
CalChamber
African American Farmers of California
The Chamber
Long Beach Area Chamber of Commerce
CALCIMA
California Construction And Industrial Materials Association
MCCV
WSPA
California Farm Bureau
Manufacturers Council of the Central Valley
American Chemistry Council
Inland Empire Economic Partnership
WTNA
Western Tree Nut Association
California Cotton Ginners and Growers Association
CCGGA
CARLSBAD
Chamber of Commerce
COBI
Council of Business & Industries
CMTA
California Manufacturers & Technology Association
California Alliance of Small Business Associations
Dedicated to Environmental Progress & Economic Growth
CCEEB
Milk Producers Council
Serving the Dairy Industry Since 1949
Greater San Fernando Valley Chamber of Commerce
Greater Coachella Valley Chamber
California Metals Coalition
safe food ALLIANCE
Western Growers
Fresh produce from our families to yours
IEA
Industrial Environmental Association
Promoting Industry and Protecting the Environment
CFCA
California Fuels + Convenience Alliance
California Food Producers
CalAPA
California Asphalt Pavement Association
CBIA
California Building Industry Association
Santa Maria Valley Chamber
NFL
Nisei Farmers League
California Citrus Mutual
California Strawberry Commission
Industrial Association
Greater High Desert Chamber of Commerce
SEMA
Specialty Equipment Market Association
Coastal Energy Alliance
California Hispanic Chambers of Commerce
CICC
Chemical Industry Council of California
Can Manufacturers Institute
California Business Properties Association
Protecting commercial real estate for over 50 years
Greater Bakersfield Chamber
Building Something Better
Kern Citizens for Energy
California Trucking Association
DFA Of California
Agricultural Council of California
Murrieta/Wildomar Chamber of Commerce
California Restaurant Association
Industry Business Council
Supply Chain Federation
Torrance Area Chamber of Commerce

July 29, 2026

Submitted via the OEHHA Comment Portal: ***Comment Submissions - Inhalation Unit Risk Factor (IUR) for Acrolein - OEHHA***

Dr. Rima Woods, Chief
Air Toxicology and Risk Assessment Section
Office of Environmental Health Hazard Assessment
1001 I Street, 12th Floor
Sacramento, CA 95814

Subject: Joint comments on OEHHA's draft Inhalation Unit Risk Factor for Acrolein

Dear Dr. Woods:

The undersigned organizations appreciate this opportunity to comment on the Office of Environmental Health Hazard Assessment's (OEHHA) draft Cancer Inhalation Unit Risk Factor (IUR) for acrolein.[1] We also thank OEHHA for allowing an additional 30 days to develop these comments in recognition of the potential impact the draft IUR could have on existing state and local air toxics programs, and OEHHA's unusual decision to release the draft acrolein IUR simultaneously with its release of a draft update to the ethylene oxide IUR, complicating the review and comment development process for organizations, industries, and businesses potentially impacted by both proposed IURs.

While the California Air Resources Board (CARB) is reasonably forthcoming regarding the many limitations in the available air monitoring data for acrolein on its Learn About Acrolein website ("acrolein website"),[2] it fails to offer any reservations regarding the preliminary findings in OEHHA's draft Technical Support Document (TSD) for the acrolein IUR. The website makes conclusory statements about the findings in OEHHA's draft TSD as if they were established scientific consensus. For example, CARB states that "Recently released draft estimates of cancer risk reflect the best available science and indicate a cause for concern." CARB also states that "acrolein is mutagenic," but it fails to offer any cautionary statements regarding uncertainty in the underlying data or in OEHHA's analysis of that data. CARB does acknowledge that "the draft IUR for acrolein will be reviewed by an independent panel of experts,"[3] (an indirect reference to the anticipated review of the draft IUR by CARB's Scientific Review Panel on Toxic Air Contaminants) but it fails to clarify that

[1] Office of Environmental Health Hazard Assessment, Air Toxics Hot Spots Program Acrolein Cancer Inhalation Unit Risk Factor, Technical Support Document for Cancer Potency Factors, Appendix B, Public Review Draft, May 2026.
[2] California Air Resources Board, Learn About Acrolein, Where It Comes From, How It Affects Your Health, and more importantly, What California Is Doing to Protect You, May 14, 2026.
[3] *Id.*, What are the potential health effects of exposure to acrolein in the air?

this review could lead to changes in OEHHA's analysis that could alter the estimated cancer risk from exposure to acrolein indicated on the acrolein website.[4]

As discussed in the analysis of OEHHA's draft TSD prepared by Intertox, Inc., which is submitted in Attachment A to this letter, there are many uncertainties and apparent deficiencies in the draft TSD that call into question the reliability of OEHHA's acrolein IUR derivation. These include, but are not limited to, the following issues:

- **The proposed IUR relies heavily on one chronic inhalation bioassay, with limited support from the broader animal cancer database or from human evidence.** OEHHA's quantitative IUR derivation is based primarily on the Matsumoto et al. (2021)/Japan Bioassay Research Center (JBRC) rat and mouse whole-body inhalation study. The broader animal database does not show a consistent carcinogenic response across studies, species, routes, or tumor sites. The only other inhalation cancer study identified by OEHHA and available in the literature database, Feron and Kruysse (1977), used a single high acrolein concentration in hamsters for 52 weeks and did not show a clear carcinogenic response, and older oral studies were generally negative or difficult to interpret. Prior assessments generally concluded that acrolein was not classifiable as to its carcinogenic potential in humans, or that the database was inadequate for quantitative cancer assessment. Although the International Agency for Research on Cancer's (IARC) 2021 Group 2A classification represents a major shift following availability of the Matsumoto/JBRC inhalation bioassays, IARC still concluded that human cancer evidence was inadequate. Accordingly, the proposed IUR rests primarily on OEHHA's interpretation and modeling of a single animal study, rather than on independent human dose-response evidence or a robust, consistently positive animal cancer database.
- **OEHHA's selected value is driven by a female mouse multisite analysis that combines biologically different tumor endpoints.** The IUR is based on a multisite analysis combining female mouse nasal cavity adenoma and lymph node malignant lymphoma. The nasal adenoma response is the most mechanistically plausible animal cancer endpoint for inhaled acrolein because it occurs at the portal of entry (nose) and is consistent with acrolein's local reactivity, irritation, inflammation, and epithelial hyperplasia. By contrast, lymph node malignant lymphoma is a systemic endpoint with a less direct biological connection to inhaled acrolein, limited and

[4] *Id.*, What is the cancer risk associated with acrolein in the air in California? "Based on OEHHA's draft cancer IUR and CARB's statewide monitoring, the average excess cancer risk is estimated to be approximately 1,300 in a million statewide.

uncertain human support, and a less robust dose-response pattern. Based on OEHHA's reported modeling, use of nasal adenoma alone would reduce the IUR by roughly 47 percent. This decision is one of the most significant quantitative drivers of the proposed IUR and yet it is one of the most uncertain and methodologically challenged aspects of OEHHA's IUR derivation.

- **The female mouse nasal tumor response was high-dose only and occurred in the context of local respiratory tract toxicity, raising questions about OEHHA's linear low-dose extrapolation approach.** Female mouse nasal cavity adenomas occurred only at the highest exposure concentration (0/50, 0/50, 0/50, and 16/50 at 0, 0.1, 0.4, and 1.6 parts per million (ppm), respectively). The accompanying noncancer nasal changes—including inflammation, abnormal cell growth, tissue remodeling, and repair—indicate that the tumors may have developed in response to repeated local injury in the nasal tissues. Although there is some evidence of genotoxic potential, the relevance of that evidence to low-dose inhalation exposures or to the specific tumor endpoints used for the IUR requires more thorough examination. OEHHA should explain why this high-dose only, tissue-injury-associated tumor response supports a linear low-dose cancer model rather than a nonlinear or threshold interpretation.
- **Animal-to-human extrapolation should address respiratory tract dosimetry, not just default body-weight scaling.** For a highly reactive inhaled gas such as acrolein, target-tissue dose depends on nasal anatomy, airflow patterns, nasal versus oral breathing, regional deposition, local uptake, and detoxification. Rodent nasal tumors may be relevant for hazard identification, but quantitative extrapolation to humans requires consideration of species differences. OEHHA's derivation does not appear to adequately account for chemical-specific inhalation dosimetry or the relevance of rodent portal-of-entry dose to humans.
- **Several conservative or uncertain assumptions are compounded without adequate sensitivity analysis.** In addition to endpoint selection, multisite modeling, linear low-dose extrapolation, and animal-to-human extrapolation, the IUR reflects use of several other assumptions such as use of a 5% benchmark response (BMR) rate, adjustment of intermittent chamber exposures to lifetime average exposures, and study-duration adjustment for female mice. While some of these choices may be individually defensible in the context of standard cancer risk modeling methodologies, OEHHA should at least show how the IUR changes under reasonable alternative assumptions and justify application of the assumptions included in the draft IUR derivation.

These and other deficiencies in OEHHA's draft IUR require additional justification and sensitivity analysis, which may lead to a different IUR derivation, and this work should be completed before OEHHA's IUR is used to support any regulatory reviews or interventions.

We encourage careful and thorough consideration of these comments by OEHHA, CARB, and the Scientific Review Panel on Toxic Air Contaminants (SRP), and we look forward to reviewing a revised draft IUR that addresses the technical deficiencies discussed in Attachment A. If you have any questions, please do not hesitate to contact Jon Kendrick of the California Chamber of Commerce at (916) 594-6540.

Sincerely,

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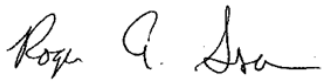

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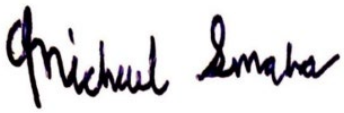

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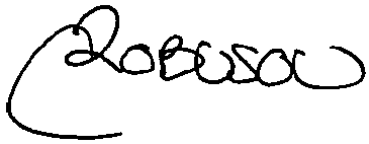

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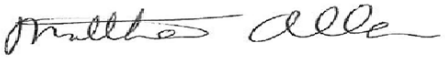

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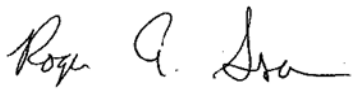

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Attachments

cc: Dr. Kristina Thayer, Director – Office of Environmental Health Hazard Assessment
Dr. David Edwards, Chief Deputy Director – OEHHA
Lauren Sanchez, Chair, California Air Resources Board
CARB Members

Dr. Steven Cliff, Executive Office – CARB
Rajinder Sahota, Deputy Executive Officer – CARB
Edie Chang, Deputy Executive Officer – CARB

Attachment A

Technical Analysis of OEHHA's Draft Technical Support Document for the Acrolein Cancer Inhalation Unit Risk (IUR) Factor

July 28, 2026

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List of Acronyms

Acronym	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike information criterion (a model-fit statistic)
ATSDR	Agency for Toxic Substances and Disease Registry
BBDR	Biologically based dose-response (model)
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence Limit
BMDS	Benchmark Dose Software (U.S. EPA)
BMDU	Benchmark dose upper confidence limit
BMR	Benchmark response
CAS / CASRN	Chemical Abstracts Service (Registry Number)
CEMA*	Carboxyethylmercapturic acid (a urinary acrolein/acrylonitrile metabolite biomarker)
CFD	Computational fluid dynamics
CRAVE*	Cancer Risk Assessment Verification Endeavor (historical U.S. EPA workgroup)
CSF	Cancer slope factor
DFG	Deutsche Forschungsgemeinschaft (German research foundation)
DNA	Deoxyribonucleic acid
DOI	Digital Object Identifier
EPA	Environmental Protection Agency (U.S.)
HPMA*	3-Hydroxypropylmercapturic acid (a urinary acrolein metabolite biomarker)
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System (U.S. EPA)
IUR	Inhalation unit risk
JBRC	Japan Bioassay Research Center
MAK	Maximale Arbeitsplatzkonzentration (German Maximum Workplace Concentration Commission)
MOA	Mode of action
MOE	Margin of exposure
MRL	Minimal Risk Level (ATSDR)
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment

Acronym	Definition
PAH	Polycyclic aromatic hydrocarbon
PMID	PubMed Identifier
PPRTV	Provisional Peer-Reviewed Toxicity Value (U.S. EPA)
REL / RELs	Reference exposure level(s) (OEHHA)
RfC	Reference concentration (U.S. EPA)
RGDR	Regional gas dose ratio
TSD	Technical Support Document

EXECUTIVE SUMMARY

On behalf of the undersigned organizations, these technical comments address the California Office of Environmental Health Hazard Assessment's (OEHHA) May 2026 Public Review Draft proposing an inhalation unit risk (IUR) value for acrolein. The comments do not challenge evaluation of acrolein as a potential carcinogenic hazard; rather, they focus on whether OEHHA has adequately supported the specific numerical IUR it proposes. That value depends on a series of quantitative and qualitative judgments made in interpreting and modeling a single bioassay, including tumor endpoint selection, use of a lymphoma-inclusive multisite analysis, linear low-dose extrapolation, benchmark response selection, a study-duration adjustment, and default animal-to-human extrapolation.

OEHHA's proposed IUR is derived from a single chronic inhalation bioassay, the Matsumoto/Japan Bioassay Research Center (JBRC) study. That study is important for evaluating portal-of-entry nasal tumors, but the broader animal database does not show a replicated, consistently positive carcinogenic response, and the human epidemiology database provides no acrolein-specific dose-response basis for validating the proposed value. No other authoritative body, including the International Agency for Research on Cancer (IARC), American Conference of Governmental Industrial Hygienists (ACGIH), National Institute for Occupational Safety and Health (NIOSH), or National Toxicology Program (NTP), has derived a quantitative cancer potency value for acrolein. IARC's 2021 Group 2A classification is the most significant recent development; it supports a hazard concern, but it does not validate OEHHA's endpoint selection, modeling approach, or numerical result.

Three key issues limit the scientific support for the proposed numerical value: 1) how OEHHA combined two biologically distinct tumor endpoints; 2) whether OEHHA has adequately justified linear low-dose extrapolation, rather than a nonlinear or threshold approach, for the tumor endpoints that determine the proposed IUR; and 3) whether default extrapolation assumptions adequately account for acrolein's portal-of-entry toxicokinetics and target tissue dosimetry. The significance of these issues is summarized below.

Key Issue 1: OEHHA Combines Two Biologically Distinct Tumor Types to Develop the IUR. OEHHA selected a female mouse multisite analysis that combines observed incidences of nasal cavity adenoma and lymph node malignant lymphoma as the quantitative basis for the IUR because it produced the highest potency estimate. The nasal tumor endpoint is the more biologically intuitive portal-of-entry finding for inhaled acrolein. Lymph node malignant lymphoma, by contrast, is a systemic tumor endpoint with a less direct relationship to acrolein's expected site-of-contact toxicity. In the Matsumoto/JBRC study, the lymphoma response also showed a nonmonotonic incidence pattern, no statistically significant pairwise increase compared with controls, no incidence above the JBRC historical-control range, and no established biological pathway linking inhaled acrolein exposure to lymphoid tumor formation. Considered separately rather than in combination, lymphoma

alone would yield an IUR nearly identical to OEHHA's proposed value, while nasal adenoma alone would yield an IUR of roughly half that value. The proposed IUR therefore reflects the lymphoma finding far more than the nasal tumor finding, even though nasal tumors are the more biologically relevant and expected portal-of-entry effect of inhaled acrolein. OEHHA should not use the lymphoma-inclusive multisite estimate as the primary basis for the IUR unless it provides a clear biological, statistical, and risk-assessment justification for combining these endpoints. Absent that justification, OEHHA should derive the IUR using the female mouse nasal cavity adenoma endpoint alone and present the lymphoma-inclusive result, at most, as a sensitivity or upper-bound analysis.

Key Issue 2: OEHHA Has Not Justified Linear Low-Dose Extrapolation for the Tumor Endpoints That Drive the IUR. OEHHA's use of linear low-dose extrapolation rests on its determination that acrolein's mode of carcinogenic action is genotoxic. That determination, however, was not reached through the tissue-specific weight-of-evidence analysis that OEHHA's own adopted framework requires: OEHHA's *Technical Support Document for Cancer Potency Factors* defers to the U.S. Environmental Protection Agency's (EPA's) *Guidelines for Carcinogen Risk Assessment*, which call for evaluation of mode-of-action evidence in the relevant target tissue, not merely a general finding that a chemical can be genotoxic. OEHHA's cited genotoxicity evidence for acrolein comes largely from other tissue types — including buccal/oral cells and unrelated cell lines — not nasal respiratory tissue. Consistent with this data gap, the nasal tumor response occurred only at the highest exposure concentration, in association with nonneoplastic nasal lesions, glutathione depletion, and a saturable respiratory-tract uptake pattern more consistent with a cytotoxicity-driven, threshold-type process than a proportional low-dose mutagenic one. U.S. EPA's 2024 *IRIS Toxicological Review of Formaldehyde (Inhalation)*, involving a mechanistically analogous nasal tumor, illustrates the type of tissue-specific, mechanistically integrated analysis that is needed here. EPA evaluated genotoxicity and cytotoxic proliferation together rather than treating genotoxic potential alone as sufficient. OEHHA's acrolein draft does not perform a comparable analysis for the endpoints that determine the proposed IUR. OEHHA should justify its use of linear low-dose extrapolation for these endpoints or conduct a comparable tissue-specific mode-of-action and dose-response analysis.

