris.epa.gov/document/&deid=363363

the International Agency for Research on Cancer (IARC) (IARC 2006, 2012), which classifies it as “carcinogenic to humans (Group 1)”.

Therefore, the human health risk assessment for formaldehyde should include a quantitative cancer risk assessment using appropriate cancer data, rejecting the use of sensory irritation as being protective of cancer hazard.

The long-standing scientific consensus is that formaldehyde is a direct-acting genotoxic carcinogen. According to US EPA (2024a), “Mechanistic data suggest that URT [upper respiratory tract] cancers are likely the result of genotoxicity and mutagenicity, cytotoxicity, and cell proliferation”. Consistent with US EPA (2024a), the NTP Report on Carcinogens[2] (2021) concludes that mechanisms by which formaldehyde causes cancer “most likely involve several modes of action” and lists several key events associated with formaldehyde exposure, including “DNA reactivity, gene mutation, chromosomal breakage, aneuploidy, epigenetic effects… and cytotoxicity-induced cellular proliferation”. Specifically, NTP (2021) concluded:

> “**Formaldehyde is a direct-acting genotoxic compound** and has given positive results for almost all genetic end points evaluated in bacteria, yeast, fungi, plants, insects, nematodes, and cultured mammalian cells. It caused base-pair gene mutations in Salmonella typhimurium and DNA adducts, DNA-protein crosslinks, DNA-DNA crosslinks, DNA single-strand breaks, unscheduled DNA synthesis, inhibition of DNA repair, gene mutations, cell transformation, and cytogenetic effects (sister chromatid exchange, chromosomal aberrations, and micronucleus formation) in cultured mammalian cells (NTP 2010).” (emphasis added)

NTP went on to summarize evidence of genetic damage in the nasal tissues of both animals and humans exposed by inhalation, including detection of DNA-DNA and DNA-protein crosslinks[3].

NASEM conducted consensus panel scientific peer review of the US EPA IRIS document (US EPA 2022, external review draft for US EPA 2024a) and confirmed that US EPA (2022) used state-of-practice methods in synthesizing the evidence on MOA for upper respiratory tract cancers. Specifically, NASEM summarized EPA’s approach and expressed agreement as follows:

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[2] The NTP Report on Carcinogens (RoC), mandated by Congress, is one of the most authoritative scientific documents in the United States regarding cancer hazards. Its authority is rooted in Section 301(b)(4) of the Public Health Service Act (1978) and an extensive, multi-agency peer-review process. For more information, see https://ntp.niehs.nih.gov/research/assessments/cancer/roc

[3] See page 4 of NTP (2021), available at: https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/profiles/formaldehyde.pdf

> "Key conclusions are that (1) strong, consistent evidence from rodent and non-Human primate models supports the role of **both direct** (i.e., potentially DNA–protein crosslink or hypermethylated DNA adduct-associated) **mutagenicity, as well as indirect genotoxicity, mutagenicity, and regenerative proliferation resulting from respiratory tissue pathology, in rodent upper respiratory tract carcinogenesis**; (2) **mutagenicity is presumed to be a relevant component of upper respiratory tract carcinogenesis in humans**, supported by consistent observations of direct genotoxicity and mutagenicity from human epidemiological studies; and (3) increased nasal epithelial cell proliferation (in rats and nonhuman primates) coincides anatomically with progressive, proliferative lesions in the nasal/buccal epithelium and nasopharynx of chronically exposed humans. Finally, the Draft Assessment notes that mechanistic data provide strong and consistent evidence supporting the **contribution of both direct genotoxicity and mutagenicity and cytotoxicity-induced regenerative proliferation as primary mechanistic events**. EPA concluded that these mechanisms were highly relevant for informing quantification of nasal cancers in experimental animals following chronic formaldehyde exposure." (emphasis added)

In other words, NASEM agrees with US EPA's conclusion that the mechanisms for formaldehyde include direct genotoxicity and mutagenicity. NASEM's views are in contrast with the non-consensus view of TSCA's Science Advisory Committee on Chemicals (SACC) that it is not a direct mutagen, or that cytotoxicity is the rate-limiting biological step (SACC, 2024). Further, the conclusions presented in the 2024 IRIS assessment were developed following the IRIS Program's seven-step process[4], that includes review by US EPA Program and Regional Offices, other Federal Agencies (including the Executive Branch) and external consensus-panel peer review. The conclusions presented by some (but not all) SACC members have not undergone such a rigorous peer review process. Given the evidence that formaldehyde is a direct-acting genotoxic carcinogen and that it likely acts through multiple carcinogenic mechanisms, a no-threshold approach should be used in developing the cancer dose response assessment (see NTP 2021, US EPA 2005, Kirsch-Volders et al. 2000, Lovell 2000, Nohmi 2018).

