November 25, 2025

Submitted via oehha.ca.gov

California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
1001 I Street
Sacramento, CA 95814

Re: **Comments on Proposed Public Health Goal for 1,4-Dioxane**

To Whom It May Concern:

I. INTRODUCTION

The Dow Chemical Company (Dow) appreciates this opportunity to provide comments regarding the California Office of Environmental Health Hazard Assessment's (OEHHA) proposed Public Health Goals (PHG) for 1,4-Dioxane in Drinking Water.

Dow's product portfolio of plastics, industrial intermediates, coatings, and silicones delivers a broad range of differentiated, science-driven products and solutions for its customers in high-growth market segments, such as packaging, infrastructure, mobility, and consumer applications. Dow has studied 1,4-dioxane for years and many of its 1,4-dioxane studies have been determined by the U.S. Environmental Protection Agency (EPA) to be of high quality. Based on Dow's considerable scientific expertise, Dow is pleased to share these comments. As discussed more fully below, Dow believes that OEHHA's approach to developing a proposed PHG for 1,4-dioxane in drinking water is legally and scientifically flawed and would result in a misleading standard if it moves forward as proposed. Dow urges OEHHA to withdraw the proposed PHG for 1,4-dioxane as it is scientifically indefensible, needlessly and unduly conservative, and duplicative of existing and ongoing federal actions to evaluate the risk to human health and the environment from potential 1,4-dioxane exposure.[1] Alternatively, given the significant deficiencies with the

[1] The brevity of the comment period, even with the modest 15-day extension, has deprived Dow and other stakeholders of an adequate opportunity to comment and submit relevant scientific information. Despite the extension, OEHHA also did not correspondingly adjust the date of the public workshop that was held on November 13, 2025, preventing stakeholders from engaging meaningfully with OEHHA scientists and other interested stakeholders in that forum when they must simultaneously prepare comments in this compressed timeframe. It is a basic due process right for the government to provide adequate notice and an opportunity to be heard and to do less, as here, arbitrarily deprives the public of a protected interest and denies due process. An adequate comment period must be provided to ensure informed agency decision-making. Dow reserves all rights to supplement and/or amend these comments.

way OEHHA derived this PHG as explained in these comments, Dow urges OEHHA to revise the PHG to address these deficiencies to meet OEHHA's own legal and scientific requirements.

II. BACKGROUND

On September 24, 2025, OEHHA announced the availability of a draft document describing a proposed PHG for 1,4-dioxane in drinking water.[2] The proposed PHG is in response to a request made in 2019 by California's State Water Resources Control Board (SWRCB) that OEHHA establish a PHG for 1,4-dioxane.[3]

Under the California Safe Drinking Water Act of 1996 (Health and Safety Code Section 116365(c)), a PHG is an "estimate of the level of the contaminant in drinking water that is not anticipated to cause or contribute to adverse health effects, or that does not pose any significant risk to health."[4] For contaminants that are considered to be a carcinogen or other substance that may cause chronic disease, the PHG "shall be set at the level that, based upon currently available data, does not pose any significant risk to health."[5] PHGs are not enforceable regulatory standards, but SWRCB is directed to set maximum contaminant levels (MCL) for drinking water at a level as close to the PHG as is technologically and economically feasible, "placing primary emphasis on the protection of public health."[6]

The proposed 1,4-dioxane PHG is 0.04 micrograms per liter (µg/L; or 0.04 parts per billion (ppb)).[7] In addition to the PHG of 0.04 ppb, OEHHA proposes a noncancer health-

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2 OEHHA, Public Health Goals, First Public Review Draft, 1,4-Dioxane in Drinking Water (Sept. 2025) (Proposed PHG Document), https://oehha.ca.gov/sites/default/files/media/2025-09/1%2C4-dioxane%20PHG%20draft%20092625.pdf.

3 Memorandum from Darin Polhemus, P.E., Deputy Director, DIVISION OF DRINKING WATER, SWRCB, to Lauren Zeise, Ph.D., Director, OEHHA, and Melanie Marty, Ph.D., Deputy Director for Scientific Affairs, OEHHA (Jan. 22, 2019) (SWRCB request memo), https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/14dioxane/14-dioxane_phg_request_memo_signed.pdf.

4 Cal. Health & Safety Code § 116365(c).

5 Cal. Health & Safety Code § 116365(c)(1)(B).

6 Cal. Health & Safety Code § 116365(a).

7 Proposed PHG Document at 5.

protective concentration value of 33 ppb for 1,4-dioxane based on studies indicating liver and kidney degeneration and necrosis in male rats.

OEHHA states that the proposed PHG is based on hepatic tumors in female mice (Kano *et al.* 2009)[8] and multiple tumor types in male mice that have been questioned (Kasai *et al*. 2009).[9] In addition to review of animal studies, OEHHA states that it "performed a systematic literature search of human and animal toxicity and pharmacokinetics studies published from 2009 onward, just prior to the US EPA (2010) assessment. OEHHA also reviewed health assessments by US EPA (2013a) and the Agency for Toxic Substances and Disease Registry (ATSDR (2012), where studies published before 2009 were identified."[10]

III. TO MAKE DEFENSIBLE DECISIONS, OEHHA IS OBLIGATED TO FOLLOW LEGAL REQUIREMENTS AND SCIENTIFIC PRINCIPLES THAT IT HAS IGNORED OR MISAPPLIED IN THE PROPOSED PHG

A. OEHHA Has Ignored or Not Considered Adequately or Appropriately Applicable Legal Requirements

OEHHA has failed to comply with legal requirements and standards for developing PHGs, resulting in a proposed PHG for 1,4-dioxane that is scientifically flawed, legally deficient, and inappropriate for use in developing any future regulation. In setting a PHG, the statute directs OEHHA to engage in rational and transparent decision-making based on the best available science. OEHHA has failed to follow this statutory requirement for 1,4-dioxane by ignoring the most current data, much of which were developed after 2020, but well before OEHHA's proposal, and by not engaging in a scientific assessment consistent with OEHHA's statutory directive on cancer risk evaluation. OEHHA's PHG Guide states, "The process for establishing a PHG for a chemical contaminant in drinking water is very rigorous. OEHHA scientists first compile all relevant scientific information available, which includes studies of the chemical's effects on laboratory animals and studies of humans who have been exposed to the chemical." If OEHHA had relied upon the most current data and followed its own policies on cancer risk evaluation, it would have calculated a safe dose response threshold for cancer. Instead of developing that threshold, OEHHA utilizes a default cancer risk assessment method that mischaracterizes and overstates cancer risk,

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8 Kano H, Umeda Y, Kasai T, *et al*. (2009). Carcinogenicity studies of 1,4-dioxane administered in drinking-water to rats and mice for 2 years. Food Chem Toxicol 47(11): 2776-2784, https://doi.org/10.1016/j.fct.2009.08.012.

