VINYL ACETATE COUNCIL

1250 Connecticut Avenue, NW • Suite 700 • Washington, DC 20036

September 18, 2023

Kiana Vaghefi
Office of Environmental Health Hazard Assessment
1001 I Street, 23rd Floor
Sacramento, California 95814

Re: Request for Relevant Information on Vinyl Acetate Monomer

Dear Ms. Vaghefi:

The Vinyl Acetate Council (VAC) is responding to the request by the California Office of Environmental Health Hazard Assessment (OEHHA) for information regarding the carcinogenicity potential of vinyl acetate monomer (VAM; CAS 108-05-4) for review by the Carcinogen Identification Committee's (CIC) 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 a volatile, flammable, and reactive substance that is used as a monomer in the manufacture of various polymers and copolymers that have a wide variety of industrial and commercial applications, including polymers used in water-based coatings and adhesives. Given it characteristics, VAM is tightly controlled during manufacture, shipping, handling and use to avoid the potential for fires, uncontrolled polymerization, release and exposure. The VAC and its members provide guidance on the safe handling and use of VAM including publishing a Vinyl Acetate Safe Handling Guide (www.vinylacetate.org).

Below, the VAC has identified information relevant to evaluating the carcinogenicity potential of VAM:

Local Irritation

VAM is classified as a respiratory tract irritant based on the significant irritation noted in both short-term and chronic inhalation studies in rats and mice (Hazelton1987; Bodganffy 1994a). Exposed workers were reported to exhibit local irritant reactions of the skin, eyes and respiratory tract (Deese & Joyner,1969; EU RAR, 2008). However, standard skin and eye irritation assays and skin sensitization assays do not indicate a hazard for classification.

Genetic Toxicity

Key *in vitro* studies evaluating the genotoxicity of VAM include the bacterial reverse mutation assays (McCann et al., 1975, Jung et al., 1992; Watanabe et al., 1998), a mammalian cell cytogenetic assay (Jantunen et al., 1986), a human cell micronucleus assay (Budinsky et al., 2013), and a human cell gene mutation assay in the TK locus (Budinsky et al., 2013) with a

supporting investigation. A human cell gene mutation assay in the HPRT locus is also available, although experimental methodology is limited (Budinsky et al., 2013).

Animal Carcinogenicity Testing

In a lifetime inhalation study in rats, a limited number of benign and malignant nasal tumors were observed in the terminal sacrifice group (2 years of exposure). Seven nasal tumors were observed out of 59 male rats and 4 nasal tumors out of 60 female rats at the highest concentration of 600 ppm. These findings were considered statistically significant. One benign papilloma occurred in 1 of 29 male rats exposed to 200 ppm VAM; this result was not statistically significant. There were no observed effects at 50 ppm (Hazelton 1987; Bogdanffy 1994a). No such effects were observed in a mouse study of comparable design (Bogdanffy 1994a). Based on the findings of severe chronic nasal irritation in this study and in follow-up mechanistic research inhalation studies, these tumor formations appear to be the result of nasal tissue cytotoxicity coupled with regenerative cell proliferation, metaplasia and dysplasia. These effects occur at concentrations of 200 ppm and above with a clear dose-response relationship indicating a threshold for irritation, cytotoxicity and tumor formation. Recent research evaluating DNA adducts shows that exogenous DNA adduct formation only exceeds endogenous DNA adducts at concentrations of 200 ppm VAM and higher. This research also shows that these adducts are not systemically distributed and that exogenous adduction formation is non-detectable below concentrations of 10 ppm VAM (Liu 2021; Hsiao 2022).

VAM has also been tested in both rats and mice in 2-year drinking water studies which are summarized in Bogdanffy et al. (1994b).

Epidemiology

There are no human studies indicating a cancer concern for VAM. In a case-control study of vinyl acetate chemical operators in 3 production units of a Gulf Coast chemical plant, exposure concentrations of VAM in air (under normal working conditions) of 5 to 10 ppm VAM were estimated for the duration of their service. The mean service length of the 21 operators was 15 years and from review of medical records, recent multiphasic examinations and personal questionnaires, there was no evidence to suggest any chronic effects of VAM at the long-term levels of 5 -10 ppm (Dees and Joyner 1969).

Among male workers from two chemical companies (n=29,139), a nested case-control study was conducted to evaluate associations between exposure to 21 unique chemicals and the development of a subset of cancers (Union Carbide 1989). There was no observed increased risk of lymphatic or hematopoietic tissue cancer in workers “ever” exposed to VAM relative to those “never” exposed, while the odds ratios (ORs) for non-Hodgkin’s lymphoma, myeloma, nonlymphocytic leukemia, and lymphocytic leukemia for VAM were 1.2 (7 cases), 1.6 (3 cases), 0.5 (2 cases), and 1.8 (2 cases), respectively. As concluded in a draft toxicological profile of VAM by ATSDR (2023), the study offers little insight into VAM-related cancer risk due to co-

exposure of the worker population to multiple chemicals and lack of control for confounding factors.

Mode of Action and Mechanistic Research

Recent testing on the formation of acetaldehyde DNA adducts following exposure to inhaled VAM vapors shows exogenous adduct formation is below endogenous background levels at concentrations under 200 ppm and is non-detectable at concentrations under 10 ppm (Liu 2021; Hsiao 2022).

Prior Reviews

There are several relatively recent comprehensive regulatory reviews of VAM conducted by the authorities in Canada, the European Union and the United States.

The Canadian review determined that VAM did not meet the health (or environmental) criteria in Section 64 of the Canadian Environmental Protection Act (CEPA) as a "toxic substance" and thus it was not added to CEPA Schedule 1 (Canada 2008). VAM is regulated as a hazardous substance in Canada based on its volatility, flammability and reactivity.

The European Union released a final substance evaluation in October 2020 (EU 2020) and concluded that no further action is required on VAM.

> *Taking into account the information contained in the registration dossier1, the Competent Authority… was able to conclude on every endpoint of concern and found no potential, inadequately controlled risks.*
>
> *The exposure data did not suggest indications of a risk to consumers.*
>
> *[T]here is no need for follow-up action at EU level due to this substance evaluation.*

A recent draft toxicological profile of VAM by the Agency for Toxic Substances and Disease Registry (ATSDR; 2023) noted, "U.S. Environmental Protection Agency (EPA) (IRIS 1990) and the Department of Health and Human Services (HHS) (NTP 2021) have not classified the potential for vinyl acetate to cause cancer in humans."

1 The REACH dossier for vinyl acetate can be accessed at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15530

We would be happy to address any questions OEHHA or the CIC may have regarding VAM toxicology and risk assessment, including any of the referenced studies. Please contact me at andrew@vinylacetate.org or (301) 461-9695.

Best regards,

Andrew Jaques, Executive Director
Vinyl Acetate Council

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