November 25, 2025

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
P.O. Box 4010, MS-12B
1001 I Street
Sacramento, California 95812-4010
Attention: PHG Program (Hermelinda Jimenez)
https://oehha.ca.gov/comments

Subject: Comments on OEHHA's First Public Review Draft Proposed Public Health Goal for 1,4-Dioxane in Drinking Water

Dear Ms. Jimenez:

The undersigned organizations hereby submit the following comments in response to the Office of Environmental Health Hazard Assessment's (OEHHA) First Public Review Draft Public Health Goal (PHG) for 1,4-Dioxane in Drinking Water ("draft PHG"). We appreciate OEHHA's action to extend the public comment period by an additional two weeks to allow for a more thorough review of, and development of comments on, the draft PHG.

Our organizations represent companies that have used 1,4-Dioxane (1,4-DX) or parent compounds in industrial applications or in manufacturing commercial and consumer products, and companies that manufacture personal care and cleaning products using surfactants that may generate trace amounts of 1,4-DX as an unintended by-product. We also represent companies that are water users and wastewater dischargers, and companies that own and operate their own water systems, a subset of public water systems known as non-transient, non-community (NTNC) water systems.[1] Our members are committed to addressing contamination affecting their NTNC water systems and providing safe drinking water to those they serve. Based on our in-depth review of the draft PHG for 1,4-DX, we have identified a number of technical and science policy deficiencies that must be addressed in a revised draft PHG to satisfy OEHHA's express statutory obligations to establish the PHG "at the level that, based upon currently available data, does not pose any significant risk to health." Addressing these issues also helps OEHHA ensure that it is not improperly leading the State Water Resources Control Board (SWRCB) to establish a future primary drinking water standard at a level lower than necessary to avoid posing a significant health risk, which would impose unnecessary costs on water purveyors and wastewater treatment system operators.

Public water systems, including NTNC water systems, are subject to enforceable maximum contaminant levels (MCLs) developed by the State Water Resources Control Board (SWRCB) and applied to chemical contaminants in sources of drinking water and in wastewater discharges. In the latter case, MCLs are incorporated by reference into Regional Water Quality Control Board (RWQCB) basin plans and National Pollution Discharge Elimination System (NPDES) direct discharge permits. OEHHA plays a critical role in the development of MCLs by adopting PHGs to estimate "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."[2] While PHGs are not enforceable drinking water or wastewater discharge standards, they are a key consideration in setting MCLs. Public water systems are also required to provide information to the public about potential health risks from exposure

[1] Health & Saf. Code, § 116275(k): "Nontransient noncommunity water system" means a public water system that is not a community water system and that regularly serves at least 25 of the same persons over six months per year.
[2] Health & Saf. Code, § 116365(c)(1).

to drinking water contaminants that exceed their corresponding PHGs, and about the cost of treatment to achieve PHGs, in annual Consumer Confidence Reports.[3]

The California Safe Drinking Water Act (CSDWA) requires the SWRCB to set the MCL for a given contaminant "as close as feasible to the corresponding public health goal" placing primary emphasis on protection of public health and technological and economic feasibility.[4] Since assuming responsibility for the state drinking water program in 2014, the State Water Resources Control Board (SWRCB) has emphasized achieving PHGs when it establishes MCLs, including by prioritizing reviews of existing MCLs set above their corresponding PHGs, and by lowering detection limits for reporting purposes (DLRs) to investigate the feasibility of achieving MCLs that are closer to their corresponding PHGs.[5]

We recognize that OEHHA must take steps to mitigate uncertainties in the scientific evidence it uses to characterize health risk from exposure to drinking water contaminants. The CSDWA anticipates these challenges in the requirements it imposes on OEHHA for purposes of developing PHGs. It requires OEHHA, in the course of setting PHGs, to prepare risk assessments "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."[6] It also requires OEHHA to set PHGs at the "safe dose response threshold" if "adequate scientific evidence" demonstrates that such a threshold exists for the subject contaminant.[7] These requirements are particularly relevant to this PHG because, as we discuss in greater detail in the attached technical comments, the weight of evidence demonstrates that a safe dose response threshold does exist for cancer effects from exposure to 1,4-DX in drinking water. This conclusion is further supported by peer-reviewed studies and public health assessments published over the past three decades, including several published in just the past five years (see Attachment A for a list of these studies), many of which were not considered by OEHHA in the Technical Support Document. This accumulated weight of evidence supporting a threshold MOA for liver tumors (generally recognized as the most sensitive cancer endpoint), coupled with the statutory requirements

