August 30, 2019

Ms. Meredith Williams
Acting Director
Department of Toxic Substances Control
11001 I Street
Sacramento, CA 95814-2828

Re: 1,4-Dioxane in Personal Care and Cleaning Products

Dear Ms. Williams:

The 1,4-Dioxane Panel of the American Chemistry Council submits these comments in response to the Department's request for information on its consideration of 1,4-dioxane in personal care and cleaning products under the state's Safer Consumer Products (SCP) program. The Panel includes companies with a common interest in the use of the best scientific information in developing regulatory standards such as those under consideration by the Department.

The Panel opposes the Department's plan to consider listing personal care and cleaning products containing low levels of 1,4-dioxane as Priority Products under the SCP regulations. The available toxicological information indicates that 1,4-dioxane does not present a health risk at current environmental exposure levels. A recently completed sub-chronic study sponsored by the Panel provides additional support for this conclusion. Given the absence of evidence of health effects at current exposures and concerns about the ability to detect low levels of the substance, moreover, DTSC's suggestion to use a default practical quantification limit of 1 part per million (ppm) as the alternative assessment threshold is not appropriate.

1,4-Dioxane Does Not Present a Health Risk at Current Environmental Exposure Levels

DTSC relies on the evaluation by the US Environmental Protection Agency (USEPA) in determining that 1,4-dioxane presents a cancer risk at environmental exposures.[1] The USEPA evaluation fails to fully consider established key events in the mode of action (MOA) of 1,4-dioxane, however, leading to the conclusion that application of the default low-dose risk model is inappropriate for evaluating 1,4-dioxane carcinogenicity. Although USEPA acknowledges the

[1] DTSC. Work plan implementation - 1,4-Dioxane in Personal Care and Cleaning Products (May 23, 2019), at 2.

available evidence for a threshold MOA in its recent draft risk evaluation of 1,4-dioxane,[2] it concludes that the information is not sufficiently robust and defaults to the genotoxic MOA in characterizing risk from 1,4-dioxane exposure.

Based on the currently available evidence, however, the genotoxic MOA is inappropriate primarily because 1,4-dioxane is not genotoxic. This conclusion is the result of extensive testing with *in vitro* assay systems with prokaryotic organisms, non-mammalian eukaryotic organisms, mammalian cells, and *in vivo* genotoxicity assays. In addition, there are well designed animal studies providing evidence that the development of tumors only occurs when dosing exceeds the threshold of metabolic saturation (see Figure 1). Studies confirm that, while the substance is readily metabolized and quickly eliminated from the body, the metabolic pathway becomes saturated at higher exposure levels of 1,4-dioxane.

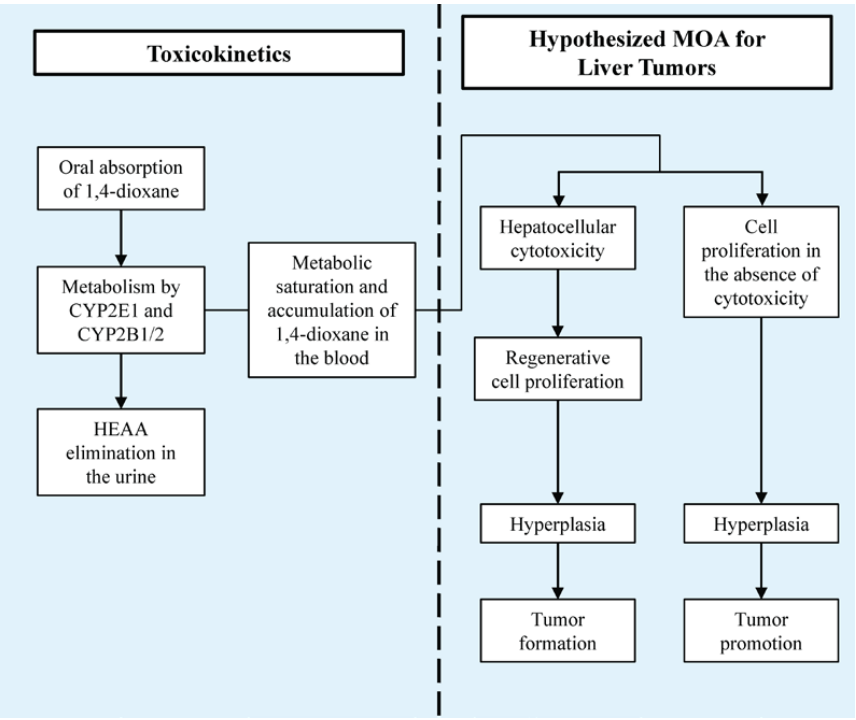

Figure 1. Identification of key events in liver tumor formation following exposure to 1,4-dioxane[3]

