american cleaning institute®

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Office of Environmental Health Hazard Assessment (OEHHA)
California Environmental Protection Agency (CalEPA)
1001 I St.
Sacramento, CA 95814

Submitted via OEHHA's public comment portal: https://oehha.ca.gov/water/comments/comment-submissions-proposed-public-health-goal-phg-14-dioxane-drinking-water

RE: First Public Review Draft – Public Health Goal – 1,4-Dioxane in Drinking Water

The American Cleaning Institute (ACI) appreciates the opportunity to provide the Office of Environmental Health Hazard Assessment (OEHHA) with comments on its "Proposed Public Health Goal for 1,4-Dioxane in Drinking Water" (Review Draft)[1] as OEHHA works to fulfill its mission to protect and enhance the health of Californians and the state's environment. We also appreciate the extension of the public comment period from November 10 to November 25, which afforded stakeholders the opportunity to hear and consider remarks from OEHHA and others in the November 13 hybrid public workshop before submitting their comments.

ACI is the home of the U.S. Cleaning Products Industry® and represents the $60 billion U.S. cleaning product supply chain. ACI members include the manufacturers and formulators of soaps, detergents, and general cleaning products used in household, commercial, industrial and institutional settings; companies that supply ingredients and finished packaging for these products; and chemical distributors. ACI serves the growth and innovation of the U.S. cleaning products industry by advancing the health and quality of life of people and protecting our planet. ACI achieves this through a continuous commitment to sound science and being a credible voice for the cleaning products industry.[2] Our members actively work to reduce the presence of 1,4-dioxane in their products, including for compliance with New York States's household cleansing products content limits, and have a vested interest in related policies.

[1] First Public Review Draft – Public Health Goal 1,4-Dioxane in Drinking Water, available at: https://oehha.ca.gov/water/crnr/proposed-public-health-goal-phg-14-dioxane-drinking-water.
[2] For more information: www.cleaninginstitute.org.

Summary

ACI members have concerns with the approach reflected and conclusions in the Review Draft to derive the proposed Public Health Goal (PHG) limits of 0.04 ppb for cancer and 33 ppb for noncancer, respectively. As PHGs form the basis of California's Maximum Contaminant Levels (MCLs) for drinking water, it is important to set appropriate PHGs based on evaluations that reflect credible and current evidence and understanding of the state of the science. The Review Draft takes a linear (non-threshold) approach to the mode of action (MOA) for carcinogenicity for 1,4-dioxane, but we believe this is not the appropriate model and overestimates exposure risk. Studies and assessments both included and not included in the Review Draft do provide mechanistic data for OEHHA, supporting a pathway involving metabolic saturation and other threshold events that contribute to the weight of evidence for a threshold MOA for carcinogenicity for 1,4-dioxane.

ACI believes that a revised draft and proposed PHG would significantly benefit from OEHHA taking the following steps:

- *Reconsider its quality assignment and reliance on Kano et al. (2009)*. As discussed in our comments, this reevaluation has significant deficiencies and does not represent the best available science.
- *Review and include additional studies and reviews, including the work of Chappell et al. (2021)*[3]*, Lafranconi et al. (2023)*[4] *and Kirman et al. (2026)*.[5] Chappell et al. (2021) and Lafranconi et al. (2023) were available online within the literature search period. While Kirman et al. was more recently published online, it serves as an additional body of evidence for OEHHA to consider as the science on 1,4-dioxane has evolved and consensus continues to build on the MOA for carcinogenicity for 1,4-dioxane. We believe these will help address issues with the Review Draft dataset and total body of evidence available for each type of cancer risk and provide even stronger evidence for a non-linear (threshold) approach.
- *Review and consider the evaluations of other regulatory agencies and authoritative bodies around the world, such as Health Canada (2021),*[6] *European Chemicals Agency's (ECHA)*

[3] Chappell et al. (2021) *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*, Current Research in Toxicology, Vol. 2, available at: https://doi.org/10.1016/j.crtox.2021.01.003.

[4] Lafranconi et al. (2023) *An Integrated Assessment of the 1,4-Dioxane Cancer Mode of Action and Threshold Response in Rodents*, Regulatory Toxicology and Pharmacology, Vol. 142, available at: https://doi.org/10.1016/j.yrtph.2023.105428.