Key Issue 3: OEHHA Relies on Default Body-Weight Scaling Rather Than Chemical-Specific Respiratory-Tract Dosimetry. To extrapolate the animal findings to humans, OEHHA relies on default body-weight scaling rather than a chemical-specific respiratory-tract dosimetry approach, even though target-tissue dose for a reactive portal-of-entry gas depends on respiratory tract anatomy, airflow, uptake efficiency, detoxification, and regional tissue dose, not body weight alone. This concern is heightened because OEHHA applies default body-weight scaling to a combined multisite slope factor that includes biologically distinct tumor types. For nasal epithelial tumors, the relevant issue is regional respiratory tract dose; for lymphoma, the relevant issue would be systemic or lymphoid tissue dose,

which OEHHA has not established. A single default scaling factor does not support endpoint-specific extrapolation for both tumor types. OEHHA also does not provide sensitivity analyses showing how the proposed IUR would change under reasonable alternative assumptions, such as excluding lymphoma, using alternative benchmark responses, or applying alternative dose metrics.

The proposed IUR is also difficult to reconcile with measured ambient acrolein concentrations reported by OEHHA. Applying the proposed IUR directly to CARB's statewide monitoring data—a mean of 0.57 micrograms per cubic meter (µg/m³) in 2024 and 1.05 µg/m³ in 2019, with site averages up to 9.4 µg/m³—implies lifetime excess cancer risks from acrolein alone ranging from roughly 1-in-2,200 at the statewide mean to 1-in-135 at the highest monitored site average, for essentially the entire California population. Even the cleanest available rural background measurement implies a cancer risk at or above 100 per million (1×10^{-4}), a level generally at or above the upper end of what regulatory risk-management programs typically treat as acceptable for a single chemical. OEHHA should reconcile this population-level implication with the absence of any documented cancer signal attributable to acrolein.

In sum, while the Matsumoto/JBRC study supports evaluation of acrolein's carcinogenic potential, particularly for portal-of-entry nasal tumors, it does not by itself support the specific numerical IUR OEHHA has proposed. Before finalizing the IUR, OEHHA should exclude lymph node malignant lymphoma from the critical quantitative analysis unless it provides a clear biological, statistical, and risk-assessment justification for including that endpoint; conduct an endpoint-specific mode-of-action and dose-response evaluation; address chemical-specific respiratory-tract dosimetry and endpoint-specific animal-to-human extrapolation; and provide sensitivity analyses showing how the proposed value changes under scientifically supportable alternative assumptions.

1.0 INTRODUCTION

On behalf of the signatory organizations, Intertox respectfully submits the following technical comments on the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment's (OEHHA) May 2026 Public Review Draft, *Acrolein Cancer Inhalation Unit Risk Factor, Technical Support Document for Cancer Potency Factors, Appendix B*.

OEHHA's draft reflects a review of experimental animal data, epidemiological information, toxicokinetics, inhalation dosimetry, genotoxicity, and other mechanistic evidence. These comments focus on the scientific support for the proposed quantitative inhalation unit risk (IUR). In particular, the comments address whether the proposed IUR is adequately supported by the available database, whether the selected tumor endpoints and modeling assumptions are sufficiently robust to support the proposed numerical IUR, and whether OEHHA has adequately characterized uncertainty and reasonable alternative interpretations.

Acrolein is a highly reactive aldehyde and a potent respiratory irritant. Its toxicity is strongly influenced by portal-of-entry reactions, local respiratory tract uptake, glutathione depletion, cytotoxicity, inflammation, DNA and protein adduct formation, and regenerative responses. These properties are central to evaluating both the qualitative relevance of the animal tumor findings and the quantitative extrapolation of those findings to low-dose human inhalation exposure.

In deriving the IUR, OEHHA reviewed available animal, epidemiological, toxicokinetic, dosimetry, and mechanistic information, and concluded that the available human studies were not suitable for quantitative dose-response assessment. Consequently, the proposed IUR is based on two-year inhalation carcinogenicity studies in rats and mice conducted by the Japan Bioassay Research Center (JBRC) and summarized in Matsumoto et al. (2021). To derive the IUR, OEHHA modeled tumor incidence data for selected female rat and female mouse tumor endpoints. For female rats, OEHHA modeled nasal cavity squamous cell carcinoma, nasal cavity rhabdomyoma, and combined nasal cavity squamous cell carcinoma plus rhabdomyoma. For female mice, OEHHA modeled nasal cavity adenoma, lymph node malignant lymphoma, and a multisite combination of nasal cavity adenoma plus lymph node malignant lymphoma.

OEHHA determined that acrolein's likely mode of carcinogenic action is genotoxic and used a multistage cancer model with linear low-dose extrapolation. OEHHA used a benchmark response (BMR) of 5% extra risk and calculated animal cancer slope factors as 5% (0.05) divided by the benchmark dose level (BMDL). OEHHA then converted intermittent chamber concentrations to time-adjusted continuous concentrations and average daily doses, applied a study-duration adjustment for the female mouse data because the mouse study was terminated at 99 weeks rather than 104 weeks, converted animal slope factors to human-equivalent slope factors using body-weight scaling, and converted the selected human-

equivalent slope factor to an IUR using its default human breathing rate and body weight assumptions.

OEHHA selected the female mouse multisite tumor analysis as the critical basis for the proposed IUR because it produced the highest modeled human-equivalent cancer slope factor among the evaluated endpoints. The selected value resulted in a proposed cancer slope factor of 2.8 (milligrams per kilogram per day (mg/kg-d))$^{-1}$ corresponding to an IUR of 7.9×10^{-4} per µg/m³, equivalent to 3.4×10^{-4} per part per billion (ppb).

While these comments do not dispute that the Matsumoto/JBRC inhalation bioassay provides important information for evaluating acrolein cancer hazard, particularly with respect to portal-of-entry nasal tumors, they address whether OEHHA has adequately justified the additional quantitative decisions required to derive the proposed IUR, including tumor endpoint selection, combination of nasal and systemic tumor endpoints, linear low-dose extrapolation, benchmark response selection, study-duration adjustment, and animal-to-human extrapolation for a highly reactive inhaled gas.

These comments are organized around three key issues that, in combination, most affect the scientific support for OEHHA's proposed numerical IUR. **Key Issue 1: Tumor Endpoint Combination** addresses whether OEHHA has adequately justified combining a portal-of-entry nasal tumor with a systemic lymphoid tumor in a single multisite analysis. **Key Issue 2: Linear Low-Dose Extrapolation** addresses whether OEHHA has adequately justified using linear low-dose extrapolation, rather than a nonlinear or threshold approach, for the tumor endpoints that determine the proposed IUR, including whether its genotoxic mode-of-action determination follows OEHHA's own adopted analytical framework. **Key Issue 3: Animal-to-Human Dosimetry** addresses whether default body-weight scaling adequately accounts for acrolein's portal-of-entry toxicokinetics. Each issue is developed in detail below, and Table 1 summarizes these and other assumptions affecting the proposed IUR.

2.0 Overview of Key IUR Assumptions

OEHHA's proposed IUR reflects a sequence of study-selection, endpoint-selection, modeling, low-dose extrapolation, exposure-adjustment, study-duration, and animal-to-human extrapolation decisions. Several of these decisions appear to rely on conservative default assumptions rather than a balanced evaluation of the available compound-specific evidence. Because these choices are applied sequentially and materially affect the final IUR, OEHHA should provide the scientific rationale for each, show how scientifically supportable alternatives would affect the final value, and revise the derivation where the selected approach is not supported by the available evidence.

Table 1 summarizes the major assumptions affecting OEHHA's proposed IUR and identifies where each issue is discussed in these comments.

Table 1. Key Modeling and Extrapolation Decisions Affecting OEHHA's Proposed IUR

IUR assumption and Comment Report section	OEHHA approach	Why the approach requires additional scientific support
Study selection (Section 2.0)	Used the Matsumoto/JBRC rat and mouse two-year inhalation bioassays as the primary quantitative basis for the IUR.	The Matsumoto/JBRC study provides important hazard information, particularly for portal-of-entry nasal tumors. However, the broader animal database does not show a replicated or consistently positive carcinogenic response across studies, species, exposure routes, or tumor sites. Human epidemiology also does not provide an acrolein-specific inhalation dose-response basis for deriving or independently validating the proposed IUR. OEHHA should address how limitations in the overall acrolein carcinogenicity database affect confidence in the proposed quantitative value.
Critical tumor endpoint and tumor combination selection (Section 3.0)	Selected the female mouse multisite endpoint, combining nasal cavity adenoma and lymph node malignant lymphoma, as the quantitative basis for the IUR.	Endpoint selection materially affects the final IUR. The multisite estimate is far closer to the lymphoma-only estimate than to the nasal adenoma-only estimate. OEHHA's Cancer Potency Factors Technical Support Document (OEHHA, 2009) distinguishes between combining tumor types that represent progression from a common original normal cell type (which does not apply here) and combining treatment-related tumors at multiple sites. The first basis does not apply because nasal cavity adenoma and lymph node malignant lymphoma do not share a common tissue or cellular origin. OEHHA has also not coherently demonstrated that the second basis for tumor combination—multisite summation of treatment-related tumors—applies. OEHHA did not establish that lymph node malignant lymphoma is treatment-related, biologically plausible, statistically supported, human-relevant, or appropriate for summation with nasal adenoma. Without that demonstration, OEHHA's selected multisite endpoint does not satisfy the

IUR assumption and Comment Report section	OEHHA approach	Why the approach requires additional scientific support
		conditions for tumor combination under OEHHA's own guidance, calling into question the scientific basis for the critical point of departure and the resulting IUR.
Low-dose extrapolation (Section 4.0)	Used a multistage cancer model with linear low-dose extrapolation.	The female mouse nasal tumor response occurred only at the highest exposure concentration and in the context of local nasal toxicity, including epithelial injury, inflammation, hyperplasia, metaplasia, and repair. This pattern supports biological plausibility for a portal-of-entry tumor response, but it also raises questions about whether the response is better characterized as a high-concentration, tissue-injury-associated process rather than a linear low-dose process. OEHHA's own 2009 *Technical Support Document* requires an affirmative weight-of-evidence evaluation before assuming linearity, and U.S. EPA's 2024 *IRIS Toxicological Review of Formaldehyde*, involving a mechanistically analogous portal-of-entry nasal tumor, performed that analysis, integrating cytotoxic proliferation with genotoxicity rather than treating genotoxic potential alone as sufficient. OEHHA should explain why generalized evidence of genotoxic potential supports linear extrapolation for the specific tumor endpoints selected for IUR derivation, or conduct a comparable tissue-specific mode-of-action and dose-response analysis.

IUR assumption and Comment Report section	OEHHA approach	Why the approach requires additional scientific support
Dose metric/ Exposure adjustment (Section 4.0)	Converted intermittent chamber exposures to time-adjusted continuous concentrations and average daily doses.	For a highly reactive portal-of-entry irritant, lifetime average daily dose may not be the most biologically relevant dose metric. Local exposure concentration, peak concentration, time above a tissue-injury threshold, or regional respiratory tract tissue dose may be more directly related to nasal tissue injury and tumor formation. OEHHA should justify the dose metric used for modeling and discuss whether alternative dose metrics would better reflect acrolein's mode of action.
Animal-to-human extrapolation (Section 5.0)	Used default body-weight scaling to convert animal slope factors to human-equivalent slope factors.	Target-tissue dose for a reactive inhaled gas depends on respiratory tract dosimetry, not body weight alone. Relevant factors include species differences in nasal anatomy, airflow patterns, breathing route, uptake efficiency, detoxification, and regional respiratory tract tissue dose. OEHHA's calculation methodology used only body-weight-ratio scaling with no discussion of regional gas dose ratios or the Category 1 (reactive gas) dosimetry approach that U.S. EPA's 1994 methodology for derivation of inhalation reference concentrations (RfCs) prescribes for exactly this situation. For nasal tumors, the relevant extrapolation issue is regional respiratory tract dose; for lymphoma, the relevant issue would be systemic or lymphoid tissue dose, which OEHHA has not established. OEHHA should provide a dosimetry-informed analysis and uncertainty characterization unless it can identify additional evidence demonstrating that default body-weight scaling is appropriate for a reactive inhaled gas and for the biologically distinct tumor endpoints included in the selected multisite analysis.

IUR assumption and Comment Report section	OEHHA approach	Why the approach requires additional scientific support
Sensitivity to alternative modeling assumptions (Section 6.0)	Selected the highest modeled human-equivalent potency estimate in the final IUR; used a 5% BMR, BMDL-based linear slope calculation, and a female mouse study-duration adjustment from 99 to 104 weeks.	OEHHA should provide analysis showing how the proposed IUR changes under reasonable alternative modeling assumptions. These should include nasal tumors alone, lymphoma alone, exclusion of lymphoma, female mouse versus female rat nasal tumor endpoints, 5% versus 10% BMR, BMD versus BMDL-based estimates, alternative acceptable model forms, results with and without the female mouse study-duration adjustment, average daily dose versus alternative dose metrics, default body-weight scaling versus dosimetry-informed alternatives, and linear versus nonlinear or margin-of-exposure presentation. These analyses are especially important because the selected endpoint includes a biologically uncertain lymphoma component and the nasal tumor response is high-dose-only.
Consistency with risk-assessment guidance and other authoritative assessments (Section 7.0)	Relied on accepted cancer modeling tools and cited IARC's Group 2A cancer classification, but provided limited explanation of how the specific IUR derivation comports with U.S. EPA cancer, benchmark dose, and inhalation dosimetry guidance.	OEHHA should distinguish cancer hazard classification from quantitative IUR derivation. IARC's Group 2A classification supports a cancer hazard concern, but it does not validate OEHHA's selected tumor endpoint, lymphoma-inclusive multisite modeling approach, low-dose extrapolation method, animal-to-human scaling approach, or final numerical IUR. OEHHA's draft shows that is employs U.S. EPA benchmark dose guidance for model-fit selection, which makes it more notable that it has not applied comparable mode-of-action and endpoint-combination principles from U.S. EPA's 2005 cancer risk assessment guidelines.

BMDL – Benchmark dose level; BMR – Benchmark response

The following sections address the database context for the proposed IUR and the key assumptions applied in the derivation that are summarized in Table 1. In brief, the proposed IUR is derived from selected tumor findings in the Matsumoto/JBRC inhalation bioassay,

while the broader animal database, human epidemiology database, and other authoritative assessments do not independently corroborate the proposed numerical value.

2.1 The Proposed IUR Relies Heavily on One Chronic Inhalation Bioassay, with Limited Support from the Broader Animal Cancer Database

OEHHA's IUR is derived from the Matsumoto et al. (2021)/JBRC two-year whole-body inhalation studies in rats and mice, summarized above in the Introduction. In both species, nasal tumors occurred only at the highest exposure concentration and primarily in females. Nonneoplastic nasal lesions, including inflammation, epithelial hyperplasia, squamous metaplasia, regeneration, and other local tissue changes, were also increased at higher exposure levels in the respiratory tract. In female mice, the reported trend for lymph node malignant lymphoma was not accompanied by a statistically significant pairwise increase at any exposure level.

The Matsumoto/JBRC study has several strengths for evaluating chronic inhalation carcinogenicity, including two-year exposure duration, evaluation of two rodent species and both sexes, multiple exposure concentrations, examination of respiratory tract tissues, and a design generally consistent with carcinogenicity testing guidelines. However, it remains a single study. Reliance on this study for quantitative IUR derivation should therefore be considered in the context of the broader cancer database, which does not show a consistent carcinogenic response across studies, species, exposure routes, or tumor sites.

The portal-of-entry nasal findings are consistent with acrolein's high reactivity and observed local respiratory tract effects. However, because the nonneoplastic nasal lesions were reported from necropsy evaluations rather than from interim time points, they support an association with local tissue injury but do not establish that the lesions preceded tumor development. The high-dose-only nasal tumor response, occurring in the same target tissue as local injury and repair-related changes, raises questions about whether this rodent tumor response should be extrapolated quantitatively to low-dose human environmental exposures without additional analysis of dose-response, mode of action, and respiratory tract dosimetry.

The only other inhalation cancer study identified by OEHHA is Feron and Kruysse (1977), which used a single high acrolein concentration in hamsters for 52 weeks. In this study, Syrian golden hamsters (18 per sex per exposure level) were exposed by whole-body inhalation to 0 or 4 ppm acrolein for 7 hours/day, 5 days/week, for 52 weeks. The study reported nasal irritation-related changes, including epithelial hyperplasia and metaplasia in the nasal cavity, but no neoplastic changs in the respiratory tract or other tissues that could be attributed to acrolein were observed. The study authors concluded that acrolein exposure under the conditions tested did not produce tumors. However, the study is limited for cancer assessment because it used only one acrolein exposure concentration, had a shorter-than-

lifetime exposure duration, and included limited pathological reporting (mostly limited to respiratory tract) by current standards.

One other, likewise limited, chronic inhalation study for acrolein was identified in the literature database. In a study in female Sprague Dawley rats, 20 animals were exposed to a single concentration of acrolein (8 ppm; 18 milligrams per cubic meter (mg/m^3)) via whole body inhalation for 1-hour daily for up to 18 months (Le Bouffant et al., 1980). Histological examination of major tissues and organs (including nasal fossae, larynx, trachea and lungs) revealed no evidence of tumors or metaplasia except for small lesions described as of the epidermoid type in the large bronchi of two animals.

Earlier oral animal studies (Table 2), which are not discussed in detail in OEHHA's draft, also provide limited support for quantitative inhalation cancer potency derivation or for inclusion of a systemic tumor endpoint such as lymph node malignant lymphoma in the IUR analysis. This is expected, to some extent, because acrolein is highly reactive, and route and portal of entry are important: oral studies do not directly inform local respiratory tract tissue dose, nasal injury, or nasal tumor formation following inhalation exposure. However, the oral studies also do not corroborate a concern for lymphoma or other systemic cancer effects. The principal positive oral finding—increased adrenal cortical neoplasms in high-dose female rats in the Lijinsky and Reuber (1987) drinking-water study—was not confirmed in the later Parent et al. (1992a) rat gavage study and has been questioned by U.S. EPA (2003) because of exposure-characterization, pathology, and historical-control issues. Other oral studies in mice, rats, and dogs did not report treatment-related tumor increases.

