VINYL ACETATE COUNCIL

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Review of Pre-regulatory Draft No Significant Risk Level for
Vinyl Acetate Monomer under Proposition 65
October 21, 2026

I. Introduction

The Vinyl Acetate Council (VAC)[1] is pleased to provide the following comments to the Office of Environmental Health Hazard Assessment (OEHHA) regarding its pre-regulatory draft No Significant Risk Level ('draft NSRL') for vinyl acetate monomer (VAM; CAS 108-05-4) under the Safe Drinking Water and Toxic Enforcement Act of 1986 or Proposition (Prop) 65.

VAC represents manufacturers of VAM and vinyl acetate-based polymers and products. VAM is used as a monomer in the manufacture of various polymers and copolymers that have a wide variety of industrial and commercial applications. Many of the products produced using VAM-based polymers and copolymers support environmental initiatives in California, such as reducing VOCs in coatings and consumer products through the development of water-based applications. The monomer, VAM, is tightly controlled during its handling and use to avoid the potential for fires, uncontrolled polymerization, release and exposure. There is no direct consumer or public use of VAM. The VAC and its members provide guidance on the safe handling and use of VAM including publishing a Vinyl Acetate Safe Handling Guide (https://www.vinylacetate.org/safe-handling-guide).

The VAC and its members have a long history of product stewardship and research on VAM, sponsoring dozens of studies, commissioning independent reviews, and publishing numerous papers in the peer-reviewed literature. After VAM was listed on Prop 65, the VAC commissioned a triple-blinded expert panel to review the toxicology and related research on vinyl acetate monomer and derive an NSRL. The panel independently decided to derive two separate NSRLs for VAM, one for oral exposure (110,000 µg/day) and one for inhalation exposure (20,000 µg/day). This expert panel review was published earlier this year as Kirman et al. (2026). The VAC believes that the expert panel's review is more comprehensive than OEHHA's since it considered all of the available cancer studies and associated data sets and thus the NSRLs derived by the expert panel are more representative of the best available science on the cancer risk of VAM than the draft NSRL presented by OEHHA.

To further inform OEHHA's NSRL derivation, the VAC also just commissioned these same experts to provide their assessment of the available VAM cancer studies to use in deriving NSRLs. A detailed analysis of the panelists study reviews is attached and summarized below. The VAC believes that, based on the judgement of these experts, OEHHA has errored in using the Lijinsky and Reuber (1983) study for deriving the draft NSRL.

[1] The members of the Vinyl Acetate Council are the Celanese Corporation, The Dow Chemical Company, Kuraray America, Inc. and LyondellBasell Acetyls, LLC.

The VAC also believes that OEHHA has not adequately justified the decision to use a drinking water study to derive an NSRL for all routes of exposure. Based upon mode of action considerations and VAM's observed effects at the point of contact, a key conclusion from the expert panel was that an inhalation study was the most appropriate study for establishing an NSRL for inhalation exposure.

II. Study Selection for NSRL Derivation

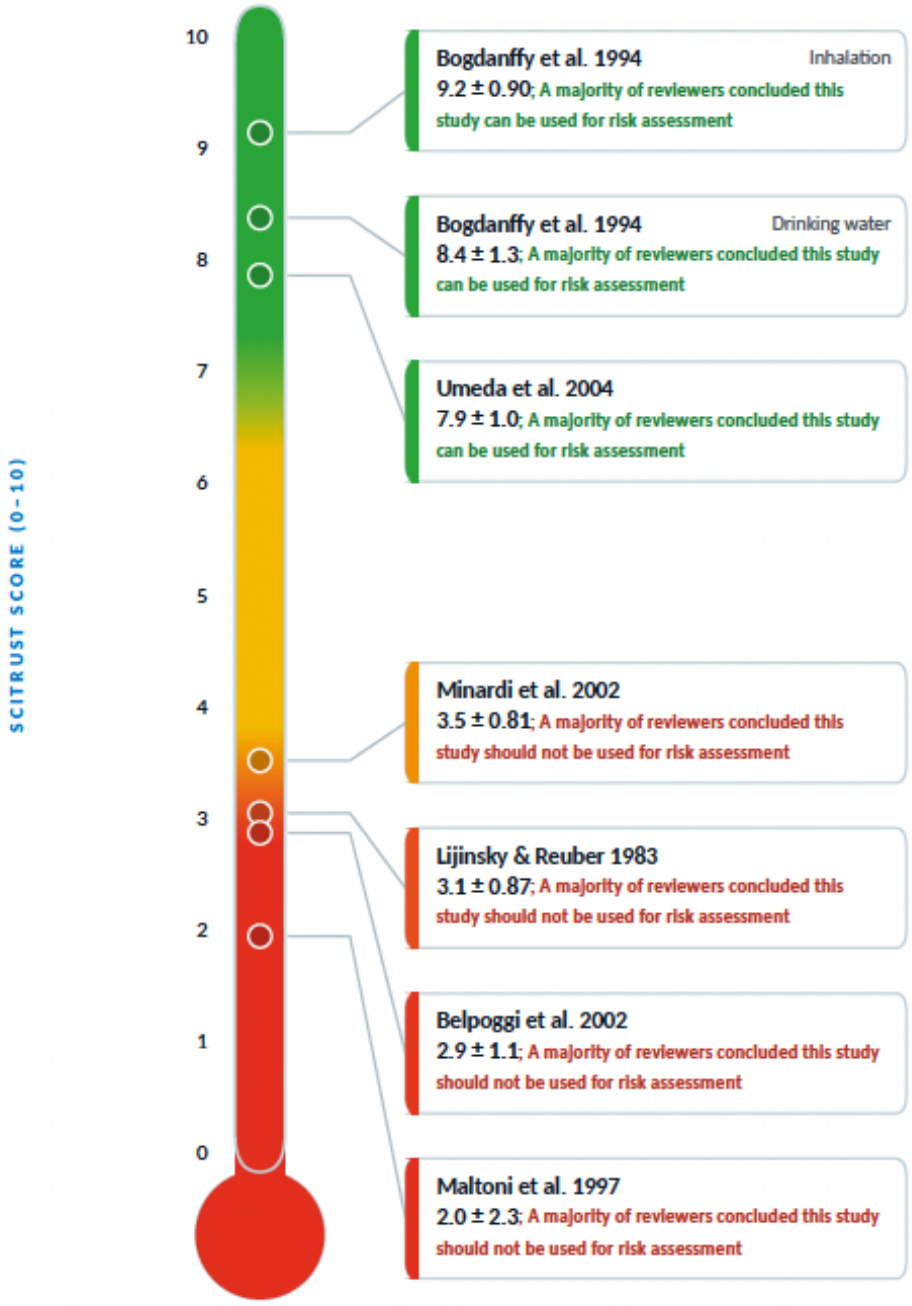
Expert Panel Review of Available Cancer Studies