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[2] USEPA. Draft risk evaluation for 1,4-dioxane (CASRN: 123-91-1). EPA-740-R1-8007. Office of Chemical Safety and Pollution Prevention (June 2019). https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/draft-risk-evaluation-14-dioxane

[3] USEPA. Toxicological review of 1,4-Dioxane (with inhalation update) (CAS No. 123-91-1) in support of summary information on the Integrated Risk Information System (IRIS.) EPA-635/R-11/003-F. Washington, DC (2013), at 95. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0326tr.pdf

The available evidence demonstrates that toxicity occurs only after the clearance pathway becomes saturated and the parent compound accumulates in the blood. Although 1,4-dioxane has been reported to evoke multiple tumors, the increased tumor incidences occur at the highest dose only, and all are consistent with a threshold-based non-mutagenic mode of action. The threshold MOA is recognized by authoritative bodies worldwide and has led authorities in Australia, Canada, Europe, and Japan to apply threshold assumptions when characterizing risk.

In its 2018 draft guideline for 1,4-dioxane in drinking water, for example, Health Canada concludes that –

> Analysis of the weight of evidence indicates that 1,4-dioxane is not a mutagen but promotes tumours through non-genotoxic mechanisms, which is supported by a MOA analysis indicating the progression from non-cancer to cancer effects after exposure to 1,4-dioxane. Thus, the assessment of 1,4-dioxane in drinking water considers the cancer and non-cancer effects together using a threshold approach. Liver effects that are early events of cancer are the most sensitive endpoints for both cancer and non-cancer toxicity associated with oral exposure to 1,4-dioxane. [4]

Using this approach, Environment and Health Canada concluded that the margin of exposure (MOE) from all environmental media (including drinking water) ranged from 7,600 to greater than 50,000.[5] This range is well above that considered to be adequately protective of human health, even after accounting for uncertainties in the risk assessment for both cancer and non-cancer effects. The Ministers of Health and Environment concluded that 1,4-dioxane –

- is not harmful to the health of the general population at current levels of exposure; and
- is not entering the environment in a quantity or under conditions that constitute a danger to the environment.

Based on its assessment, Health Canada has proposed a maximum allowable concentration of 50 µg/l for 1,4-dioxane in drinking water.

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[4] Health Canada. 1,4-Dioxane in drinking water. Guideline technical document for public consultation (2018). https://www.canada.ca/en/health-canada/programs/consultation-1-4-dioxane-drinking-water/document.html

[5] Screening Assessment for the Challenge – 1,4-Dioxane. Environment Canada, Health Canada (2010). The screening assessment used a drinking water concentration of 10 µg/L, the limit of detection, although all samples were below this limit. http://www.ec.gc.ca/ese-ees/default.asp?lang=En&xml=2051DAE2-3883-F0F6-D5A9-E46DBD26BA33.

In establishing its drinking water guideline for 1,4-dioxane in 2005, WHO considered both linear and non-linear models to estimate cancer risks. Using a conservative risk assessment approach, the World Health Organization (WHO) also concluded that a guideline of 50 µg/L was protective of both cancer and non-cancer effects.[6]

The Results of the ACC-Sponsored Drinking Water Study Support a Threshold MOA

USEPA's decision to discount the evidence for a threshold MOA for 1,4-dioxane was primarily the result of observations from a study in female mice. To help further characterize the MOA, ACC sponsored a recently completed study to further investigate potential key events and responses related to the MOA for female mouse liver tumors following 1,4-dioxane drinking water administration. This study was designed to examine biological responses at specified, interim time points within the overall 90-day exposure period. Groups of ten female B6D2F1 mice were given drinking water at concentrations up to 6000 parts per million (ppm) 1,4-dioxane for a duration of at least 7, 28, or 90 days. A summary of the results of this study were presented at the June 28 public meeting and the lab report from this study is included with this comment (**Enclosure 1**).