US EPA's 2005 Cancer Risk Assessment Guidelines[5] specifies that linear extrapolation (no-threshold approach) should be used for carcinogens that fulfill the following criteria, or when there is insufficient evidence to support a nonlinear extrapolation procedure in the absence of evidence of DNA reactivity.

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[4] https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process
[5] See US EPA (2005) and US EPA webpage on "Risk Assessment for Carcinogenic Effects" https://www.epa.gov/fera/risk-assessment-carcinogenic-effects

> "• agents that are DNA-reactive and have direct mutagenic activity, or
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> • agents for which human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process, so that background exposures to this and other agents operating through a common mode of action are in the increasing, approximately linear, portion of the dose-response curve.
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> When the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data, linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective approach. Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained."

This is consistent with OEHHA's guidance for cancer risk assessment, which specifies that "the low dose linearity assumption is a general default for any carcinogen, and it is unlikely to be altered for genotoxic carcinogens" (OEHHA, 2009).

The current knowledge of formaldehyde's MOA (MOA not established for myeloid leukemia or upper respiratory tract cancers; direct genotoxicity and mutagenicity and cytotoxicity-induced regenerative proliferation likely being primary mechanistic events for upper respiratory tract cancers) fits into the following scenario as described by US EPA (2005) guidelines:

> "When the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data, linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective approach. **Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained.** Where alternative approaches with significant biological support are available for the same tumor response and no scientific consensus favors a single approach, an assessment may present results based on more than one approach." (emphasis added)

In the case of formaldehyde, there has been no scientific consensus on any alternative biological evidence supporting a threshold approach, as evidenced by the different

opinions expressed by different SACC members (SACC, 2024)[6]. Therefore, OEHHA recommends that a linear extrapolation be used in cancer risk assessment.

2. Selection of sensory irritation as the critical effect is not health protective.

The use of an acute inhalation point of departure (POD) of 0.3 ppm based on sensory irritation as being protective of all other potential health hazards, including cancer, is not scientifically supportable. Risk assessment guidelines do not support using an acute, non-permanent outcome to be supportive of cancer and chronic non-cancer endpoints. For example, the US EPA (2002) Guidance on Reference Dose and Reference Concentration Process states that "reference values should be derived to be protective of all types of effects for a given duration of exposure". Acute sensory irritation is a subjective endpoint that can be influenced by odor (SACC, 2024) which can produce adverse effects on its own, and should not be used for chronic exposures. Multiple lines of evidence on formaldehyde indicate that an acute sensory irritation POD is insufficient for protecting public health, especially when considering cancer and chronic non-cancer effects. For example, US EPA (2024a) determined that there are more sensitive non-cancer PODs (e.g., decreased pulmonary function, prevalence of current asthma or degree of asthma control, and allergic conditions) from studies with higher confidence. Additionally, US EPA (2024b) carefully considered this issue and did not find evidence to support the assertion in the Draft Memo that sensory irritation is upstream of other health effects (e.g., cancer, respiratory tract pathology, reproductive toxicity) caused by formaldehyde inhalation. Overall, sensory irritation as the sensitive effect protective of all other health hazards from exposure to formaldehyde is not consistent with the current knowledge base or existing US EPA assessments (US EPA 2024a, 2024b) and is not health protective. For evaluation of non-cancer risk, OEHHA recommends selecting a more sensitive and objective POD that is consistent with the well-established science conventions.

[6] See pages 62-64 on various opinions from committee members regarding MOA. For example, on page 64 the document states 'A minority of members agreed with the EPA's conclusion that "there is sufficient evidence that a mutagenic mode of action contributes to risk of nasopharyngeal cancer (NPC) from inhaled formaldehyde"'.

3. Elimination of the interindividual variability factor is inconsistent with the current state of knowledge and is not health protective.