9 Kasai T, Kano H, Umeda Y, *et al.* (2009). Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. Inhal Toxicol. Sep;21(11):889-97. doi: 10.1080/08958370802629610. PMID: 19681729.

10 Proposed PHG Document at 6.

resulting in a proposed PHG that is unnecessarily and indefensibly low. The proposed PHG also misleads the public in falsely suggesting the existence of a public health threat, undermining one key reason for developing PHGs. It also undermines another other key reason for developing a PHG, which is informing the development of an MCL, by making it virtually certain that the MCL value will not be at or near the PHG.

1. OEHHA Cannot Ignore the Best Available Data

OEHHA must develop PHGs by following the requirements set forth in the law, implementing regulations, and related guidance. These legal standards have been established to ensure that OEHHA's risk assessments are based upon best available, sound science, and the most current principles, practices, and methods.

California's Health and Safety Code Section 116365(c)(1) states that OEHHA's "risk assessment shall be prepared using the most current principles, practices, and methods used by public health professionals who are experienced practitioners in the fields of epidemiology, risk assessment, and toxicology." OEHHA's Proposed PHG Document states: "PHGs are developed for chemical contaminants based on the best available data in the scientific literature and using the most current principles, practices, and methods used by public health professionals."[11]

As discussed in more detail in Section IV, OEHHA has not based its proposed PHG for 1,4-dioxane on the best and most current data, principles, practices, or methods. As examples:

- OEHHA conducted a limited literature search and review that included studies published prior to August 2023. As a result, OEHHA excluded new studies that were published after August 2023, in clear violation of OEHHA's requirement to ensure that it is basing the PHG on the best available data in the scientific literature consistent with Section 116365(c) and OEHHA's own policies and statements. In addition, OEHHA missed a number of key mechanistic studies that should have been identified as

[11] Proposed PHG Document at ii.

published before August 2023, such as Chappell *et al.* (2021)[12], Corton *et al*. (2020)[13], and Wang *et al.(*2022)[14].

- OEHHA determined that there were not adequate data to support a non-genotoxic mode of action (MOA) for cancer effects for 1,4-dioxane and applied its default linear extrapolation approach to assess cancer risk, in opposition of the conclusions made by other authoritative bodies based on the weight of evidence for the MOA of 1,4-dioxane such as ECHA RAC, 2022; Health Canada, 2021, and US EPA Risk Evaluation, 2020 assessments.
- OEHHA's PHG does not reflect the latest scientific research, that demonstrates that the default OEHHA cancer risk assessment methods and assumptions mischaracterize and overstate cancer risk from exposure to 1,4-dioxane in drinking water.

2. The PHG Is Significantly Lower Than Required, Undermining the Communicative Value and Purpose of PHGs

As a result of OEHHA's flawed scientific process and assumptions in the Proposed PHG Document that overstate risks, the proposed PHG level is indefensibly low. The statute requires OEHHA, in setting a PHG, to engage in rational and transparent decision-making based on the best available science. Instead of developing a scientifically sound threshold, however, OEHHA utilizes a default cancer risk assessment method that mischaracterizes and overstates

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12 Chappell, G. A., Heintz, M. M., & Haws, L. C. (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*, *2*, 30–41. https://doi.org/10.1016/j.crtox.2021.01.003

13 Corton, J. C., Hill, T., Sutherland, J. J., Stevens, J. L., & Rooney, J. (2020). A set of six gene expression biomarkers identify rat liver tumorigens in short-term assays. *Toxicological Sciences: An Official Journal of the Society of Toxicology*, *177*(1), 11–26. https://doi.org/10.1093/toxsci/kfaa101

14 Wang, Y., Charkoftaki, G., Davidson, E., Orlicky, D. J., Tanguay, R. L., Thompson, D. C., Vasiliou, V., & Chen, Y. (2022). Oxidative stress, glutathione, and CYP2E1 in 1,4-dioxane liver cytotoxicity and genotoxicity: Insights from animal models. *Current Opinion in Environmental Science & Health*, *29*, 100389. https://doi.org/10.1016/j.coesh.2022.100389

cancer risk, resulting in a legally flawed PHG that is lower than would otherwise be required under the statute.

This indefensibly low value undermines one of the primary purposes of PHGs: a communication tool for California to advise its citizens of the existence of legitimate public health threats, based upon best available data and sound science. Public water systems, for example, use PHGs to provide information in annual reports to customers about drinking water contaminants that may pose health risks. The flawed risk assessment sends an inaccurate, alarmist, and confusing message to citizens that will undermine public confidence in the accuracy of future public health warnings.

3. Testing Is Not Reliable at the Proposed PHG Level, Frustrating the Ability of California to Use the Value in Developing Future Regulation

The development of PHGs is a process based on health considerations. Feasibility and other considerations come into play later when SWRCB sets an MCL that aims to align as much as possible the PHG. While OEHHA may not be required to consider feasibility at this stage, the SWRCB will be challenged to develop an MCL that can be achieved based on this PHG.

If California were to establish a future MCL at the proposed PHG level (or close to it), the resulting testing efforts would inevitably lead to prolific data quality/false positive test results undermining efforts to ensure safe drinking water and causing undue public concern. While the EPA Method 522 specifies a Minimum Reporting Level (MRL) of 0.036 and 0.047 µg/L, this is not a common MRL among our preferred lab network. From our survey of four labs that conduct EPA Method 522, we've observed that their Reporting Levels range from 0.07 to 0.2 µg/L. Therefore, implementing a reporting level below this range, such as 0.04 µg/L, would be challenging. Because these reporting levels are so close to the proposed PHG, data at levels approaching the PHG would not be considered reliable, and at the very least, be incapable of distinguishing true detections from false positives. Testing to these levels would also require substantial additional investments in high-end analytical instruments, dedicated lab space and analysts to avoid contamination from the environment, and sophisticated sample preparation procedures, all of which will make testing costs prohibitively expensive.