[3] Health & Saf. Code, § 116470(b) requires public water systems with more than 10,000 service connections that detect contaminants above their PHGs to provide PHG exceedance reports every three years and to hold public hearings regarding their reports. See also SWRCB, Consumer Confidence Reports (CCRs), available at https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/CCR.html (last accessed Oct. 17, 2025).
[4] Health & Saf. Code, § 116365(a).
[5] "DDW [SWRCB Division of Drinking Water] is continuing work to evaluate the potential for reporting concentrations closer to PHGs, beginning with metals. As lower reporting levels are determined to be feasible, staff proposes revising DLRs to allow occurrence data collection to better inform the MCL review process. A preliminary proposal based on the results of surveys of Environmental Laboratory Accreditation Program (ELAP) certified laboratories was presented at a November 2022 workshop. A courtesy pre-publication Department of Finance review was completed in November 2023. Laboratory surveys regarding costs and capabilities for analysis of organic compounds are anticipated to start in 2025, following release of the metal DLRs notice of proposed rulemaking." (See SWRCB, Board Meeting Session, Division of Drinking Water (Feb. 19, 2025), Item 3, p. 4, available at https://www.waterboards.ca.gov/board_info/agendas/2025/feb/021925_3.pdf.)
[6] Health and Safety Code §116365(c)(1).
[7] Health and Safety Code §116365(c)(1)(D).

for OEHHA to use "the most current principles, practices, and methods," and to base the PHG "upon currently available data," requires OEHHA in developing this PHG to reject the default cancer risk assessment methods and assumptions it has historically used. Failure to comply with these statutory requirements leads OEHHA to rely on assumptions that mischaracterize cancer risk from exposure to 1,4-DX in drinking water. In turn, this may cause SWRCB to establish an MCL that is lower than necessary to avoid any known or anticipated adverse effects on public health from toxic substances with an adequate margin of safety, and lower than necessary to avoid any significant risk to public health from carcinogens or substances that may cause chronic disease, which increases compliance costs for water systems but does not actually improve public health protections.

1,4-DX presents several practical challenges that necessitate a more rigorous approach to the development of the PHG. The available literature on remediation of 1,4-DX demonstrates that it is resistant to conventional water treatment technologies, especially at levels approaching California's current 1 microgram per liter (µg/L) DLR.[8] In addition to industrial and other sources of 1,4-DX, the generation of trace amounts of 1,4-DX as a byproduct of the manufacture of consumer products, which are washed down drains and into sanitary sewers and septic systems during their normal use, means that the occurrence of 1,4-DX in potable reuse and groundwater recharge systems, and ultimately in sources of drinking water, is likely to be more widespread than the available occurrence data indicates.[9] A new MCL set at or close to the draft PHG would create significant new barriers for water recycling programs, which are a lifeline for many communities struggling with climate-induced water supply constraints, and would conflict with the state's water recycling policy goals.[10] In addition, the advanced chemical-specific and energy-intensive treatment necessary to remove small concentrations of 1,4-DX from wastewater and sources of drinking water would likely be cost-prohibitive for systems serving small and disadvantaged communities,[11] some of which are already designated by the SWRCB as failing, or at-risk of failing, to provide safe drinking

[8] SWRCB, Groundwater Fact Sheet, 1,4 Dioxane (Nov. 2019), p. 3, available at https://www.waterboards.ca.gov/gama/docs/coc_1_4_dioxane.pdf; US EPA, Treatment Technologies for 1,4-Dioxane: Fundamentals and Field Applications (Dec. 2006), p. 2-1, available at https://www.epa.gov/sites/default/files/2015-08/documents/treatment_for_1-4-dioxane_542r06009.pdf.

[9] Department of Toxic Substances Control, Product-Chemical Profile for Personal Care Products and Cleaning Products Containing 1,4-Dioxane, August 2025 Final Version, pp. 45-47; available at https://dtsc.ca.gov/wp-content/uploads/sites/31/2025/05/14-Dioxane_Final_Profile_Accessible_Version.pdf.

[10] Governor Newsom just signed SB 31 (McNerny, 2025), which is intended to help achieve California's Water Supply Strategy goal of using 1.8 million acre-feet of recycled water by 2040 (https://leginfo.legislature.ca.gov/faces/billPdf.xhtml?bill_id=202520260SB31&version=20250SB3192CHP).

[11] The most prevalent form of treatment for 1,4-Dioxane in drinking water sources appears to be Advanced Oxidation Processes (AOP) using ultraviolet light and hydrogen peroxide (UV/H_2O_2). These systems require substantial capital investments and have high operation and maintenance (O&M) costs related to high energy and hydrogen peroxide demand and specialized operator training and certification. For example, the City of Santa Monica operates a UV-AOP system that treats 1.9 million gallons per day with an annual O&M cost of $1.1 million.

water.[12] A PHG (and eventual MCL) for 1,4-DX based on default cancer risk assessment methods will impose an unnecessary burden on those systems.

