September 18, 2023

Carcinogen Identification Committee
Attention: Kiana Vaghefi
Office of Environmental Health Hazard Assessment
1001 I Street, 23rd Floor
Sacramento, California 95814

Submitted electronically at: *https://oehha.ca.gov/comments*

Re: Request for relevant information on the carcinogenicity of vinyl acetate

Dear Carcinogen Identification Committee:

The American Chemistry Council (ACC)[1] is pleased to respond to the request for information for vinyl acetate.

Please contact Jessica Ryman-Rasmussen at 202-249-6406 or jessica_ryman-rasmussen@americanchemistry.com if you have any questions about this submission.

Sincerely,

Karyn M. Schmidt
Senior Director, Regulatory & Scientific Affairs
American Chemistry Council
Karyn_Schmidt@americanchemistry.com

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the multibillion-dollar business of chemistry. ACC members apply the science of chemistry to make innovative products, technologies and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health, safety and security performance through Responsible Care®; common sense advocacy addressing major public policy issues; and health and environmental research and product testing. ACC members and chemistry companies are among the largest investors in research and development, and are advancing products, processes and technologies to address climate change, enhance air and water quality, and progress toward a more sustainable, circular economy.

Submission of the American Chemistry Council
Request for information for vinyl acetate
September 18, 2023

ACC has identified a 2023 Draft ATSDR Tox Profile and certain, relevant literature and information of which OEHHA and the CIC should be aware:

- ATSDR Draft Toxicological Profile for Vinyl Acetate;[2]
- Budinsky R, Gollapudi B, Albertini RJ, Valentine R, Stavanja M, Teeguarden J, Fensterheim R, Rick D, Lardie T, McFadden L, Green A, Recio L. Environ Mol Mutagen. 2013 Dec;54(9):755-68. doi: 10.1002/em.21809. Epub 2013 Aug 28. PMID: 24038327;
- EFSA Scientific Opinion on the safety of polyvinylpyrrolidone-vinyl acetate copolymer for the proposed uses as a food additive. EFSA Journal 2010;8(12):1948. Please note that although this Opinion is on polymers, EFSA does provide information related to the genotoxicity of vinyl acetate (please see #4 below);
- Hsiao YC, Liu CW, Hoffman G, Fang C, Lu K. Molecular Dosimetry of DNA Adducts in Rats Exposed to Vinyl Acetate Monomer. Toxicol Sci. 2022 Jan 24;185(2):197-207. doi: 10.1093/toxsci/kfab140. PMID: 34904679; PMCID: PMC8795904;
- Latvia (Evaluating Member State). SUBSTANCE EVALUATION CONCLUSION as required by REACH Article 48 and EVALUATION REPORT for Vinyl acetate EC No 203-545-4. CAS No 108-05-4. 1 October 2020. EC No 203-545-4;
- Liu CW, Hsiao YC, Hoffman G, Lu K. LC-MS/MS Analysis of the Formation and Loss of DNA Adducts in Rats Exposed to Vinyl Acetate Monomer through Inhalation. Chem Res Toxicol. 2021 Mar 15;34(3):793-803;
- Lu K, Hsiao YC, Liu CW, Schoeny R, Gentry R, Starr TB. A Review of Stable Isotope Labeling and Mass Spectrometry Methods to Distinguish Exogenous from Endogenous DNA Adducts and Improve Dose-Response Assessments. Chem Res Toxicol. 2022 Jan 17;35(1):7-29. doi: 10.1021/acs.chemrestox.1c00212. Epub 2021 Dec 15. PMID: 34910474.