B. OEHHA and SWRCB Should Defer to Actions on 1,4-Dioxane at the Federal Level

1. EPA Has Determined That an MCL for 1,4-Dioxane in Drinking Water Is Not Warranted

In 2021, EPA's Office of Water (OW) announced its decision under Section 1412 of the Safe Drinking Water Act (SDWA) not to regulate 1,4-dioxane in drinking water.[15] This

[15] EPA. "Announcement of Final Regulatory Determinations for Contaminants on the Fourth Drinking Water Contaminant Candidate List," 86 Fed. Reg. 12272 (Mar. 3, 2021),

decision was supported by an extensive analysis of available information, including nationally representative drinking water monitoring data collected through EPA's Unregulated Contaminants Monitoring Rule 3 (UCMR3). Although EPA OW identified health effects data indicating the potential for adverse human health effects, importantly, EPA did not find conclusive information that 1,4-dioxane "occurs in public water systems with a frequency and at levels of public health concern and whether there is a meaningful opportunity for public health risk reduction by establishing an NPDWR…."[16]

Notably, EPA OW estimated less than two baseline cancer cases per year attributable to 1,4-dioxane in drinking water.[17] EPA acknowledged that this number was derived in a manner intended to reflect a high-end estimate of the number of national cancer cases, meaning that the actual number may be lower.[18] EPA also identified a need for additional information on other adverse health effects following exposure to 1,4-dioxane. In a 2024 joint memo with EPA's Office of Chemical Safety and Pollution Prevention (OCSPP), OW committed to continue to collect occurrence information under the UCMR program and to keep 1,4-dioxane on future Contaminant Candidate Lists to determine whether there would be a meaningful opportunity at some future date for health risk reduction for persons served by public water systems by regulating 1,4-dioxane in drinking water.[19]

2. EPA's Efforts to Regulate Upstream Sources of 1,4-Dioxane Are Ongoing

OCSPP recently completed a risk evaluation for 1,4-dioxane under the Toxic Substances Control Act (TSCA), encompassing a broad set of circumstances regarding the manufacture, processing, distribution in commerce, use, and disposal of 1,4-dioxane.[20] The risk

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https://www.federalregister.gov/documents/2021/03/03/2021-04184/announcement-of-final-regulatory-determinations-for-contaminants-on-the-fourth-drinking-water

16 86 Fed. Reg. at 12287.

17 86 Fed. Reg. at 12287.

18 86 Fed. Reg. at 12287.

19 EPA. "Coordinated Risk Management Action on 1,4-Dioxane under Section 9(b) of the *Toxic Substances Control Act*" (Nov. 5, 2024) (OCSPP/OW 2024 Joint Memo), https://www.epa.gov/system/files/documents/2024-11/1_4-dioxane-tsca-9b-memo_november-2024.pdf.

20 EPA. "Supplement to the Risk Evaluation for 1,4-Dioxane," EPA Document # EPA-740-R-24-013 (Nov. 2024), https://www.epa.gov/system/files/documents/2024-11/1.-1-4-dioxane-.-supplement-to-the-risk-evaluation-.-public-release-.-hero.-nov-2024.pdf.

evaluation also considers risks to human health and the environment. Those findings can be used in a wider range of risk mitigation options, beyond drinking water. TSCA requires EPA to propose a risk management rule to address any identified unreasonable risks within one year of completing its risk evaluation. Appropriate regulatory action at the federal level will result in a single, uniform national standard that can provide consistency, improve compliance, and increase nationwide confidence in the safety of this chemical moving forward.

3. Continuing Another Scientific and Regulatory Process for 1,4-Dioxane in Drinking Water Is Not an Efficient Use of California's Taxpayer Resources

Given the prior and ongoing federal efforts involving 1,4-dioxane, continuing this initiative is unnecessary and a misuse of limited taxpayer resources. The California Environmental Protection Agency (CalEPA), which includes OEHHA and SWRCB, as an agency of the state government, has a duty to be transparent and accountable for how it uses taxpayer funds and is required to ensure the efficient and appropriate use of revenue and expenditures. CalEPA's foundational mission requires the agency to ensure "economic vitality" in California, providing an implicit mandate that it properly steward taxpayer dollars entrusted to it.[21]

Here, the use of taxpayer dollars to duplicate ongoing federal efforts for an assessment of potential risks from 1,4-dioxane in drinking water is fiscally irresponsible. Neither OEHHA nor SWRCB appear to be coordinating their efforts with those happening at the federal level, a mandate expressly required under CalEPA's programs, policies, and standards in California Public Resources Code Section 71110.[22]

For example, SWRCB knew, or should have known, that at the time it submitted a request that OEHHA initiate the process for development of a PHG in 2019, EPA was already in the process of considering whether to regulate 1,4-dioxane under SDWA. Likewise, OEHHA knew, or should have known, that EPA had already published its preliminary (2020)[23] and final (2021)[24] regulatory determinations for 1,4-dioxane under SDWA -- determining that an MCL was not warranted -- at the time that OEHHA published its proposed PHG (2025). Yet OEHHA's references to EPA scholarship in the technical support document for the PHG fail to acknowledge the determinations under SDWA, the accompanying analyses, or the federal position on the ability of an MCL to meaningfully reduce public health risks. This willful indifference to significant,

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21 CalEPA. "Our Mission," https://calepa.ca.gov/about/.

22 Cal. Pub. Res. Code § 71110(e).

23 EPA. "Announcement of Preliminary Regulatory Determinations for Contaminants on the Fourth Drinking Water Contaminant Candidate List," 85 Fed .Reg. 14098 (Mar. 10, 2020), https://www.federalregister.gov/documents/2020/03/10/2020-04145/announcement-of-preliminary-regulatory-determinations-for-contaminants-on-the-fourth-drinking-water.

24 86 Fed. Reg. at 12272.

preexisting, and ongoing federal regulatory and scientific efforts so duplicative of OEHHA's efforts is mystifying.

Finally, because both the California and the federal processes under TSCA and SDWA are happening simultaneously, interested stakeholders are compromised. These initiatives dilute the bandwidth of California citizens and others meaningfully to participate in disparate, duplicative, and resource-demanding administrative initiatives. Dow urges OEHHA to focus its limited scientific resources and expertise on participating in and collaborating with these ongoing federal processes.

IV. THE PROPOSED PHG IS SCIENTIFICALLY FLAWED AND OEHHA MUST WITHDRAW ITS PROPOSAL

A. OEHHA Is an Outlier on Its Interpretation of the Direct Genotoxic MOA for 1,4-Dioxane

Multiple global competent authorities agree that 1,4-dioxane is a threshold-based carcinogen. OEHHA used a linear low-dose extrapolation for deriving its Points of Departure (POD), which are orders of magnitude lower than those derived by other authoritative regulatory agencies that evaluated the same data and concluded that 1,4-dioxane is not a direct-acting genotoxic carcinogen and, hence, a threshold approach can be considered. EPA requires a linear approach be used where there is evidence of a genotoxic MOA. Because there is no evidence (or very weak evidence) of direct genotoxicity, the linear approach is not supported and inappropriately overestimates risk. This is bolstered by the use of threshold approaches by other global regulatory agencies.

- **World Health Organization (WHO):** In 2005, WHO summarized genotoxicity and related endpoints with "[t]he weight of evidence indicates that 1,4-dioxane is probably non-genotoxic"[25] and calculated a drinking water guideline value for 1,4-dioxane using both a linear low-dose extrapolation and tolerable daily index approach. The two approaches resulted in equivalent guideline values at 50 µg/L (ppb) in drinking water.[26]

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25 WHO (2005). *1,4-Dioxane in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality*, WHO/SDE/WSH/05.08/120, 12 pp., at 5, https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/dioxane-bd.pdf.

