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PUBLIC COMMENTS
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
Proposition 65: Vinyl Acetate Pre-Regulatory Workshop
Proposed No Significant Risk Level (NSRL) of 11 µg/day

October 21, 2026

Re: Comments on the Pre-Regulatory Draft Proposal Establishing an NSRL of 11 µg/day for Vinyl Acetate (CAS No. 108-05-4)

Dear OEHHA Staff:

The following comments address the pre-regulatory proposal to establish a No Significant Risk Level (NSRL) of 11 micrograms *per* day (µg/day) for vinyl acetate (VA; vinyl acetate monomer, VAM; CAS No. 108-05-4) under Title 27, California Code of Regulations, section 25705(b), and the related proposed addition of a new section 25901 clarifying analytical methods for the residual monomer.

Vinyl acetate was listed as a carcinogen under Proposition 65 effective January 3, 2025, based on the Carcinogen Identification Committee's determination. The proposed NSRL was derived from a human cancer slope factor of 0.065 $(mg/kg\text{-}day)^{-1}$ based on the female Fischer 344 rat drinking-water bioassay reported by EPL (1982) and Lijinsky and Reuber (1983). The slope factor was developed using a multistage model fit in EPA Benchmark Dose Software (BMDS), with a benchmark response corresponding to 5% extra cancer risk (*i.e.*, BMR = 5% of BMR_5) and linear low-dose extrapolation from the model-derived point of departure (POD) to a cancer risk level of 10^{-5} (OEHHA 2026 workshop slides; OEHHA 2024).

We respectfully submit that the proposed NSRL of 11 µg/day is not supportable under the applicable regulatory standard, the weight of the scientific evidence, or best available science regarding the mode of action of vinyl acetate.

The selected study does not meet the regulatory requirement that the NSRL be based on the most sensitive study of sufficient quality. More robust bioassays and extensive mechanistic data supporting a portal-of-entry, dose-dependent mode of action provide a scientific basis for substantially higher NSRLs.

We support the proposed clarifying language regarding residual monomer versus polymer-derived material.

I. Regulatory Standard Requires a Science-Based Assessment of Sufficient Quality

Title 27, California Code of Regulations, section 25703 provides the quantitative risk assessment procedures for determining NSRLs. Subsection (a) states:

> "*A quantitative risk assessment which conforms to this section shall be deemed to determine the level of exposure to a listed chemical which, assuming daily exposure at that level, poses no significant risk.*
>
> *The assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause cancer.*
>
> *In the absence of principles or assumptions scientifically more appropriate, based upon the available data, the following default principles and assumptions shall apply in any such assessment:*"

Subsection (a)(1) requires that animal bioassay studies meet generally accepted scientific principles, including thoroughness of experimental protocol, the degree to which dosing resembles expected human exposure, temporal exposure pattern, duration of study, purity of test material, number and size of exposed groups, route of exposure, and extent of tumor occurrence.

Subsection (a)(3) states: "*Risk analysis shall be based on the most sensitive study deemed to be of sufficient quality.*"

Subsection (a)(5) specifies one of the default principles:

> "*The absence of a carcinogenic threshold dose shall be assumed and no-threshold models shall be utilized. A linearized multistage model for extrapolation from high to low doses, with the upper 95 percent confidence limit of the linear term expressing the upper bound of potency shall be utilized. Time-to-tumor models may be appropriate where data are available on the time of appearance of individual tumors, and particularly when survival is poor due to competing toxicity.*"

Because this provision is expressly conditioned on the absence of more appropriate principles, the linearized multistage model and no-threshold assumption are defaults, not absolute requirements.

Subsection (a)(7) further supports the use of mode-of-action information when the data are of sufficient quality:

"*When available data are of such quality that physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the risk assessment for inter-species, inter-dose, and inter-route extrapolations.*"

OEHHA's public materials reinforce this flexibility. The agency states that the adopted safe-harbor NSRLs "*do not preclude the use of alternative levels that can be demonstrated by their users as being scientifically valid."* OEHHA's 2026 workshop materials and 2024 Hazard Identification Document correctly restate the "*most sensitive study deemed to be of sufficient quality*" criterion.

However, the selection of the EPL 1982 / Lijinsky and Reuber 1983 female F344 rat study as the critical study prioritizes perceived sensitivity over quality and scientific appropriateness. The resulting cancer slope factor of 0.065 $(mg/kg\text{-}day)^{-1}$ and NSRL of 11 µg/day are driven by this choice and by application of the default linear no-threshold model without adequate consideration of the mode-of-action data that constitute scientifically more appropriate principles under section 25703(a).