Notably, the ATSDR Draft Tox Profile derived MRLs only for inhalation, and oral MRLs were not derived due to insufficient data:

- Oral MRLs (acute, sub-chronic (intermediate), and chronic) were not derived due to insufficient data.[3] This indicates that the oral database for vinyl acetate is insufficient to support regulatory actions for this route of exposure.
- Inhalation MRLs (acute, sub-chronic (intermediate), and chronic) were derived using nasal lesions in rodents as the critical effect.[4]

The ATSDR Draft Tox Profile indicates that vinyl acetate is a skin and eye irritant. It is therefore reasonable to assume that dermal exposure will be self-limiting in an occupational

[2] Draft Toxicological Profile for Vinyl Acetate. ATSDR. August 2023. https://www.atsdr.cdc.gov/ToxProfiles/tp59.pdf.
[3] Ibid. A-24 to A-26.
[4] Ibid. A-11 to A-14.

setting. Since there is no direct consumer use of vinyl acetate and only negligible consumer exposures to vinyl acetate residuals in vinyl acetate-derived polymers and co-polymers, consumer exposures to vinyl acetate are not a health concern.

The Draft Tox Profile cited occupational case reports of blisters or severe irritation but that not enough data was available to determine LOAELs or NOAELs for dermal effects in humans. The Draft Tox Profile noted that vinyl acetate liquid is a skin irritant in rabbits and that vinyl acetate vapor is an eye irritant in humans and rodents. Taken together, these data indicate that prolonged occupational exposures to high concentrations of vinyl acetate would be unlikely, because even relatively short exposures to vinyl acetate (on the order of minutes) at above 5 ppm concentrations are reported by ATSDR as irritating to the eyes in some individuals. As such, due to the reported skin and eye irritancy of vinyl chloride, it is reasonable to assume that dermal exposures would be self-limiting due to the use of PPE or the avoidance of exposure altogether.

For non-occupational (consumer) exposures, Latvia (as the Evaluating Member State for the October 2020 Substance Evaluation for vinyl acetate, page 13) determined:

> "Negligible consumer exposure to residual levels of vinyl acetate monomer present in adhesives and sealants, cosmetics and personal care products, air care products, fillers, putties, plasters, modelling clay and polymers."

The ATSDR Draft Tox Profile and this literature and information support the interpretation that neoplastic transformation only occurs in portal-of entry tissues (gastrointestinal and respiratory) and is a threshold-based effect. It occurs only in animals at high doses to which humans are not exposed. Neoplastic transformation is driven by cytotoxicity-related cell proliferation and not genotoxicity from acetaldehyde. As such, vinyl acetate exposures in the concentration ranges experienced by humans from all routes of human exposure are not likely to result in carcinogenicity and therefore vinyl acetate should not be listed for cancer under Prop 65.

The ATSDR Draft Tox Profile describes that the carcinogenic mechanism indicated by the available literature is a threshold-based mechanism whereby oral or inhalation exposure to portal-of-entry tissues (GI or respiratory tract) results in:

- Hydrolysis of vinyl acetate to acetic acid and acetaldehyde;
- Tissue acidification resulting in cytotoxicity;
- Regenerative and/or mitotic cell division;
- Mutagenesis (spontaneous and/or acetaldehyde-induced: acetaldehyde induced not considered sufficient for carcinogenesis);
- Neoplastic transformation.

The information below further supports the interpretation that neoplastic transformation is a threshold effect, that cell proliferation is more sensitive tha genotoxic effects, and that these effects of vinyl acetate are limited to portal-of-entry tissues:

- Budinsky R *et al.* 2013: Cytotoxicity observed before micronuclei formation *in vitro*;

- Hsiao YC *et al.* 2022: An elegant, *in vivo* isotopic labeling study via the inhalation route to discern endogenous from vinyl acetate-induced DNA adducts showed that no exogenous adducts were detected up to 1 ppm, that adducts increased non-linearly between 100 to 600 pm (indicative of a threshold), and that adducts were not detectable in distant, non-portal of entry tissues;
- The EFSA Scientific Opinion on the safety of polyvinylpyrrolidone-vinyl acetate copolymer for the proposed uses as a food additive cites the EU Risk Assessment Report on Vinyl Acetate regarding the genotoxic potential of vinyl acetate (excerpt below, Section 3.2.3.3):

3.2.3.3. Genotoxic potential of vinylacetate (VA)

There is an EU Risk Assessment Report on VA (EU RAR, 2008) in which the evaluation of mutagenicity is described as follows:

"*Vinyl acetate is not mutagenic to bacteria, but it induces chromosomal aberrations, gene mutations and SCE in several tests with mammalian cells from different sources in culture.*

Furthermore, at high concentrations the formation of DNA-protein-cross links and DNA-DNA-cross links is shown with mammalian cells. The in vivo genotoxicity of vinyl acetate appears to be limited to toxic doses thus it may be reasonable to assume a threshold mechanism of action for germ cell mutagenicity. Taking into account the exposure estimates resulting for a point source from a worst case calculation and from regional background concentrations it may be concluded that there is presently no concern regarding in vivo mutagenicity."