26 WHO (2005) at 9.

- **European Union:** 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 acting by a non-genotoxic mode of action. Therefore, a threshold approach is appropriate."[27] Further, 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 non-linear (threshold) risk assessment approach is considered appropriate"[28] in support of the recommended occupational exposure level (OEL) of 6 parts per million (ppm) (22 milligrams per cubic meter (mg/m^3)) for an 8-hour time-weighted average (TWA) and a short-term exposure limit (STEL) of 20 ppm (73 mg/m^3).

- **Canada:** Health Canada concluded in its 2021 Guideline Technical Document for Public Consultation on 1,4-Dioxane in Drinking Water that "since 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,"[29] resulting in a maximum acceptable concentration (MAC) of 0.050 milligrams per liter (mg/L) (50 µg/L) for 1,4-dioxane in drinking water.[30]

Table 1 summarizes the health protective values for 1,4-dioxane from global regulatory bodies with consensus on a threshold approach for cancer hazard.

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27 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 91, https://echa.europa.eu/documents/10162/a4e83a6a-c421-4243-a8df-3e84893082aa.

28 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 8, https://echa.europa.eu/documents/10162/7937606/1_final_opinion_oel_1_4_dioxane_en.pdf.

29 Health Canada (2021). Guidelines for Canadian Drinking Water Quality: Guideline Technical Document - 1,4-Dioxane, ISBN: 978-0-660-37417-8, at 39-40, 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.

30 Health Canada (2021) at 1.

Table 1: Health Protective Values for 1,4-dioxane.

Authoritative Body	Route of Exposure	Health Protective Value for 1,4-dioxane
WHO (2005)	Drinking water	50 µg/L (ppb)
ECB (2002)	Inhalation/dermal	Exposure scenario analysis only
ECHA (2022)	Inhalation	OEL = 6 ppm (22 mg/m^3) STEL = 20 ppm (73 mg/m^3)
Health Canada (2021)	Drinking water	MAC = 0.050 mg/L (50 µg/L or ppb)

There is general scientific consensus that 1,4-dioxane is not a direct genotoxicant based on the large body of *in vitro* and *in vivo* data that OEHHA describes in the Proposed PHG Document for 1,4-dioxane. OEHHA's determination of a direct genotoxic MOA (based on 1,4-dioxane or its metabolite(s)' reactivity with DNA) is deeply questionable given that other regulatory agencies around the world have determined that the carcinogenic MOA for 1,4-dioxane supports application of a non-linear approach (*i.e.*, a threshold). OEHHA's use of a linear low-dose extrapolation for carcinogenic risk assessment is misleading given the reasonably available information that informs the carcinogenic MOA for 1,4-dioxane and supports a threshold approach to cancer risk assessment and does not distinguish between direct and indirect genotoxic effects of the substance, as outlined in EPA's 2005 Guidelines for Carcinogen Risk Assessment.[31] Even EPA's (2020) risk evaluation concluded that although "there is some evidence for genotoxicity *in vivo* at high doses, but there is insufficient evidence to conclude that 1,4-dioxane is mutagenic or induces cancer through a mutagenic mode of action."[32]

This highlights the disagreement between OEHHA's conclusion of a mutagenic MOA and the overwhelming scientific consensus across global authoritative bodies. OEHHA's failure to explain why it has departed from the scientific conclusions of these other competent authorities, including the EPA (2020) risk evaluation, further underscores the arbitrary nature of OEHHA's decision. OEHHA failed to conduct an accurate and transparent systematic review of the available data set and omitted review of a significant portion of peer-reviewed literature within the identified time periods. EPA requires a linear approach be used where there is evidence of a genotoxic MOA. EPA has set this standard because if there is no evidence (or very weak evidence) of genotoxicity, the linear approach is not supported and inappropriately overestimates risk. This is bolstered by the use of threshold approaches by other regulatory agencies.

B. OEHHA Improperly Relies on a "Characteristics of Carcinogens" Approach, Rather than a Structured MOA Analysis

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31 EPA (2005). Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/011F https://www.epa.gov/sites/default/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

32 EPA (2020). Final Risk Evaluation for 1,4-Dioxane. https://www.epa.gov/sites/default/files/2020-12/documents/1._risk_evaluation_for_14-dioxane_casrn_123-91-1.pdf.

OEHHA outlines key characteristics of 1,4-dioxane as a potential carcinogen and states "these data support 1,4-dioxane is genotoxic (KC 2), induces chronic inflammation (KC 6), and alters cell proliferation (KC 10) but does [not] modulate receptor-mediated effects (KC 8)."[33] Becker *et al.*, 2017,[34] in contrast, showed that the Smith *et al.*, 2016[35] "characteristics of carcinogens" were no better at predicting carcinogenicity than chance alone, indicating that structured MOA analysis is required to understand and characterize carcinogenicity. Instead of the "characteristics of carcinogens" approach, OEHHA should apply a well-established MOA framework, such as International Life Sciences Institute's (ILSI) Key Events Dose-Response Framework [36] or EPA's Guidelines for Carcinogen Risk Assessment.

OEHHA does not address this shortcoming, nor does it provide conclusions regarding the mechanism or direct genotoxic MOA of 1,4-dioxane in carcinogenicity. OEHHA instead states that "[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."[37] All of these would cause indirect DNA damage and would be evident at high doses where DNA repair and detoxification mechanisms would become saturated: a high-dose phenomenon such as those seen in published peer-reviewed literature and consistent with other authoritative assessment conclusions for 1,4-dioxane. OEHHA concludes with an ambiguous

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33 Proposed PHG Document at 44.

34 Richard A. Becker, David A. Dreier, Mary K. Manibusan, Louis A. (Tony) Cox, Ted W. Simon, James S. Bus *How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?*, Regulatory Toxicology and Pharmacology, Volume 90, 2017, Pages 185-196, ISSN 0273-2300, https://doi.org/10.1016/j.yrtph.2017.08.021.

35 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: 10.1289/ehp.1509912. Epub 2015 Nov 24. PMID: 26600562; PMCID: PMC4892922. https://pubmed.ncbi.nlm.nih.gov/26600562/.

36 Julien, E., Boobis, A. R., Olin, S. S., & The ILSI Research Foundation Threshold Working Group (2009). The Key Events Dose-Response Framework: A Cross-Disciplinary Mode-of-Action Based Approach to Examining Dose-Response and Thresholds. Critical Reviews in Food Science and Nutrition, 49(8), 682–689. https://doi.org/10.1080/10408390903110692.