As OEHHA is aware, there are 9 carcinogenicity studies of vinyl acetate monomer (VAM) in animals; 6 in the rat and 3 in mice. Seven of these studies were administered via drinking water and two are inhalation studies. These 9 studies are presented in 7 publications: Belpoggi et al., 2002; Bogdanffy et al., 1994a, (inhalation); Bogdanffy et al. 1994b (drinking water); Lijinsky and Reuber, 1983; Maltoni et al. 1997; Minardi et al., 2002; Umeda et al., 2004. Given these available studies, the VAC was surprised at OEHHA's focus on 3 rat drinking water studies in the draft NSRL document. While the draft NSRL document asserts that the selected studies are of "sufficient quality" under section 25703(a)(4), it does not document or evaluate the quality of these studies nor does it compare the relative strength and weaknesses of each cancer study in the VAM database.

In order to provide a systematic evaluation of these carcinogenicity studies, the VAC has commissioned an independent review of the quality and reliability of all VAM cancer studies. Given their familiarity with the VAM database, the same independent experts used in the expert panel review (Kirman et al., 2026) were asked to review and score these studies. The full assessment is provided in Attachment 1 and key conclusions are summarized below.

The panel independently scored each publications on a 0–10 scale across three components (Methods, Results, and Discussion/Conclusions) from which an overall score was calculated. The results, expressed as mean ± standard deviation with n denoting the number of panelists scoring each study (panelists were randomly assigned 4 specific publications, and were permitted to review additional publications as their time permitted; for this reason n varies across studies), were as follows: Bogdanffy et al. (1994a; inhalation), 9.2 ± 0.90 (n = 4); Bogdanffy et al. (1994b; drinking water), 8.4 ± 1.3 (n = 5); Umeda et al. (2004; drinking water), 7.9 ± 1.0 (n = 4); Minardi et al. (2002; drinking water), 3.5 ± 0.81 (n = 5); Lijinsky and Reuber (1983; drinking water), 3.1 ± 0.87 (n = 3); Belpoggi et al. (2002; drinking water), 2.9 ± 1.1 (n = 4); and Maltoni et al. (1997; drinking water), 2.0 ± 2.3 (n = 4) (**Figure 1; Attachment 1**). The three studies selected by OEHHA, Lijinsky and Reuber (1983), Belpoggi et al. (2002), and Maltoni et al. (1997), are the three lowest-scoring studies in the database (average score of 2.6 out of 10). As such, these studies fail to meet the "sufficient" quality standard required for their use in setting an NSRL for VAM. In contrast, the three highest-scoring studies in the VAM cancer database (Bogdanffy et al., 1994a,b; Umeda et al., 2004) (average score of 8.5 out of 10) are clearly of sufficient quality, but were not considered in OEHHA's draft NSRL.

Figure 1. Summary of SciTrust Scores for the Cancer Bioassays Conducted for Vinyl Acetate Monomer



The panel was unanimous in its favorable assessment of both Bogdanffy et al. (1994a,b) studies, with no dissenting views recorded. Cited strengths included the use of two species and both sexes,

adequate group sizes, multiple exposure concentrations plus concurrent controls, 104-week duration, interim sacrifices, thorough characterization of the test material including purity and stability verification, comprehensive pathology with independent review of the primary site, and appropriate statistical treatment including survival adjustment. Bogdanffy et al. (1994b) scored 8.4, with panelists specifically highlighting daily preparation of dosing solutions with five percent overformulation to offset decomposition, periodic verification of VAM stability in the drinking water, health screening and vaccination of study animals, and dose selection supported by evidence that the high dose represented an appropriate maximum tolerated dose. The panel agreed that the study was negative, with tumor rates in the highest dose group falling within the historical control range. Umeda et al. (2004), a GLP-compliant two-year drinking water study in both rats and mice with 50 animals per group, scored 7.9; one panelist noted that the increases in systemic tumor incidence observed in that study were neither dose-dependent nor statistically significant.