[5] Kirman et al. (2026) *Expert panel evaluation of the tumor modes of action for 1,4-dioxane and their implications for human risk assessment*, Regulatory Toxicology and Pharmacology, Vol. 164, available at: https://doi.org/10.1016/j.yrtph.2025.105950.

[6] Health Canada (2021) *Guidelines for Canadian Drinking Water Quality Guideline Technical Document 1,4-Dioxane*, available at: https://www.canada.ca/content/dam/hc-sc/documents/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-1-4-dioxane/1-4-dioxane-pdf-eng.pdf.

Committee for Risk Assessment (RAC) (2022),[7] *Japan's Ministry of Health, Labour and Welfare (MHLW),* [8] *and the World Health Organization (WHO)*.[9] These have determined that the carcinogenic MOA for 1,4-dioxane supports a threshold-dose model.

- *Conduct a more thorough review of current consumer products and support or revise assumptions on human exposure.* The Review Draft does not support its statement that residual 1,4-dioxane in consumer products is a "significant source of human exposure" or consider the current landscape, which impacts exposure assumptions and the PHG.
- *Update the Review Draft after a review and consideration of the above*. This will enable the final PHG to reflect both the current understanding of 1,4-dioxane toxicity across various modalities and the latest analyses of its MOA for carcinogenicity.

Chronic Studies and Cancer Studies in Animals

The Review Draft explains that it selected Kano et al. (2009), among other sources, as one of the "candidate critical studies because they were the best quality studies. These studies had large numbers of animals per dose group, multiple dose groups, adequate reporting of results including pathology, and were the most sensitive." In the Review Draft's Summary, OEHHA notes that the proposed PHG is based in part on hepatic tumors in female mice as reported in this source. However, the Review Draft does not include a clear explanation of what tumor types were considered treatment related and the weight-of-evidence assessment that was conducted to conclude that these tumors were treatment related, which is foundational to a cancer assessment and performed before a cancer slope factor is derived. Using the weight of the evidence to evaluate and inform a decision on the likely MOA is also consistent with EPA's 2005 Guidelines for Carcinogen Risk Assessment, which "encourages assessments to be performed using [these] alternative procedures" that have "significant biological support" and where feasible.[10]

The Review Draft references Health Canada (2021) in a table of health advisory or regulatory values, but does not mention Health Canada's questioning in that document the results of the

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[7] ECHA (2022) Committee for Risk Assessment, RAC, Opinion on Scientific Evaluation of Occupational Exposure Limits for 1,4-Dioxane, ECHA/RAC/OEL-O-0000007101-89- 01/F 18/03/2022, European Chemicals Agency (ECHA), 10 pp., at p. 8 (PDF p. 8), available at: https://echa.europa.eu/documents/10162/7937606/1_final_opinion_oel_1_4_dioxane_en.pdf.

[8] MHLW (2015) *Drinking Water Quality Standards in Japan (April 2015~)*, Japanese Ministry of Health, Labour and Welfare (MHLW), available at: https://www.mhlw.go.jp/english/policy/health/water_supply/dl/4a.pdf.

[9] World Health Organization (2005) *1,4-Dioxane in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality*. WHO/SDE/WSH/05.08/120, available at: https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/dioxane-bd.pdf?sfvrsn=1910104c_4.

[10] EPA (2005) Guidelines for Carcinogen Risk Assessment, Risk Assessment Forum, U.S. Environmental Protection Agency (EPA), EPA/630/P-03/001F, available at: https://www.epa.gov/sites/default/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

Kano et al. (2009) reevaluation, noting the "large degree of uncertainty [that] exists regarding the liver tumour occurrence in female mice [citations omitted] at >66 mg/kg bw per day," that "liver tumours were generally reported at higher doses (LOAELs of 274-1599 mg/kg bw per day) in the other chronic studies…[, and] [t]he absence of non-cancer histopathological changes and the concomitant increase in liver enzymes in the [Japan Bioassay Research Center] JBRC studies despite the presence of both endpoints in the sub-chronic studies from the same group…."[11] Though the Kano et al. (2009) reevaluation was performed by the JBRC, Japan does not use it as the basis for its drinking water standard for 1,4-dioxane and instead appears to rely on the World Health Organization's (WHO) guideline value of 0.05 mg/L.[12,13]

EPA's Office of Pollution Prevention and Toxics (OPPT) is the only regulatory body in the world known to rely, at least at present, upon the Kano et al. (2009) reevaluation. ACI is raising here the same concerns we expressed to EPA, in that the reevaluation has significant deficiencies and does not represent the best available science; this is detailed in an analysis[14] undertaken and submitted in response to EPA's proposed "2023 Draft Supplement to the 1,4-Dioxane Risk Evaluation."[15] Comments specific to hepatocellular toxicity and hyperplasia are provided below.

Hepatocellular Toxicity

In addition to consideration of the above, we ask that OEHHA review and incorporate Lafranconi et al. (2023), which noted issues with Kano et al. (2009) including:

> "There are three important considerations for this reported response that, taken together, undermine the usefulness of mouse liver tumor incidence findings from this study.
>
> 1) The Kano et al. (2009) study in Crj:BDF1 female mouse demonstrated a near maximum liver tumor response (e.g., 70%) at the lowest dosage tested (66 mg/kg/d) that increased modestly to 92% at the highest dosage (964 mg/kg/d). In contrast, the 1978 [National Cancer Institute] NCI study in B6C3F1 female mice demonstrated a more abrupt increase in treatment-related liver tumors, where tumor incidence increased from 44% at 380 mg/kg/d to 95% at 860 mg/kg/d.

[11] Health Canada (2021).
[12] MHLW (2015).
[13] World Health Organization (2005).
[14] ACI (2023) Appendix A Analysis at https://www.regulations.gov/comment/EPA-HQ-OPPT-2016-0723-0119 and https://www.regulations.gov/comment/EPA-HQ-OPPT-2022-0905-0066.
[15] United States, Environmental Protection Agency. (2023). 1,4-Dioxane; Draft Supplement to the TSCA Risk Evaluation; Science Advisory Committee on Chemicals (SACC) Meeting; Notice of Meeting and Request for Comment. *Federal Register*, 88 Fed. Reg. 43562-43565, available at: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032.

2) The 13-week mouse drinking water study (Kano et al., 2008) reported non-neoplastic liver pathology that was inexplicably not reported in the 2-year study. In addition, similar non-neoplastic findings were also observed in the re-read of the liver slides from the NCI study (Dourson et al., 2014) indicating that the reporting of pre-neoplastic findings from the chronic study by Kano was incomplete.
3) The diagnostic criteria used in the original JRBC report (JBRC, 1990) and associated conference proceeding (Yamazaki et al., 1994) changed in the subsequent peer-reviewed publication of the same study (Kano et al., 2009)."[16]

Kano et al. (2009) appears to be an outlier in the available chronic oral toxicity data on 1,4-dioxane in mice and rats. The underlying basis for the 70% tumor response in female Crj:BDF1 mice observed at a dose nearly six-fold lower than the dose causing a 44% increase in tumor response in female B6C3F1 mice is unclear; this could represent a unique susceptibility of female Crj:BDF1 mice to the effects from 1,4-dioxane or may reflect an issue with the subsequent change in classification of tumors, as reported by Kano et al. (2009).

Despite well-documented issues regarding its quality, OPPT assigned Kano et al. (2009) a data quality rating of "High" using its 2018 document for the application of systematic review in TSCA risk evaluations (2018 SR Document) – a document which, based on the feedback it received from its requested National Academies of Science, Engineering, and Medicine (NASEM) review, OPPT stated it "is not using, and will not again." NASEM concluded that "[t]he OPPT approach to systematic review does not adequately meet the state-of-practice"[17] and that OPPT was aware of the 2018 SR Document deficiencies prior to the NASEM review.

Hyperplasia

ACI maintains concerns with the Kano et al. (2009) reevaluation and hyperplasia that warrant consideration by OEHHA, consistent with our submissions to other agencies. In 2020, 'OPPT stated that "Hepatocyte hyperplasia was reported in rats and mice following 1,4-dioxane exposure in several studies [citations omitted]; however, the hyperplasia originally reported by Yamazaki et al. and JBRC was subsequently reexamined histopathologically and changed to hepatocellular adenoma and altered hepatocellular foci Kano et al. (2009)."[18] OPPT further stated that "it

[16] Lafranconi et al. (2023).
[17] NASEM (2021) *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, Consensus Study Report, Highlights*, (Feb. 2021), available at: https://nap.nationalacademies.org/resource/25952/TSCA 4-pager final.pdf.
[18] EPA (2020) *Final Risk Evaluation for 1,4-Dioxane CASRN: 123-91-1*, EPA Document # EPA-740-R1-8007, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency (EPA), available at: https://www.epa.gov/sites/default/files/2020-12/documents/1._risk_evaluation_for_14-dioxane_casrn_123-91-1.pdf.

considered previously unavailable incidence data from Kociba et al. 1974) [sic]. This new data suggests there may be a dose-response relationship between 1,4-dioxane and bile duct epithelial hyperplasia, but [they] did not show a dose-response relationship between 1,4-dioxane and hepatocellular hyperplasia or demonstrate hyperplasia precedes tumor formation."'[19] ACI notes that other authoritative regulatory agencies, such as Health Canada, reviewed these same data and did not rely on them. We also note that the data from Kociba et al. (1974)[20] in rats support the MOA developed by Lafranconi et al. (2023), which "suggest cytotoxicity is a late developing [key event] KE in the cancer MOA of 1,4-DX."[21] OPPT's own summary of the histopathology incidence data from Kociba et al. (1974) supports this given the dose-dependent increase in hepatocellular vacuolar degeneration and necrosis observed in male and female rats.'[22]

Mode of Action and Mechanistic Considerations

The Review Draft summarizes discussion on the MOA and mechanistic considerations by stating "… the available evidence for a singular predominant mechanism for 1,4-dioxane carcinogenesis is not conclusive… [as] [m]ultiple mechanisms appear involved based on evidence for genotoxicity in in vivo studies, increased oxidative stress, induction of chronic inflammation, and increased cell proliferation" and concludes that OEHHA's "default linear low-dose extrapolation is appropriate for cancer dose-response analysis."

This Review Draft section offers the following explanation: "1,4-[d]ioxane causes tumors in multiple sites in rodents (liver, nasal cavity, mammary gland, subcutis and peritoneum). The 1,4-dioxane carcinogenic mode of action (MOA) is not well understood; however, mechanistic studies have been conducted to elucidate the MOA for liver tumor formation. In this section… data support 1,4-dioxane is genotoxic (KC 2), induces chronic inflammation (KC 6), and alters cell proliferation (KC 10) but does modulate receptor-mediated effects (KC 8). Other proposed MOAs and mechanisms not related to the KCs (such as metabolic saturation, cytotoxicity and activation of transcription profiling) are also be [sic] discussed."

ACI is concerned that OEHHA relied on Smith et al. (2016)[23] qualitative "characteristics of carcinogens" approach. Rather, OEHHA should apply a well-established International Life

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[19] *Id*.

[20] Kociba RJ, McCollister SB, Park C, Torkelson TR, Gehring PJ (1974). *1,4-Dioxane. I. Results of a 2-year ingestion study in rats*. Toxicol Appl Pharmacol 30(2): 275-286.

[21] Lafranconi et al. (2023).

[22] EPA (2020).

[23] Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K. *Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis*. Environ Health Perspect. 2016 Jun;124(6):713-21. doi:

Sciences Institute's (ILSI) MOA Key Events Dose-Response Framework or EPA's 2005 Guidelines for Carcinogen Risk Assessment.

Genotoxicity

The Review Draft refers to its earlier Genetic Toxicity section and states that "1,4-[d]ioxane is not mutagenic in the majority of in vitro systems tested; however, it is possible that metabolites of 1,4-dioxane are mutagenic. The in vitro studies are limited, as they do not adequately capture the complete metabolism of 1,4-dioxane and in vivo studies show mixed results." ACI would like to point out that the current dataset (Stott et al. 1981, Totsuka et al. 2020, Lafranconi et al. 2021) argues against a reactive metabolite that is able to alkylate DNA; rather the DNA damage and mutation is secondary to activation of biological responses such as Cyp2E1, oxidative stress, cytotoxicity and even chronic inflammation that cause indirect DNA damage.

The Review Draft discussion also includes that "[i]n vivo genetic toxicity studies show mixed results. The majority of in vitro studies indicate that 1,4-dioxane is not genotoxic, as shown in Table 4. In the risk evaluation by US EPA (2013a), the authors concluded that 1,4-dioxane is nongenotoxic or weakly genotoxic based on results from in vitro studies. However, in a recent risk assessment, US EPA (2020) concluded that 1,4-dioxane is genotoxic in vivo at high doses based on bone marrow micronucleus assays, which are included in Table 3."

It is unclear how OEHHA viewed the results which formed the basis for EPA's conclusion, which were only at very high doses and with no observed toxicity at lower doses and secondary to inducible biological responses such as Cyp2E1 activation, oxidate stress, cytotoxicity and even chronic inflammation.

The Review Draft's table of drinking water health advisory or regulatory values includes Health Canada's 2021 "Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – 1,4-Dioxane," but this genetic toxicity section does not mention or address Health Canada's conclusion in section 9.2.4 of their document which states that "[b]ased on the weight of evidence provided below [in the document], 1,4-dioxane is not genotoxic at low doses."[24]

In vivo gene mutation assays in OEHHA's evaluation included Gi et al. (2018) and Itoh and Hattori (2019), which were also reviewed by EPA's OPPT. OPPT noted that Itoh and Hittori (2019), which assessed gene mutations with the Pig-a assay, was negative; Gi et al. (2018), which assessed gene mutations in gpt delta transgenic F344 rats, was positive at greater than 1000 ppm or about 92

10.1289/ehp.1509912. Epub 2015 Nov 24. PMID: 26600562; PMCID: PMC4892922. https://pubmed.ncbi.nlm.nih.gov/26600562/.

[24] Health Canada (2021).

mg/kg/d for A-to-T transversions and A-to-G transitions at 5000 ppm or about 440 mg/kg/d; in the study, the no observed genotoxic effect level (NOGEL) value was 92 mg/kg/d for *gpt* delta mutation frequency. ACI notes that OPPT agreed with the conclusions of the authors of both studies, including those of Gi et al. (2018) that "no genotoxic or mutagenic effect [was identified] in transgenic animals in the lowest dose group (18.7 mg/kg/day)."[25] Further, ACI notes the recent evaluation from Health Canada (2021) concluded, after evaluating Gi et al (2018), that "1,4-dioxane acts through a non-genotoxic MOA."[26]

Oxidative Stress

Building on the previous discussion of genotoxicity, there is confidence in available studies and assessments that oxidative stress induces carcinogenicity; e.g.:

> 'Lafranconi *et al*. (2023) performed a critical review of Gi *et al*. (2018) and noted that these authors "suggested that the increased expression of methylguanine methyltransferase (MGMT) repair protein at the high dose of 5000 ppm is the key line of evidence for a mutagenic MOA."[citation omitted] Lafranconi *et al*. (2023) further noted that "MGMT prevents G-to-A mutations, and those transitions were not increased in the Gi *et al*. (2018) study. Instead, [Gi et al., 2018] found mutations at the A:T base pair, specifically A-to-G and A-to-T mutations, predominating as a result of 1,4-DX treatment (Gi et al., 2018)." [citation omitted] This finding is consistent with other more recent findings that identified a possible role of oxidative stress in the formation of DNA adducts of 1,4-DX treated animals. For example, Totsuka *et al*. (2021)[citation omitted] reviewed their previous research[citation omitted] on 1,4-DX where they performed an untargeted DNA adductome study on frozen liver samples from 1,4-DX treated *gpt* delta rats (*i.e.*, samples from Gi *et al*., 2018). The authors identified three candidate adducts that were characteristic of 1,4-DX treatment, including two that contained thymine or cytidine/uracil and a third identified as 8-hydroxy-2'-deoxyguanosine (8-oxo-dG). The authors interpreted their finding as suggesting that "oxidative stress responses could account for the increased frequency of mutations resulting from 1,4-dioxane treatment." [citation omitted] It is noteworthy that Totsuka et al. (2020) discussed the absence of an increase in 8-oxo-dG in their previous evaluation of livers of gpt delta rats, as reported by Gi et al. (2018). Totsuka et al. (2020) stated that the discrepancy between their work and previous evaluation for 8-oxo-dG performed by Gi et al. (2018) was unclear and that "differences in sample preparation and detection methods may have influenced the results." Further, the research of Chen et al. (2022) showed that

[25] EPA (2020).
[26] Health Canada (2021).

lipid peroxidation and oxidative stress were likely the operational mechanisms through which 1,4-DX causes liver carcinogenicity in mice.[citation omitted]'[27]

The above further supports that the carcinogenic MOA for 1,4-dioxane involves a threshold with mutagenicity occurring as a secondary effect to oxidative stress.

Receptor Mediated Effects

The Review Draft includes the only study investigating receptor mediated effects of 1,4-dioxane that was identified, Gi et al. (2018), and notes that "[t]he authors concluded that the carcinogenic mechanism of 1,4-dioxane is not likely to be mediated via CAR, PXR, PPARα, or AhR."

ACI agrees. We note that Lafranconi et al. (2023) evaluated the potential role of nuclear receptors in the carcinogenic MOA for 1,4-DX, concluding that the reasonable available information "are not indicative of a NR-mediated rodent hepatocarcinogen but clearly indicate the dose- and temporal-threshold nature of hepatocellular proliferation, along with shifts in metabolism."[28] ACI also notes that Chappell et al. (2021)[29] determined that 1,4-dioxane treatment in mice did not increase CYP-encoding genes that are common indicators of CAR, AhR, or PPARα activation. A significant upregulation of the PXR-related Cyp3a11 (human homolog CYP3A4) in mice at the highest treatment dose (6000 ppm) was noted but only observed at the 90-day timepoint; the dose- and temporal-nature lend further support that nuclear receptor activation is unlikely to play a role in the carcinogenic MOA of 1,4-dioxane.

Cell Proliferation

The Review Draft includes a table summary of animal studies of 1,4-dioxane that measured effects on replicative DNA synthesis, an indicator of cell proliferation, and states that those studies show that "1,4-dioxane causes increased DNA synthesis in the liver of rats."

ACI maintains that experiments conducted by Lafranconi et al. (2021) and Chappell et al. (2021) help inform questions about 1,4-dioxane and the dose-response relationship for induction of cell proliferation, whether increased rates of DNA synthesis "represent a true increase in cellular proliferation rates or if this increase is a cellular response to DNA damage and the repair of those lesions," and "whether observed cell proliferation is a direct response to cytotoxicity and whether it is caused by 1,4-dioxane or a metabolite."[30] Lafranconi et al. (2023) summarize this as follows:

[27] ACI (2023).
[28] Lafranconi et al. (2023).
[29] Chappell et al. (2021).
[30] ACI (2023).

> ‘Lafranconi et al. (2021) evaluated both the dose-response and time course of hepatic events of female B6D2F1 mice treated with 20, 40, 200, 600, 2000 or 6000 ppm 1,4-DX in drinking water for 7, 28 or 90 days. Liver weight increases after 90 days of exposure were accompanied by evidence of increased pan-lobular hepatocellular proliferation as determined by increased BrdU incorporation. Other than limited evidence of single-cell necrosis typical of apoptosis, there was no histological or biochemical evidence of cytotoxicity at any of the exposures used in this study. There was evidence of changes in genomic signaling only at 2000 ppm (337–391 mg/kg/d) and 6000 ppm (895–1063 mg/kg/d) from whole transcriptome analyses consistent with mitotic events (Chappell et al., 2021).’[31]

When considering cell proliferation in the absence of cytotoxicity, ACI has noted the following:

> ‘Lafranconi *et al*. (2021) determined through experimentation that their results “provide further evidence for the metabolic saturation of clearance pathways as a KE leading to accumulation of systemic 1,4-DX.”[citation omitted] The study authors also noted “a time- and dose-dependent threshold for this saturation and the development of the subsequent KE [i.e., a direct mitogenic response].” The study authors found that “the direct mitogenic stimulation observed in this study, approximately a five-fold increase in liver proliferation (labeling index) in the 6000 ppm exposure group after 90 days, occurs prior to the development of cytotoxicity and regenerative repair that is a cornerstone of the regenerative hyperplasia MOA.”[citation omitted] Lafranconi et al. (2023) concluded that “the current compilation of data sets from mice and rats demonstrate that 1,4-DX causes an early and direct mitogenic response absent cytotoxicity; this reduced the need for cytotoxicity-driven regenerative repair in the MOA sequence.”[citation omitted] These authors further concluded that “The evidence of cytotoxicity from shorter-term studies is less compelling and suggest cytotoxicity is a late developing KE in the cancer MOA of 1,4-DX.”[citation omitted]’[32]