II. The Selected Critical Study (EPL 1982 / Lijinsky and Reuber 1983) Is not of Sufficient Quality

The 100-week drinking-water study in Fischer 344 rats used only 20 animals *per* sex *per* group. Animals were exposed to 0, 1000, or 2500 ppm vinyl acetate 5 days/week with observation for up to an additional 30 weeks (Lijinsky and Reuber 1983, EPL 1982, OEHHA 2024). OEHHA (2024) estimated average daily doses from the lifetime administered doses reported by Lijinsky and Reuber (1983) as 0, 50, and 124 mg/kg bw/day for males, and 0, 80, and 200 mg/kg bw/day for females.

No treatment-related tumors were reported in the males.

For the females, OEHHA (2026) reconstructed the following incidences from the combined EPL (1982) pathology review and Lijinsky and Reuber 1983:

- Hepatocellular adenoma (neoplastic nodule): 0/20, 0/20, 6/20
- Uterine adenocarcinoma: 0/18, 1/20, 4/20
- Endometrial stromal polyp: 0/18, 3/20, 5/20
- Thyroid C-cell adenoma: 0/17, 2/19, 5/20
- Pituitary adenoma: 6/17, 8/19, 12/18.

However, there are fundamental quality deficiencies that preclude reliance on this study as the basis for quantitative risk assessment, including:

- Groups of 20 animals are substantially below current standards and limit the reliability of tumor incidence estimates and trend analyses from the data reported in this study, especially for rare tumors. As OEHHA (2024) noted, the EPL (1982) / Lijinsky and Reuber (1983) study tested small numbers of animals/dose, as did other studies OEHHA selected for modelling and derivation of the proposed NSRL.

- The peer-reviewed publication (Lijinsky and Reuber 1983) did not examine or report all tissues in all test animals of the study. Histology slides were subsequently submitted for independent review by EPL (1982), which prepared additional slides from previously unexamined tissues. EPL (1982) documented anomalies, including missing slides for some animals and the submission of mouse tissues under a female rat identifier containing an alveolar/bronchiolar adenoma typical of aged mice. Variations in the reported denominators reflect these issues.

- Vinyl acetate hydrolyzes readily in aqueous solution. Lijinsky and Reuber (1983) reported a decomposition rate of approximately 8.5% *per* day at room temperature and 5% *per* day at 4°C. Drinking-water solutions were prepared weekly and dispensed every three days. These authors noted that the animals likely received lower, but at least half, of the intended dose. This factor introduces substantial uncertainty about the dose metric used for OEHHA's cancer potency calculations. Hydrolysis of vinyl acetate generates acetaldehyde and acetic acid. Thus, the animals were exposed to vinyl acetate together with hydrolysis products, including acetaldehyde and acetic acid, rather than exclusively to unchanged vinyl acetate.

- The liver findings were originally described as "neoplastic nodules." OEHHA (2024) reclassified them as hepatocellular adenomas.

- Pituitary adenomas are common spontaneous tumors in aged F344 rats.

- The multi-site modeling that produced the highest potency involved combining liver, uterine (adenocarcinoma and stromal polyp), thyroid C-cell, and pituitary endpoints. None of these lesions are portal-of-entry lesions for oral exposure. The portal-of-entry sites for oral administration include the oral cavity, esophagus, forestomach, and stomach. None of the tumors the OEHHA modeled from this study arise at the site of first contact. This pattern does not align with the consistent portal-of-entry squamous-cell tumors observed in higher-quality studies reported later.

An additional substantive limitation of the EPL (1982) / Lijinsky and Reuber (1983) drinking-water study is the inadequate characterization of the vinyl acetate test material. The authors described the

material only as a "commercial product with no significant impurities" but did not report a quantitative purity specifications, impurity profile, or analytical characterization of the test article (Lijinsky and Reuber 1983; EPL 1982, as summarized in OEHHA 2024). Such information is important for interpreting whether observed effects can be attributed to vinyl acetate itself rather than to unidentified contaminants, as well as degradation products.

ATSDR (2025) identified potential contaminants in commercial-grade vinyl acetate of undetermined purity, together with small group size and uncertainty regarding exposure stability, as limitations of the EPL (1982) / Lijinsky and Reuber (1983) study. Separately, VAC (2024) raised analogous concerns regarding the characterization of test materials used in the Ramazzini Institute oral carcinogenicity studies. These observations underscore broader questions about test-article characterization across portions of the oral carcinogenicity database.

The limitations of the Lijinsky and Reuber (1983) study were recognized in subsequent regulatory evaluations. The European Union Risk Assessment Report (2008) placed greater weight on later carcinogenicity studies, including Umeda *et al.* (2004), which were conducted in accordance with more modern study designs and provided more consistent evidence of portal-of-entry tumor formation following oral exposure.

Consequently, even if the EPL (1982) / Lijinsky and Reuber (1983) study is considered informative for hazard identification, its limitations materially diminish its suitability as the basis for quantitative potency estimation when more comprehensive and better-characterized studies are available. The available regulatory evaluations place greater weight on the later studies because they provide more robust dose-response information and a tumor profile that is more consistent with an established mode of action of vinyl acetate.

III. Other Studies Selected for Modeling (also Have Significant Limitations)

OEHHA modeled 5 sex/species datasets, selecting the female F344 rat dataset from EPL (1982) and Lijinsky and Reuber (1983) because it yielded the highest human cancer slope factor (0.065 [mg/kg bw/day]$^{-1}$).

The remaining datasets were derived from Ramazzini Institute studies reported by Belpoggi *et al.* (2002) (male and female F1 Wistar rats) and Maltoni *et al.* (1997) (male and female F1 Swiss mice). These studies involved *in utero* exposure followed by lifetime exposure to drinking water containing 0, 1000, or 5000 ppm vinyl acetate. OEHHA (2026) modeled multisite tumor responses, including tumors of the oral cavity, forestomach, esophagus, and other tissues, and derived lower human cancer slope factors ranging from approximately 0.0098 to 0.025 (mg/kg bw/day)$^{-1}$ than those obtained from the female F344 rat study.

The Ramazzini Institute studies continued until the spontaneous death of the animals after an exposure period ranging from 78 to 104 weeks. This lifetime-to-natural death design has been criticized in EFSA reviews and other scientific assessments. The combination of advanced age at death, elevated background rates of lesions, and practical challenges of pathology examinations at terminal stages (including autolysis as well as age-related lesions), reduces the reliability of tumor diagnoses for quantitative risk assessment. These concerns further support the use of data from higher-quality studies that terminated at a standard 104-week endpoint with complete necropsy of all animals (*e.g.*, Umeda *et al.* 2004).

Regulatory and scientific reviews have generally placed greater emphasis on the later drinking-water studies and supporting mechanistic evidence demonstrating dose-related squamous-cell neoplasms at portal-of-entry tissues of the upper digestive tract, especially the bioassay of Umeda *et al.* (2004). These findings are consistent with the established portal-of-entry mode of action for orally administered vinyl acetate and have therefore been regarded as especially relevant for dose-response assessment of vinyl acetate carcinogenicity (EU RAR 2008; Bogdanffy *et al.* 2004).

Tumors of the forestomach have limited relevance to human risk assessment because humans lack a forestomach. Consistent with the current understanding of vinyl acetate carcinogenicity, forestomach tumors are generally interpreted as secondary to local metabolism, irritation, cytotoxicity, and regenerative cell proliferation at sites of direct contact, rather than as evidence of a systemic carcinogenic mechanism (IARC 1995; EU Risk Assessment Report 2008).

Moreover, adrenal pheochromocytomas (or pheochromoblastomas) reported in some Ramazzini Institute studies, including Belpoggi *et al.* (2002), arise in tissues remote from the site of first contact and are not readily reconciled with the portal-of-entry mode of action supported by the broader vinyl acetate database. In contrast, the most consistent treatment-related neoplastic response across drinking-water studies is the occurrence of squamous-cell tumors in directly-exposed tissues of the upper digestive tract, including the oral cavity and esophagus.

Therefore, multisite models that combine forestomach tumors, which have limited relevance to humans, with distant-site tumors for which the relationship to the established mode of action of vinyl acetate is less well established may yield potency estimates that are not driven primarily by the tumor responses most clearly associated with vinyl acetate exposure. From a biological and risk-assessment perspective, greater weight should be assigned to the consistent portal-of-entry squamous neoplasms observed in directly-exposed tissues of the upper digestive tract, which represent the most coherent and reproducible carcinogenic response across the vinyl acetate database.

IV. Higher-Quality Studies Support a Portal-of-Entry, High-Dose Response

The published studies with larger group sizes, improved dose characterization, and protocols generally consistent with contemporary carcinogenicity testing standards provide a more reliable basis for hazard identification and dose-response assessment.

Umeda *et al.* (2004)[1] evaluated groups of 50 male and 50 female F344/DuCrj rats and Crj:BDF1 mice exposed to vinyl acetate in drinking water at concentrations of 0, 400, 2000, or 10,000 ppm for 104 weeks. Treatment solutions were prepared twice weekly, and analytical measurements demonstrated that actual concentrations were lower than nominal values because of evaporation and hydrolysis. Acetic acid concentrations increased with increasing vinyl acetate concentrations, consistent with degradation of the parent compound.

Statistically significant increases in combined oral cavity squamous-cell papillomas and carcinomas occurred predominantly at the highest exposure concentration (*e.g.*, 7/50 male rats, 16/50 male mice, and 18/50 female mice). Additional squamous-cell tumors of the esophagus and forestomach were observed in high-dose mice. No consistent treatment-related increases in the critical oral-cavity lesions were observed at the lower exposure concentrations.

The study authors and subsequent evaluations reported benchmark-dose lower confidence limits ($BMDL_{10}$s) of approximately 440 to 477 mg/kg bw/day for combined oral-cavity squamous-cell tumors. EFSA (2010, 2013) and the European Union Risk Assessment Report (2008) regarded these findings as providing a robust basis for characterizing the carcinogenic effects of oral administration of vinyl acetate.

For example, EFSA (2013) noted that VA is used as a starting material in the manufacture of PVA-PEG graft copolymer used as a food additive and that the applicant proposed a specification limit of 20 mg/kg for residual, unreacted VA. In an earlier evaluation, the (2010) derived a $BMDL_{10}$ of 440 mg/kg bw/day based on the combined incidence of oral-cavity squamous-cell papillomas and carcinomas in mice and rats reported by Umeda et al. (2004). Using this point of departure and assuming a maximum residual VA concentration of 20 mg/kg in the copolymer, the Panel calculated margins of exposure (MOEs) of approximately 2.2×10^6 for adults and 2.5×10^6 for children. On this basis, the Panel concluded that the presence of residual VA in PVA-PEG graft copolymer at concentrations up to 20 mg/kg does not raise a safety concern.

Consistent with the reported $BMDL_{10}$ values, OEHHA (2024) estimated average daily vinyl acetate intakes of 0, 21, 98, and 442 mg/kg bw/day for male rats and 0, 31, 146, and 575 mg/kg bw/day for female rats. Notably, statistically significant increases in oral-cavity squamous-cell tumors were observed primarily in the highest dose groups, corresponding to average daily intakes of

[1] Full laboratory study report: Japan Bioassay Research Center (JBRC) 1995.

approximately 442 mg/kg bw/day in male rats and 575 mg/kg bw/day in female rats, which is consistent with the reported $BMDL_{10}$ values for these lesions.

Chronic inhalation studies conducted by Bogdanffy *et al.* (1994a) in rats and mice (0, 50, 200, or 600 ppm, 6 hours/day, 5 days/week for 104 weeks) produced nasal squamous-cell papillomas and carcinomas only at the highest exposure concentration in rats. These tumors were associated with pronounced cytotoxicity, epithelial metaplasia, and sustained regenerative hyperplasia of the olfactory and respiratory epithelium. A parallel oral study that included *in utero* exposure (Bogdanffy *et al.* 1994b) produced few, if any, treatment-related neoplastic responses at concentrations up to 600 ppm.

Extensive mechanistic investigations by Bogdanffy and colleagues subsequently demonstrated that vinyl acetate is rapidly hydrolyzed by local carboxylesterases, resulting in intracellular acidification, tissue injury, compensatory cell proliferation, and ultimately tumor formation at sites of direct contact with the chemical and its metabolites (Bogdanffy *et al.* 1994a, 1998, 1999, 2001, 2002; Lantz *et al.* 2003; Nakamoto *et al.* 2005; Plowchalk *et al.* 1997).

In sum, these studies support a portal-of-entry mode of action in which tumor formation occurs only after prolonged high-dose contact sufficient to induce sustained cytotoxicity and regenerative cell proliferation in directly exposed tissues. The available animal, mechanistic, and toxicokinetic evidence does not provide comparable support for a generalized multisite systemic carcinogenic response at lower exposure levels. Thus, portal-of-entry tumor responses warrant primary consideration in evaluating the carcinogenic potential of vinyl acetate and conducting quantitative dose-response assessment.

V. Mode of Action Supports a Threshold and Constitutes Scientifically More Appropriate Principles

Vinyl acetate is rapidly hydrolyzed by widely distributed carboxylesterases to yield acetaldehyde and acetic acid as intermediate metabolites (Bogdanffy and Taylor 1993; Bogdanffy *et al.* 1998, 1999; Hinderliter *et al.* 2005; Albertini 2013).

The weight of evidence supports the following sequence of key events at the portal of entry:

1. Local hydrolysis of vinyl acetate to acetaldehyde and acetic acid.
2. Intracellular acidification and metabolic stress resulting in epithelial cytotoxicity and cell death in directly exposed tissues (nasal cavity or upper gastrointestinal tract).
3. Sustained regenerative cell proliferation in response to tissue injury.
4. Formation of acetaldehyde-derived DNA-protein cross-links and other adducts at sufficiently high local concentrations, especially when detoxification pathways (including aldehyde dehydrogenase-mediated metabolism) are saturated or overwhelmed.

5. Development of neoplastic lesions following prolonged exposure associated with persistent cytotoxicity and regenerative proliferation.

This mode of action is supported by extensive *in vitro* and *in vivo* evidence demonstrating local acidification, cytotoxicity, regenerative cell proliferation, formation of acetaldehyde-derived DNA lesions, and the dependence of these effects on carboxylesterase-mediated metabolism (Bogdanffy 2002; Bogdanffy and Valentine 2003; Kuykendall *et al.* 1993; Lantz *et al.* 2003; Nakamoto *et al.* 2005; Albertini 2013).

Collectively, these data support a portal-of-entry, cytotoxicity-driven mode of action with an important dose-dependent aspect and provide limited evidence that vinyl acetate acts through a generalized systemic carcinogenic mechanism at low exposure levels.

Acetaldehyde is an endogenous metabolite that is also present in many foods and beverages. Available toxicokinetic and mechanistic data indicate that acetaldehyde is efficiently metabolized by aldehyde dehydrogenase and other detoxification pathways, resulting in a nonlinear relationship between exposure and biologically effective dose at low exposure levels (Albertini 2013; Budinsky *et al.* 2013; EU Risk Assessment Report 2008).

Consistent with this understanding, *in vitro* mutagenicity studies of both vinyl acetate and acetaldehyde have demonstrated nonlinear, threshold concentration-response relationships, with genotoxic effects becoming evident primarily at concentrations associated with saturation of cellular detoxification and protective mechanisms (Budinsky *et al.* 2013; Albertini 2013).

Moreover, the available *in vivo* data provide limited evidence for systemic genotoxicity at non-cytotoxic exposure levels. Genotoxic and carcinogenic responses are observed predominantly at sites of direct contact or under experimental conditions involving high local tissue concentrations, supporting the conclusion that tissue injury, regenerative cell proliferation, and local metabolism are important determinants of vinyl acetate carcinogenicity (Albertini 2013; EU Risk Assessment Report 2008).

Taken together, these findings are more consistent with a portal-of-entry mode of action characterized by dose-dependent saturation of detoxification and tissue homeostasis than with a potent systemic genotoxic mechanism active at low exposure levels.

The European Union Risk Assessment Report (2008), Health Canada's Screening Assessment (2008), and numerous peer-reviewed reviews have concluded that the carcinogenic effects of vinyl acetate are most plausibly explained by a portal-of-entry mode of action involving rapid hydrolysis to acetaldehyde and acetic acid, local cytotoxicity, regenerative cell proliferation, and, at sufficiently

high exposures, secondary genotoxic effects associated with acetaldehyde formation (Albertini 2013; EU Risk Assessment Report 2008; Health Canada 2008; SCHER 2008).

IARC (1995) classified vinyl acetate as Group 2B ("possibly carcinogenic to humans") based on what was deemed to be sufficient evidence of carcinogenicity in experimental animals and inadequate evidence in humans. The animal evidence was characterized predominantly by tumors occurring at sites of direct contact following exposure to relatively high concentrations of vinyl acetate.

Collectively, the toxicological, mechanistic, and toxicokinetic data provide a scientifically supported basis for considering mode-of-action information to evaluate the dose-response relationship for vinyl acetate. Such information is directly relevant to the provision in Title 27, California Code of Regulations, section 25703(a), which states that the default assumptions apply only "[i]*n the absence of principles or assumptions scientifically more appropriate, based upon the available data.*"

In addition, these data are consistent with the considerations described in section 25703(a)(7), under which physiologic, pharmacokinetic, and metabolic information may be incorporated into risk assessment when available data are of sufficient quality and confidence.

Accordingly, the available evidence supports evaluation of whether the default no-threshold assumption and linearized multistage extrapolation model appropriately reflect the biological behavior of vinyl acetate at low exposure levels. Because the observed carcinogenic response is associated with portal-of-entry toxicity, regenerative proliferation, and dose-dependent metabolic processes, linear low-dose extrapolation may yield risk estimates that are more conservative than would be predicted by the weight of the mechanistic and toxicokinetic evidence.

Independent expert-panel analyses that incorporate mode-of-action information, toxicokinetic data, and threshold considerations have derived substantially higher NSRLs, on the order of tens to hundreds of thousands of µg/day for oral and inhalation exposures (Kirman *et al.* 2026).

Moreover, even when applying a conventional linear multistage approach to the oral cavity squamous-cell tumor data from the higher-quality study of Umeda *et al.* (2004), estimated NSRLs are substantially greater than the 11 µg/day value proposed by OEHHA (2026). Based on our calculations using the oral-cavity squamous-cell tumor data from Umeda *et al.* (2004), estimated NSRLs fall in the range of approximately 180-330 µg/day, depending on benchmark-response selection, extrapolation assumptions, and treatment of forestomach tumors. These estimates are based on tumor responses occurring at the portal of entry and are therefore more consistent with the established mode of action of vinyl acetate than potency estimates driven by multisite modeling of systemic tumor endpoints.

VI. Lack of Justification for the 5% Extra-Risk Benchmark Response

OEHHA's workshop slides (2026) state that cancer potency was estimated using the multistage polynomial model in EPA's Benchmark Dose Software (BMDS) and present an example labeled "*1st Degree Multistage Model with BMR of 5% Extra Risk for BMD and 95% Lower CI for BMDL*."