Lijinksy and Reuber Study is a Poor Choice for NSRL

The critical study selected for the draft NSRL (EPL, 1982; Lijinsky and Reuber, 1983) is a pre-GLP chronic toxicity study evaluating only 20 animals per group, 2 dose groups, conducting incomplete tissue examinations, mislabeled pathology slides, mishandling pathology samples resulting in incomplete pathology assessments, inadequate drinking water formulation preparation, and no measured body weight or water consumption data. As such, it is one of the weakest studies in the available database for a quantitative potency estimate. Some of the noted concerns with this study are:

- Drinking water formulations were only prepared weekly as opposed to daily in the higher quality study of Bogdanffy et al., 1994b and twice per week in the higher quality study of Umeda et al. (2004). This is a significant concern for drinking water study reliability, as VAM could hydrolyze or volatilize from the formulation. Per study authors, test article instability was high (8.5% decomposition rate/day at room temperature storage; 5% when refrigerated), with estimations that animals received half the nominal dose, which further leads to questions as to what potential mixture of degradants or even polymerized forms of vinyl acetate the animals may have been exposed.

- Animals were examined only after natural death.

- Inconsistent survival pattern of the controls compares to dosed animals (i.e., twice the number of dosed females made it to Week 130 than control females). This could have a significant impact on the statistical analysis, particularly since spontaneous tumorigenesis is known to increase with age in laboratory animals (Bode 1985).

- The numbers reported in Table 1 of the pre-regulatory draft and Table 11of HID are not consistent with the number examined tissues in EPL 1982. For example, Table 1 notes that 5 out of 20 top dose females were reported to have c-cell adenomas in the thyroid; however, EPL reports that only 2 thyroid samples were available from 20 top dose females. Thus it

appears that the results reported in Table 1 of the draft NSRL and Table 11 of the HID are taken directly from Table 2 of Lijinsky and Reuber 1983. At a minimum these tables are mislabeled by indicating EPL 1982 as a reference. However, the far larger issue here is the extremely poor preservation of the tissue samples in this study. EPL 1982 notes this problem specifically when it states that the "tissues [preserved for examination] were less consistently present for all groups of treated male and female rats." The many tissues missing from the data set across a large percentage of study animals represent clear and serious errors in sample identification, disposition, and chain of custody and further call into question the reliability of the pathology conclusions made on this study. If conducted during the time of GLP, these errors would have been considered serious GLP violations and likely invalidated the study.

- The wrong species (mouse) was found on some of the pathology slides reported by EPL 1982 as evidenced by the presence of a gall bladder and other anatomical indicators of mice. Again, this calls into question the overall reliability of the study as these pathology samples were supposed to be from a rat study.

The independent panel (**Attachment 1**) also noted the following issues with this study:

- Asked to identify the study's strengths, one panelist responded that its "sole strength is the authors' admission that the study was flawed." A second concluded that the study was "performed according to standards in the late 1970s with limited resources" and "can only be used as descriptive." A third credited only that "it appears to be the first attempt to look at the chronic effects of VAM in rodents," adding that NCI studies of that period "frequently … shared control animals with other chronic studies which compounds interpretation of the results."

- On the characterization of dose — the parameter on which the entire potency calculation depends — one panelist concluded: "Limited description of stability of VAM in water, composition and contaminants not given, replacement of solutions did not account for kinetics of decomposition. Animals likely exposed to substantial amounts of decomposition products. Drinking water intake not determined, dose received cannot be determined. Estimated doses stated in manuscript do not make sense." A second panelist recorded that "body weights of the rats were not measured" and that "ongoing water intake was not measured, only estimated." A third observed that the authors, "instead of actually measuring the concentration of VAM in the water," merely "believed each animal received at least half the administered dose." These observations are significant because OEHHA did not take the administered dose for this study from the study record; it reconstructed it. The pre-regulatory draft states that body weight "was calculated based on the author's report of the lifetime intake of vinyl acetate," and that default water consumption values from Gold and Zeiger (1997) were used because none of the selected studies reported water consumption. An independent expert has concluded that the dose received "cannot be determined" and that the manuscript's estimated doses "do not make sense."

- The panelists were also uniform on group size and the absence of statistical analysis. One characterized the number of animals per group as "low, << in guidance"; a second stated that "20 per dose group—too small"; and a third listed as the first weakness that "the experimental design included only 20 rats per group." On statistics, panelists recorded that "No statistical analysis was performed on any of the results" and that there were "No statistics at all." Every p-value and trend test appearing in Table 1 of the pre-regulatory draft was therefore generated by OEHHA, not by the study authors.

- On the dosing regimen, one panelist noted that "the dose selection was poorly described and not adequate," that "because of inadequate resources preliminary dose range finding studies were not performed," and that "treatment was for 5 days on and 2 days off. No explanation for the interruption in treatment was provided. Since this was a drinking water study, it is not clear why treatment was not continuously for 7 days."

- In the initial panel engagement (Kirman et al., 2026), a panelist also noted that Lijinsky and Reuber (1983) cannot support dose-response analysis at all, observing that "the study design precluded any dose-response analysis" and that "one of the Bradford-Hill considerations is a biological gradient that was not possible in this study."

- Finally, two panelists independently observed that the study authors themselves called for better work, noting that the "only solid conclusion is that a better study be conducted" and that the "authors suggest performing another study with adequate numbers and improved study design." That the original investigators regarded their own study as preliminary is a substantial argument against building a safe harbor level upon it four decades later. As noted above, better studies (Bogdanffy et al., 1994a,b; Umeda et al., 2004) have been conducted after Linjinsky and Reuber (1983) was published.

- The panel independently identified a fundamental problem with the pathology underlying this study. One panelist, expressly flagging the item as "IMPORTANT," reported a direct conflict between the published manuscript and the EPL (1982) pathology report prepared on the same tissues. The panelist wrote that there "appears to be a disconnect between the reported increase in treatment related tumors reported in this manuscript and the pathology report by EPL (1982) of the tissues from this study," and quoted the EPL report as stating: "A variety of neoplastic and nonneoplastic lesions were present in male and female control rats and in rats treated with Vinyl Acetate. The incidence of neoplastic nodules of the liver in male and female rats and neoplasms of the uterus in female rats was greater in treated groups when compared with control groups. NO treatment-related differences in the incidence, distribution and severity of other lesions were observed among control and treated groups. These lesions had a similar incidence and distribution of those known to occur spontaneously in untreated Fischer 344 rats of similar age."

- The panelist concluded that, "in contrast to that reported in the manuscript, the EPL pathology report found no increase in thyroid tumors with treatment," while the EPL evaluation did identify "treatment related neoplastic nodules (probably liver adenomas using today's criteria) in both male and female treated rats." Uterine tumors were confirmed in both evaluations. The panelist characterized these "discrepancies in histopathology evaluations" as "disconcerting." A second panelist independently noted that "a companion analysis by EPL labs failed to show thyroid tumor, leading [to] concerns about the completeness and interpretation of the pathology reported in the manuscript."

Ramazzini Institute Studies Should Not Be Considered for NSRL Derivation

The VAC also would like to reiterate its concerns regarding the studies conducted by the Ramazzini Institute (Minardi 2002, Belpoggi 2002, and Maltoni 1997). The Ramazzini Institute has been specifically identified by EPA as having poor study conditions, unreliable quality, and that its studies are not suitable for regulatory review (EPA 2010). Moreover, carcinogenicity studies conducted at the Ramazzini Institute have been repeatedly questioned regarding their interpretation, in addition to recurring chronic infections, which limits the credibility and reliability of these three studies (NTP 2011, Haighton 2019). These studies also employed the unusual practice of exposing animals until natural death, rather than a set period of time for all animals on study. Such study designs are flawed as it relates to high background incidence of spontaneous tumors and challenges with study interpretation (Hayes et al., 2011, Haighton 2019). As noted above, the independent panel assigned these studies low scores (2.0-3.5 out of 10) and therefore they are not of sufficient quality to support an NSRL for VAM.

Dose Equivalence Considerations Do Not Support Study Selected for Draft NSRL

When equivalent doses of VAM (~297 mg/kg) were administered to rats (same strain, sex, number) via inhalation and oral routes of administration, equivalent absorption, distribution and excretion was observed (Strong 1980; EPA 1989). Despite these findings, sensitivity of rats to systemic tumor formation via both routes was shown to be unique, per OEHHA's HID document, in that systemic tumors were observed in rats (F344; Lijinsky and Reuber 1983) dosed chronically via the oral route at 57 mg/kg/day, yet rats (Sprague Dawley; Bogdanffy et al., 1994b) dosed chronically via inhalation up to 371 mg/kg did not exhibit a systemic tumor, despite the same tissues being histologically examined. As a result, three interpretations are possible:

1. There are major strain differences in vinyl acetate sensitivity to systemic tumor elicitation, regarding specific routes of administration (i.e., Oral F334 > inhalation Sprague Dawley), for reasons unknown.
2. The tumors observed in the Lijinsky and Reuber study are not test article related and/or were misidentified.
3. The inhalation route leads to reduced sensitivity of rodents to systemic tumor elicitation.

The VAC is unaware of any scientific evidence suggesting interpretation #1 is valid. Assuming interpretations 2 and/or 3 are believed to be the most scientifically justified, then another oral study should be relied on for the oral NSRL and a separate inhalation NSRL should be developed for

VAM to address exclusively the risk of developing inhalation portal-of-entry nasal tumors.