When administered via drinking water, the data collected for 1,4-dioxane indicate a clear time- and dose-dependent threshold for hepatic effects. The molecular and apical treatment-induced biological changes correlate with increased quantifiable concentrations of 1,4-dioxane in the blood and a potential shift in metabolism over time. After 28 and 90 days, liver weight increases in the highest dose groups were correlated with histopathological findings of increased centrilobular vacuolation, hypertrophy, and apoptosis. Notably, the magnitude of hepatocellular proliferative induction (~5-fold) at the highest dose is comparable to other mitogenic, non-genotoxic hepatocarcinogens (*e.g.*, phenobarbital). Collectively, these data indicate that, after an extended period of administration at metabolically saturating doses of 1,4-dioxane, a mitogenic response is triggered in the liver of female mice. This mitogenic response occurs relatively early and likely contributes to the regenerative repair that is suggested with the slight increase in single cell necrosis (apoptosis) seen in this study and in earlier studies.

The ACC-sponsored study also investigated the molecular basis of key events in the MOA by utilizing transcriptomic analyses. The results of the transcriptomics analysis of liver tissue demonstrate an increase in signals related to induction of xenobiotic metabolism, a subtle, yet, significant dose- and time-responsive increase in mitotic cell cycle and cellular proliferation, and a decrease in complement cascade processes and lipid metabolism. The

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[6] WHO. 1,4-Dioxane in drinking water. Background document for development of WHO Guidelines for Drinking-water Quality. WHO/SDE/WSH/05.08/120 (2005). http://www.who.int/water_sanitation_health/water-quality/guidelines/chemicals/14dioxane0505.pdf?ua=1.

signals for proliferative response only occur at exposures of 2000 ppm or greater, while alterations related to xenobiotic metabolism occur as low as 600 ppm. Importantly, signals related to activation of DNA damage response and/or repair mechanisms were not evident at any of the concentrations and time points evaluated thus reinforcing the conclusions that 1,4-dioxane is not genotoxic. There were no significant changes in signaling pathways/gene sets at concentrations below 600 ppm.

1 ppm is not an Appropriate Threshold for 1,4-Dioxane in Personal Care and Cleaning Products

Although the Safer Consumer Products program is primarily intended to address the intentional use of Chemicals of Concern (COC) to manufacture products, the SCP regulations provide for the listing of products based on the presence of a COC as a contaminant. In deciding to list such a product, the regulations suggest that listing "will likely be" because the COC is found "in concentrations that present potential adverse impacts and potential exposures."[7] This is clearly not the case for 1,4-dioxane for which authoritative bodies around the world have established drinking water limits well above those suggested by DTSC's analysis.[8]

In listing products based on contamination with a COC, DTSC will establish a threshold for conducting an alternatives analysis, which is set at the practical quantification limit (PQL) by default. In explaining the basis for setting the default at the PQL, DTSC notes that "because some chemicals (*e.g.*, carcinogens) cause adverse impacts at very low levels, at or near zero, it is unsuitable to use a higher default level of quantification for policy setting and/or regulatory decision-making."[9] As evidenced by the available scientific evidence summarized above, and as confirmed by numerous authoritative bodies, 1,4-dioxane does not present a risk of adverse health impacts at 1 ppm in consumer products. Given this fact, and the concerns expressed about the ability to achieve a PQL of 1 ppm for many personal care and cleaning products, additional investigation is warranted before moving ahead with regulations.

The available scientific evidence do not support listing personal care and cleaning products containing 1,4-dioxane as a contaminant as a Priority Product under the SCP regulations. As outlined in these comments, authoritative bodies around the world have concluded that 1,4-dioxane does not present a cancer risk at the levels currently encountered

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7 Final Statement of Reasons, Safer Consumer Products, at 233.

8 DTSC's analysis focuses on the contribution of personal care and cleaning products to 1,4-dioxane levels in drinking water sources. Although the Department does not address the potential for health effects from the use of these products, available evidence indicates that such risks are not significant.

9 FSOR, at 234.

in personal care and consumer products and drinking water. We urge the Department to reconsider its proposal to list these products under the SCP regulations.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

Enclosure