The resulting human cancer slope factor of 0.065 $(mg/kg\text{-}day)^{-1}$ for the female F344 rat dataset from Experimental Pathology Laboratories (EPL 1982) and Lijinsky and Reuber (1983) was used to derive the proposed NSRL of 11 µg/day.

Neither the workshop slides nor the accompanying explanatory materials identify a scientific rationale for selecting a benchmark response corresponding to 5% extra risk (BMR_5) rather than a 10% extra-risk benchmark response (BMR_{10}), which is commonly used as the default benchmark response for quantal cancer endpoints in benchmark-dose modeling unless a different value is scientifically justified.

Proposition 65 regulations require that the final NSRL correspond to a lifetime excess cancer risk of one in 100,000 under Title 27, California Code of Regulations, section 25703. However, the regulations do not specify a required benchmark response level for the underlying dose-response modeling. Rather, the benchmark response is a scientific modeling choice used to establish the point of departure (POD) from which potency is estimated.

For a given dataset and model, selection of a 5% extra-risk benchmark response generally produces a lower benchmark dose (BMD) and benchmark-dose lower confidence limit (BMDL) than selection of a 10% extra-risk benchmark response. All else being equal, this tends to increase the resulting cancer potency estimate and decrease the derived NSRL.

Because the proposed NSRL is sensitive to the choice of benchmark response level, it would be informative for OEHHA to provide the scientific basis for selecting BMR_5 and to present a sensitivity analysis comparing the resulting potency estimates and NSRL values obtained using alternative benchmark responses, including BMR_{10}. In the absence of such information, interested parties cannot readily evaluate the degree to which the proposed NSRL reflects the underlying tumor data versus the modeling assumptions.

VII. Human Relevance and Exposure Context

Occupational and consumer exposures to residual vinyl acetate monomer are generally low. Available information indicates that residual vinyl acetate monomer concentrations in products manufactured from vinyl acetate-based polymers are typically low and decline further through volatilization and hydrolysis during manufacture, storage, and use (Health Canada 2008; Vinyl Acetate Council submissions).

Vinyl acetate is rapidly metabolized following exposure and does not bioaccumulate, as explained above. Its disposition is characterized by rapid hydrolysis to acetaldehyde and acetic acid and subsequent metabolism through normal endogenous pathways (EU Risk Assessment Report 2008; Albertini 2013).

Epidemiological studies of exposed workers have not provided clear or consistent evidence of an increased cancer risk attributable to vinyl acetate exposure (OEHHA 2024; EU Risk Assessment Report 2008).

The proposed language in section 25901 focuses exposure assessment, enforcement, and warning obligations on exposure to residual free vinyl acetate monomer under realistic conditions of consumer use. By requiring that exposure allegations be based on the listed chemical itself (vinyl acetate monomer) and by excluding monomer generated through artificial degradation of vinyl acetate-containing polymers under conditions not representative of consumer exposure, the proposal is consistent with the toxicological evidence, the listed chemical, and the actual exposure scenarios relevant to Proposition 65.

Accordingly, we support the proposed clarification in section 25901. The proposed provision would help ensure that exposure assessments are based on reasonably anticipated consumer exposures to vinyl acetate monomer rather than on analytical artifacts generated through testing conditions that do not reflect normal product use.

VIII. Requested Action

We respectfully request that OEHHA:

1. Decline to adopt the NSRL of 11 µg/day based on the current proposal.

2. Re-evaluate study selection under the "*sufficient quality*" criterion of Title 27, California Code of Regulations, section 25703(a)(3), giving primary consideration to studies that provide the most robust and reliable basis for quantitative dose-response assessment. The latter include Umeda *et al.* (2004) and the studies of Bogdanffy and colleagues, which employed larger group sizes, more comprehensive dose characterization, and study designs consistent with contemporary carcinogenicity testing practices.

3. Reconsider reliance on the female F344 rat dataset from Experimental Pathology Laboratories (1982) and Lijinsky and Reuber (1983) as the basis for the proposed cancer potency estimate, given the study's limitations regarding dose characterization, pathology evaluation, and consistency with the broader vinyl acetate database.

4. Evaluate whether the extensive toxicokinetic, mechanistic, and mode-of-action evidence for vinyl acetate constitutes "*principles or assumptions scientifically more appropriate, based upon the available data*" within the meaning of section 25703(a), and whether those data support an approach other than the default linearized multistage extrapolation described in section 25703(a)(5).

5. Provide sensitivity analyses comparing cancer potency estimates and resulting NSRLs across alternative benchmark responses, including BMR_5 and BMR_{10}, together with a scientific rationale for the selected benchmark response level.