The latest scientific research reinforces the weight of evidence demonstrating that default cancer risk assessment methods and assumptions mischaracterize, and likely substantially overstate, cancer risk from exposure to 1,4-DX in drinking water. We encourage OEHHA to use the development of this PHG as an opportunity to progress the goals stated in the most recent update of its Strategic Plan, including to "advance the science for the evaluation of risks posed to the public health and environment," in part through activities that "develop, improve, and define methods and sources of information for risk assessment, such as databases and models, to enhance and streamline efforts of CalEPA, its boards and departments, and others, to predict the effects of chemicals on humans and wildlife."[13] Achieving these goals in the context of PHG development will provide greater confidence that the final PHG will prevent "any significant risk to health." This outcome would satisfy OEHHA's statutory obligations and is more likely to result in an MCL that provides meaningful additional public health protection without imposing unnecessary additional costs on water systems and ratepayers and making it more difficult for California to ensure the availability of affordable and accessible safe drinking water for everyone.

We appreciate OEHHA's solicitation of public comments on critical areas of scientific expertise and charge questions for the external scientific peer review that will follow the close of the comment period on the draft PHG. For your consideration, our recommended peer reviewer areas of expertise and charge questions are set out in Attachment B to this letter.

Thank you for consideration of these comments and recommendations. We look forward to reviewing a substantially revised PHG. If you have any questions regarding this letter, please contact Tim Shestek, American Chemistry Council, at tim_shestek@americanchemistry.com.

Sincerely,

Tim Shestek, Senior Director, State Affairs, Western Region

American Chemistry Council

[12] SWRCB, 2025 Drinking Water Needs Assessment (June 2025), available at https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/needs/2025needsassessment.pdf.

[13] OEHHA, Strategic Plan: 2018 Update (Jan. 2018), Goal 2, pp. 10 and 14, available at https://oehha.ca.gov/sites/default/files/media/strategicplan2018.pdf.

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Chris Reardon, Vice President

California Farm Bureau Federation

Daniel Hartwig, President

California Fresh Fruit Association

Katie Litte, Director of Government Affairs

California League of Food Producers

Elizabeth Esquivel, Vice President of Government Relations

California Manufacturers & Technology Association

Rick Tomlinson, President

California Strawberry Commission

Mike Montna, President/CEO

California Tomato Growers Association

Anastasia Swearingen, Executive Director

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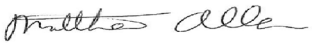
Craig Johns, Program Manager

Partnership for Sound Science in Environmental Policy



Matthew Allen, Vice President, State Government Affairs

Western Growers Association

Renee Pinel, President/CEO

Western Plant Health Association

Attachment A: Technical Comments on OEHHA's First Public Review Draft PHG for 1,4-Dioxane in Drinking Water

Attachment B: Recommendations on Areas of Expertise and Charge Questions for External Peer Reviewers of OEHHA's First Public Review Draft PHG for 1,4-Dioxane in Drinking Water

cc: Dr. Kristine Thayer, Director, OEHHA
Dr. David Edwards, Chief Deputy Director, OEHHA
Dr. Kimberly Gettmann, Deputy Director for Scientific Programs
Dr. Amy Gilson, Deputy Director for External and Legislative Affairs, OEHHA
Yana Garcia, Secretary for Environmental Protection, CalEPA
Scott Lichtig, Deputy Secretary for Environmental Policy, CalEPA
Anna Naimark, Deputy Secretary and Special Counsel for Water Policy, CalEPA
Joaquin Esquivel, Chair, SWRCB
Dorene D'Adamo, Vice Chair, SWRCB
Laurel Firestone, Member, SWRCB
Nichole Morgan, Member, SWRCB
Sean Maguire, Member, SWRCB
Eric Oppenheimer, Executive Officer, SWRCB
Darrin Polhemus, Deputy Director, Division of Drinking Water, SWRCB

Attachment A

Technical Comments on OEHHA's First Public Review Draft PHG for 1,4-Dioxane in Drinking Water

November 25, 2025

Systematic Review

OEHHA's literature review for the draft PHG does not qualify as a "systematic review," as that term is defined by authoritative bodies such as the National Institute of Health and the National Academies of Sciences,[14] and the gaps in OEHHA's methodology, summarized in Appendix A, compromise the transparency of the literature review, the risk assessment, and the PHG calculation.

OEHHA did not document its systematic review process sufficiently to allow other scientists, including external peer reviewers, to replicate the agency's work. Although the Population, Exposure, Comparator, and Outcome (PECO) statement, search strategy, and search terms were provided, there is no description of how OEHHA evaluated the risk of bias and methodological quality of the studies it screened, or the subset of studies it selected to support development of the draft PHG. In addition, despite OEHHA having conducted updated literature searches in August 2021 and August 2023, key studies were either excluded or not referenced, including, for example:

- 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
- 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
- Lafranconi, M., