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Independent Regulatory Review Commission

American Chemistry Council

November 21, 2023

Ms. Bevin Buchheister
Acting Deputy Secretary
Office of Water Programs
Department of Environmental Protection
Rachel Carson State Office Building
400 Market Street
Harrisburg, PA 17101

Re: Triennial Review of Water Quality Standards, Proposed Human Health Criterion for 1,4-Dioxane

Dear Ms. Buchheister:

The 1,4-Dioxane Panel of the American Chemistry Council (ACC) submits the following comments on the proposed ambient water quality criterion for human health protection for 1,4-dioxane (1,4-DX). The ACC Panel represents companies interested in the application of the best available science and the weight of the scientific evidence to the assessment of the potential health effects of 1,4-DX.

As documented in the Department's April 2022 rationale document, the proposed criterion of 0.3 micrograms per liter (µg/L) is based on the assessment of potential cancer risk conducted by the US Environmental Protection Agency (USEPA) as part of its Integrated Risk Information System (IRIS) originally published in 1988 and confirmed in 2013. The USEPA assessment applies a default linear non-threshold (LNT) assumption for a genotoxic mode of action (MOA) in characterizing the cancer risk from 1,4-DX exposure after concluding that the cancer MOA has not been established for the substance.

Based on the available evidence, however, the application of the default genotoxic MOA is inappropriate since 1,4-DX is neither directly genotoxic nor mutagenic. Moreover, there is ample evidence supporting use of threshold models for assessing cancer risk from exposure to 1,4-DX. This conclusion is based on numerous reports demonstrating that tumors observed in laboratory animal tests only occur after exposure to 1,4-DX exceeds a threshold. This evidence has been recognized by authoritative bodies worldwide, including both Health Canada, the European Union, and the World Health Organization (WHO).

There is no information suggesting that 1,4-DX is bioactivated to reactive intermediate metabolites capable of directly impacting DNA to produce mutations. This conclusion is supported by extensive testing with *in vitro* assay systems with prokaryotic organisms, non-mammalian eukaryotic organisms, mammalian cells, and most *in vivo* genotoxicity assays. Instead, 1,4-DX's

metabolism is well-documented to proceed to a stable, nongenotoxic/non-mutagenic metabolite, 2-hydroxyethoxyacetic acid (HEAA). Metabolism studies confirm, moreover, that while 1,4-DX is readily metabolized and quickly eliminated from the body the metabolic pathway becomes saturated at higher exposure levels of 1,4-DX. The available evidence demonstrates that toxicity occurs only after the clearance pathway becomes saturated and the parent compound accumulates in the blood and target tissues.

Although 1,4-DX has been reported to evoke multiple tumors, the increased tumor incidence tends to occur at the highest dose only, and all reported incidences are consistent with a threshold-based, non-mutagenic MOA. This finding is supported by extensive histopathology for both liver and nasal tissue providing a robust set of key events - pre-cancerous changes consistent with mitogenesis leading to genotoxicity and cytotoxicity and a threshold MOA for 1,4-DX-induced tumors. Chronic and subchronic studies in laboratory animals exposed to levels above metabolic saturation have consistently demonstrated a threshold response of pre-neoplastic events and subsequent tumor formation after chronic exposure.

Although some of the metabolism information was available to USEPA for its 2020 evaluation under the Toxic Substances Control Act, a considerable amount of new and relevant information has been published since that time. We have enclosed a list of recent publications that we urge the Department to consider before it finalizes a human health criterion for 1,4-DX.

Please feel free to contact me at srisotto@americanchemistry.com or at (202) 249-6727 if you have questions about the enclosed information or wish to discuss it further.

Sincerely,

*Steve Risotto*

Stephen P. Risotto
Senior Director

Enclosure

**List of References Relevant to Cancer Mode of Action for 1,4-Dioxane Published Since 2020**


Chappell GA *et al.* Transcriptomic analyses of livers from mice exposed to 1,4-dioxane for up to 90 days to assess potential mode(s) of action underlying liver tumor development. *Curr Res Toxicol* 2:30-41 (2021). https://doi.org/10.1016/j.crtox.2021.01.003

Charkoftaki G *et al.* Identification of Dose-Dependent DNA Damage and Repair Responses from Subchronic Exposure to 1,4-Dioxane in Mice Using a Systems Analysis Approach. *Toxicol Sci* 183(2):338-351 (2021). https://doi.org/10.1093/toxsci/kfab030

Chen Y *et al.* Oxidative stress and genotoxicity in 1,4-dioxane liver toxicity as evidenced in a mouse model of glutathione deficiency. *Sci Total Environ* 806(2):150703 (2022). https://doi.org/10.1016/j.scitotenv.2021.150703

Cho E *et al.* AOP report: development of an adverse outcome pathway for oxidative DNA damage leading to mutations and chromosomal aberrations. *Environ Mol Mutagen* 63:118–134 (2022). https://doi.org/10.1002/em.22479

European Chemical Agency (ECHA). ECHA Scientific Report for Evaluation of Limit Values for 1,4-dioxane at the Workplace. Helsinki, Finland (2021). https://echa.europa.eu/documents/10162/ffebd37d-e38c-0b15-7376-229481dd9619

Ginsberg G *et al.* Mechanistic considerations in 1,4-dioxane cancer risk assessment. *Curr Opin Environ Sci Health* 30:100407 (2022). https://doi.org/10.1016/j.coesh.2022.100407

Health Canada. Guidelines for Canadian Drinking Water Quality Guideline Technical Document 1,4-Dioxane. Ottawa. ISBN: 978-0-660-37417-8 (2021). https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-1-4-dioxane.html

Lafranconi M *et al.* A 90-day drinking water study in mice to characterize early events in the cancer mode of action of 1,4-dioxane. *Reg Toxicol Pharma* 119:104819 (2021).https://doi.org/10.1016/j.yrtph.2020.104819

Lafranconi M. *et al.* An integrated assessment of the 1,4-dioxane cancer mode of action and threshold response in rodents. *Reg Toxicol Pharma* 142:105428 (2023). https://doi.org/10.1016/j.yrtph.2023.105428

Wang Y *et al.* Oxidative stress, glutathione, and CYP2E1 in 1,4-dioxane liver cytotoxicity and genotoxicity: insights from animal models. *Curr Opin Env Sci Health* 29:100389 (2022) https://doi.org/10.1016/j.coesh.2022.100389