6. Evaluate NSRL derivations based on the portal-of-entry squamous-cell tumor data from Umeda *et al.* (2004), which are more closely aligned with the established mode of action of vinyl acetate and the predominant tumor response observed across the animal database.

7. Finalize the proposed section 25901 language clarifying that exposure assessments and analytical measurements should address residual vinyl acetate monomer under realistic consumer-use conditions and should not rely on monomer generated through artificial degradation of vinyl acetate-containing polymers under conditions not representative of consumer exposure.

A scientifically supported NSRL derived either from the portal-of-entry tumor data reported by Umeda *et al.* (2004) using conventional benchmark-dose methods or from an approach that incorporates the substantial mode-of-action and toxicokinetic evidence for vinyl acetate would likely be substantially higher than the proposed value of 11 µg/day. Such an NSRL would remain protective of public health while better reflecting the totality of the carcinogenicity, mechanistic, and exposure evidence available for vinyl acetate.

We appreciate the opportunity to provide these comments and would be pleased to provide any additional information, analyses, or supporting references that may assist OEHHA in its evaluation of the proposed NSRL and related regulatory provisions.

Respectfully submitted,



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References

Albertini RJ (2013). Vinyl acetate monomer (VAM) genotoxicity profile: Relevance for carcinogenicity. Critical Reviews in Toxicology 43(8): 671-706. https://doi.org/10.3109/10408444.2013.827151

Agency for Toxic Substances and Disease Registry (ATSDR) (2025). Toxicological Profile for Vinyl Acetate. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
American Chemistry Council (2023). Response to OEHHA Request for Relevant Information on the Carcinogenicity of Vinyl Acetate. September 18, 2023.

American Chemistry Council (2023). Response to OEHHA Request for Relevant Information on the Carcinogenicity of Vinyl Acetate. September 18, 2023.

Belpoggi F, Soffritti M, Minardi F, Ciliberti A, Padovani M, Cattin E, Maltoni C (2002). Results of a long-term carcinogenicity bioassay on vinyl acetate monomer in Wistar rats. European Journal of Oncology 7(4): 279-293.

Bogdanffy MS (2002). Vinyl acetate-induced intracellular acidification: Implications for risk assessment. Toxicological Sciences 66(2): 320-326.

Bogdanffy MS, Dreef-van der Meulen HC, Beems RB, Feron VJ, Cascieri TC, Tyler TR, Vinegar MB, Rickard RW (1994a). Chronic toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse. Fundamental and Applied Toxicology 23(2): 215-229.

Bogdanffy MS, Gladnick NL, Kegelman TP, Frame SR (1997). Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhalation Toxicology 9(4): 331-350.

Bogdanffy MS, Plowchalk DR, Sarangapani R, Starr TB, Andersen ME (2001). Mode-of-action-based dosimeters for interspecies extrapolation of vinyl acetate inhalation risk. Inhalation Toxicology 13(5): 377-396.

Bogdanffy MS, Sarangapani R, Kimbell JS, Frame SR, Plowchalk DR (1998). Analysis of vinyl acetate metabolism in rat and human nasal tissues by an *in vitro* gas uptake technique. Toxicological Sciences 46(2): 235-246.

Bogdanffy MS, Sarangapani R, Plowchalk DR, Jarabek AM, Andersen ME (1999). A biologically based risk assessment for vinyl acetate-induced cancer and noncancer inhalation toxicity. Toxicological Sciences 51(1): 19-35.

Bogdanffy MS, Taylor ML (1993). Kinetics of nasal carboxylesterase-mediated metabolism of vinyl acetate. Drug Metabolism and Disposition 21(6): 1107-1111.

Bogdanffy MS, Tyler TR, Vinegar MB, Rickard RW, Carpanini FMB, Cascieri TC (1994b). Chronic toxicity and oncogenicity study with vinyl acetate in the rat: *in utero* exposure in drinking water. Fundamental and Applied Toxicology 23(2): 206-214.

Bogdanffy MS, Valentine R (2003). Differentiating between local cytotoxicity, mitogenesis, and genotoxicity in carcinogen risk assessments: The case of vinyl acetate. Toxicology Letters 140-141: 83-98.

Budinsky R, Gollapudi B, Albertini RJ, Valentine R, Stavanja M, Teeguarden J, Fensterheim R, Rickard D, Lardie T, McFadden L, Green A, Recio L (2013). Nonlinear responses for chromosome and gene level effects induced by vinyl acetate monomer and its metabolite, acetaldehyde in TK6 cells. Environmental and Molecular Mutagenesis 54(9): 755-768.

European Food Safety Authority (EFSA) (2010). Scientific Opinion on the safety of polyvinylpyrrolidone-vinyl acetate copolymer for use in food-contact applications. EFSA Journal.