37 Proposed PHG Document at 51.

statement that reflects a lack of critical review and interpretation of the available science for 1,4-dioxane: "[T]he available evidence for a singular predominant mechanism for 1,4-dioxane carcinogenesis is not conclusive."[38]

EPA's Guidelines for Carcinogenic Risk Assessment -- a comprehensive and authoritative cancer risk assessment guidance documents -- explain that linear extrapolation is appropriate when "the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data."[39] OEHHA's finding that the weight of evidence is not conclusive for a singular mechanism does not indicate that a genotoxic MOA is plausible based on the available data, so OEHHA's application of the default linear extrapolation conflicts with the EPA guidance.

OEHHA ultimately defaults to linear low-dose extrapolation, despite clear evidence of a non-genotoxic MOA, which discounts secondary effects caused by oxidative stress such as DNA strand breaks at 8-OH-dG DNA lesions as summarized and discussed in Lafranconi *et al.* (2023)[40] and general agreement across multiple global competent authorities.

C. Systemic 1,4-Dioxane Levels above the Metabolic Threshold Initiate a Cascade of Events That Result in Tumor Formation

OEHHA's summary of the cancer MOA is flawed. Saturation of metabolic clearance and subsequent mitogenesis are the initiating and primary key events in 1,4-dioxane carcinogenicity, which is a threshold-based mechanism driving cancer hazard. There is supporting evidence for each key event in the literature that are summarized and presented as a step-wise mechanism in Lafranconi *et al.*, 2023.

OEHHA should consider Lafranconi *et al.*, 2023 and Kirman *et al.*, 2026[41], review articles of the cancer MOA of 1,4-dioxane, to ensure the best available data are applied in a manner

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38 Proposed PHG Document at 51.

39 EPA (2005), Guidelines for Carcinogen Risk Assessment at 3-21.

40 Mark Lafranconi, Janet Anderson, Robert Budinsky, Lisa Corey, Norman Forsberg, Joanna Klapacz, Matthew J. LeBaron, *An integrated assessment of the 1,4-dioxane cancer mode of action and threshold response in rodents*, Regulatory Toxicology and Pharmacology, Volume 142, 2023, 105428, ISSN 0273-2300, https://doi.org/10.1016/j.yrtph.2023.105428.

41 C.R. Kirman, J.S. Bus, S. Gupta, J.E. Klaunig, M.E. Meek, S.M. Hays, *Expert panel evaluation of the tumor modes of action for 1,4-dioxane and their implications for human*

consistent with the weight of scientific evidence and supports the role of direct mitogenesis as an early key event in the carcinogenic MOA of 1,4-dioxane. The cancer MOA of 1,4-dioxane is "dependent on exceeding the metabolic clearance of absorbed 1,4-dioxane, direct mitogenesis, elevation of Cyp2E1 activity and oxidative stress leading to genotoxicity and cytotoxicity followed by sustained proliferation driven by regenerative repair and progression of heritable lesions to tumor development."[42]

- **Biological Threshold:** Lafranconi *et al.* (2021) determined through experimentation that their results "provide further evidence for the metabolic saturation of clearance pathways as an initiating key event (KE) leading to accumulation of systemic 1,4-DX."[43] 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]."[44] *See* Figure 1.

  In a recent review article, Lafranconi *et al*. (2023) clearly describe the body of data supporting metabolic saturation at 30-100 milligrams per kilogram per day (mg/kg-day) in rats and 200- >400 mg/kg-day in mice.[45]

  > The plasma levels reported in the 13-week inhalation study by Kasai *et al.* (2008) achieved average values of 48 and 80 µg/ml at the lowest exposure level of 400 ppm for males (approximately 158 mg/kg) and females (approximately 167 mg/kg), respectively. The other exposures used in this study, 800, 1,600, and 3200 ppm, all generated blood levels exceeding the estimated metabolic threshold and are in the range of exposures that caused tumors in the two-year

risk assessment, Regulatory Toxicology and Pharmacology, Volume 164, 2026, 105950, ISSN 0273-2300, https://doi.org/10.1016/j.yrtph.2025.105950.

42 Kirman *et al*. (2026) at 4 (PDF).

43 Mark Lafranconi, Robert Budinsky, Lisa Corey, Joanna Klapacz, James Crissman, Matthew J. LeBaron, Rachel Golden, Richard Pleus (2021). *A 90-Day Drinking Water Study in Mice to Characterize Early Events in the Cancer Mode of Action of 1,4-Dioxane*, REGULATORY TOXICOLOGY AND PHARMACOLOGY, Vol. 119, 8 pp., at 5 (PDF), https://doi.org/10.1016/j.yrtph.2020.104819.

44 Lafranconi *et al*. (2021) at 5 (PDF).

45 Lafranconi *et al*. (2023) at 11 (PDF).

inhalation study by the same authors (Kasai *et al.*, 2009). Inhalation exposures of 50, 250 and 1250 ppm (approximately 19, 97, 488 mg/kg/d) were used in a two-year follow-up study by the same investigators (Kasai *et al*., 2009). Based on the plasma levels generated in the 13-week study, it is reasonable to expect the highest exposure, 1,250 ppm, would generate blood levels above the metabolic saturation threshold. Unfortunately, blood or plasma levels of 1,4-DX were not reported to confirm this.

Across the rat bioassays (Torkelson *et al*., 1974[46]; Kasai *et al*., 2009; Kociba *et al*., 1974[47]; NCI, 1978; Kano *et al*., 2009), the results show that the incidence of all treatment-related tumors (*i.e.,* nasal cavity squamous cell carcinoma, hepatocellular adenoma and carcinoma, differed significantly from controls starting at lifetime average daily doses in excess of 30 mg/kg. This point of departure aligns with current understanding that 1,4-DX metabolism/clearance saturation occurs somewhere between 30 and 100 mg/kg/d (Young *et al.*, 1978)[48]. This is also true for the dose-response analysis of tumor formation for mice in which the point of departure, determined by the LOEL, exceeds the metabolic/clearance threshold of 200 to >400 mg/kg/d projected for mice (Lafranconi *et al*., 2021; Sweeney *et al.*, 2008). In mice, doses resulting in tumors after chronic exposure to 1,4-DX typically are in excess of 200–400 mg/kg/d.

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46 Torkelson, TR; Leong, BKJ; Kociba, RJ; Richter, WA; Gehring, PJ. (1974). 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. Toxicol Appl Pharmacol 30: 287-298. http://dx.doi.org/10.1016/0041- 008X(74)90100-8

47 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. https://doi.org/10.1016/0041-008X(74)90099-4.

48 Young, JD; Braun, WH; Gehring, PJ. (1978a). The dose-dependent fate of 1,4-dioxane in rats. J Environ Pathol Toxicol 2: 263-282. http://dx.doi.org/10.1080/15287397809529693

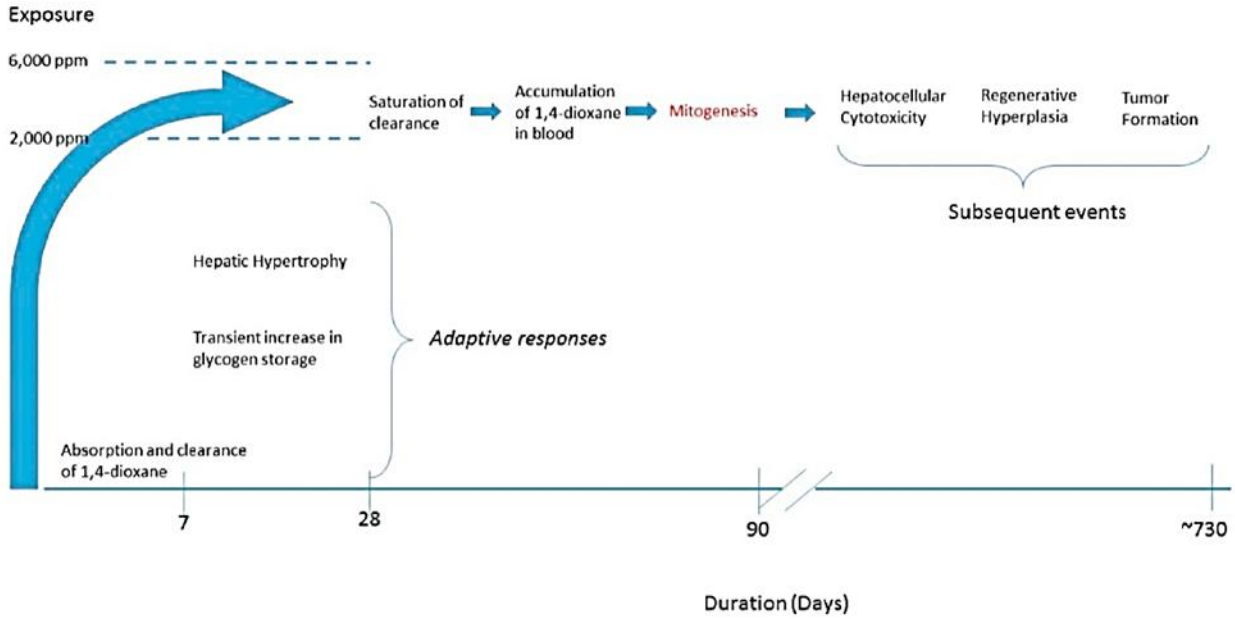

Figure 1: MOA of 1,4-dioxane induced development of hepatic tumors (Lafranconi *et al*., 2021).

- **Key Event 1 -- Mitogenesis:** Lafranconi *et al*. (2021) found that "the 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."[49] 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."[50]

- **Key Event 2 -- Elevation of Cyp2E1 Activity and Oxidative Stress:** Sustained activation of Cyp2E1 is recognized as a molecular initiating event (MIE) that leads to liver cancer and has a well-developed adverse outcome

[49] Lafranconi *et al*. (2021) at 6 (PDF).

[50] Lafranconi *et al*. (2023) at 13 (PDF).

pathway (AOP)[51] that is endorsed by the Organisation for Economic Co-operation and Development (OECD; *i.e.*, AOP: 220).[52]

- **Key Event 3 -- Genotoxicity and Cytotoxicity:** Data generated from *in vivo* studies show genotoxicity to be the result of elevated generation of reactive oxygen species (ROS) and subsequent oxidative DNA damage based on a recognized AOP (Cho *et al.*, 2022[53]). Lafranconi *et al.* (2023) 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-dioxane"[54] based on data from Kociba *et al*. (1974)[55] in rats.

These data support the view that the carcinogenic MOA for 1,4-dioxane involves a threshold response occurring as a downstream effect of direct mitogenesis, oxidative stress, and subsequent genotoxicity and cytotoxicity, yet OEHHA dismisses this evidence with a perfunctory statement that "the available evidence […] is not conclusive."[56] Lafranconi *et al*. (2021) showed that saturation of clearance of 1,4-dioxane and accumulation in the blood leads to direct mitogenesis and subsequent events leading to eventual tumor formation (*See* Figure 1).

D. OEHHA Incorrectly Determined Genotoxicity As a Relevant MOA Based on Micronucleus Formation

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51 Webster *et al*. (2023). *Cyp2E1 Activation Leading to Liver Cancer*, AOP: 220, Last modified on April 29, 2023, AOP Wiki, https://aopwiki.org/aops/220#prototypical-stressors.

52 Webster *et al*. (2023).

53 E. Cho, A. Allemang, M. Audebert, V. Chauhan, S. Dertinger, G. Hendriks, M. Luijten, F. Marchetti, S. Minocherhomji, S. Pfuhler, D.J. Roberts, K. Trenz, C.L. Yauk. *AOP report: development of an adverse outcome pathway for oxidative DNA damage leading to mutations and chromosomal aberrations*, Environ. Mol. Mutagen., 63 (2022), pp. 118-134, https://doi.org/10.1002/em.22479.

54 Lafranconi *et al*. (2023) at 13.

55 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. https://doi.org/10.1016/0041-008X(74)90099-4.

56 Proposed PHG Document at 51.

Micronucleus formation in bone marrow and hepatocytes, an indicator of potential genotoxicity, only occurs at elevated doses that are likely to saturate the systemic metabolic capacity for 1,4-dioxane in study animals and express in oxidative DNA damage. The resulting effects include an array of oxidative DNA lesions (with 8-OH-dG being the most prevalent), DNA strand breaks, and g-H2AX histone phosphorylation).
The body of evidence for micronucleus formation, which OEHHA highlights as a key finding in EPA's updated 2020 risk evaluation for 1,4-dioxane[57], reflects this high-dose, indirect mechanism. EPA concluded "1,4-dioxane is genotoxic *in vivo* at high doses based on bone marrow micronucleus assays." EPA has indicated, however, that it plans to revisit its TSCA risk evaluation so this conclusion may be subject to revision.

OEHHA's perfunctory dismissal of the evidence that it did consider, and failure to consider more recent and directly relevant studies demonstrates that the PHG was not 'prepared using the most current principles, practices, and methods used by public health professionals who are experienced practitioners in the fields of epidemiology, risk assessment, and toxicology' as required by the statute.

In the epidemiology section, OEHHA discussed two population studies that investigated potential associations with 1,4-dioxane and autism spectrum disorder (ASD). OEHHA cites two fatally flawed studies with diverging conclusions as to any reasonable association trends. Furthermore, 1,4-dioane exposure was based on zip code air concentrations and no other, more relevant routes of exposure to the outcomes. OEHHA should make clear that the existing epidemiological dataset does not allow any meaningful analysis or conclusions on biological plausibility of the ASD association with the substance. At the very least, OEHHA should remove the word 'firm' and note that the exposure analyses and conclusions as to ASD association are extremely limited.