Table 2. Summary of Animal Oral Carcinogenicity Studies for Acrolein

Study	Design	Reported cancer findings	Interpretation
Lijinsky and Reuber, 1987	F344 rats exposed to 0, 100, 250, or 625 milligrams per liter (mg/L) acrolein in drinking water for 5 days per week (d/wk) for 104–124 weeks; U.S. EPA reported average daily intakes of 0, 1.9, 5.0, and 12.5 milligrams per day (mg/d) (males) or 0 and 12.5 mg/d (females), but mg/kg-d dose estimates are uncertain.	No treatment-related increase in neoplasms was reported. Common tumor incidences were similar between treated and control rats, and isolated uncommon tumors did not generally show a consistent or dose-related pattern. Increased adrenal cortical lesions in high-dose females given 625 mg/L, including 5/20 adrenal cortical adenomas and 2/20 hyperplastic nodules. Other tumor findings, including forestomach papillomas in males, were sporadic or not dose-related.	This is the main earlier "positive" oral study, but findings were later questioned. Limitations include uncertainty in actual dose, limited high-dose female-only adrenal findings, and later pathology review and conclusion that cortical tumors were within the range of historical control (U.S. EPA, 2003). Study findings contributed to U.S. EPA's earlier possible-human-carcinogen classification (U.S. EPA, 1992), but were later questioned by U.S. EPA (2003) which characterized the study as inadequate to determine acrolein's carcinogenic potential.
Parent et al., 1991	CD-1 mice dosed with acrolein by gavage for 18 months, at 0, 0.5, 2.0, or 4.5 mg/kg-d.	No treatment-related tumor increase based on histopathological evaluation, including major organs, respiratory and gastrointestinal tissues, endocrine organs, lymphoid tissues, reproductive tissues, and gross lesions.	The study does not support a generalized systemic carcinogenic response to acrolein.
Parent et al., 1992a	Sprague-Dawley rats dosed with acrolein by gavage for 102 weeks, at 0, 0.05, 0.5, or 2.5 mg/kg-d.	No treatment-related tumor increase was observed based on broad histopathological evaluation of major organs, adrenal glands, lymphoid tissues, respiratory/GI tissues, reproductive/endocrine tissues, and gross lesions, which did not identify acrolein-related carcinogenicity.	In a detailed analysis of the adrenal cortex, the adrenal tumor finding reported by Lijinsky and Reuber (1987) was not reproduced.

Study	Design	Reported cancer findings	Interpretation
Parent et al., 1992b	Beagle dogs given acrolein orally for one year, at 0, 0.1, 0.5, or 1.5 mg/kg-d, with the high dose increased to 2 mg/kg-d after 4 wks.	No treatment-related tumor increase; broad histopathology of major organs, adrenal glands, lymphoid tissues, respiratory/GI tissues, reproductive/endocrine tissues, and gross lesions did not identify acrolein-related carcinogenicity.	Although not a standard lifetime carcinogenicity bioassay, it does not support a generalized systemic carcinogenic response to acrolein.

OEHHA should explain how these limitations in the broader animal database affect confidence in the proposed IUR.

2.2 The Human Epidemiology Database Does Not Independently Support the Proposed Numerical IUR

OEHHA reviewed occupational and population-based epidemiological studies, including studies considered by IARC and studies published after the IARC review. OEHHA appropriately concludes that the human epidemiology database remains inadequate overall for quantitative dose-response assessment. The available occupational studies are limited by lack of quantitative acrolein exposure assessment, co-exposures to other chemicals, and small numbers of exposed cases. The available population-based studies are limited by reliance on biomarkers or modeled ambient exposure estimates, potential confounding, collinearity with other air toxics, reverse causation in some case-control designs, single-time-point exposure measurements, and limited ability to isolate acrolein-specific effects.

The principal epidemiological studies discussed by OEHHA are summarized in Table 3. None provides an acrolein-specific inhalation exposure-response relationship or a consistent cancer endpoint.

Table 3. Summary of Epidemiological Studies Evaluating Acrolein Exposure and Cancer Outcomes

Study	Population / exposure metric	Cancer endpoint(s)	Key findings	Primary limitations for IUR derivation
Bittersohl, 1975	Occupational cohort / case series of aldehyde factory workers with presumed acrolein exposure.	Oral cavity, bronchial, stomach, and intestinal cancers were reported.	OEHHA/IARC considered the study uninformative for acrolein-specific carcinogenicity.	No quantitative acrolein exposure assessment, no suitable comparison group or effect estimate, and multiple chemical co-exposures.
Ott et al., 1989a,b	Occupational nested case-control study of chemical workers.	Non-Hodgkin lymphoma, multiple myeloma, leukemia.	Positive associations for lympho-hematopoietic cancers but based on very small numbers of exposed cases; confidence intervals were wide and included 1.	Very small, exposed case counts, potential bias and confounding, high correlation with other chemicals, and co-exposures to known carcinogens.
Yuan et al., 2012	Nested case-control study in smokers using urinary HPMA as an acrolein metabolite biomarker.	Lung cancer.	The association disappeared after adjustment for other tobacco-related biomarkers, and after adjustment for polycyclic aromatic hydrocarbon (PAH) metabolites, tobacco nitrosamines, and cotinine.	Strong smoking-related confounding; biomarker reflects multiple exposure sources; does not establish direct etiological role for acrolein.
Yuan et al., 2014	Nested case-control study in nonsmokers using urinary acrolein metabolites.	Lung cancer.	No clear positive association after adjustment for confounders.	Biomarker-based exposure assessment, limited external exposure information, and potential secondhand smoke or other exposure limitations.
Tsou et al., 2019	Case-control study measuring acrolein-DNA adducts in buccal/oral samples.	Oral cancer.	Higher adduct levels in cases/ tumor tissues, but no association with external exposure sources, e.g., tobacco, betel chewing.	Mechanistic or biomarker study; samples collected after diagnosis; does not provide external inhalation exposure-response information.

Study	Population / exposure metric	Cancer endpoint(s)	Key findings	Primary limitations for IUR derivation
Hong et al., 2020	Case-control study in patients with chronic kidney disease.	Urothelial carcinoma.	Reported differences in acrolein-related biomarkers.	Small sample size, poor external exposure assessment, possible reverse causation, and design limitations.
Etemadi et al., 2024	Nested case-control in Iran using urinary acrolein metabolites CEMA and HPMA.	Esophageal squamous cell carcinoma.	Increased risk reported among non-current tobacco users; no increased risk in current tobacco users.	Biomarker-based; not inhalation-specific; potential confounding by diet, combustion products, environmental exposures, and other aldehydes/toxicants.
Feng et al., 2024	Prospective National Health and Nutrition Examination Survey (NHANES)-based cohort using urinary acrolein metabolites.	All-cancer mortality.	Associations reported for all-cause and cancer mortality.	Not site-specific for cancer, biomarker reflects multiple sources, potential residual confounding, and limited ability to infer causation or dose-response.
Heck et al., 2024	Multiethnic cohort in Los Angeles using modeled residential ambient air toxics exposure.	Breast cancer.	Positive association for modeled acrolein exposure; acrolein had the highest health risk among evaluated traffic-related pollutants.	Interpretation constrained by collinearity with other air toxics, uncertainty in modeled exposure estimates, possible unmeasured correlated pollutants, and incomplete lifetime exposure history.
Rodriguez et al., 2024	Small case-control using urinary HPMA and other biomarkers.	Pancreatic ductal adenocarcinoma.	Higher HPMA and other toxicant biomarkers were reported in cases.	Very small study, single urine sample near diagnosis, potential reverse causation, multiple correlated toxicants.
Peterson et al., 2025	Small case-control of current nonsmokers using urinary HPMA.	Urothelial carcinoma.	No significant difference in HPMA between cases and controls.	Small sample size, single time-point exposure measurement, hospital controls.

Study	Population / exposure metric	Cancer endpoint(s)	Key findings	Primary limitations for IUR derivation
Nalini et al., 2026	Nested case-cohort study using urinary CEMA/HPMA.	Lung cancer.	Associations in current smokers attenuated after adjustment for smoking-related biomarkers; no clear positive association in non-current smokers.	Smoking confounding, biomarker nonspecificity, and limited relevance to acrolein-specific inhalation dose-response.

CEMA – N-acetyl-S-(2-carboxyethyl)-L-cysteine; HPMA – N-acetyl-S-(3-hydroxypropyl)-L-cysteine [Both are urinary mercapturic acid metabolites used as biomarkers of acrolein exposure, although they may reflect multiple exposure sources and are not specific to inhalation exposure].

These studies provide limited qualitative support for hazard plausibility, particularly when considered together with mechanistic evidence that acrolein can form DNA adducts and produce other key characteristics of carcinogens. However, they do not demonstrate reliable acrolein-specific inhalation exposure-response relationships, do not identify a consistent human cancer endpoint, and do not provide a suitable point of departure for IUR derivation.

The epidemiology database also does not independently validate OEHHA's selected animal-based point of departure. Specifically, the human data do not validate the quantitative inclusion of lymph node malignant lymphoma as a critical endpoint, nor do they establish that acrolein cancer risk is linear at low environmental exposure levels or confirm the relative magnitude of OEHHA's proposed IUR.

OEHHA should state these limitations explicitly in the draft.

2.3 Other Authoritative Assessments Do Not Broadly Corroborate OEHHA's Proposed Quantitative IUR

Other authoritative assessments provide important context for evaluating OEHHA's proposed IUR. Currently, OEHHA is the only body that has proposed a quantitative cancer potency value for acrolein. Other bodies either classify cancer hazard, decline to classify, or derive noncancer values focused on point-of-contact toxicity. For inhalation, those values generally focus on respiratory irritation or nasal lesions (e.g., U.S. EPA (2003) derived an inhalation RfC based on upper respiratory tract and lung lesions in rats and the Agency for Toxic Substances and Disease Registry (ATSDR) (2025) derived acute, intermediate, and chronic inhalation minimal risk levels (MRLs) based on nose/throat irritation, decreased respiratory rate, and nasal respiratory gland metaplasia; OEHHA (2008) previously derived acute, 8-hour, and chronic noncancer reference exposure levels (RELs) based on ocular irritation and respiratory epithelial lesions[1]). For oral exposure, U.S. EPA (2003) and ATSDR (2025) have derived noncancer values based on increased mortality or gastrointestinal epithelial effects, with the underlying toxicology reflecting acrolein's high reactivity and local tissue injury at sites of first contact.

Prior to publication of the Matsumoto/JBRC chronic inhalation bioassay, authoritative bodies generally concluded that acrolein was not classifiable as to carcinogenicity, was only a possible or suspected carcinogen, or had an inadequate database for quantitative cancer assessment. Following publication of that study (Matsumoto et al., 2021), IARC classified

[1] Examples of noncancer inhalation values for acrolein include U.S. EPA's RfC of 0.020 µg/m³ based on upper respiratory tract/lung lesions; ATSDR's acute inhalation MRL of 6.9 µg/m³ based on nose/throat irritation and decreased respiratory rate and chronic/intermediate inhalation MRL of 0.92 µg/m³ based on nasal respiratory gland metaplasia; and OEHHA's acute, 8-hour, and chronic RELs of 2.5, 0.70, and 0.35 µg/m³, respectively, based on ocular irritation or respiratory epithelial lesions.

acrolein as Group 2A, probably carcinogenic to humans, based on "sufficient" evidence in experimental animals and "strong" mechanistic evidence, but concluded that the human evidence remained "inadequate" (IARC, 2021).

A hazard classification indicates that a chemical may cause cancer under some conditions, but it does not determine which tumor endpoint should be modeled, whether low-dose extrapolation should be linear, how animal results should be extrapolated to humans, or what numerical IUR should result.

As summarized below, with the exception of OEHHA, no other authoritative body has derived a quantitative cancer potency value for acrolein. Several earlier assessments predated the Matsumoto/JBRC chronic inhalation bioassay and emphasized limitations in the cancer database. The more recent assessments, particularly IARC's 2021 Group 2A classification, provide important hazard context. However, these assessments do not independently evaluate or corroborate OEHHA's specific quantitative choices, including selection of the critical tumor endpoint, use of a lymphoma-inclusive multisite analysis, low-dose extrapolation approach, animal-to-human extrapolation method, or final numerical IUR. It is also noteworthy that, based on publicly available information, OEHHA's draft IUR appears to be the only pending derivation of a quantitative cancer potency value for acrolein in the five years since IARC issued its Group 2A classification.

- U.S. EPA Carcinogen Risk Assessment Verification Endeavor (CRAVE) (1992, summarized in U.S. EPA, 2003)—classified acrolein as Group C (possible human carcinogen) based on an oral finding later determined unreliable, but did not derive a quantitative value.
- Health Canada/Environment Canada (2000) and German MAK/DFG (2001)—did not classify acrolein as a carcinogen or derive a cancer-based value and instead emphasized site-of-contact toxicity and an inadequate database.
- U.S. EPA Provisional Peer-Reviewed Toxicity Value (PPRTV) (2002) and IRIS Toxicological Review (2003)—found the database inadequate to derive cancer potency values; emphasized portal-of-entry respiratory effects.
- ACGIH (2019) and NIOSH (1991, 2019)—presented occupational exposure guidance, not public-health cancer potency values.
- IARC (2021)—classified acrolein as Group 2A, probably carcinogenic to humans, based on sufficient evidence in experimental animal studies and strong mechanistic evidence, including the Matsumoto/JBRC study, while concluding that human evidence was inadequate.
- NTP (2021)— did not list acrolein as a known or reasonably anticipated human carcinogen in the 15th Report on Carcinogens. However, given the timing of the

report relative to publication of the Matsumoto/JBRC study and IARC's evaluation, it is unclear whether NTP considered this evidence.

- ATSDR (2025) Toxicological Profile—discussed the Matsumoto/JBRC study and referenced IARC's Group 2A classification, but ATSDR generally does not assign independent cancer classifications or derive cancer potency values; its inhalation MRLs for acrolein are noncancer values based on nasal irritation and lesions.

The proposed IUR is a quantitative estimate derived primarily from OEHHA's interpretation and modeling of selected Matsumoto/JBRC animal tumor endpoints, informed by supporting mechanistic evidence and limited qualitative epidemiological information. The broader assessment context supports careful evaluation of acrolein's carcinogenic potential, particularly the portal-of-entry nasal tumor findings. However, it does not independently confirm the numerical IUR proposed by OEHHA or the specific quantitative choices underlying that value.

2.4 Recommended Revisions

OEHHA should revise the draft to:

1. justify reliance on the Matsumoto/JBRC study for quantitative IUR derivation while acknowledging that the broader animal database is limited and inconsistent;
2. summarize older oral carcinogenicity studies and acknowledge that they do not provide consistent corroboration for a generalized systemic carcinogenic response or for the quantitative cancer potency derivation;
3. state explicitly that human epidemiology is inadequate for deriving or validating the proposed IUR; and
4. distinguish evidence supporting acrolein cancer hazard characterization from evidence sufficient to support a quantitative cancer potency value and clarify that IARC's 2021 Group 2A classification does not, by itself, validate OEHHA's selected tumor endpoint, modeling approach, or proposed numerical IUR.

These revisions are needed because the proposed IUR is derived from OEHHA's interpretation and modeling of selected tumor findings from the Matsumoto/JBRC study, not from a broadly consistent animal cancer database or from human dose-response evidence. OEHHA should characterize the proposed IUR accordingly. Where the broader database does not support the selected endpoint or modeling approach, OEHHA should revise the derivation and explicitly characterize the resulting uncertainty..

3.0 Key Issue 1: Tumor Endpoint Combination

This section develops the first of the three key issues introduced in Section 1.0: OEHHA's combination of two biologically distinct tumor endpoints, nasal cavity adenoma and lymph node malignant lymphoma, into a single multisite analysis, selected because it produced the

highest potency estimate. Combining these endpoints, especially in the absence of stronger justification, is scientifically inappropriate because they differ in anatomical site, biological plausibility, dose-response pattern, statistical support, and relevance to inhaled acrolein exposure, as discussed in the subsections below.

3.1 The Female Mouse Multisite Point of Departure Combines Tumor Types with Different Biological Plausibility and Dose-Response Patterns

OEHHA's selected multisite analysis combines incidences of female mouse nasal cavity adenoma and lymph node malignant lymphoma at each exposure level. Before combining these endpoints quantitatively, OEHHA should at least evaluate each endpoint separately and demonstrate that each is treatment-related, biologically plausible, supported by a relevant mode of action, statistically and dose-response supported, and relevant to human inhalation exposure. OEHHA should then explain why the two endpoints should be combined, including whether they share a common or related mode of action and whether their risks can reasonably be treated as additive.

Table 4 summarizes the tumor incidence data for the two female mouse endpoints included in OEHHA's selected multisite analysis.

Table 4. Female Mouse Tumor Incidences Used in OEHHA's Multisite Analysis

Acrolein exposure	Approximate acrolein concentration	Nasal cavity adenoma	Lymph node malignant lymphoma
0 ppm	0 mg/m³	0/50	12/50 (24%)
0.1 ppm	0.2 mg/m³	0/50	8/50 (16%)
0.4 ppm	0.9 mg/m³	0/50	6/50 (12%)
1.6 ppm	3.7 mg/m³	16/50 (32%)	17/50 (34%)

As shown in Table 4, nasal cavity adenomas occurred only at the highest exposure concentration. This endpoint is anatomically and toxicologically consistent with inhaled acrolein's portal-of-entry toxicity. In the same study, the nasal tumor response occurred in the context of nonneoplastic nasal lesions, including inflammation, hyperplasia, metaplasia, regeneration, and other tissue repair/remodeling changes. These findings support the nasal cavity as a target tissue for inhaled acrolein, but they also suggest that the nasal tumor response may be linked to repeated local tissue injury and repair at high exposure concentrations. This raises separate questions about low-dose extrapolation, discussed in Section 4.0.

Lymph node malignant lymphoma shows a much different pattern. Incidences were lower than controls at the low and mid exposure levels and higher than controls only at the highest exposure concentration. Because lymphoma is not a portal-of-entry tumor and does not follow the same response pattern as nasal adenoma, OEHHA should not combine these tumors with the high dose nasal cavity adenomas unless it can provide an affirmative biological rationale for treating lymphoma as an acrolein exposure-related endpoint. More specifically, OEHHA's proposed approach is not scientifically valid unless it can identify evidence that inhaled acrolein, or biologically relevant downstream effects of acrolein exposure, can plausibly produce a lymphoid tumor response under the study conditions, which it has not done.

The quantitative importance of lymphoma is shown by OEHHA's endpoint-specific potency estimates. Based on OEHHA's reported human-equivalent cancer slope factors (OEHHA, 2026, Table 7), the multisite estimate is much closer to the lymphoma-only estimate than to the nasal adenoma-only estimate (Table 5).

Table 5. Comparison of Female Mouse Endpoint-Specific Potency Estimates

Female mouse endpoint	Human-equivalent CSF, per mg/kg-d	Implied IUR, per µg/m³	Comparison to final IUR
Nasal cavity adenoma alone	1.47	~4.2×10^{-4}	~53% of final IUR
Lymph node malignant lymphoma alone	2.64	~7.5×10^{-4}	~95% of final IUR
Nasal adenoma + lymph node malignant lymphoma multisite	2.76	~7.9×10^{-4}	100% of final IUR
OEHHA selected final IUR	2.8, rounded CSF	7.9×10^{-4}	100%

CSF –Cancer slope factor

This comparison shows that the multisite IUR is only slightly higher than the lymphoma-only IUR but substantially higher than the nasal adenoma-only IUR. Thus, although the multisite endpoint includes the biologically plausible nasal tumor response, the final potency estimate is heavily dependent on inclusion of lymphoma.

This point is important for transparency. The multisite analysis may give the appearance that the final IUR is supported by a combined tumor response, when the resulting potency estimate is driven largely by the biologically implausible lymphoma endpoint. OEHHA should remove the lymphoma data from the IUR derivation or clearly explain the contribution of each endpoint to the multisite estimate and discuss how uncertainty in lymphoma treatment-relatedness, biological plausibility, and human relevance affects confidence in the final proposed IUR.

3.2 Lymph Node Malignant Lymphoma Lacks Statistical and Historical-Control Support

The lymphoma incidence pattern is non-monotonic and statistically weak on the study authors' own terms. Incidence was 12/50, 8/50, 6/50, and 17/50 across the four exposure groups, lower than the concurrent control at the low and mid doses and higher only at the highest dose, with no statistically significant pairwise increase in any group. Matsumoto et al. (2021) did not find this pattern significant by Fisher's exact test at any individual dose; the response depends entirely on a trend test, in contrast to nasal adenoma, which was significant on both the trend test and Fisher's exact test at the high dose. A trend test can be relevant evidence of a dose-related response, but it does not, by itself, establish that an endpoint is sufficiently robust to serve as a critical quantitative basis for the IUR, particularly given this non-monotonic pattern.

Historical-control context further weakens confidence in this endpoint. JBRC reports a historical-control range of 28–46% for malignant lymphoma in female B6D2F1/Crlj mice across 11 carcinogenicity studies (169 tumor-bearing animals among 500 examined, average 33.8%), and the concurrent control incidence in this study was itself 24%. Every dose group in the study, including the high-dose group's 34% incidence, falls within or below this historical range. This is consistent with the broader pathology literature: malignant lymphoma is among the most common spontaneous tumors in aging B6D2F1 mice, with incidence that varies substantially by strain, sex, age, and laboratory and sometimes exceeds 50% independent of any exposure (Frith et al., 1993). By the same historical-control logic that OEHHA and JBRC apply to evaluate rare tumors, a common tumor occurring within its expected background range should not be attributed to treatment without additional support.

OEHHA's own draft shows it is willing to exclude a statistically significant tumor finding on this same reasoning. Female mice also had a significant increase in histiocytic sarcoma at the mid dose, which OEHHA excluded from dose-response modeling because IARC (2021) considered it only possibly treatment-related "due to the lack of a clear dose-response relationship" (OEHHA, 2026, p. 43). Lymphoma presents the same basic problem—a non-monotonic pattern with no significant pairwise increase at any dose—yet OEHHA included it in the critical multisite analysis rather than excluding it on the same basis. OEHHA should explain why a "lack of a clear dose-response relationship" warranted excluding histiocytic sarcoma but not lymphoma, and more generally why the observed incidence pattern and its position within the JBRC historical-control range support treating lymphoma as a robust, treatment-related quantitative endpoint.

3.3 Lymph Node Malignant Lymphoma Lacks Biological Plausibility as an Acrolein-Related Endpoint

Acrolein is highly reactive and is expected to act primarily at sites of first contact; a nasal tumor response is therefore biologically intuitive for inhaled acrolein, but a systemic lymphoid tumor response is not, and should not be assumed without evidence of systemic delivery, lymphoid tissue exposure, immunotoxicity, lymphoid precursor lesions, or another plausible lymphomagenic pathway. OEHHA does not identify such evidence. Occupational epidemiology has reported limited and uncertain associations between acrolein exposure and lymphohematopoietic cancers, but these findings are not specific enough to validate the female mouse lymphoma endpoint and are limited by small numbers, co-exposures, and exposure-classification uncertainty.

Acrolein's own reactivity and near-complete nasal scrubbing argue against sufficient systemic delivery to drive a lymphoid tumor. Nasal uptake efficiency data show the upper respiratory tract extracts a large majority of inhaled acrolein before it can travel further, with efficiencies commonly exceeding 50% and reaching roughly 98% at lower, more environmentally relevant concentrations (Struve et al., 2008; Morris, 1996). The same chemistry that makes acrolein an efficient local nasal toxicant argues against meaningful delivery to lymph nodes, spleen, or bone marrow: Dorman et al. (2008) state that inhaled acrolein has "very limited systemic delivery" (citing Beauchamp et al., 1985).

Further, the two tumor types also share no documented tissue origin, cell lineage, or mechanism. Nasal adenoma is an epithelial tumor preceded by a well-documented local sequence of cytotoxic injury—inflammation, hyperplasia, and metaplasia. Malignant lymphoma arises in an entirely different lineage and anatomic compartment, with no cytotoxic precursor lesion reported anywhere in the acrolein literature; Matsumoto et al. (2021) propose a specific biological explanation for how the nasal tumors arise, linking repeated local tissue injury and regeneration to tumor formation, but offer no comparable explanation for how inhaled acrolein could plausibly cause lymphoma. Testing whether the two tumors co-occurred in the same animals more often than chance would require individual-animal data, but Matsumoto et al. (2021) reports only group-level incidence; in the absence of that evidence, treating co-occurrence in the aggregate dataset as meaningful is not supportable.

Given this lack of shared tissue origin or mechanism, lymphoma also does not satisfy the same-tissue-type combination criterion discussed below, further undermining OEHHA's basis for pooling it with nasal adenoma in a single multisite analysis.

3.4 BMDS Multisite Modeling Does Not Resolve Uncertainty in Endpoint Selection or Endpoint Combination

U.S. EPA's Benchmark Dose Software (BMDS) multitumor procedure provides a statistical method for estimating the BMD/BMDL associated with the risk of developing one or more selected tumor endpoints (U.S. EPA, 2026). However, the method depends on endpoint-selection and endpoint-combination assumptions that must be justified by the assessor. U.S. EPA's BMDS User Guide describes the multitumor option as a special application of dichotomous modeling for evaluating the combined effect of two or more independent dichotomous responses and states that the method estimates the risk of responding with one or more of the endpoints under analysis. The User Guide also identifies key assumptions: the tumors are statistically independent, a multistage model is appropriate for each tumor separately, and the assessor is interested in estimating the risk of developing one or more of the tumors under analysis.

OEHHA's own draft undercuts this multisite combination on its own terms. OEHHA states that "tumors of the same histological cell type or tissue type were combined for dose-response assessment (McConnell et al., 1986; Brix et al., 2010)" (OEHHA, 2026, p. 43), and applied that principle to combine female rat nasal cavity squamous cell carcinoma and rhabdomyoma, two histologically distinct tumors that nonetheless share the same tissue of origin. For female mice, however, OEHHA did not apply that same-tissue-type principle. Instead, it fit a separate multistage model to each tumor type and summed the maximum-likelihood parameter estimates (β_i) across those two models (not the tumors' incidence data, and not their individually computed BMDs) to build a single combined model using the BMDS multisite tumor module's profile-likelihood method (OEHHA, 2026, p. 43), a purely statistical combination that does not require, and here does not have, a shared tissue of origin. OEHHA should explain why the same-tissue-type criterion it invokes for the rat nasal tumors does not apply to, or was not required for, the mouse multisite analysis.

U.S. EPA's BMDS guidance also makes clear that the user should investigate each tumor individually and determine the appropriate multistage model for each tumor, considering the usual model-fit considerations, including AIC and related diagnostics. The User Guide further states that it is ultimately the user's responsibility to ensure that model degree and other modeling selections are appropriate for the dataset.

U.S. EPA's broader Benchmark Dose Technical Guidance similarly emphasizes that study and endpoint selection remain risk-assessment judgments (U.S. EPA, 2012). Endpoints selected for modeling should be relevant to the exposure scenario and should generally show a biologically or statistically significant dose-related trend. The guidance also notes that datasets with only the highest dose showing a response may provide limited information about the shape of the dose-response relationship and that fitting multiple models can help evaluate uncertainty in the BMD estimate.

U.S. EPA's cancer guidance is also relevant (U.S. EPA, 2005). U.S. EPA states that, when an agent induces multiple tumor types, dose-response assessment should include analysis of tumor types followed by an overall synthesis that considers risk estimates across tumor types, the strength of mode-of-action information for each tumor type, and anticipated human relevance. U.S. EPA also states that, if multiple tumor sites have different modes of action, the corresponding dose-response approach should be used at each site.

These guidance statements support a clear distinction between the ability of BMDS to calculate a multisite BMD/BMDL and the scientific appropriateness of the tumor endpoints selected for combination. For acrolein, OEHHA should demonstrate that nasal cavity adenoma and lymph node malignant lymphoma are each treatment-related, adequately modeled individually, statistically independent, relevant to human inhalation exposure, and appropriate to treat as additive tumor risks arising from the same exposure. OEHHA should also explain whether the endpoints share a common or related mode of action, or whether they are being combined solely because doing so produces the highest potency estimate.

If individual-animal data are available, OEHHA should report whether nasal adenoma and lymph node malignant lymphoma occurred in the same animals, whether the endpoints appear independent, and whether survival adjustment affects the endpoint-specific and combined results. If only aggregate tumor incidence data are used, OEHHA should acknowledge that the independence and additivity assumptions cannot be directly evaluated from the published summary data.

Accordingly, the BMDS multisite result should not be treated as self-validating. The key issue is whether the selected endpoints are scientifically appropriate inputs to the model. Unless OEHHA provides stronger support for combining a portal-of-entry nasal epithelial tumor with a systemic lymphoid tumor, the lymphoma-inclusive multisite result should be presented as a sensitivity analysis or upper-bound alternative rather than as the primary basis for the proposed IUR.

3.5 OEHHA Should Base the IUR on the Female Mouse Nasal Cavity Adenoma Endpoint Unless the Basis for Combining Endpoints Is Established

OEHHA should present the female mouse nasal adenoma, lymph node malignant lymphoma, and multisite results side-by-side, including BMD, BMDL, animal cancer slope factor, study-duration-adjusted animal slope factor, human-equivalent slope factor, implied IUR, and percent contribution relative to the selected final IUR. This would allow reviewers to understand how much of the proposed IUR is attributable to the portal-of-entry nasal tumor endpoint and how much depends on inclusion of lymphoma.

Without stronger biological and statistical rationale for combining the nasal cavity adenoma and lymphoma endpoints, OEHHA should derive the proposed IUR using only the female

mouse nasal cavity adenoma endpoint, the more directly relevant portal-of-entry tumor response for inhaled acrolein. Absent concrete evidence addressing the statistical, biological, and risk-assessment deficiencies identified above, OEHHA should not include lymph node malignant lymphoma in the critical estimate.

3.6 Recommended Revisions

OEHHA should revise the draft to:

1. evaluate female mouse nasal cavity adenoma and lymph node malignant lymphoma separately before combining them quantitatively;
2. provide endpoint-specific BMD, BMDL, animal slope factor, human-equivalent slope factor, implied IUR, and model-fit information for each endpoint and for the multisite analysis;
3. either acknowledge that there is no statistical basis for treating lymph node malignant lymphoma as treatment-related, or provide additional evidence explaining the statistical basis for this assumption, including trend test results, pairwise comparisons, model-fit statistics, and survival adjustment methods;
4. discuss the JBRC historical-control incidence for malignant lymphoma in female B6D2F1/Crlj mice and either acknowledge that the high-dose incidence does not support treatment-relatedness or provide additional evidence explaining how this interpretation is supported despite malignant lymphoma for this mouse strain falling within the reported historical-control range;
5. provide a biological rationale for lymphoma as an acrolein-related endpoint, including evidence for systemic delivery, lymphoid tissue exposure, immunotoxicity, lymphoid precursor lesions, or another plausible lymphomagenic pathway;
6. explain whether nasal adenoma and lymphoma can reasonably be treated as independent but additive tumor risks arising from the same inhalation exposure;
7. state whether individual-animal tumor co-occurrence data were available and used to evaluate independence or additivity;
8. explain how OEHHA's use of the BMDS multisite model comports with OEHHA's tumor-combination guidance and U.S. EPA BMDS and cancer guidance, including the need to evaluate each tumor endpoint separately and consider mode-of-action and human-relevance support for each tumor type;
9. present a sensitivity analysis showing the impact of alternative endpoint selections, including nasal adenoma alone, lymphoma alone, the lymphoma-inclusive multisite estimate, and exclusion of lymphoma from the critical IUR derivation; and
10. absent a stronger biological and statistical rationale for combining the endpoints, exclude lymph node malignant lymphoma from the critical quantitative analysis and derive the IUR using the female mouse nasal cavity adenoma endpoint alone.

These revisions are needed to align the IUR derivation with OEHHA's own tumor-combination guidance and with the experimental evidence. The critical IUR should be based on the tumor endpoint most directly supported by the Matsumoto/JBRC study unless OEHHA provides a clear biological, statistical, and risk-assessment justification for including lymphoma in the multisite analysis. Without that justification, the lymphoma-inclusive multisite estimate should not serve as the primary basis for the IUR and should be presented, at most, as a conservative sensitivity or upper-bound analysis.

4.0 KEY ISSUE 2: OEHHA HAS NOT JUSTIFIED LINEAR LOW-DOSE EXTRAPOLATION FOR THE TUMOR ENDPOINTS THAT DRIVE THE IUR

This section addresses the second key issue introduced in Section 1.0: whether OEHHA has adequately justified using linear low-dose extrapolation, rather than a nonlinear or threshold approach, for the tumor endpoints that determine the proposed IUR. OEHHA's choice of a linear approach rests on its determination that acrolein's mode of carcinogenic action is genotoxic. OEHHA states in its draft that it "determined that acrolein's likely mode of carcinogenic action is via genotoxicity" and, on that basis, "adopted the linear low-dose hypothesis" (OEHHA, 2026, pp. 39–40). But that determination was not reached through the tissue-specific analysis OEHHA's own adopted framework requires, and as discussed below, the underlying tumor and mechanistic data are more consistent with a threshold-type, cytotoxicity-driven process than with a proportional low-dose mutagenic one.

4.1 Evidence of Genotoxic Potential Does Not, by Itself, Establish That the Selected Tumor Endpoints Operate Linearly at Low Doses

OEHHA's Technical Support Document for Cancer Potency Factors states that its dose-response methodology "is similar to those described by U.S. EPA (2005a)" and "refers to U.S. EPA (2005a) for explanation of detailed procedures" (OEHHA, 2009). Under that framework, a conclusion that a chemical's mode of carcinogenic action is mutagenic—sufficient to support the default assumption of low-dose linearity—requires an affirmative weight-of-evidence evaluation of the mechanistic data for the tumor response at issue. It is not enough to show that the chemical can act as a genotoxicant under some experimental conditions. OEHHA's draft does not provide that endpoint- and tissue-specific weight-of-evidence analysis for the tumor responses that drive the proposed IUR.

OEHHA relies on mechanistic evidence, including DNA adduct formation, genotoxicity, oxidative stress, chronic inflammation, and altered cell proliferation or cell death, to support its cancer hazard evaluation and its conclusion that acrolein's likely mode of carcinogenic action is genotoxic. These data are relevant to hazard identification and biological plausibility. However, OEHHA should distinguish between evidence that acrolein has

genotoxic potential and evidence that the specific tumor endpoints selected for IUR derivation are driven by a mutagenic process that operates linearly at low doses.

That distinction is particularly important because the nasal tumor response is observed only at high exposure concentrations and occurs in the context of local nasal toxicity. A general conclusion that acrolein is genotoxic is not the same as demonstrating that female mouse nasal adenomas, lymph node malignant lymphomas, or a combined multisite endpoint should be extrapolated linearly to low environmental concentrations. OEHHA should justify linearity for the specific endpoints driving the IUR, rather than relying on a generalized characterization of acrolein as genotoxic.

The relevant questions are whether genotoxic effects are observed in the respiratory target tissues where tumors occur, whether those effects occur at exposure concentrations below those causing cytotoxicity or inflammation, whether they are dose-related in the low-dose region, and whether they are sufficient to explain the observed tumor pattern. OEHHA should also evaluate whether genotoxicity occurs independently of local tissue injury, or whether DNA damage may occur secondarily through oxidative stress, inflammation, cytotoxicity, depletion of local protective mechanisms, or regenerative proliferation.

The available genotoxicity evidence appears to support biological plausibility, but it does not resolve the low-dose extrapolation question. Acrolein is a reactive electrophile and can form DNA adducts and produce genotoxic responses in experimental systems. However, the most relevant evidence for the proposed IUR would be dose-related genotoxicity in nasal or other respiratory target tissues following inhalation exposure, particularly at concentrations that do not also cause cytotoxicity, inflammation, or regenerative proliferation. In the absence of such evidence, OEHHA should not treat generalized genotoxic potential as sufficient to establish linear low-dose extrapolation for the selected tumor endpoints.

OEHHA also should not treat evidence of genotoxic potential as automatically overriding the importance of portal-of-entry tissue injury. If genotoxic effects occur primarily in the context of cytotoxicity, oxidative stress, inflammation, or depletion of local protective mechanisms, the mode of action may be mixed rather than purely mutagenic. A mixed mode of action may still support a cancer hazard conclusion, but it requires a more nuanced discussion of whether linear low-dose extrapolation is the only scientifically supportable approach.

OEHHA's own draft appears to leave this issue unresolved. The genotoxicity studies cited in support of a mutagenic mode of action are drawn primarily from oral or buccal mucosal cells and from cell lines unrelated to the respiratory tract, rather than from nasal or other respiratory epithelium following inhalation exposure. OEHHA's draft does not identify a positive genotoxicity finding measured directly in nasal tissue at exposure concentrations relevant to the tumor response. Given that gap, the available genotoxicity data support the conclusion that acrolein can act as a genotoxicant in some systems, but do not establish that the female mouse nasal adenoma, lymph node malignant lymphoma, or combined multisite

endpoint result from a mutagenic mechanism operating in the tissue where the tumors occur.

4.2 OEHHA Should Evaluate Whether the Nasal Tumor Response Is Better Explained by a High-Concentration Local Tissue-Injury Process

The Matsumoto/JBRC nasal tumor response occurred with local nasal toxicity. Nonneoplastic nasal lesions reported in rats and mice included inflammation, epithelial hyperplasia, squamous metaplasia, regeneration, atrophy, and related tissue changes. These findings are consistent with a portal-of-entry injury-and-repair process. For a reactive inhaled irritant such as acrolein, repeated high-concentration exposure may deplete local defenses, produce sustained tissue injury, and increase cell proliferation, all of which can contribute to tumor development.

OEHHA should evaluate whether the nasal tumor response is better characterized as a high-concentration effect associated with local tissue damage and repair, rather than as a response expected to increase proportionally at low ambient concentrations. This evaluation should include the anatomical co-location of nonneoplastic lesions and tumors, the dose-response for precursor or related lesions, evidence of glutathione depletion or detoxification saturation, and whether the tumor response is absent at exposures below those that produce appreciable local tissue toxicity.

The nasal tumor data are consistent with the need for this evaluation. The female mouse nasal adenoma response was absent across all lower-exposure groups and present only at the high-exposure concentration. That pattern does not make the endpoint irrelevant, but it does make the low-dose slope highly dependent on model assumptions rather than observed low-dose tumor data. OEHHA should explain whether the modeled low-dose slope reflects biological evidence for low-dose linearity or default application of a linear cancer model to a high-dose tumor response.

The female rat nasal tumor endpoint shows the same dependence on model extrapolation beyond the observed data. OEHHA reports that, for the female rat nasal squamous cell carcinoma endpoint, low tumor incidence in the high-exposure group (2 of 50 animals) meant that "BMD modeling resulted in the BMD (i.e., 5% tumor response) that was greater than the highest exposure concentration" tested (OEHHA, 2026, p. 44, Table 7, note a). In other words, for this endpoint the benchmark dose itself lies outside the range of concentrations actually administered to the animals, underscoring that the low-dose slope is a product of the model's assumed shape rather than of observed tumor incidence at or near that dose.

OEHHA should also more clearly explain why it rejected nonlinear or threshold-like interpretations of the acrolein nasal tumor response. Potentially informative alternatives

include a nonlinear mode-of-action interpretation for portal-of-entry nasal tumors, a margin-of-exposure comparison using the nasal tumor or nasal lesion point of departure, a dual presentation of the linear IUR and a nonlinear sensitivity analysis, or comparison of low-dose risk estimates under linear and nonlinear assumptions. If OEHHA concludes that linear extrapolation remains the preferred approach, it should explain why that conclusion is supported for the specific tumor endpoints used in the IUR.

The Matsumoto/JBRC study's own nonneoplastic lesion data are informative on this point. Nasal tumors in female mice occurred only in the same high-exposure group that also showed the most severe and extensive nonneoplastic nasal pathology, while lower-exposure groups without nasal tumors showed a less severe, dose-related pattern of the same lesion types. This step-function correspondence between precursor-lesion severity and tumor incidence is consistent with a local injury-and-repair process rather than a mutagenic process expected to produce risk proportional to dose at all exposure levels. This pattern is consistent with subchronic rat nasal toxicity data showing a clear no-observed-adverse-effect level of 0.2 ppm for respiratory epithelial hyperplasia/inflammation/metaplasia, below which lesion incidence was essentially absent, with incidence rising sharply above that level, a signature of threshold-like rather than smoothly graded toxicity (Dorman et al., 2008).

OEHHA's draft also documents acrolein's rapid conjugation with glutathione and evidence of saturable respiratory-tract uptake at higher exposure concentrations, both of which are mechanistically relevant to a threshold-like, cytotoxicity-driven process. Reported respiratory-tract uptake efficiency itself is nonlinear with concentration, averaging roughly 98% at 0.6 ppm versus roughly 50% at 3.6 ppm in one nasal dosimetry study, with a similar concentration-dependent decline (though different absolute values) reported in an earlier study, indicating a saturable process governs tissue dose before any injury response is considered (Struve et al., 2008; Morris, 1996). Reported glutathione depletion likewise scales with concentration, with respiratory epithelial glutathione reduced by roughly a third at 1.8 ppm and by roughly three-quarters at 3.6 ppm, at levels associated with nasal pathology (Struve et al., 2008). Depleted or saturated local detoxification capacity, rather than a proportionally low genotoxic risk, is a more parsimonious explanation for a tumor response confined to the highest-exposure group. OEHHA's draft does not connect this glutathione-depletion and uptake-saturation evidence, which appears elsewhere in its own document, to its mode-of-action or dose-response model selection for the nasal tumor endpoint.

4.3 U.S. EPA's 2024 Reassessment of Formaldehyde—Involving A Mechanistically Analogous Portal-of-Entry Tumor—Illustrates the Weight-of-Evidence Analysis OEHHA Has Not Performed

The kind of tissue-specific weight-of-evidence analysis described above is not a hypothetical or unreasonably demanding standard. *U.S. EPA's 2024 Toxicological Review of Formaldehyde (Inhalation)* (U.S. EPA, 2024a), a chemical that, like acrolein, produces a portal-of-entry

rat/mouse nasal tumor preceded by dose-related nonneoplastic precursor lesions, performed a tissue-specific, mechanistically integrated analysis that is instructive by comparison.

OEHHA's own draft already invites this comparison. In discussing the proposed acrolein IUR, OEHHA notes that "the OEHHA Hot Spots IURs for formaldehyde and acetaldehyde are 6.0×10^{-6} and 2.7×10^{-6} $(\mu g/m^3)^{-1}$, respectively" (citing OEHHA, 2025) and concludes that "acrolein is a more potent aldehyde" (OEHHA, 2026, p. 46). Having drawn that comparison itself, OEHHA should be expected to apply comparable methodological rigor to the mode-of-action analysis underlying acrolein's proposed potency, which is precisely where the comparison below shows a gap.

U.S. EPA's mutagenic mode-of-action conclusion for formaldehyde was supported by "strong mechanistic support…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" (U.S. EPA, 2024a). Critically, U.S. EPA did not treat genotoxicity and cytotoxic cell proliferation as competing, mutually exclusive explanations requiring a single choice of model. It integrated both mechanisms quantitatively: a separate reference concentration was derived specifically "for cytotoxicity-induced regenerative cell proliferation, one of the mechanisms contributing to nasal cancer development…estimated to be between 0.006 and 0.018 mg/m^3" using biologically based dose-response (BBDR) modeling (U.S. EPA, 2024a).

OEHHA's own 1992 potency derivation for formaldehyde, which is based on the same category of rat nasal squamous cell carcinoma, preceded by dose-related "rhinitis, epithelial dysplasia and hyperplasia, squamous hyperplasia, and cellular atypia" (described in OEHHA, 2009), likewise did not rely on a single linear mutagenic model. OEHHA derived that value using both the standard linearized multistage procedure and the Moolgavkar-Knudson two-stage clonal expansion model, which "takes into account the proliferation of premalignant cells due to the formaldehyde exposure" (OEHHA, 2009); i.e., OEHHA itself has previously folded a cytotoxicity/cell-proliferation mechanism into a quantitative potency estimate for a mechanistically comparable nasal tumor, rather than treating a genotoxic pathway as the only permissible model.

The point of this comparison is not that OEHHA must adopt a nonlinear or threshold model for acrolein. It is that OEHHA's own 2009 methodology and its sister federal agency's 2024 reassessment both demonstrate that a tissue-specific, mechanistically integrated weight-of-evidence analysis—one that accounts for cytotoxicity and regenerative proliferation alongside genotoxicity—is a routine and achievable component of a nasal tumor mode-of-action determination for a reactive inhaled irritant. OEHHA's acrolein draft, by contrast, asserts a mutagenic mode of action without performing that analysis for the tumor endpoints that determine the proposed IUR. OEHHA should conduct a comparable tissue-

specific, mechanistically integrated evaluation for acrolein, or explain specifically why that analysis, which was conducted for formaldehyde, is unnecessary or inapplicable here.

We note that OEHHA's own posted formaldehyde value is not on equal analytical footing with the comparison drawn here: OEHHA's current formaldehyde IUR still reflects its 1992 derivation and has not been updated to reflect U.S. EPA's 2024 reassessment. The methodological comparison above is to U.S. EPA's current formaldehyde analysis, not to OEHHA's own formaldehyde number, and should not be read to suggest the two agencies' formaldehyde values are presently aligned.

4.4 OEHHA Should Justify the Dose Metric Used for Low-Dose Extrapolation

OEHHA converted intermittent chamber exposures to time-adjusted average daily doses and used those values to derive the cancer slope factor. OEHHA should explain why the lifetime average daily dose is the most appropriate dose metric for a highly reactive portal-of-entry irritant whose key events may depend on exposure concentration, local tissue uptake, detoxification capacity, tissue injury, and regional respiratory tract dose.

For chemicals whose effects are driven by cumulative systemic dose, lifetime average daily dose may be an appropriate metric. For acrolein, however, the relevant biological events for nasal tumors may depend more directly on local respiratory tract concentration and tissue dose. A short-term or repeated high-concentration exposure may produce local injury, inflammation, or depletion of protective mechanisms in ways not captured by an average daily dose metric.

OEHHA should therefore discuss whether exposure concentration, peak concentration, time above a tissue-injury threshold, or regional nasal tissue dose would be more biologically relevant for the portal-of-entry nasal tumor response. OEHHA should also explain whether the use of average daily dose affects interpretation of the high-dose-only tumor response and whether alternative dose metrics would alter the modeled point of departure or low-dose extrapolation.

Rodent-human respiratory tract dosimetry also bears on this issue because the target-tissue dose associated with a given chamber concentration may differ between rodents and humans. That issue is addressed in more detail in Section 5.0.

Finally, OEHHA should evaluate the low-dose extrapolation assumption in the context of the other assumptions used in the IUR derivation. Linear extrapolation is only one part of the overall derivation; the final IUR also reflects endpoint selection, inclusion of lymphoma, use of a 5% BMR, reliance on a BMDL-based slope, study-duration adjustment, and assumptions about animal-to-human extrapolation. The combined effect of these assumptions is addressed in Section 6.0.

4.5 Recommended Revisions

OEHHA should revise the draft to:

1. clearly distinguish evidence of genotoxic potential from evidence supporting linear extrapolation for the specific tumor endpoints used to derive the IUR;
2. reevaluate whether the female mouse nasal adenoma response, which occurred only at the highest exposure concentration and in association with local nasal toxicity, actually supports linear extrapolation to low environmental concentrations;
3. evaluate whether the nasal tumor response is better explained by a high-concentration, portal-of-entry process involving cytotoxicity, inflammation, detoxification depletion, and regenerative proliferation;
4. provide a concise endpoint-specific genotoxicity evaluation addressing target-tissue relevance, in vivo versus in vitro evidence, dose-response, cytotoxicity, endogenous background, and relevance to the selected tumor endpoints;
5. explain whether genotoxic effects occur independently of cytotoxicity and local tissue injury or as part of a mixed mode of action;
6. evaluate nonlinear or threshold-like alternatives, including margin-of-exposure analyses or sensitivity analyses based on nasal lesions or nasal tumors;
7. reevaluate whether lifetime average daily dose is an appropriate metric for a reactive respiratory irritant whose key events may be driven by exposure concentration, peak concentration, duration above a local-effect threshold, or regional respiratory tract tissue dose;
8. explain how chemical-specific respiratory tract dosimetry affects confidence in low-dose extrapolation;
9. coordinate the low-dose extrapolation discussion with the sensitivity analyses requested in Section 6.0; and
10. explain whether OEHHA has conducted, for acrolein, the same kind of tissue-specific, mechanistically integrated weight-of-evidence analysis, accounting for cytotoxicity and regenerative proliferation alongside genotoxicity, that U.S. EPA performed for a mechanistically comparable nasal tumor in its 2024 formaldehyde reassessment, or explain why that analysis is unnecessary or inapplicable here.

These revisions are needed because OEHHA has not adequately demonstrated that linear low-dose extrapolation is appropriate for the nasal tumor response used to support the IUR. The female mouse nasal adenomas occurred only at the highest exposure concentration and in the same target tissue in which local injury and repair-related changes were reported. General evidence of genotoxic potential does not, by itself, establish that this high-dose, portal-of-entry tumor response should be treated as linear at low environmental concentrations. OEHHA should either provide an endpoint-specific mode-of-action and

dose-response justification for linear extrapolation or present nonlinear, threshold-like, or margin-of-exposure alternatives as part of the quantitative assessment.

5.0 KEY ISSUE 3: ANIMAL-TO-HUMAN DOSIMETRY

This section develops the third key issue introduced in Section 1.0: whether OEHHA's default interspecies extrapolation approach adequately accounts for acrolein's portal-of-entry toxicokinetics. OEHHA converted animal cancer slope factors to human-equivalent cancer slope factors using default body-weight scaling, an approach that may be appropriate for systemic dose metrics but does not directly address the dose delivered to regional respiratory tract tissue from a reactive portal-of-entry gas. Rodent nasal tumors may be qualitatively relevant to human hazard evaluation, but qualitative relevance does not establish that the same external concentration produces a comparable respiratory target-tissue dose in rodents and humans, as discussed below.

5.1 Default Body-Weight Scaling Does Not Address Regional Respiratory Tract Tissue Dose

Rodents and humans differ in respiratory tract anatomy and breathing physiology in ways that can materially affect target-tissue dose for acrolein. Rodents are obligate nasal breathers with complex nasal turbinates and relatively large nasal surface areas, while humans may breathe through the nose, mouth, or both depending on activity level, exertion, congestion, and other conditions. These differences can affect whether acrolein is delivered primarily to nasal tissues, lower airways, or both.

For a reactive gas, regional uptake and "scrubbing" in the upper respiratory tract can strongly influence the dose delivered to downstream tissues. If uptake is greater in rodent nasal tissues than in human nasal tissues, rodent nasal tumor data may overpredict human nasal tissue dose at the same external concentration. Conversely, if human oral breathing bypasses nasal scrubbing, human lower-airway tissues may receive greater exposure than would be predicted from rodent nasal-breathing models. Either way, default body-weight scaling does not resolve the relevant dosimetry question.

OEHHA's draft does not address this question. OEHHA's own calculation methodology performs animal-to-human extrapolation using only default body-weight-ratio scaling ($CSF_h = CSF_a \times (BW_h \div BW_a)^{1/4}$) justified solely by reference to general interspecies differences in "pharmacokinetics (e.g., breathing rate, metabolism)" and "pharmacodynamics" (OEHHA, 2026, pp. 44–45, citing U.S. EPA, 2005). That section contains no discussion of regional gas dose ratios, human-equivalent concentrations, respiratory tract regions, or the Category 1 (reactive, water-soluble gas) dosimetry approach that U.S. EPA's RfC methodology (U.S. EPA, 1994) specifically prescribes for a chemical with acrolein's portal-of-entry properties, and it does not explain why that approach was not used.

OEHHA should explain why it relied on default body-weight scaling rather than a respiratory-tract dosimetry approach for acrolein. If OEHHA concludes that the available information is insufficient to derive a chemical-specific dosimetric adjustment, it should still characterize the uncertainty introduced by relying on default body-weight scaling for a portal-of-entry nasal tumor endpoint.

5.2 Available Acrolein Dosimetry Information Should Be Used to Characterize Uncertainty

OEHHA discusses several acrolein-specific dosimetry studies, but the proposed IUR derivation does not appear to use those data quantitatively to adjust animal-to-human extrapolation. These studies do not necessarily provide a complete chemical-specific human-equivalent concentration, but they do provide important information about upper respiratory tract uptake, species differences in nasal extraction, concentration dependence, oral versus nasal breathing, and potential lower-airway delivery. Table 6 summarizes the acrolein dosimetry information that OEHHA should address in characterizing uncertainty in the proposed IUR.

Table 6. Acrolein Dosimetry Information Relevant to Animal-to-Human Extrapolation

Study/ Information Type	Key dosimetry finding	Implication for OEHHA's IUR
Struve et al., 2008	Isolated rat upper respiratory tract studies indicate substantial uptake of acrolein in the rat upper respiratory tract, with uptake efficiency affected by concentration, airflow, and exposure duration.	Supports the importance of upper respiratory tract uptake and raises questions about whether chamber concentration or mg/kg-day dose adequately represents nasal tissue dose.
Schroeter et al., 2008	Computational fluid dynamics (CFD) modeling predicted consistently lower nasal extraction of acrolein in humans than in rats across exposure concentrations under modeled resting nasal-breathing conditions.	Supports the need to distinguish qualitative relevance of rodent nasal tumors from quantitative human nasal tissue dose.

Study/ Information Type	Key dosimetry finding	Implication for OEHHA's IUR
Asgharian et al., 2012	Human lung dosimetry modeling predicted that acrolein can penetrate into distal conducting airways and to a limited extent the alveolar region, with the location and magnitude of uptake affected by ventilation rate. The model also indicated that local tissue concentration, not just the rate of delivery to the airway surface or external exposure concentration, may be important for evaluating respiratory tract dose.	Supports the need for a dosimetry-informed animal-to-human extrapolation for acrolein. The findings suggest that human target-tissue dose may vary by airway region and breathing conditions and may not be adequately represented by default body-weight scaling alone. Differences in lower-airway dose in rodents vs. humans point to uncertainty in extrapolating rodent nasal tumors to human respiratory tract risk, but don't support combining nasal epithelial tumors with lymph node malignant lymphoma.
Xi et al., 2018	Modeling suggested that acrolein-water interactions, particle/agglomerate behavior, or concentration-related changes may influence deposition and diffusivity.	Supports evaluating whether uptake and tissue dose are concentration-dependent rather than proportional to lifetime average dose.
Human breathing-route considerations	Humans may breathe nasally, orally, or oronasally; rodents are obligate nasal breathers. Oral or oronasal breathing can bypass some nasal uptake and alter the distribution of acrolein dose within the respiratory tract.	Supports the need for respiratory-tract dosimetry rather than default body-weight scaling alone. Breathing route may affect the relative dose delivered to the nasal passages versus lower airways in humans, creating uncertainty in extrapolating rodent nasal tumor findings to human risk.

The available dosimetry information does not make rodent nasal tumors irrelevant. Rather, it shows that animal-to-human extrapolation is not straightforward. OEHHA should explain whether the available acrolein dosimetry studies support default body-weight scaling, suggest an alternative human-equivalent concentration approach, or introduce uncertainty that should be reflected qualitatively and quantitatively.

OEHHA should also clarify whether the proposed IUR is intended to estimate risk for the same target tissue observed in rodents, namely nasal epithelium, or whether it is intended as a more general inhalation cancer potency estimate. If the former, OEHHA should explain how rodent nasal tissue dose was translated to human nasal tissue dose. If the latter, OEHHA

should explain how potential differences in human airway deposition, including lower-airway delivery during oral breathing, affect confidence in the selected rodent nasal tumor point of departure.

5.3 Recommended Revisions

OEHHA should revise the draft to:

1. either acknowledge that default body-weight scaling is not appropriate for a reactive inhaled gas whose animal tumor findings include a portal-of-entry nasal epithelial tumor and, in the selected multisite analysis, a systemic lymphoid tumor, or provide sufficient evidence supporting application of default body-weight scaling;
2. discuss how species differences in nasal anatomy, airflow, nasal surface area, uptake efficiency, detoxification, and breathing route affect animal-to-human extrapolation for acrolein;
3. evaluate whether available acrolein dosimetry studies support, limit, or modify use of default body-weight scaling;
4. clarify the target-tissue dose metric underlying the proposed IUR, including whether the extrapolation is intended to represent nasal epithelial dose, broader respiratory tract epithelial dose, systemic/internal dose, or a combined cancer potency estimate across biologically distinct tumor types;
5. evaluate the animal-to-human extrapolation basis for nasal adenoma and lymph node malignant lymphoma separately, including the relevant exposure-dose relationship and target-tissue dose metric, reevaluate whether there is sufficient scientific justification for the critical multisite analysis, and revise the IUR derivation accordingly; and
6. provide sensitivity analyses, where feasible, comparing default body-weight scaling with alternative dosimetry-informed assumptions.

OEHHA's current animal-to-human extrapolation should be revised. The draft applies default body-weight scaling to a combined multisite slope factor that includes biologically distinct tumor types, without adequately addressing animal-human differences in acrolein dosimetry or how those differences affect target-tissue dose. For nasal epithelial tumors, the relevant issue is regional respiratory tract dose, while for lymphoma, the relevant issue is systemic or lymphoid tissue dose, which OEHHA has not established. A single default scaling factor does not support endpoint-specific extrapolation for different tumor types. OEHHA should provide that justification or revise the IUR derivation to rely on the endpoint and extrapolation approach best supported by the evidence.

6.0 Sensitivity and Real-World Plausibility Analyses

OEHHA's proposed IUR reflects a sequence of endpoint selection, modeling, low-dose extrapolation, study duration, dose metric, and animal-to-human extrapolation assumptions. Some of these assumptions may be consistent with OEHHA practice or accepted default risk assessment methods. However, several factors materially affect the final IUR, including selection of the female mouse multisite endpoint, inclusion of lymph node malignant lymphoma, use of a 5% benchmark response, reliance on a BMDL-based linear slope, adjustment of the female mouse study duration from 99 to 104 weeks, and default body-weight scaling for animal-to-human extrapolation. This section presents two related but distinct types of checks on the proposed IUR: (1) sensitivity analyses showing how the IUR would change under alternative, scientifically supportable modeling assumptions, and (2) a comparison of the proposed IUR to the lifetime cancer risk it implies for measured, real-world ambient acrolein concentrations, to test whether the resulting value is plausible in light of real-world exposure.

6.1 OEHHA Should Conduct Sensitivity Analyses to Show How the IUR Changes Under Key Alternative Assumptions

OEHHA should provide sensitivity analyses showing how the final value would change under reasonable alternative assumptions. This is particularly important because the critical tumor responses are sparse, high-dose-driven, and/or biologically uncertain. Sensitivity analyses would allow reviewers to distinguish between conclusions supported directly by the observed tumor data and conclusions that depend more heavily on model form, endpoint selection, or default extrapolation assumptions.

Table 7 identifies the sensitivity analyses that should be provided.

Table 7. Requested Sensitivity Analyses for Major Assumptions in the Proposed Acrolein IUR

Sensitivity analysis requested	Purpose	Information OEHHA should provide	Expected direction of effect
Female mouse nasal adenoma alone vs. lymph node lymphoma alone vs. nasal adenoma + lymphoma multisite	Shows how much endpoint selection and tumor combination drive the IUR.	Endpoint-specific BMD, BMDL, animal slope factor, human-equivalent slope factor, and IUR.	Inclusion of lymphoma likely increases IUR relative to nasal adenoma alone.
Excluding lymphoma from the critical estimate	Tests the impact of the more biologically uncertain systemic endpoint.	IUR based on nasal adenoma alone and comparison with selected multisite IUR.	Likely decreases IUR.

Sensitivity analysis requested	Purpose	Information OEHHA should provide	Expected direction of effect
Female mouse endpoints vs. female rat nasal tumor endpoints	Shows whether other portal-of-entry tumor endpoints support a similar potency estimate.	Rat and mouse endpoint-specific results using consistent modeling assumptions.	Unknown; should be shown.
Linear low-dose extrapolation vs. nonlinear or MOE presentation	Shows how the risk characterization changes under plausible alternative interpretations of the mode of action.	Linear IUR and alternative nonlinear/MOE characterization, where feasible.	Nonlinear/MOE approach would not produce the same low-dose IUR.
5% vs. 10% BMR	Tests sensitivity to benchmark response selection.	BMD, BMDL, slope factors, and IURs for both BMRs.	5% BMR likely increases IUR relative to 10% BMR.
BMD vs. BMDL-based slope	Shows the influence of statistical uncertainty in the point of departure.	Parallel slope factors and IURs calculated from the BMD and BMDL.	BMDL-based slope likely increases IUR relative to BMD-based slope.
Alternative acceptable model forms	Tests sensitivity to model selection and curve shape.	Model-fit statistics, AIC values, scaled residuals, visual fits, and resulting IURs.	Unknown; should be shown.
With and without female mouse study-duration adjustment	Shows the quantitative effect of the 99-to-104-week adjustment.	Exact adjustment factor and IURs with and without the adjustment.	Adjustment appears likely to increase IUR by ~16%.
Average daily dose vs. exposure concentration or tissue-dose metrics	Evaluates whether the lifetime average dose is appropriate for a reactive portal-of-entry irritant.	Alternative dose-metric analyses or an explanation why they cannot be performed.	Unknown; should be shown or characterized.
Default body-weight scaling vs. inhalation dosimetry-informed alternatives	Tests the effect of animal-to-human extrapolation assumptions.	Estimates using RGDRs, CFD-informed approaches, other respiratory tract dosimetry methods, or qualitative uncertainty analysis.	Unknown; may differ by target tissue and breathing route.

AIC – Akaike information criterion; BMD – Benchmark dose; BMDL – Benchmark dose lower confidence limit; CFD – Computational fluid dynamics; MOE – Margin of exposure; RGDR – Regional gas dose ratio

The potential effect of alternative tumor endpoint selection is discussed above in Section 3.0. With regard to other parameters, the effect of alternative parameters should also be presented. For example, OEHHA calculated cancer slope factors as 0.05 divided by the BMDL, using a 5% extra-risk BMR, the value OEHHA states is "recommended by OEHHA (2008) for the BMD and the 95% lower confidence bound" for "large datasets that contain 50 rodents/group/sex" (OEHHA, 2026, p. 43). Use of a 5% BMR may be consistent with OEHHA practice, but OEHHA should show the sensitivity of the proposed IUR to this choice. This is especially important for high-dose-only or sparse tumor responses, where the estimated low-dose slope may be influenced substantially by the selected model form, the selected BMR, and the lower confidence bound on the BMD.

OEHHA should also show the quantitative effect of the female mouse study-duration adjustment. OEHHA applied this adjustment because the female mouse study was terminated at 99 weeks rather than 104 weeks, using the formula CSF_a = CSF_a-unadjusted × (104 weeks/study duration)^3 (OEHHA, 2026, p. 44, citing OEHHA, 2009). For the female mouse data, that formula corresponds to multiplication by $(104/99)^3 \approx 1.16$, confirming our estimate that the adjustment increases the slope factor by approximately 16%. Using OEHHA's selected IUR of 7.9×10^{-4} per µg/m^3, removing that adjustment would reduce the IUR to approximately 6.8×10^{-4} per µg/m^3. This adjustment is not trivial. OEHHA should provide IURs with and without the study-duration adjustment and explain whether the adjustment is warranted given the reason for early study termination and the reported survival pattern. If the mouse study was terminated early because survival was reduced across groups, rather than because of an acrolein-specific mortality pattern limited to exposed animals, OEHHA should explain why increasing the potency estimate improves comparability to a standard 104-week study.

As Table 7's final column shows, most of these assumptions are expected to increase the final IUR relative to reasonable alternatives; the effect of a dosimetry-informed animal-to-human extrapolation is less predictable and should be evaluated explicitly.

6.2 OEHHA Should Reconcile the Proposed IUR with the Population-Level Risk Implied by Measured Ambient Acrolein Concentrations

OEHHA's own draft provides detailed information on measured ambient acrolein concentrations in California, which allows the proposed IUR to be checked against real-world exposure levels rather than evaluated only in the abstract. OEHHA reports that CARB's statewide air-monitoring network measured a mean acrolein concentration of 0.57 µg/m^3 in 2024, the most recent year with complete statewide data, with individual site averages ranging from 0.34 to 3.2 µg/m^3. In 2019, the prior year with complete monitoring data, the statewide mean was 1.05 µg/m^3, with site averages up to 9.4 µg/m^3 (OEHHA, 2026, citing CARB, 2025a). Specialized sampling conducted in California in 2013, using a method

designed to avoid known quality-control problems affecting standard canister sampling, found remote, rural, and coastal concentrations generally at or below the method detection limit (up to 0.16 µg/m³) and Los Angeles Basin concentrations of 0.23 to 0.41 µg/m³, with a median of 0.32 µg/m³ (OEHHA, 2026, citing Cahill, 2014).

Applying OEHHA's proposed IUR of 7.9×10^{-4} per µg/m³ directly to these measured concentrations illustrates the following lifetime excess cancer risks the proposed values imply for ordinary ambient exposure, without any facility-specific, occupational, or indoor-source contribution:

- 2024 statewide mean (0.57 µg/m³): approximately 4.5×10^{-4}, or roughly 1 in 2,200.
- 2024 highest monitored site average (3.2 µg/m³): approximately 2.5×10^{-3}, or roughly 1 in 400.
- 2019 statewide mean (1.05 µg/m³): approximately 8.3×10^{-4}, or roughly 1 in 1,200.
- 2019 highest monitored site average (9.4 µg/m³): approximately 7.4×10^{-3}, or roughly 1 in 135.
- Rural/remote background measurement (Cahill, 2014; up to 0.16 µg/m³): approximately 1.3×10^{-4}, or roughly 1 in 7,900.

For additional context, OEHHA also reports acrolein concentrations of 2.3 to 275 µg/m³ in indoor environments with active smoking, such as bars and taverns. These are not lifetime, continuous exposure scenarios appropriate for direct application of a lifetime-average IUR, but they illustrate that measured acrolein concentrations span several orders of magnitude across real-world settings, all of which the proposed potency value would characterize as posing appreciable cancer risk.

Every ambient concentration OEHHA reports, including the lowest and most carefully measured rural background level in the available data, implies a lifetime excess cancer risk from acrolein alone that is at or above 1×10^{-4}— a risk level generally treated as at or above the upper end of the risk range that California's own risk-management programs, including the Air Toxics Hot Spots Program, typically use to characterize acceptable cancer risk from a single chemical. The statewide mean concentrations that essentially the entire California population breathes on an ongoing basis imply a lifetime excess cancer risk from acrolein alone of roughly 1 in 1,200 to 1 in 2,200; peak monitored site averages imply risks approaching or exceeding 1 in 150.

OEHHA should reconcile these implications with the absence of any documented population-level cancer signal attributable to acrolein, despite decades of measured ambient exposure at these levels across a large population. Although, as discussed above, the available epidemiological studies have well-documented limitations, including lack of acrolein-specific exposure assessment, confounding by co-exposures and smoking, and small sample sizes, that would likely prevent detection of even a substantial population-level excess risk, the

scale of the population-level burden implied by the proposed IUR, applied to the reported ambient concentrations, is large enough that OEHHA should directly address whether this is a plausible, intended consequence of the proposed potency value, or whether it instead indicates that one or more of the modeling choices addressed in these comments—endpoint selection and combination, mode-of-action assumptions, or animal-to-human dosimetry—may be substantially overestimating acrolein's carcinogenic potency.

6.3 Recommended Revisions

OEHHA should revise the draft to:

1. provide sensitivity analyses for the major assumptions used to derive the proposed IUR, including tumor endpoint selection, tumor combination, BMR selection, model form, study-duration adjustment, dose metric, low-dose extrapolation, and animal-to-human extrapolation;
2. show results for female mouse nasal cavity adenoma alone, female mouse lymph node malignant lymphoma alone, the selected female mouse multisite endpoint, and relevant female rat nasal tumor endpoints;
3. present sensitivity analyses using alternative acceptable model forms and provide model-fit statistics, AIC values, scaled residuals, visual fits, and model-selection rationale;
4. present IURs with and without the female mouse study-duration adjustment and explain why OEHHA believes the adjustment is appropriate given the early termination circumstances and survival pattern;
5. characterize whether the proposed IUR should be viewed as a central estimate, plausible upper-bound estimate, or highly conservative estimate; and
6. reconcile the proposed IUR with the lifetime excess cancer risk it implies when applied to California ambient acrolein concentration data, and explain whether that population-level implication is an intended consequence of the proposed potency value or indicates that one or more of the modeling assumptions may overestimate acrolein's carcinogenic potency.

These revisions are needed to distinguish the components of the proposed IUR that are directly supported by the observed tumor data from those that depend on conservative or uncertain modeling assumptions. They would also allow OEHHA and reviewers to evaluate whether the resulting potency value is consistent with real-world ambient exposure information or whether the proposed IUR is being driven by assumptions that produce implausibly high population-level risk estimates.

7.0 CONSISTENCY WITH U.S. EPA GUIDANCE

BMD modeling, use of a BMDL, and linearized cancer risk assessment are accepted tools in quantitative cancer risk assessment. However, OEHHA should more clearly justify their application in this specific assessment, particularly because the proposed IUR depends on a female mouse multisite endpoint that combines a portal-of-entry nasal tumor with a systemic lymphoma endpoint; high-dose-only nasal tumor responses occurring in the context of local tissue injury; selection of a 5% BMR; study-duration adjustment; and default body-weight scaling for a reactive inhaled gas.

OEHHA should explain how its approach is consistent with, or departs from, U.S. EPA guidance on hazard characterization, mode-of-action evaluation, tumor endpoint selection, benchmark response selection, model-fit evaluation, low-dose extrapolation, uncertainty characterization, and inhalation dosimetry for portal-of-entry gases. This section does not repeat the endpoint-specific, low-dose extrapolation, or dosimetry comments provided in Sections 4.0 through 7.0. Rather, it identifies areas where OEHHA should more clearly connect its quantitative choices, including the three key issues introduced in Section 1.0, to relevant risk-assessment guidance.

7.1 U.S. EPA Cancer and Benchmark Dose Guidance Supports Endpoint-Specific Justification, Not Just Default Modeling

U.S. EPA's cancer guidelines allow linear low-dose extrapolation under certain circumstances, including when data indicate a linear component below the point of departure or when the mode of action for a tumor site is not established and linear extrapolation is used as a health-protective default. U.S. EPA also recognizes that nonlinear approaches may be appropriate when adequate mode-of-action data support nonlinearity, and that both linear and nonlinear approaches may be used when different tumor sites or modes of action are involved.

That guidance does not mean that evidence of genotoxic potential automatically resolves the dose-response question. For acrolein, OEHHA should explain how it evaluated possible competing or mixed modes of action, including direct DNA reactivity, oxidative stress, cytotoxicity, inflammation, and regenerative proliferation. This is particularly important because the nasal tumor response occurred only at the highest exposure concentration and in the context of local tissue injury and repair.

U.S. EPA guidance also supports evaluating tumor endpoints individually before synthesizing across tumor types. When multiple tumor sites are observed, the assessment should consider the strength of the evidence for each tumor type, mode-of-action information for each endpoint, human relevance, and whether endpoints should be modeled separately, combined, or presented as a range. For acrolein, this means OEHHA should explain why female mouse nasal adenoma and lymph node malignant lymphoma are each appropriate for

quantitative modeling and why they are appropriate to combine in the selected multisite analysis.

U.S. EPA benchmark dose guidance is also relevant to OEHHA's BMR selection and model evaluation. OEHHA should justify use of a 5% BMR for the tumor endpoints modeled, provide comparison to a 10% extra-risk BMR where feasible, and present endpoint-specific BMD, BMDL, BMDU, model-fit, model-selection, and uncertainty information. This is particularly important for high-dose-only or sparse tumor responses, where the modeled low-dose slope may be influenced substantially by model form and confidence-bound selection.

OEHHA's draft shows that it does employ U.S. EPA benchmark dose guidance for some purposes: it reports using "US EPA's BMD guidelines and software (version 3.3.2)" (OEHHA, 2026, p. 42, citing U.S. EPA, 2024b) to run the multistage models, and selected among first- and second-degree model fits based on "BMD technical guidance (US EPA, 2022)" (OEHHA, 2026, p. 43). That OEHHA applies U.S. EPA benchmark dose guidance to model-fit selection makes it more notable that OEHHA does not apply the comparable mode-of-action and endpoint-combination guidance in U.S. EPA's 2005 cancer risk assessment guidelines described above.

7.2 U.S. EPA Inhalation Guidance Supports Respiratory Tract Dosimetry Considerations for Reactive Portal-of-Entry Gases

U.S. EPA inhalation risk assessment guidance recognizes that portal-of-entry effects require attention to respiratory tract dosimetry. For reactive or highly water-soluble gases, target-tissue dose may depend on regional uptake, respiratory tract anatomy, airflow, breathing route, exposure concentration, and local tissue reactivity. These considerations are directly relevant to acrolein because the most biologically plausible animal tumor findings are nasal tumors associated with local respiratory tract injury.

OEHHA's draft discusses acrolein's reactivity and available respiratory tract dosimetry information, but the proposed IUR appears to rely on default body-weight scaling rather than a chemical-specific or regional respiratory tract dosimetry approach. OEHHA should explain why default body-weight scaling is appropriate for a portal-of-entry nasal tumor endpoint, or alternatively provide a dosimetry-informed extrapolation or uncertainty analysis.

OEHHA should also explain how the human breathing route affects animal-to-human extrapolation. Rodents are obligate nasal breathers, whereas humans may breathe nasally, orally, or oronasally depending on activity and conditions. Oral or oronasal breathing may bypass some nasal uptake and alter the regional distribution of acrolein dose within the human respiratory tract, including potential delivery to lower-airway epithelium. This does not make rodent tumors irrelevant, but it does mean that quantitative extrapolation from rodent nasal tumors to human inhalation risk should be explicitly justified.

OEHHA should also explain how human breathing route affects animal-to-human extrapolation. Rodents are obligate nasal breathers, whereas humans may breathe nasally, orally, or oronasally depending on activity and conditions. Oral or oronasal breathing may bypass some nasal uptake and alter the regional distribution of acrolein dose within the human respiratory tract, including potential delivery to lower-airway epithelium. This does not make the rodent nasal tumor findings irrelevant, but it does underscore the need for respiratory-tract dosimetry when extrapolating portal-of-entry tumor findings to humans. It also does not support OEHHA's lymphoma-inclusive multisite approach. OEHHA should explain the target-tissue dose metric and animal-to-human extrapolation basis for each tumor type separately and then determine whether it is appropriate to include both nasal adenoma and lymph node malignant lymphoma in the critical multisite analysis. A single default body-weight scaling approach applied to a combined multisite animal slope factor does not address whether the relevant human dose metric is regional respiratory epithelial dose for nasal tumors, systemic/internal dose for lymphoma, or some other endpoint-specific measure.

Table 8 summarizes the principal U.S. EPA guidance issues that OEHHA should address in explaining the proposed IUR.

Table 8. U.S. EPA Guidance Issues Relevant to OEHHA's Proposed Acrolein IUR

Guidance issue	Relevance to acrolein	Clarification OEHHA should provide
Tumor endpoint selection	Selected IUR depends on female mouse multisite endpoint.	Whether nasal adenoma and lymphoma are both treatment-related, human-relevant, and appropriate for quantitative modeling.
Multiple tumor sites / modes of action	Nasal adenoma and lymphoma differ in site and biological plausibility.	Whether endpoints share a common or related MOA and whether risks should be combined.
Linear vs nonlinear extrapolation	Nasal tumors are high-dose-only and associated with local tissue injury.	Whether the available evidence supports linear low-dose extrapolation over nonlinear/MOE alternatives.
BMR selection	OEHHA used 5% extra risk.	Why OEHHA believes 5% is appropriate, and how the results compare with 10%.
Model fit and uncertainty	Sparse/high-dose-driven responses may be model-sensitive.	Endpoint-specific BMD, BMDL, BMDU, fit statistics, scaled residuals, AIC, and visual fits.
Inhalation dosimetry	Acrolein is reactive and acts at portal-of-entry tissues.	Whether the available evidence supports default body-weight scaling and how dosimetry-informed alternatives affect the IUR.

7.3 Recommended Revisions

OEHHA should revise the draft to:

1. compare its approach more explicitly with applicable U.S. EPA cancer risk assessment, benchmark dose, and inhalation dosimetry guidance;
2. distinguish clearly between evidence supporting acrolein cancer hazard classification and evidence sufficient to support a specific quantitative inhalation cancer potency value;
3. provide an endpoint-specific mode-of-action evaluation for each modeled tumor endpoint, including whether female mouse nasal adenoma and lymph node malignant lymphoma share a common or related mode of action and whether they are appropriate to combine in a multisite analysis;
4. reevaluate whether OEHHA's lymphoma-inclusive multisite analysis is appropriate in light of apparent conflicts with U.S. EPA guidance and OEHHA's own tumor-combination guidance, including the need to establish that each included endpoint is treatment-related, biologically plausible, statistically supported, and human-relevant, and revise the IUR derivation accordingly; and
5. provide dosimetry-informed alternatives and uncertainty analysis in lieu of default body-weight scaling or provide sufficient evidence demonstrating that the default approach is appropriate for a reactive inhaled gas and for the biologically distinct tumor endpoints included in the selected multisite analysis .

These revisions are needed because OEHHA has not adequately demonstrated that its selected endpoint, lymphoma-inclusive multisite analysis, linear low-dose extrapolation, and default animal-to-human scaling are consistent with applicable risk-assessment guidance as applied to the acrolein database. OEHHA should revise the IUR derivation to use the endpoint, modeling approach, and extrapolation method that are best supported by the evidence.

8.0 Summary of Requested Revisions

To provide a scientifically supportable basis for the proposed acrolein IUR, OEHHA should revise the draft document to address the following issues:

Database Foundation

1. Explain how limitations in the animal, human, mechanistic, and dosimetry evidence streams affect confidence in the IUR derivation, including the fact that the quantitative derivation relies on selected tumor findings from a single chronic inhalation bioassay that is not broadly corroborated by the broader animal or human cancer database.

2. Distinguish evidence supporting acrolein cancer hazard classification from evidence sufficient to support a specific quantitative inhalation cancer potency value, and clarify that IARC's 2021 Group 2A classification does not, by itself, validate OEHHA's selected tumor endpoint, modeling approach, or proposed numerical IUR.

Key Issue 1: Tumor Endpoint Combination

3. Exclude lymph node malignant lymphoma from the critical quantitative analysis and derive the IUR using the female mouse nasal cavity adenoma endpoint alone, unless OEHHA provides a clear biological, statistical, and risk-assessment justification for treating lymphoma as a treatment-related, human-relevant endpoint appropriate for multisite summation with nasal adenoma under OEHHA's own tumor-combination guidance.

Key Issue 2: Linear Low-Dose Extrapolation and Dose Metric

4. Conduct and document an endpoint-specific weight-of-evidence mode-of-action analysis for the tumor endpoints that drive the proposed IUR, consistent with OEHHA's adopted cancer risk assessment framework, rather than relying on generalized evidence that acrolein can be genotoxic.
5. Address the tissue-specificity limitations in the genotoxicity evidence, including the extent to which available data are from buccal/oral cells or in vitro systems rather than nasal respiratory tissue, and explain how the glutathione-depletion and saturable-uptake evidence in the draft affects OEHHA's proposed mode-of-action and dose-response model selection.
6. Either conduct the same kind of tissue-specific, mechanistically integrated weight-of-evidence analysis for acrolein that U.S. EPA performed for a mechanistically comparable nasal tumor in its 2024 formaldehyde reassessment or explain why that analysis is unnecessary here.
7. Reevaluate the dose metric used for modeling, or provide adequate scientific justification for converting chamber concentrations to time-adjusted average daily dose, including discussion of whether exposure concentration, peak concentration, time above a local-effect threshold, or regional respiratory tract tissue dose would be more biologically relevant for a reactive portal-of-entry irritant.

Key Issue 3: Animal-to-Human Dosimetry

8. Provide a respiratory-tract dosimetry-informed analysis and uncertainty characterization, or provide evidence showing why default body-weight scaling is appropriate for a reactive inhaled gas and for the biologically distinct tumor endpoints included in the selected multisite analysis.
9. Clarify the target-tissue dose metric underlying the proposed IUR, including whether the extrapolation is intended to represent nasal epithelial dose, broader respiratory

tract epithelial dose, systemic or lymphoid tissue dose, or a combined cancer potency estimate across biologically distinct tumor types.

Consistency with U.S. EPA Guidance

10. Compare OEHHA's approach more explicitly with applicable U.S. EPA cancer risk assessment, benchmark dose, and inhalation dosimetry guidance.
11. Provide a mode-of-action and tumor combination evaluation for each modeled tumor endpoint, including whether female mouse nasal adenoma and lymph node malignant lymphoma share a common or related mode of action, whether each endpoint is treatment-related and human-relevant, and whether their risks can reasonably be combined under U.S. EPA guidance and OEHHA's own tumor-combination guidance.

Cross-Cutting Support

12. Provide sensitivity analyses for major assumptions, including endpoint selection, exclusion of lymphoma, BMR selection, BMD versus BMDL, alternative acceptable model forms, the female mouse study-duration adjustment, dose metric, low-dose extrapolation approach, and animal-to-human extrapolation approach.
13. Reconcile the proposed IUR with the population-level lifetime excess cancer risk it implies when applied to California ambient acrolein concentration data, and explain whether that implication supports the proposed potency value or indicates that one or more modeling assumptions may overestimate acrolein's carcinogenic potency.

In making these revisions, OEHHA should clearly distinguish cancer hazard classification from quantitative cancer potency derivation. The proposed IUR should not be presented as a value independently confirmed by human dose-response evidence, a consistent multi-study animal cancer database, or other authoritative quantitative cancer assessments. If OEHHA cannot provide endpoint-specific support for inclusion of lymphoma, linear low-dose extrapolation, and default animal-to-human scaling, the IUR derivation should be revised to rely on the endpoint, dose metric, and extrapolation approach best supported by the available evidence.

9.0 CONCLUSIONS

The Matsumoto/JBRC inhalation bioassay provides important evidence relevant to acrolein cancer hazard evaluation, particularly for portal-of-entry nasal tumors. It does not, however, resolve the three issues that most affect the proposed IUR's potency and uncertainty: whether lymph node malignant lymphoma should be combined quantitatively with nasal tumors; whether OEHHA's genotoxic mode-of-action determination reflects the tissue-specific weight-of-evidence analysis required under OEHHA's own adopted framework; and whether OEHHA's default body-weight scaling adequately accounts for acrolein's portal-of-entry respiratory tract dosimetry. These issues are especially important because U.S. EPA conducted a more tissue-specific, mechanistically integrated analysis for a mechanistically comparable nasal tumor endpoint in its 2024 formaldehyde reassessment.

The broader database does not independently resolve these uncertainties. Earlier oral and inhalation studies do not provide a consistent independent pattern of carcinogenicity, the human epidemiology database does not provide an acrolein-specific inhalation dose-response basis for the IUR, and no other authoritative body has derived a quantitative cancer potency value for acrolein. IARC's Group 2A classification supports a cancer hazard concern, but it does not validate OEHHA's selected tumor endpoint, multisite modeling approach, low-dose extrapolation method, or final numerical IUR.

The proposed IUR is also difficult to reconcile with measured ambient acrolein concentrations OEHHA itself reports. Applied to CARB's statewide monitoring data, the proposed value implies lifetime excess cancer risks from acrolein alone of roughly 1 in 2,200 to 1 in 135 for the general California population, and even the cleanest available rural background measurement implies a risk at or above a level generally treated as the upper bound of acceptable risk for a single chemical. OEHHA should reconcile this population-level implication with the absence of a documented cancer signal attributable to acrolein.

Before finalizing the proposed IUR, OEHHA should conduct the tissue-specific mode-of-action analysis described above, provide endpoint-specific and sensitivity analyses, and revise the IUR derivation as appropriate. Unless OEHHA provides adequate biological, statistical, and risk-assessment justification for combining nasal adenoma and lymphoma, the critical IUR should be based on the female mouse nasal cavity adenoma endpoint alone, with the lymphoma-inclusive multisite result presented only as a sensitivity or upper-bound analysis. OEHHA should also show how much of the proposed value reflects observed tumor data versus conservative modeling choices, including the selected BMR, study-duration adjustment, dose metric, and default body-weight scaling for animal-to-human extrapolation.

These revisions would not preclude OEHHA from considering acrolein a potential carcinogenic hazard. Rather, they are needed to ensure that the final quantitative IUR is based on the endpoint, dose metric, mode-of-action interpretation, and animal-to-human extrapolation approach best supported by the available evidence.

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Attachment B

Policy Arguments Supporting Reconsideration of OEHHA's draft IUR for Acrolein

Overview

OEHHA and CARB have taken the unusual step of releasing two IURs for different chemicals at the same time. Among the commonalities between acrolein and EO are their apparent ubiquity in ambient air and the magnitude of the cancer potency estimated by OEHHA. If OEHHA adopts final IURs at or close to the draft levels, each of these chemicals would, by itself, present a cancer risk in many areas of the state that is greater than the cancer risk from all other state-regulated toxic air contaminants (TAC) combined. Taken together, they would represent an unprecedented health threat that would demand immediate actions and dedication of substantial resources by CARB and the air districts to mitigate the presumed cancer risk.

Given these significant impacts, it is critically important that development of an IUR is based on and supported by strong scientific evidence. However, the scientific evidence supporting the draft acrolein IUR is very limited and OEHHA's interpretation of the limited evidence is speculative. As indicated in Attachment A, OEHHA's IUR derivation relies on data from a single study, and disregards current guidance and best practices in human health risk assessment by combining tumors observed in different target tissues. It also incorporates default assumptions in lieu of available data for other aspects of the IUR derivation, such as extrapolation of high dose animal effects to potential effects in humans at much lower exposure levels, which have a compounding effect on the IUR estimate.

These methodological flaws suggest that OEHHA is focused on deriving a more stringent value, rather than on establishing value that more accurately and precisely reflects human health risk. The objective of health risk assessment should be to predict potential adverse health outcomes as accurately as possible and then apply a margin of safety that reasonably addresses uncertainty in the underlying data and variability in the exposed population. Health risk estimates should not be predicated on data that is not fit for purpose, nor intentionally overstated in the interest of driving more stringent regulatory outcomes. Particularly where, as here, health risk assessment results are intended to support regulatory decisions and will have real world consequences, improper and speculative risk assessment will result in regulatory decisions that impose higher societal costs than are necessary to protect public health. Any such action that is likely to

exacerbate existing affordability challenges without delivering a commensurate public health benefit should be strictly avoided.

This approach could also jeopardize public health protection by redirecting limited agency staff time and funding from identification and mitigation of documented health risks toward identification and mitigation of increasingly theoretical health risks. It is all the more concerning when one considers that many potential anthropogenic sources of acrolein are already highly regulated, and natural sources are inherently difficult if not impossible to control. For example, CARB states in its acrolein website that it "is implementing the most advanced mobile source emissions control program in the nation to reduce emissions from cars, trucks, off-road equipment and freight sources" and that air districts "have been addressing air toxics and combustion-related emissions through a variety of regulatory, permitting, monitoring, and risk reduction programs." CARB also credits air districts with regulations and control measures addressing more diffuse sources, such as agricultural burning, residential wood burning, commercial cooking operations, and open burning. For the majority of these combustion sources, all technologically and economically feasible controls, including conversion to zero emissions technologies, have already been implemented, or are being phased in over time. Also, as CARB has acknowledged, acrolein emissions are not always a by-product of fuel combustion. One such example is cooking with fats and oils, where acrolein emissions are a function of the high temperatures necessary for food preparation. In these cases, there may not be a technology-based solution that can reduce acrolein emissions at the source.[6] It is unclear how CARB would reconcile the state's very high preliminary health risk estimates with subsequent findings that there are very limited opportunities to meaningfully reduce risks from exposures to acrolein.

CARB has acknowledged that it does not have adequate information on the various sources of acrolein, much less an understanding of which sources are the primary drivers for ambient acrolein concentrations. It is likely that significant time, staff resources, and funding will be dedicated to this task and it is equally likely that CARB and the air districts will conclude that there is little opportunity for additional risk reduction for many sources beyond actions that have already been taken or are under development. At a minimum, and before making this commitment at the expense of other regulatory priorities, CARB and the air districts must be certain that OEHHA's IURs are based on a reasonable

[6] Jiayu Li et al., Air pollutant exposure concentrations from cooking a meal with a gas or induction cooktop and the effectiveness of two recirculating range hoods with filters. Indoor Environments, December 2024: "VOCs did not significantly differ between gas and induction.";
https://www.sciencedirect.com/science/article/pii/S2950362024000444.

interpretation of adequate and reliable scientific evidence, and that fundamental flaws in existing emissions data are resolved.

Limitations in acrolein monitoring data should preclude speculation about potential cancer risks

The agencies acknowledge that the draft cancer risk estimate presented on CARB's acrolein website[7] is "based on limited air monitoring data with known limitations and notable uncertainties." We particularly appreciate CARB's acknowledgement of the many shortcomings in the existing acrolein monitoring data, including:[8]

- A lack of understanding of the amount of acrolein each potential source emits.
- The current emissions inventory "relied on emission factors from a source test method that is now known to have high uncertainty and chemical profiles that were developed for the purpose of modeling ozone, not for evaluating air toxic emissions."
- Many of the existing chemical profiles "were developed decades ago, are not representative of sources today, or do not capture the suite of toxics that would be expected to be emitted."
- The "range of concentrations … uses measurements with known limitations and notable uncertainties."
- "There is less certainty in historic acrolein concentrations and overall trends because of changes in laboratory methods and practices."
- "Research has shown that acrolein can form or break down inside the [air sampling] canister, which can make the results uncertain. Uncertainty increases when the true concentration is very low, near the detection limit."
- "The laboratory methods used to measure acrolein may not be sensitive enough to reliably measure acrolein at the low concentrations that matter for health assessments."

CARB further states that "it does not consider this information an appropriate or accurate measure of what is emitted in California." While we appreciate CARB's acknowledgement of these many data limitations, and the Newsom Administration's $2.5 million research initiative to "fill the scientific gaps surrounding acrolein and ethylene oxide," at least in the case of acrolein, we fail to understand why these deficiencies were not corrected following

[7] Id., "Based on OEHHA's draft cancer IUR and CARB's statewide monitoring, the average excess cancer risk is estimated to be approximately 1,300 in a million statewide."
[8] Id., How well are acrolein emissions in California understood? How much acrolein is in the air according to air monitoring? What are the challenges of measuring acrolein in the air?

OEHHA's adoption of a non-cancer health reference value for acrolein in 2008. For reasons neither CARB nor OEHHA has disclosed, it has taken the state 18 years to publicly acknowledge critical data limitations and to begin to take the necessary steps to address deficiencies in the information it has presumably been using to inform air toxics risk assessments and regulatory decisions.

Given the substantial shortcomings the agencies have identified in the existing emissions data, their inability to obtain accurate measurements at the present time, and the many scientific deficiencies in the draft acrolein IUR identified in Attachment A, it is irresponsible for the agencies to speculate about potential cancer risks from ambient exposures to acrolein.[9] Such assertions tend to incite fear and anger among community representatives, much of which is directed toward known and potential sources, especially those specifically identified by regulatory agencies. This approach is also likely to foster greater distrust of CARB, OEHHA, and the air districts if future research proves the initial speculation to be misdirected or unfounded. The agencies should publicly withdraw these statements pending completion of the IUR development process, and the research necessary to fill the many data gaps noted above.

CARB and OEHHA should be more forthcoming about potential impacts on existing air toxics programs

CARB and OEHHA fail to explain the potential impact of the draft IURs for EO and acrolein on state and local air toxics programs in the agencies' public-facing informational materials. CARB states on its acrolein website that "an IUR can impact implementation for a broad number of programs that consider health impacts of air toxics," and then proceeds to describe in general terms the process for developing IURs and how they are used in those state and local air toxics programs. What it fails to address, however, is the high probability of significant impacts on existing work streams that would stem from the extremely high risk estimates attached to these particular TACs, or how future agency responses involving reallocation of resources within state and local air toxics programs could impact public health locally, regionally, and at the state level.

Given the preliminary cancer risk estimates cited by the agencies for exposure to ambient acrolein and EO (1,300 in one million and 980 in one million and respectively), CARB, and particularly the air quality management districts, are likely to face an increase in workload under the Toxic Air Contaminant Identification and Control Program and the Air Toxics Hot

[9] Id., "The average excess cancer risk from acrolein is estimated to be more than 10 times higher than the cancer risk from benzene and puts it on par with the cancer risk diesel exhaust posed when it was first elevated as a major concern two decades ago — both well-known toxic air contaminants."

Spots Program that is arguably unlike anything they have experienced since CARB listed diesel exhaust particulate as a TAC in 1998. And as CARB separately acknowledges, the air districts will face the additional challenge of incorporating evaluation of cancer risks from these chemicals into their air toxics new source review programs. This probable step-change impact in workload is a function of both the relative magnitude of the cancer risk estimates for acrolein relative to those of other state regulated carcinogenic TACs, and the agencies' limited understanding of acrolein and EO concentrations in ambient air and contributions from various anthropogenic and natural emissions sources. This concern was previously expressed by the South Coast Air Quality Management District (SCAQMD) in comments it submitted to OEHHA in June 2023 on OEHHA's first draft IUR for EO.[10]

> "… if EtO indeed has the cancer potency that OEHHA is proposing, there are significant consequences for all Californians. The potential cancer risk at background levels would be about 1,000 chances in-a-million, more than double the cancer risk from all other pollutants and sources combined in South Coast AQMD. It is currently unclear what sources are contributing to background levels of EtO …"
>
> "With population-wide risks of this level, we believe it is imperative that CalEPA take a much more active role in identifying the sources of the risk, as well as appropriate measures to reduce it. This effort will take significant coordination among the state, air districts, and others as well as substantial resources."

The $2.5 million earmarked in the fiscal year 2026-2027 state budget to address the data gaps acknowledged by CARB and OEHHA is only a small down payment on the funding and agency resource commitments that will be necessary to support the development and deployment of new air quality monitoring methods, statewide and regional emissions inventory updates, source assessment and apportionment, facility-specific emissions inventory updates, new health risk assessments, additional public notifications, development of new risk management plans and risk mitigation measures, new source review for new and modified sources of acrolein and EO, new state and local rulemakings, and other regulatory actions.

If, as indicated in the analyses of the draft acrolein IUR in Appendix A, the science underpinning the proposed acrolein IUR is speculative, then the resource shifting and new

[10] Letter from South Coast Air Quality Management District to the California Air Resources Board dated June 14, 2023, commenting on the Office of Environmental Health Hazard Assessment's first draft IUR for Ethylene Oxide: https://oehha.ca.gov/sites/default/files/media/dockets/21072/21122-south_coast_aqmd/oehha_eto_-_south_coast_aqmd_comment_letter_6-14-23.pdf

spending that would result from this proposal is likely to create gaps in public health protection by diverting limited resources from regulation of other TACs and criteria pollutants where the public health basis for regulation is more clearly established. At a minimum, CARB and the air districts should evaluate the potential programmatic impacts of both the draft acrolein and EO IURs, including but not limited to additional staffing and funding needs and the potential for shifting resources from current areas of focus to assessment and management of health risks from acrolein and EO, and disclose that information to the public.

CARB should clarify the potential role and limitations of mobile monitoring data as a potential guidepost for future regulatory actions

CARB's acrolein website notes that CARB collected acrolein data as part of the Statewide Mobile Monitoring Initiative (SMMI) and then states that this "high time resolution data is expected to support improved understanding of pollutant variability and potential sources of acrolein." Apart from the extensive limitations in the available acrolein data acknowledged by CARB, this language appears to overstate the potential utility of the acrolein data collected through the SMMI. CARB has posted separate information on its SMMI webpage highlighting the appropriate uses and limitations of mobile monitoring data. For example, CARB has posted a Frequently Asked Questions document on its SMMI website, last updated on June 24, 2026,[11] which includes the following statements to guide interpretation and future use of the SMMI data:

> "Not intended for regulatory determinations: Mobile monitoring is best for screening, mapping, and prioritizing follow up. Regulatory decisions under the Clean Air Act rely on fixed site monitors that use U.S. EPA approved Federal Reference or Equivalent Methods (FRM/FEM) and meet siting criteria.
>
> If results are needed for regulatory purposes, a follow-up study using U.S. EPA approved methods would be required."
>
> "Mobile sensor data also shouldn't be used to quantify individual or community health risks, and U.S. EPA does not set health-based standards for the short-term sampling typical of many sensor readings."
>
> "The mobile sensors' ability to collect accurate results can also be affected by temperature, humidity, co-pollutants, and variable environmental conditions so routine checks, calibration, and corrections are needed."

[11] California Air Resources Board, Statewide Mobile Monitoring Initiative (SMMI): Frequently Asked Questions, June 24, 2026: https://ww2.arb.ca.gov/resources/fact-sheets/smmi-frequently-asked-questions-faq

> "Depending on the source of concern and pollutants to be measured, monitoring was assigned to Aclima's vehicles or to Partner Mobile Laboratories (PMLs). The three PMLs—operated by UC Berkeley, UC Riverside, and Aerodyne—collected air toxics measurements and were deployed to high-priority areas identified through community engagement. Because PMLs are limited, communities received only a few days of these specialized measurements."
>
> "While the dataset may help inform future work, it is not intended to directly drive regulatory or policy decisions."
>
> "Before releasing [SMMI] results, CARB must complete extensive quality checks and prepare plain-language explanations and visuals so the public can use the information confidently. This kind of dataset is both powerful and easy to misinterpret without clear context. Mobile sensor data involve short, non-continuous samples and lower-cost instruments, which expand coverage but add uncertainty. Because of this, the results require extra interpretive care compared with fixed-site monitors. Taking time to review, verify, and contextualize the findings helps ensure the results are reliable and actionable."
>
> "This data provides a starting point, especially in communities that previously lacked sufficient air-monitoring data, so that future monitoring can investigate the air quality benefits of actions to reduce emissions."

While not expressly stated in the SMMI FAQ, these limitations support the conclusion that SMMI data is not appropriate for quantifying localized ambient concentrations of individual TACs or for source attribution analysis.

It is unclear why CARB did not carry the guidance in the SMMI FAQ forward into the informational materials it is now presenting on acrolein, but as a matter of transparency and consistency in interpretation of available data, it should immediately remedy that oversight. To the extent that CARB continues to reference SMMI data as a source of information to help inform future regulatory actions related to acrolein, we strongly recommend that CARB include this information in all of its public-facing materials on these substances.

CARB should complete state-funded research before air districts incorporate final IURs into their Hot Spots regulatory programs

Local air district regulations implementing the Air Toxics Hot Spots Program, such as the Bay Area District's Regulation 11, Rule 18, and the South Coast Air Quality Management District's Rule 1402 include a public notification component which is triggered in cases where cancer risks from individual stationary sources exceed 10 in one million at receptors beyond the facility fenceline (e.g., homes, schools, hospitals, other businesses). These sources will be targets of opportunity for community groups and air districts, even if CARB concludes that the majority of emissions for both acrolein and EO originate from mobile, indirect, and natural sources.

The adoption of new IURs for acrolein and EO will likely result in air districts reprioritizing facilities subject to the Hot Spots program, which will result in requirements for new and updated air toxics emissions inventories and facility wide health risk assessments. Facilities whose risk assessments indicate cancer risks greater than 10 in one million at receptor locations beyond the facility fenceline will be required to issue public notifications stating that facility operations are exposing individuals at the identified locations to an excess cancer risk. To the extent the draft IURs are based on overstated health risks that cause affected facilities to exceed air district public notification thresholds, new notifications will cause unnecessary and counter-productive public alarm in communities where the background risk from ambient concentrations of acrolein and EO may dwarf individual contributions from stationary sources.

CARB also has not addressed the potential for the IUR to be completed before the new research on acrolein and EO emissions and potential sources funded in the current state budget. A worst-case scenario would involve immediate actions by air districts under Hot Spots and air toxics new source review regulations and policies following OEHHA approval of new IURs for acrolein and EO, before the state-funded research is completed. In that scenario, air districts would be using emissions data they know to be inaccurate as a basis for estimating facility risk, and at least in some cases, imposing new regulatory requirements on affected sources. This approach would be a recipe for imposing additional and perhaps unsustainable administrative, public relations, operational, and economic burdens on affected facilities without first having a clear understanding of whether those burdens would result in a meaningful public health benefit. We strongly encourage CARB and the air districts to complete the additional state-funded research before incorporating new IURs for acrolein and EO into their air toxics programs.

CARB should refrain from using unreliable data to make inferences about particular sources

Given the presumed ubiquity of acrolein in ambient air, the diversity of potential sources cited by CARB, and conflicting results from CARB's Study of Neighborhood Air Near

Petroleum Sources (SNAPS), it is unclear why CARB would single out the results from monitoring in the Kern County community of Lost Hills as a driver for OEHHA to initiate development of an IUR for acrolein.[12] CARB cites elevated concentrations of acrolein from the Lost Hills monitoring, but fails to acknowledge that SNAPS monitoring results to date for acrolein near the Inglewood Oil Field in Los Angeles County do not show similarly elevated concentrations.[13] If, as CARB and OEHHA suggest, oil and gas operations are a dominant source of acrolein,[14] then one would expect to see comparable ambient concentrations in the communities surrounding both oil fields. This discrepancy is a real-world example of the limitations in the state's understanding of acrolein sources and the relative contributions of those sources to ambient concentrations of acrolein.

Until CARB addresses the many gaps it has identified in the existing acrolein monitoring data, including its current inability to accurately measure acrolein in ambient air or to quantify emissions from specific sources, it should not presume to identify or imply that certain sources are responsible for elevated concentrations of acrolein in any community. Statements such as these suggest an intention to selectively leverage available data to support predetermined regulatory agendas rather than an impartial, science-based approach to quantify potential public health impacts as accurately as possible and to invest limited public and private resources in mitigating significant risks.

The IUR development process is premature

CARB's acrolein website and the Governor's May Revise budget proposal[15] both acknowledge that preliminary risk estimates are predicated on limited data. The May Revise states that "critical, foundational scientific research [is] needed to support additional actions to reduce cancer risk from acrolein." OEHHA's decision to move ahead with development of an IUR, despite the Newsom Administration's recognition that the best available science currently is not sufficient to support additional action to reduce cancer risk from exposure to acrolein, is arbitrary and likely to distract OEHHA and risk managers at CARB and the air districts from more clearly established air quality and public

[12] California Air Resources Board, Learn About Acrolein, Where It Comes From, How It Affects Your Health, and more importantly, What California Is Doing to Protect You, How did monitoring in Lost Hills play a role in OEHHA's evaluation of the cancer risks of acrolein? May 14, 2026.
[13] See CARB, Study of Neighborhood Air near Petroleum Sources, January 2025 Update, Amended July 2025, Figure 8 (second data analysis update for the SNAPS air monitoring program near the Inglewood Oil Field (IOF), stating that "HQs [hazard quotients] for VOCs detected in discrete samples were all less than one (Figure 8), indicating no expected acute health risks"). It should also be noted that CARB completed monitoring in the IOF community in March 2025 but still has not released complete results to the public.
[14] Id., "The results showed acrolein concentrations in Lost Hills were higher than those measured in other parts of the Central Valley. Acrolein was also the largest contributor to non-cancer risk in the area."
[15] See: 2026-27 MR Budget Summary.

health priorities. Where the best available science is not a sufficient basis for risk assessment and risk management, OEHHA should not move forward with development of an IUR.

CARB's acrolein website states that "CARB will continue working to advance our understanding of acrolein levels in the air and will refine the cancer risk estimates as better data become available." These statements suggest that it is acceptable for the state to adopt new IURs based on limited, flawed, or otherwise inadequate scientific evidence, because CARB and OEHHA can "refine" them at a later date. The possibility that an IUR might be supported by sufficient scientific evidence in the future is not a rational basis for developing an IUR without adequate scientific support at the present time. This approach disregards the many impacts on state and local regulatory agencies and the regulated community related to emissions monitoring, risk assessment, risk management, and risk communication that an improperly derived IUR is likely to cause. The agencies' current posture also overstates the likelihood that CARB and OEHHA will promptly update an IUR based on the future availability of new scientific evidence, which has not been the agencies' practice to date.

The IARC Monograph does not support OEHHA's IUR derivation

OEHHA's draft TSD for acrolein is one of the first attempts by a regulatory agency to develop a risk-based health protective concentration for this chemical. It cites the International Agency for Research on Cancer's (IARC) 2021 classification of acrolein as a Group 2A carcinogen (probably carcinogenic to humans). According to IARC, this classification is based on findings of sufficient evidence of carcinogenicity in experimental animals but ***inadequate evidence in humans*** (emphasis added).[16] Notably, IARC observed that the JBRC 2016 study is the only available animal study assessing the carcinogenicity of acrolein that complied with good laboratory practices (GLP),[17] meaning it is the only animal study whose design and execution were subject to globally accepted standards intended to ensure data integrity, validity, and reliability. This observation underscores the limitations in the animal evidence used as a basis for OEHHA's draft IUR. More importantly, IARC monographs are limited to cancer hazard identification – a determination of whether a chemical is capable of causing cancer under a given set of circumstances. IARC does not conduct risk assessments to evaluate the likelihood of

developing cancer based on actual exposure levels and routes. IARC did not establish an IUR for acrolein, and IARC's findings in its acrolein Monograph cannot be interpreted as supporting OEHHA's analysis of the JBRC study or the science policy decisions underpinning OEHHA's derivation of the draft IUR. Thus, the deficiencies in OEHHA's draft TSD identified in Appendix A must be evaluated independently of the findings in the IARC Monograph.

Given the real-world consequences of direct application of OEHHA's IURs in local air district regulations and policies, the substantial scientific uncertainties surrounding OEHHA's IUR derivations should be resolved before regulated entities are compelled to notify the public of theoretical health risks, much less take action to reduce those risks.