European Food Safety Authority (EFSA) (2013). Scientific Opinion on the safety of polyvinyl alcohol-polyethylene glycol-*graft*-co-polymer as a food additive. EFSA Journal.

European Union Risk Assessment Report (EU RAR) (2008). Vinyl Acetate (CAS No. 108-05-4). Final Approved Version. European Chemicals Bureau, Luxembourg.

Experimental Pathology Laboratories (EPL) (1982). Bioassay of Vinyl Acetate in Fischer 344 Rats: Pathology Report Addendum, Associated Correspondence, and EPA Review Materials.

Health Canada (2008). Screening Assessment for the Challenge: Acetic Acid Ethenyl Ester (Vinyl Acetate Monomer). Environment Canada and Health Canada. November 2008.

Hinderliter PM, Thrall KD, Corley RA, Bloemen LJ, Bogdanffy MS (2005). Validation of a human physiologically based pharmacokinetic model for vinyl acetate against human nasal dosimetry data. Toxicological Sciences 85(1): 460-467.

International Agency for Research on Cancer (IARC) (1995). Vinyl Acetate. **In:** IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 63. Lyon, France.

Kirman CR, Dekan W, Dellarco VL, Dourson ML, Klaunig JE, Simon TW, Hays SM (2026). Consideration of Carcinogenicity and Mode of Action Information by an Independent Expert Panel to Support Derivation of No-Significant-Risk-Level Values for Vinyl Acetate Monomer. Independent Expert Panel Report.

Japan Bioassay Research Center (JBRC) (1995). Report on Carcinogenicity Studies on Vinyl Acetate Orally Administered (Mixed in Drinking Water) to Rats and Mice.

Kuykendall JR, Taylor ML, Bogdanffy MS (1993). Cytotoxicity and DNA-protein crosslink formation in rat nasal tissues exposed to vinyl acetate are carboxylesterase-mediated. Toxicology and Applied Pharmacology 123(2): 283-292.

Lantz RC, Orozco J, Bogdanffy MS (2003). Vinyl acetate decreases intracellular pH in rat nasal epithelial cells. Toxicological Sciences 75(2): 423-431.

Lijinsky W, Reuber MD (1983). Chronic toxicity studies of vinyl acetate in Fischer rats. Toxicology and Applied Pharmacology 68(1): $43^{-5}3$.

Maltoni C, Ciliberti A, Lefemine G, Soffritti M (1997). Results of a long-term experimental study on the carcinogenicity of vinyl acetate monomer in mice. Annals of the New York Academy of Sciences 837: 209-238.

Minardi F, Belpoggi F, Soffritti M, Ciliberti A, Lauriola M, Cattin E, Maltoni C (2002). Results of a long-term carcinogenicity bioassay on vinyl acetate monomer in Sprague-Dawley rats. Annals of the New York Academy of Sciences 982: 106-122.

Nakamoto T, Wagner M, Melvin JE, Bogdanffy MS (2005). Vinyl acetate induces intracellular acidification in mouse oral buccal epithelial cells. Toxicology Letters 158(2): 116-121.

Office of Environmental Health Hazard Assessment (OEHHA) (2024). Evidence on the Carcinogenicity of Vinyl Acetate. Reproductive and Cancer Hazard Assessment Branch, California Environmental Protection Agency.

Office of Environmental Health Hazard Assessment (OEHHA) (2026). Proposed Proposition 65 “No Significant Risk Level” (NSRL) for Vinyl Acetate. Public workshop slides (September 30, 2026) and pre-regulatory discussion draft.

Plowchalk DR, Andersen ME, Bogdanffy MS (1997). Physiologically based modeling of vinyl acetate uptake, metabolism, and intracellular pH changes in the rat nasal cavity. Toxicology and Applied Pharmacology 142(2): 386-400.

Scientific Committee on Health and Environmental Risks (SCHER) (2008). Opinion on the Risk Assessment Report on Vinyl Acetate, Human Health Part. European Commission, adopted November 17, 2008.

Umeda Y, Matsumoto M, Yamazaki K, Ohnishi M, Arito H, Nagano K, Yamamoto S, Matsushima T (2004). Carcinogenicity and chronic toxicity in mice and rats administered vinyl acetate monomer in drinking water. Journal of Occupational Health 46(2): 87-99.

U.S. Environmental Protection Agency (EPA) (2012). Benchmark Dose Technical Guidance. EPA/100/R-12/001.

U.S. Environmental Protection Agency (EPA). Integrated Risk Information System (IRIS): Vinyl Acetate (CASRN 108-05-4).

Vinyl Acetate Council (VAC) (2023). Response to OEHHA Request for Relevant Information on Vinyl Acetate Monomer. September 18, 2023.

Vinyl Acetate Council (VAC) (2024). Comments on CIC and OEHHA Proposition 65 Assessment of Vinyl Acetate. November 18, 2024.