III. Approach to NSRL Derivation

The draft acknowledges the mechanistic database for VAM but does not use it in the draft NSRL derivation. A default low-dose linear multistage model is applied despite a significant weight of evidence that supports a cytotoxicity-driven, threshold MOA (Kirman et al., 2026). Furthermore, the multisite cancer potency model used in the draft NSRL combines tumor types that are benign, high-background, age-related, non-monotonic, or without a human anatomical counterpart and of questionable relevance to human health. There are also internal numerical and statistical-notation inconsistencies in the draft NSRL that should be corrected.

A principal reason for this disconnect appears to be the analytical framework adopted in the hazard identification (HID) document (OEHHA 2024). Two panelists (Kirman 2026) independently observed that OEHHA (2024) evaluated mode of action using the key characteristics of carcinogens (KCC) rather than a causal mode-of-action analysis. One panelist noted that "OEHHA appears to be using the IARC KCCs for its evaluation of VAM's potential mode of action rather than EPA (2005) guidance." A second elaborated that the KCC approach, as applied, "functioned more as a compilation of biological events than a detailed causal analysis linking those events to cancer outcomes," and coupled this concern with "the reliance on drinking-water studies that had notable limitations." The key characteristics approach is a hazard identification tool. It catalogues properties a carcinogen may exhibit, but it does not establish the causal sequence of key events, or their dose-dependence, that a dose-response decision requires. A framework that compiles evidence of genotoxic potential without testing whether genotoxicity drives tumor formation will tend to support a default linear model regardless of what the mechanistic data show. A third panelist concluded that "the focus of the OEHHA document on mutagenicity appears misplaced," citing the Albertini et al. (2013) findings discussed in the Genotoxicity Considerations section below, including the absence of any reported gene or chromosome level mutations at VAM or acetaldehyde concentrations below 50 mM. A fourth panelist agreed that OEHHA's "focus on mutagenicity is not in line with the results obtained with VAM."

Several of the tumors should not contribute to a quantitative potency estimate at all:

- Hepatocellular adenoma is a benign lesion, and no hepatocellular carcinomas were reported.
- Uterine endometrial stromal polyps are benign proliferative lesions common in aging rats, and are of questionable relevance to humans (Davis, 2012).
- Thyroid C-cell adenoma, in addition to being inconsistently reported (EPL, 1982; Lijinsky et al., 1983), is benign with a substantial spontaneous background in F344 rats.
- Pituitary adenoma is among the most common spontaneous neoplasms in aged F344 rats, with a control incidence in the critical study of 6/17, or 35 percent, and was significant only by trend test.

- Pancreatic exocrine adenoma in male Wistar rats shows incidences of 6/86, 14/64 and 4/82, elevated at the low dose, below control at the high dose, with a trend reported as not significant, and is therefore not dose-related.
- Forestomach tumors and Zymbal's gland carcinoma have no human anatomical counterpart; four of five panelists concluded that each should not be used in human health risk assessment. Uterine adenocarcinoma, the one lesion the draft characterizes as rare, was not statistically significant by pairwise comparison with controls at either dose (0/18, 1/20, 4/20), and is significant only by trend.
- Lastly, the systemic tumors reported in the low quality study of Lijinsky and Reuber (1983) were not confirmed in the higher quality studies (Bogdanffy et al., 1994a,b; Umeda et al., 2004) conducted at a later time under GLP conditions.

In the initial panel engagement (Kirman et al., 2026), panelists were asked to indicate, for each systemic tumor site reported in the VAM database, whether the data should be used quantitatively to estimate potency, qualitatively only for cancer classification, or not at all. Across the eleven systemic target tissues presented — mammary gland, uterus, pancreas, lung, pituitary, thyroid, liver, adrenal, testes, lymphoma/leukemia and Zymbal's gland, no panelist endorsed quantitative use of any site. The panel's tissue-specific observations correspond closely to the concerns identified above. On the liver finding, one panelist noted that "a statistically significant increase in benign liver tumors was reported in one rat study, limited to females at the highest dose tested (Lijinsky and Reuber 1983), but not in other chronic rat or mouse studies." On thyroid C-cell tumors, the same panelist observed that "the Lijinsky and Reuber study is unreliable due to the sample size, a commercial product was used without rigorous purification, and the authors provide no historical control data," and that "the concurrent control incidence also appears low, at or below the lower end of the expected background for C-cell thyroid tumors in F344 females." On the pituitary finding, the panelist recorded that "a benign pituitary tumor response was reported in females only and in one rat (Fischer 344) study (Lijinsky and Reuber), but did not reach statistical significance," noting that "pituitary tumors are common spontaneous neoplasms in Fischer 344 rats." On the uterine findings in that same study, the panelist observed that "the adenocarcinoma incidences did not reach statistical significance, and endometrial stromal polyps are generally considered benign in rodents, with malignant progression being very uncommon." On Zymbal's gland, the panelist noted that it "is unique to rodents (i.e., without a human counterpart), and limits the ability to quantitatively extrapolate findings to humans." A second panelist addressed the statistical basis of these findings directly, noting that the "EPL 1982; Lijinsky and Reuber 1983 data from Table 11 of OEHHA is not SS [statistically significant] with a Fisher's exact test," and that "thus, the findings appear to be spurious." The same panelist observed that "several of these tumors are only 'significant' with a trend test, which is the weakest tool available," and that if OEHHA relies upon the trend test, it "needs to determine whether any negative trend tests were also found and then compare these two findings."