The Draft Memo proposes reducing the intrapopulation variability uncertainty factor (UF_H) from 3x to 1x. The revised draft assessment relies on several human studies[7] to derive the draft acute POD (Andersen and Mølhave, 1983; Kulle et al., 1987; Lang et al., 2008; and Mueller et al., 2013). One of the critical studies on which the acute POD is based, i.e., Mueller et al. (2013), included forty-one adult (20-40 years old) healthy humans, with approximately half of participants qualified as 'hypersensitive' individuals. The draft acute POD of 0.3 ppm is based on effect levels observed in these studies, with the application of UF_H of 1x. However, the US EPA (2024a) assessment cited a study by Zhai et al. (2013) reporting "a higher prevalence of nasal irritation and throat irritation among adults and children at concentrations above 0.08 mg/m^3 [~0.065 ppm]". These data indicate that there can be individuals in the population experiencing sensory irritation at levels 4-times below the draft revised POD. This is in line with US EPA's (2024b) observation that: "With few exceptions (i.e., large population studies encompassing a wide range of demographics, including reasonable representation of known or expected susceptible groups), the available [sensory irritation] studies are judged as unlikely to sufficiently address the identified differences in susceptibility, irrespective of the health outcome being considered."

In its review of the draft formaldehyde assessment, the SACC suggested a UF_H of 3x *or* 1x since the study population included individuals "sensitive to formaldehyde"; however, the sensitivity in the study was determined using carbon dioxide (CO_2) – not formaldehyde – therefore, there is no certainty that this study covered the range of sensitivity across the population. Importantly, the SACC did not reach consensus on the application of or the appropriate value for a UF_H. The Human Studies Review Board's review comments (HSRB 2023), as cited in the Federal Register, point to younger individuals being more sensitive than older individuals as the basis for not applying a UF_H. However, age-based sensitivities are not the only cause of human variability[8] – therefore, a UF_H is still required to protect against other variability.

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[7] The draft Human Health Risk Assessment (US EPA 2025a) cites three studies (Kulle et al., 1987; Lang et al., 2008; and Mueller et al., 2013), while the draft Human Health Hazard Assessment (2025b) and the Federal Register cite four studies (Andersen and Mølhave 1983; Kulle et al., 1987; Lang et al., 2008; and Mueller et al., 2013). The Federal Register is available at: https://www.federalregister.gov/d/2025-21776

[8] Other sources of human variability may overlap with the list of "remaining source of uncertainty" acknowledged by US EPA (2025a), including pre-existing conditions, lifestyle activities, occupational exposures, geographic factors, sociodemographic factors, genetics, aggregate exposures, and other chemical and non-chemical stressors (US EPA 2025a, Page 156 and Appendix B). Due to lack of conclusive data on how these factors can affect sensory irritation upon formaldehyde exposure, a higher uncertainty factor should be considered.

Furthermore, the revised draft assessment refers to the World Health Organization's (WHO) guidance document for indoor air quality, which included an assessment of formaldehyde with discussion around potentially sensitive populations such as asthmatics, children, and the elderly (WHO 2010). Of importance is that WHO (2010) used two of the three studies relied upon in this revised draft assessment – Lang et al., (2008) and Kulle et al., (1987) – and applied an 'assessment factor' of 5x, based on the standard deviation of nasal pungency thresholds in normal adults, to "protect the potentially more sensitive part of the population", an approach later adopted by the European Chemicals Agency (ECHA). ECHA (2019) included Mueller et al. (2013) in their review yet still chose to adopt WHO's value which applied an assessment factor of 5x.

Taken together, the UF_H of 1x used in the revised Draft Assessment for formaldehyde is not supported by the underlying data, inconsistent with the approaches of other authoritative bodies, and is not health protective. OEHHA recommends that US EPA apply an appropriate UF_H upon selection of the most sensitive non-cancer POD (see comment 2).

Summary

Overall, the revised draft risk evaluation of formaldehyde under TSCA is not consistent with scientific principles and findings of authoritative health agencies and US EPA's own guidelines and practice regarding: the lack of a quantitative, linear-extrapolation based cancer risk evaluation, the selection of a subjective endpoint (sensory irritation) as the critical non-cancer effect, and the elimination of the interindividual variability factor while using limited human data for the selected POD.

Thank you for the opportunity to comment.

Sincerely,

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Enclosure

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