E. An Independent Expert Panel Evaluation of the Tumor MOAs for 1,4-Dioxane Supports the Use of Non-Linear Extrapolation Methods for Cancer Risk

The application of a linear low-dose approach is not health protective if the science does not support the approach. Nor is this approach permitted under California law which requires OEHHA to base a safe dose threshold on "adequate scientific evidence."[58] OEHHA appears to be using a non-risk factor (its preference for a non-threshold approach) as a means of justifying its risk determination, rather than incorporating reasonably available information into the Proposed PHG Document as required by law such that it reflects the best available science and weight of scientific evidence for the carcinogenic MOA for 1,4-dioxane.

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58 Cal. Health & Safety Code § 116365(c)(1)(D).

An independent panel of six experts (Kirman *et al*., 2026) with a total of 230 years of professional experience and 1,270 publications evaluated multiple alternative MOAs, including the genotoxic MOA that OEHHA proposes in the Proposed PHG Document. The panel concluded that the most likely MOA begins with a threshold event (metabolic saturation), followed by cytotoxicity, proliferative repair processes (regenerative hyperplasia), promotion of cells with DNA damage, and tumor formation in susceptible tissues.

The independent expert panel operated under multiple controls to minimize bias and maximize transparency: triple-blinding (*i.e.*, sponsor:panel members, panel members:sponsor, panel member:panel member); used a structured, three-round, modified Delphi format for the review; tasked panelists to consider topics outside of the charge questions to avoid narrow scope bias; and published individual anonymized comments from panelists in their entirety. These review design elements reinforce the transparency of the approach and give strong validity to the panel's conclusions where:

> (1) Metabolic saturation of 1,4-DX can serve as an MIE in the MOA for 1,4-DX tumors;
> (2) MOAs involving proliferative regeneration induced by cytotoxicity and/or indirect genotoxicity are supported by the weight of evidence;
> (3) A direct genotoxic MOA is not supported by the weight of evidence for any of the tumor types considered, as indicated by negative MOA confidence score that are significantly lower than the positive score attributed to the MOAs in Conclusion 2 […]; and
> (4) Based on Conclusions 2 and 3, a threshold dose-response relationship is supported for human health risk assessment for 1,4-DX tumors.[59]

V. OEHHA Inappropriately Bases the Cancer Oral Slope Factor (OSF) for 1,4-Dioxane on Tumor Incidence Data from Kano *et al.* (2009)

OEHHA is relying on a controversial study with findings that are inconsistent with the weight of scientific evidence from other studies in rats and mice. OEHHA and EPA are the only regulatory bodies in the world to rely upon the Kano *et al.* (2009)[60] study. This study was conducted by the Japan Bioassay Research Center (JBRC), yet Japan does not base its own

[59] Kirman *et al*. (2026) at 8 (PDF).

[60] EPA (2020).

drinking water standard for 1,4-dioxane on the Kano *et al.* (2009) study and instead appears to rely on WHO's guideline value of 0.05 milligrams per liter (mg/L).[61,62]

Lafranconi *et al*. (2023) reviewed the issues with Kano *et al*. (2009), that included the following:[63]

- 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. A 2014 re-evaluation of the NCI study data by Dourson *et al.*, confirmed the lowest observable adverse effect level (LOAEL) for liver tumors at 380 mg/kg/d,[64] but there are no available histopathology slides or images available to re-review the Kano *et al.*, 2009 study. This underscores the transparency and validity of the NCI data set and highlights the opaqueness of the Kano data set and brings to question whether the data are valid.

- The 13-week mouse drinking water study (Kano *et al.*, 2008)[65] reported non-neoplastic liver pathology that was inexplicably not reported in the two-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

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

62 WHO (2005) at 9, https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/dioxane-bd.pdf.

63 Lafranconi *et al*. (2023) at 5 (PDF).

64 Dourson *et al*. (2014). Mode of action analysis for liver tumors from oral 1,4-dioxane exposures and evidence-based dose response assessment, Regul Toxicol Pharmacol, 68(3):387-401. doi: 10.1016/j.yrtph.2014.01.011.

65 Kano H, Umeda Y, Saito M, *et al.* (2008). Thirteen-week oral toxicity of 1,4-dioxane in rats and mice. J Toxicol Sci. 33(2):141-53. doi: 10.2131/jts.33.141. PMID: 18544906. https://www.jstage.jst.go.jp/article/jts/33/2/33_2_141/_pdf.

chronic study by Kano was incomplete. Health Canada similarly described the misalignment of JBRC study data with the reported outcomes: "The absence of non-cancer histopathological changes and the concomitant increase in liver enzymes in the JBRC studies despite the presence of both endpoints in the sub-chronic studies from the same group […] lend credence to the uncertainty surrounding the development of tumours at this low dose."[66]

- The diagnostic criteria used in the original JBRC report (JBRC, 1990) and associated conference proceedings (Yamazaki *et al.*, 1994) changed in the subsequent peer-reviewed publication of the same study (Kano *et al.*, 2009), but the JBRC report (1990) does not show any dose-related hyperplasia or foci (as reviewed in Dourson, *et al*., 2017).[67] These retroactive changes to histopathologic interpretation of lesions and foci, along with a lack of transparency and non-availability of images for re-review, put into question the validity and interpretation of the findings.

The Kano *et al*. (2009) study 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 and OEHHA provides no explanation although critical narratives of this 2009 publication have become available.

For example, We note that Health Canada (2021) questioned the results of Kano *et al*. (2009), as described above, and 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 JBRC studies despite the presence of both endpoints in the sub-chronic studies from the same group…"[68]

VI. OEHHA Has Failed to Meet Its Commitment to Transparency and the Dissemination of Pertinent Information

OEHHA has not provided a clear and transparent record of the scientific determinations upon which the PHG is based. This lack of transparency is inconsistent with the

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66 Health Canada (2021) at 30.

67 Dourson M, Reichard J, Nance P, *et al.* (2014). Mode of action analysis for liver tumors from oral 1,4-dioxane exposures and evidence-based dose response assessment. Regul Toxicol Pharmacol. 68(3):387-401. doi: 10.1016/j.yrtph.2014.01.011. Epub 2014 Feb 1. PMID: 24491968.

68 Health Canada (2021) at 29-30.

statute and OEHHA's claimed commitment to use the best available science. As an example, a thorough review by Lafranconi *et al.* (2023) should have been found in OEHHA's August 2023 literature search as it was published online in June 2023, but is not referenced at all in OEHHA's assessment. The 2023 review by Lafranconi *et al*. (2023) clearly integrates data from recently published studies (see Section III) to update the basis of understanding for the cancer MOA of 1,4-dioxane. There are at least nine new studies that OEHHA did not consider in their review. OEHHA has not been fully transparent in how it conducted its literature review, including how OEHHA scored study quality, precluding stakeholders' ability to understand the criteria used by OEHHA to select or reject studies from consideration.