The internal numerical and statistical-notation inconsistencies include the following. First, the narrative text gives the lifetime average daily doses for male F1 Wistar rats as 0, 64.16 and 320.82 mg/kg-day, while Table 5 gives 0, 48.00 and 240.02 mg/kg-day for the same animals, a 34 percent

discrepancy. Applying OEHHA's own equation with its Table 4 parameters (1000 mg/L × 25 mL/day ÷ (1000 mL/L × 0.5208 kg)) yields 48.00, confirming Table 5; the text value of 64.16 corresponds instead to the female parameters (20 mL/day ÷ 0.3117 kg = 64.17), indicating that the male narrative values were computed using female inputs. Second, for male F1 Swiss mice, the Table 4 body weight of 0.0431 kg and water consumption of 5 mL/day yield 116.0 mg/kg-day, whereas Table 5 reports 114.42, implying a body weight of 0.0437 kg; the corresponding female calculation (5 ÷ 0.0387 = 129.2) reproduces Table 5 exactly. Third, Tables 1 and 2 define a double asterisk as "$p < 0.1$", which likely should be "$p < 0.01$" to match Table 3 and remain consistent with a conventional significance criterion of 0.05.

VAM Tumorigenesis is Site-of-First-Contact

Multiple expert reviews (Kirman 2026, ECHA 2011, Canada 2008) have concluded that VAM tumorigenesis characteristics are best described as site-of-first-contact and not systemic. ECHA RAC noted that in both oral and inhalations studies, tumors were most consistently related to site of first contact, depending on the route of administration, and the low occurrence of systemic tumors is attributed to the limited bioavailability of VAM and its metabolites (ECHA 2011). Health Canada stated that VAM is not a systemic carcinogen (Health Canada 2008), as did Albertini 2013. All five of the independent panelists (Kirman et al. 2026) supported the use of point of contact tumors (nasal for inhalation; oral cavity for oral) using the high quality studies as the more reliable and useful basis for human health risk assessment, while the systemic tumor data from low quality studies are not suitable for quantitative risk assessment of VAM. The panel's rationale rested on VAM's rapid hydrolysis at the site of contact, with half-lives measured in seconds to minutes, such that systemic distribution and any associated cytotoxicity are expected only where enzymatic detoxification is saturated at very high administered doses. The data set chosen to establish the draft NSRL is inconsistent both with the mode of action the draft itself describes and with the endpoint basis OEHHA applied to acetaldehyde, as discussed in Section IV below.

The panel's position on systemic tumors was reached independently by each member and converged over the course of the review (Kirman 2026). After the first round, one panelist summarized the position as follows: "[b]ased on the ratings, there appears to be agreement that the reported systemic tumors should not be used for quantification," adding that "I agree with Reviewers 4 and 2 that none of the systemic tumors should be used for hazard characterization/classification." The same panelist later observed that "I think we are all in agreement regarding the systemic tumors." A second panelist concurred, stating: "I agree with the comments from 1, 2 and 3. These should be captured and included in the discussion for not considering the systemic tumors as VAM related." The panel's rationale rested on VAM's toxicokinetics. One panelist explained that "VAM is rapidly hydrolyzed and therefore unlikely to reach systemic organs unless enzymatic hydrolysis is saturated at very high doses," that the "same is true for pH changes due to proton release," and that "acetaldehyde is also rapidly detoxified." That panelist concluded that "a non-linear dose response is expected and tumors seen at high doses of VAM have little relevance for risk characterization of low dose human exposures." Another panelist stated that "exposure to VAM is greatest at the site of initial contact because of its rapid

and extensive local metabolism, which limits systemic distribution," and that "consequently, the most reliable evidence and primary targets of VAM-induced carcinogenesis occur at the portal of entry rather than at distant sites." That panelist further found that "the available data do not convincingly demonstrate that VAM acts as a systemic multi-site carcinogen when administered orally," noting that "Bogdanffy et al [1994a,b] did not find evidence of systemic tumors in their drinking water (DW) or inhalation bioassays," and that where systemic tumors have been reported in the other drinking water studies the evidence "is weak and not compelling" because such tumors "generally occurred only at very high doses, often as isolated findings," with high background incidence for some sites and "no consistent pattern across different rodent studies or strains." A further panelist noted that "none of these tumors are based on a mutagenic MOA, so any dose response assessment based on these tumors has a threshold."

Regulatory Assessments Conclude VAM Tumorigenesis Exhibit a Threshold Mode of Action

All recent regulatory assessments of VAM have concluded that it exhibits a non-linear, threshold, mode of action. ATSDR stated that mechanistic details and toxicological data indicate that VAM-induced nasal tumor formation from inhalation exposure is a threshold effect and suggested it also applied to tumors elicited via the oral route (ATSDR 2025). ECHA RAC also concluded VAM exhibited a secondary mechanism of carcinogenicity, acknowledgment that a threshold effect is associated with the observed genotoxicity and carcinogenicity, along with the fact that irritation accompanying development of nasal tumors will likely limit high VAM exposures and consequent tumor development after chronic exposure (ECHA 2011). Health Canada aligned with the ECHA RAC opinion when stating that a threshold exists for the carcinogenicity of VAM, following inhalation and oral dosing (Health Canada 2008). Health Canada also stated that the lack of consistency across the aforementioned assays fails to support a very strong weight of evidence for genotoxicity (Health Canada 2008).