<u>Other Mechanistic Considerations – Metabolic Saturation, Cytotoxicity and Proliferation</u>
The Review Draft notes other suggested possible MOA for the carcinogenicity of 1,4-dioxane, including “metabolic saturation, followed by accumulation in the blood which leads to cytotoxicity, regenerative proliferation, and the development of liver tumors (Dourson et al., 2014; Dourson et al., 2017).”

[31] Lafranconi et al. (2023).
[32] ACI (2023).

Building on our comments regarding hepatocellular toxicity, hyperplasia, cell proliferation and cytotoxicity above, we again point OEHHA to Lafranconi et al. (2023) in which the proposed MOA provides sufficient evidence to inform a linkage between metabolic saturation/1,4-dioxane accumulation in the blood and hepatocellular toxicity; more specifically, via direct mitogenesis, Cyp2E1 activation, oxidative stress, and then cellular damage. Sustained activation of Cyp2E1 is recognized as a molecular initiating event that leads to liver cancer and has a well-developed adverse outcome pathway (AOP)[33] that has been endorsed by the Organisation for Economic Co-operation and Development (OECD).[34]

Regulatory Agencies and Authoritative Bodies Worldwide Support a Threshold Approach to 1,4-Dioxane Carcinogenicity

ACI submits to OEHHA, as we have to California's Department of Toxic Substances Control (DTSC) and elsewhere, that there is ample evidence to support use of a threshold MOA that is both technically justified and sufficiently protective of human health for this endpoint.[35,36,37]

Other regulatory agencies and authoritative bodies around the world have prioritized 1,4-dioxane for assessment and reviewed scientific evidence to address potential risks associated with occupational, environmental, and/or public health exposures. Each has determined that the carcinogenic MOA for 1,4-dioxane (non-genotoxic) does not support the application of a linear approach, pointing instead to a threshold-dose model of carcinogenicity.

- The Commonwealth of Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) concluded in 1998 that "[o]verall, indications are that the primary mechanism(s) of tumourigenicity for 1,4-dioxane in animals is non-genotoxic" and that "Evidence from animal studies indicates the existence of a threshold dose for toxicity and carcinogenicity at doses where 1,4-dioxane metabolism becomes saturated."[38]
- The European Chemicals Bureau (ECB) came to the same conclusion in its 2002 *European Union Risk Assessment Report* stating that "1,4-Dioxane is considered to be a carcinogen

[33] Webster et al. (2023) *Cyp2E1 Activation Leading to Liver Cancer*, AOP: 220, Last modified on April 29, 2023, AOP Wiki, available at: https://aopwiki.org/aops/220#prototypical-stressors.
[34] Id.
[35] ACI (2023).
[36] See RFC 23002 & RFR 23002A - Toxic Substances Control Act (TSCA) Risk Evaluation for 1,4-Dioxane at https://www.epa.gov/quality/request-correction-and-reconsideration#tab-4
[37] ACI (2024) ACI - CA DTSC SCP PP for 14-DX – Comments, Document ID: #9632, available at: https://calsafer.dtsc.ca.gov/workflows/Comment/15560/?from=search.
[38] NICNAS (1998) 1,4-Dioxane Priority Existing Chemical No. 7, Full Public Report, National Industrial Chemicals Notification and Assessment Scheme (NICNAS), 129 pp., at p. 61 (PDF p. 75), available at: https://www.industrialchemicals.gov.au/sites/default/files/PEC7-1-4-Dioxane.pdf.

acting by a non-genotoxic mode of action. Therefore, a threshold approach is appropriate."[39]