VII. OEHHA Compounds Uncertainty by Applying an Uncertainty Factor for Database Deficiencies and Applying Adjustments for Early-In-Life Exposures

OEHHA establishes an uncertainty factor (UF) of square root (√) 10 for database insufficiency based on a single reproductive/developmental toxicity study. EPA (2020) determined that the study was of high quality. Study data clearly support maternal toxicity, not developmental toxicity[69] and the UF should be one for database sufficiency as there are adequate data available.

While there are no toxicokinetic data available for 1,4-dioxane exposure in children, a high-quality reproductive/developmental toxicity study in rats exists that established maternal toxicity, and not direct developmental toxicity (Giavini *et al*., 1985). OEHHA assigned a UF of "10 for pharmacokinetics variability, including infants and children with no kinetic data (OEHHA, 2008)."[70]

Early-in-life exposures are adequately captured in the risk assessment as required by OEHHA, precluding the need for additional application of UFs related to this sensitive developmental window. OEHHA accounts for the increased susceptibility of children and infants to carcinogens by applying age sensitivity factors (ASF) to the cancer potency (OEHHA, 2009). In the Proposed PHG Document, OEHHA states: "These default factors are applied regardless of the mechanism of action, unless chemical-specific data exist to better guide the risk assessment."[71] However, as described above, children are adequately protected by using a 10-fold UF for human

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69 Giavini E, Vismara C, Broccia ML (1985). Teratogenesis study of dioxane in rats. Toxicol Lett 26(1): 8588. https://doi.org/10.1016/0378-4274(85)90189-4.

70 Proposed PHG Document at 53.

71 Proposed PHG Document at 13-14.

variability[72]; OEHHA's additional assignment of an ASF thus is overly protective and unsupported by expert assessment.[73]

OEHHA's assignment of unrealistically high-age group-specific 95th percentile drinking water consumption rates multiplies the precautionary assumptions assigned in this Proposed PHG Document for 1,4-dioxane. OEHHA should revise its drinking water rates to the mean recommended values for drinking water rates as established by EPA (2019)[74] to assess accurately relative risk for infants and children over a lifetime of water consumption, similar to the WHO- recommended approach.[75]

VIII. OEHHA Applies Overly Conservative Extra Risk in the Application of Benchmark Dose (BMD) Methodology for Cancer Hazard

OEHHA's Technical Support Document (TSD) states that "Suitable polynomial fits and estimates of the benchmark may be obtained using EPA's BMDS software. The benchmark often used is the 95% lower confidence bound on the dose producing 10% tumor incidence. However, if data are available which include a significant dose-response at less than 10% tumor incidence, then that lower benchmark should be used (*e.g.*, LED_{05} or LED_{01})."[76] Tumor incidence data for 1,4-dioxane as presented by OEHHA do not have a significant dose-response at less than 10% tumor incidence, but rather illustrates a metabolic saturation threshold followed by LOAELs

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73 Giavini *et al*. (1985).

74 EPA (2019). Exposure Factors Handbook Chapter 3 (Update): Ingestion of Water and Other Select Liquids, Table 3-1 at 4, https://cfpub.epa.gov/ncea/efp/recordisplay.cfm?deid=343661.

75 WHO (2022). Guidelines for drinking-water quality: Fourth edition incorporating the first and second addenda, https://www.pseau.org/outils/ouvrages/who_guidelines_for_drinking_water_quality_4th_edition_2022.pdf.

76 OEHHA (2009). Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures at 27, https://oehha.ca.gov/sites/default/files/media/downloads/crnr/tsdcancerpotency.pdf.

for tumor incidence of 40 to 44%.[77,78] OEHHA must revise its application of 5% extra risk in the BMD model parameters to a more appropriate and justified 10% extra risk per policy guidance and application of the best scientific methods and approaches.

IX. OEHHA Disregards the Physicochemical Properties and Environmental Fate of 1,4-Dioxane in Assignment of a Relative Source Contribution (RSC) of 0.2 for Exposure via Drinking Water

In the Proposed PHG Document, OEHHA states: "The RSC of 0.2 is selected for 1,4-dioxane as the general population can be exposed to 1,4-dioxane through other sources such as air, soil, food, and consumer and industrial products, in addition to drinking water. However, data on the exposure patterns of these other sources are not available, thus the default value of 0.2 is applied."[79] Whereas in the Production, Use, and Environmental Occurrence section of the Proposed PHG Document, OEHHA highlights a reduction in environmental release since 2014, low measured air values, and low likelihood of presence in soil.

OEHHA states in the Proposed PHG Document that "[o]nce in the air, [1,4-dioxane] is quickly degraded by photo-oxidation with a reaction half-life of 6.7 hours (US EPA, 2013a)" and "[d]ue to its low organic carbon-water partition coefficient (K_{oc}), 1,4-dioxane is not expected to sorb to soil, but readily migrates to ground and surface water (ATSDR, 2012)."[80] OEHHA should assign RSCs for air and soil to zero, maintain the RSCs for food and consumer and industrial products at 0.2, and increase the drinking water RSC to 0.6. This more accurately reflects the primary RSC of 1,4-dioxane to the general population through drinking water and is supported by detection of 1,4-dioxane in ten counties in California representing about half of the state's population.[81]

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77 Kano H, Umeda Y, Kasai T, *et al*. (2009). Carcinogenicity studies of 1,4-dioxane administered in drinking-water to rats and mice for 2 years. Food Chem Toxicol 47(11): 2776-2784. https://doi.org/10.1016/j.fct.2009.08.012.

78 NCI (1978). Bioassay of 1,4-dioxane for possible carcinogenicity. National Cancer Institute Carcinogenesis Technical Report Series No. 80. Bethesda, MD. 80**:** 1-123. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr080.pdf.

79 Proposed PHG Document at 65.

80 Proposed PHG Document at 15.

81 Department of Toxic Substances Control (DTSC) (2025). Product-Chemical Profile for Personal Care and Cleaning Products Containing 1,4-Dioxane, California EPA, https://dtsc.ca.gov/wp-content/uploads/sites/31/2025/05/14-Dioxane_Final_Profile_Accessible_Version.pdf.

X. CONCLUSION

Dow urges OEHHA to withdraw the proposed PHG for 1,4-dioxane, as it is legally and scientifically indefensible and unnecessary considering prior and ongoing federal actions. Alternatively, given the significant deficiencies with the way OEHHA derived this Proposed PHG Document as explained in these comments, Dow urges OEHHA to revise it to address these deficiencies to meet OEHHA's own legal and scientific requirements.

Dow appreciates the opportunity to provide these comments for consideration. Please let us know if you have any questions.

Sincerely,

Melissa Schisler
Global Director of Product Regulatory and Scientific Expertise