The independent panel articulated the same mechanism in terms of its constituent key events. One panelist described the sequence as follows: "The primary mechanism causing cytotoxicity is the intracellular acidification due to the metabolic formation of acetic acid (i.e., accumulation of acetic acid leads to a drop in intracellular pH). The cytotoxicity triggers regenerative proliferation, and this proliferative response at the portal of entry (e.g., nasal cavity) eventually leads to tumor formation." The same panelist explained the dose-response consequence directly: "Tumor development occurs only when a biological threshold of tissue damage and sustained cell proliferation is exceeded. Accordingly, exposures below the established point of departure do not result in significant toxicity or carcinogenicity." On this basis the panel concluded that linear extrapolation of VAM's carcinogenic potential "is inappropriate given its well-characterized, threshold-based MOA."

Inhalation Studies of VAM Demonstrate Threshold Response

Chronic inhalation testing of VAM at 200 and 600 ppm produced a limited number of tumors in a 104-week rat inhalation study, primarily at 600 ppm (Bogdanffy 1994a). The tumors in the rat study included a combination of benign papillomas and carcinomas in the nasal cavity (n=12) at ≥ 200 ppm and a single carcinoma in the larynx at 600 ppm. According to ATSDR (Figure 1-3, Figure 2-2), the nasal tumor (squamous cell papilloma) observed in a single male rat at 200 ppm was not considered significant enough to influence the LOAEL designation; moreover, the tumor identified (benign exophytic papilloma) is not expected to advance to malignancy in humans (Vorasubin 2013, Xu 2024, Weindorf 2019). While the respiratory tumor findings were noted in both genders in the rat study, in a similarly designed study in mice, no tumors were observed (Bogdanffy et al. 1994a). Regarding this discrepancy, ECHA RAC stated that the insensitivity of mice to nasal tumors casts further doubt on the relevance of carcinogenic findings in the respiratory system (ECHA 2011). Not noted in the HID was the fact that interim sacrifices were conducted in the chronic rat inhalation study at 53 and 83 weeks and no tumors were observed, though there were signs of severe and chronic inflammation. These findings suggest that nasal tumors only occurred after prolonged inhalation exposure to highly irritating and cytotoxic levels. Further, supporting the determination that VAM tumorigenesis is both point-of-first-contact and a threshold response mechanism. It is worth noting how the independent panel (Kirman 2026) treated this endpoint, because the choice it made was the more conservative one available. Asked which endpoint should serve as the basis for an inhalation NSRL, all five panelists selected olfactory basal cell hyperplasia, a precursor lesion, rather than the nasal tumors themselves. The panel therefore selected an endpoint that occurs at lower exposures than the tumor response, and which consequently yields a lower and more health-protective NSRL than the tumor data would have produced.

Genotoxicity Considerations

In assessing genotoxicity, changes observed in whole mammal studies are considered more pertinent than *in vitro* methods (CIC 2001). In light of this policy, the VAC notes that the weight of evidence for *in vivo* studies suggests VAM is not genotoxic. As stated in the HID document, VAM was positive in numerous *in vitro* genotoxicity studies, including 8 sister chromatid exchange assays; an assay which was once detailed by an OECD guideline, yet was deleted in 2016 due to a lack of understanding of the mechanism(s) of action of the effect detected by the test (OECD 2017). However, *in vivo* studies showing positive effects were limited to 2 inhalation route studies (out of 7), 1 oral route study (out of 5; findings were within historical range [Gale 1979], which failed to repeat in a longer-term study [Gale 1980]) and 5 intraperitoneal route studies (out of 6). In the two inhalations studies showing effects (Liu 2021, Hsiao 2022), the observation of adducts represent DNA damage, not mutation, and therefore their progression to mutation is not inevitable, given the cell's ability to repair such lesions (Albertini 2013). In fact, there were significant levels of background acetaldehyde DNA adducts observed in non-exposed animals. Moreover, the promutagenic adduct (N2-propano-dG) was only observed in the nasal tissue at the highest concentration tested (400 ppm) in the acute dose study. As stated in Albertini 2013: *there*

is no convincing evidence that VAM or acetaldehyde induces systemic mutagenicity in vivo at non-lethal doses in normal Aldh proficient animals. Studies showing chromosome level mutations in vivo in normal mammals are restricted to those that administered VAM/acetaldehyde by non-physiological means and had associated unacceptable toxicities.