Based on these evaluations, the Panel considered that there is no concern with respect to genotoxicity of the monomers VP and VA from which the PVP/VA copolymer is derived for PVP/VA copolymer itself.

Due to differences in mechanism, it would not be scientifically justified to use IARC's 2008 mechanistic grouping of the vinyl halides and cancer classifications to read-across to vinyl acetate.

In 2008, IARC determined that vinyl chloride (Group1), vinyl fluoride (Group 2A), and vinyl bromide (Group 2A) acted through a similar mechanism.[5] The mechanism of the vinyl halides differs fundamentally from vinyl acetate with regard to metabolic activation (hepatic CYP2E1 Vs cellular esterases), target organ(s) (liver Vs. portal of entry tissues), and driver of cell proliferation (mutation of proto-oncogens/tumor suppressor genes Vs. cyctotoxicity). For these reasons, carcinogenicity data and associated classifications for the vinyl halides cannot be read across to vinyl acetate.

Although both ethanol and vinyl acetate are metabolized to acetaldehyde and alcoholic beverages and acetaldehyde are listed for cancer under Prop 65, it would not be scientifically justified to read across from acetaldehyde and/or alcoholic beverages to vinyl acetate. This is because neoplastic transformation and subsequent tumorigenesis are driven by cytotoxicity-related cell proliferation and not genotoxicity from acetaldehyde.

[5] *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* VOLUME 971,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide LYON, FRANCE 2008.

Acetaldehyde has been listed under Prop 65 for cancer since 1988 (on the basis of the State's Qualified Experts Mechanism[6]) with alcoholic beverages listed for cancer since 2011.[7] IARC last classified acetaldehyde as Group 2B in 1999[8] and classified alcohol consumption as Group 1 in 2010.[9] The 2010 IARC Monograph described several potential mechanisms for the carcinogenicity of alcoholic beverages that include DNA adducts resulting from acetaldehyde, free radical production, immunosuppression, alteration of hormone levels (in women), changes in the metabolism of endogenous and exogenous compounds, and changes in cell signaling.

- Read across from acetaldehyde to vinyl acetate to inform Prop 65 listing is not scientifically defensible. This is because neoplastic transformation and subsequent tumorigenesis are driven by cytotoxicity-related cell proliferation and not genotoxicity from acetaldehyde. In other words, acetaldehyde-induced mutagenesis is not considered sufficient for carcinogenicity. This is consistent with ATSDR 2023:

  > Additional data indicate that metabolic formation of acetaldehyde alone, without intracellular acidification, is inadequate to induce tumor formation.[10]

  The insufficiency of acetaldehyde alone is consistent with the homeostatic mechanisms (e.g., aldehyde dehydrogenases) to detoxify endogenous production of acetaldehyde, as well as exogenous acetaldehyde naturally found in foods and beverages (e.g., fruits and fruit juices) and other, exogenous sources.

- Likewise, read across from alcoholic beverages to vinyl acetate to inform Prop 65 listing is not scientifically defensible because neoplastic transformation and subsequent tumorigenesis are driven by cytotoxicity-related cell proliferation and not genotoxicity from acetaldehyde. Additionally, there are other potential mechanisms for alcoholic beverage carcinogenicity.

We note further that the Key Characteristics of Carcinogens have not been sufficiently vetted by the Carcinogen Identification Committee. On June 23, 2023, the Carcinogen Identification Committee (CIC) heard presentations from scientists on the use of the Key Characteristics of Carcinogens (KCCs) and their use in cancer hazard identification.