- Health Canada concluded in its 2021 Guideline Technical Document for Public Consultation on 1,4-Dioxane in Drinking Water that "[s]ince 1,4- dioxane acts through a non-genotoxic MOA and demonstrates dose-related non-linear kinetics, a non-linear (threshold) risk assessment approach is considered appropriate."[40]
- The European Chemicals Agency's (ECHA) Committee for Risk Assessment (RAC) concluded in its 2022 Opinion on Scientific Evaluation of Occupational Exposure Limits for 1,4-Dioxane that "[a]lthough 1,4-dioxane may have genotoxic potential, and therefore could be considered a genotoxic carcinogen, there is evidence for indirect DNA damage (from oxidative stress) as the main mechanism in tumour formation. Also, cytotoxicity, irritation and inflammation appear to be associated with tumor formation, e.g. in the nasal epithelium and liver. These thresholded mechanisms support a non-linear dose-response relationship… In weighing all the current evidence, RAC is of the opinion that at low doses, 1,4-dioxane is not mutagenic. Liver and nasal cavity tumours are reported following saturation of 1,4-dioxane metabolism or elimination. Several studies support a non-genotoxic MoA involving cytotoxicity (oxidative stress) followed by regenerative hyperplasia and stimulation of endogenously formed mutations. A non-linear (threshold) risk assessment approach is considered appropriate."[41]

Both Health Canada and the World Health Organization have concluded a drinking water level of 50 ug/L that is protective of public health.[42,43]

Consideration of Human Epidemiology Studies

ACI recommends exclusion of the "Breast cancer" and "Autism spectrum disorder (ASD)" subsections since it is OEHHA's assessment that insufficient evidence exists in both instances to draw a firm conclusion. For the "Breast cancer" section, both cited studies faced limitations that could have affected their ability to detect true associations, such as potential errors in exposure modeling and generally low levels of exposure among participants. And for ASD, OEHHA states that "firm conclusions cannot be made regarding the relationship between 1,4-dioxane and ASD from human epidemiologic studies at this time." Therefore, ACI recommends exclusion of these

[39] ECB (2002) European Union Risk Assessment Report, 1,4-Dioxane, CAS No. 123-91-1, EINECS No. 204-661-8, Institute for Health and Consumer Protection, European Chemicals Bureau (ECB), 2nd Priority List, Vol. 21, 142 pp., at p. 91 (PDF p. 101), available at: https://echa.europa.eu/documents/10162/a4e83a6a-c421-4243-a8df-3e84893082aa.

[40] Health Canada (2021).

[41] ECHA (2022).

[42] Health Canada (2021).

[43] World Health Organization (2005).

sections until future scientific inquiries are published that changes the paradigm of the current understanding of 1,4-dioxane and its impact on human epidemiology.

Human Exposure and Consumer Products

The Review Draft states that "1,4-[d]ioxane residue in consumer products is a significant source of human exposure" but does not support this claim or reflect the current product or regulatory landscape for cleaning and personal care products. 1,4-Dioxane is formed as a trace level impurity during the production of ethoxylated surfactants that can remain present in finished products as an unintentional byproduct. Reformulations and innovations have enabled ACI members to make great strides in achieving levels below 1 part per million (ppm) in household cleansing products, the limit under New York State law that went into effect on December 31, 2023.[44] We ask that OEHHA take this into consideration in its determination of the PHG and revise the Review Draft accordingly.

Additional Comments

- The Review Draft notes that "In 2010, US EPA concluded a one-in-one-million cancer risk would correspond to a 1,4-dioxane drinking water concentration of 0.35 ppb and as a result, the notification level was revised to 1 ppb. The notification level was revised to 1 ppb instead of 0.35 ppb due to limitations in accurately quantifying 1,4-dioxane at levels below 1 ppb." We appreciate OEHHA's recognition of these technical limitations and encourage continued consideration and inclusion of method capability and practical factors in this process.
- Table 18 of the Review Draft does not include New York State's ambient water quality guidance values or the MCL of 1 ppb for 1,4-dioxane. We ask that OEHHA update the table accordingly.

Closing

ACI and its members again thank OEHHA for the opportunity to provide these comments. We urge OEHHA to carefully consider the issues that should be addressed before a PHG is set. Please let us know if you have any questions.

Sincerely,

Marie Gargas
Senior Director, Regulatory and International Affairs

[44] Available at: https://dec.ny.gov/environmental-protection/help-for-businesses/household-personal-cosmetic-dioxane-limits.