HID stated that metabolism of VAM only leads to slight intracellular acidification; however, according to ATSDR, the acidification is robust enough to cause cellular damage and subsequent proliferation (ATSDR 2023). ATSDR also mentioned how data indicate that metabolic formation of acetaldehyde alone, without intracellular acidification, is inadequate to induce tumor formation, which would suggest that a non-genotoxic mechanism of action could be contributing to VAM-induced tumor formation. Albertini 2013 went so far as to state that VAM's mode of action is not via an initial key event of mutation, but rather a series of events, when stating: *The MOA for VAM's site-of-contact carcinogenicity is proposed to be metabolism with saturation of acetaldehyde detoxification as the initial gatekeeper key event. A secondary key event in the most sensitive cell type is cell proliferation. Mutation then occurs.*

Since publication of the HID, the VAC is also aware that new *in vivo* genotoxicity studies were recently added to the EU REACH dossier for VAM. These studies include an *in vivo* mammalian alkaline comet assay (OECD TG 489) combined with an *in vivo* mammalian erythrocyte micronucleus test (OECD TG 474). In the OECD 489 study, VAM did not induce treatment-related increases in DNA strand breaks in the liver, stomach or duodenum when tested up to 1200 mg/kg/day (maximum tolerated dose). In the related OECD 474 study, VAM did not induce treatment-related increases in micronucleated polychromatic erythrocytes of the bone marrow when tested up to 1200 mg/kg/day (maximum tolerated dose). Detailed summaries of these studies can be found on the ECHA Chemical Database (https://chem.echa.europa.eu/).

The weight of evidence derived from these collective studies suggests that VAM is not a mutagenic carcinogen.

IV. Considerations of Metabolic link to acetaldehyde; Reality Check for the Draft Proposed NSRL

The HID and the draft NSRL document correctly note that acetaldehyde is a metabolite of VAM. However, the document does not mention the fact that acetaldehyde is a common metabolite of a wide range of dietary components including ethanol, glucose, and other foods (Kasai and Kawai 2021, Tagaino 2019). As Lees et al. (1978) notes, acetaldehyde is a common human metabolite that is "involved in the metabolism of carbohydrate, protein, lipid, nucleic acid, and aromatic compounds" See VAC November 2024 submission for more information regarding the human metabolic relationships for acetaldehyde.

FDA notes "a daily endogenous production of 360,000 µg/day of acetaldehyde was calculated based on a constant endogenous total acetaldehyde concentration in the blood of 2.2 ±1.1 µmol/L (Ref. 3) and acetaldehyde clearance of 0.95 L/min (Ref. 5). Average acetaldehyde consumption of

up to 48,000 µg/day comes from consumption of alcoholic beverages" https://www.fda.gov/media/157451/download). Thus endogenously produced acetaldehyde is 4000 times the existing NSRL for acetaldehyde and almost 33,000 times the proposed draft NSRL for VAM.

The formation of acetaldehyde DNA adducts from VAM exposure is also briefly mentioned in the draft NSRL, but its context is not properly explained. OEHHA fails to note that the research by Liu et al. (2021) and Hsiao et al. (2022) on the formation of acetaldehyde-mediated DNA adducts following inhalation of VAM shows that these DNA adducts are not significantly systemically distributed and the levels of exogenous DNA adducts are well below endogenous levels except at very high inhalation concentrations. For example, endogenous levels are only exceeded at exposure concentrations that produce significant irritation and ultimately elicited nasal tumors (≥ 200 ppm). At 10 ppm, exogenous DNA adducts were only 3 to 9% of endogenous adducts and there were no observed increases in exogenous adducts at < 10 ppm exposures. These data reinforce a threshold effect of VAM for inducing nasal tumors following inhalation exposure and, per the authors: *nonlinear dose response model should be employed when extrapolating results from high doses of exposure to human relevant concentrations*.

V. VAC Supports Inclusion of Section 25901

The VAC fully supports the inclusion of the proposed section 25901. This section provides an important clarification for suppliers/employers in considering whether a product actually contains VAM, as opposed to a polymer derived from VAM. The following suggestions are offered for strengthening the provision.

First, the section could state affirmatively, in addition to its present negative formulation, that acceptable methods are those that quantify free, unbound monomer in the product as sold or as used — for example, static headspace gas chromatography with mass spectrometric detection, under conditions that do not depolymerize the matrix. Second, the section could make explicit that VAM generated during sample preparation is an artifact of the analytical procedure and does not constitute factual information of exposure, which would close the inference that any detection is reportable regardless of its origin. Third, the section could require that submitted factual information identify the analytical method employed, including extraction conditions, temperature and pH, so that the Attorney General is able to evaluate whether the reported concentration reflects monomer actually present in the product. Fourth, the VAC agrees with OEHHA's observation that similar issues arise for other listed monomers used in unlisted polymers and encourages OEHHA to consider a provision of general applicability in due course.

VI. Summary

Given the significant reliability and quality issues identified with Lijinsky and Reuber (1983) and the Ramizzini Institute studies identified in the draft NSRL, the VAC recommends that OEHHA reconsider its draft NSRL to use the most reliable studies available in Bogdanffy et al. (1994a,b).

These are the highest quality, guideline-compliant, GLP bioassays available in the VAM cancer database. The VAC also recommends that OEHHA develop separate NSRLs for oral and inhalation based on the recommendations from expert panel review (Kirman et al. 2026).

The VAC would like to thank the OEHHA for considering these comments. Please contact Andrew Jaques, VAC Executive Director, at andrew@vinylacetate.org or (301) 461-9695 with any questions regarding VAM toxicology and risk assessment, including any of the referenced studies.

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