- One of the presenters to the CIC was a senior-level OEHHA employee.

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[6] https://oehha.ca.gov/proposition-65/chemicals/acetaldehyde
[7] CHEMICALS KNOWN TO THE STATE TO CAUSE CANCER OR REPRODUCTIVE TOXICITY. August 11, 2023. STATE OF CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986.
[8] IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS. VOLUME 71. WORLD HEALTH ORGANIZATION INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. 1999.
[9] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 96. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon (FR): International Agency for Research on Cancer; 2010.
[10] ATSDR 2023 page 75.

- There were no presentations from scientists who have published substantial criticisms of the use of the KCCs.[11,12, 13,14]
- There were no presentations from scientists who have published on good practice for use of KCCs.[15]
- The amount of time allowed for individual public commentors (there was only one, which was ACC) was comparatively negligible. ACC's oral and written comments (which are the same) at the June 23, 2023 meeting are incorporated here by reference.[16]
- Scientific presenters were provided the opportunity to rebut the public commentor, but the public commentor was not allowed to rebut the scientific presenters.
- The result was an unbalanced June 23, 2023 CIC hearing on the KCCs that did not fully reveal the limitations of KCCs for regulatory purposes.

It is thus clear that the key characteristics of carcinogens should not be used outside of an AOP or MOA framework to inform the carcinogenic potential of vinyl acetate. While vinyl acetate is tumorigenic at high exposure levels in animals, neoplastic transformation and subsequent tumor formation are threshold effects. Exposure levels must therefore be considered. Meek and Wickoff[16] have proposed good practice that assimilates KCCs into an integrated AOP and MOA pathway construct, essentially using KCCs as a means to identify Key Events. This is consistent with conclusions stated in Becker et al., "For incorporating mechanistic data into cancer hazard evaluations, we specifically recommend adoption of the AOP (OECD, 2016) or MOA framework (Meek et al., 2014) that articulates toxicity pathways comprised of sequences of key events, starting with an initial molecular event, followed by a series of key events linked to one another, ultimately resulting in a specific adverse outcome (Meek et al., 2013, Meek et al., 2014)."

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Thank you for the opportunity to provide information responding to this request. Inquiries about these comments may be directed to Jessica Ryman-Rasmussen at 202-249-6406 or jessica_ryman-rasmussen@americanchemistry.com.

[11] Bus JS. IARC use of oxidative stress as key mode of action characteristic for facilitating cancer classification: Glyphosate case example illustrating a lack of robustness in interpretative implementation. Regul Toxicol Pharmacol. 2017 Jun;86:157-166. doi: 10.1016/j.yrtph.2017.03.004. Epub 2017 Mar 6. PMID: 28274811.
[12] Goodman J, Lynch H. Improving the International Agency for Research on Cancer's consideration of mechanistic evidence. Toxicol Appl Pharmacol. 2017 Mar 15;319:39-46. doi: 10.1016/j.taap.2017.01.020. Epub 2017 Feb 3. PMID: 28162991.
[13] Smith CJ, Perfetti TA, Hayes AW, Berry SC, Trosko JE, King JA, Goodman JI, Begley CG, Dayan A. Categorizing the characteristics of human carcinogens: a need for specificity. Arch Toxicol. 2021 Aug;95(8):2883-2889. doi: 10.1007/s00204-021-03109-w. Epub 2021 Jun 20. PMID: 34148101.
[14] Becker RA, Dreier DA, Manibusan MK, Cox LAT, Simon TW, Bus JS. How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? Regul Toxicol Pharmacol. 2017 Nov;90:185-196. doi: 10.1016/j.yrtph.2017.08.021. Epub 2017 Sep 1. PMID: 28866267.
[15] Meek MEB, Wikoff D. The Need for Good Practice in the Application of Mechanistic Constructs in Hazard and Risk Assessment. Toxicol Sci. 2023 Apr 19:kfad039. doi: 10.1093/toxsci/kfad039. Epub ahead of print. PMID: 37074944.
[16] https://oehha.ca.gov/media/downloads/crnr/americanchemistrycouncilpubliccomment.pdf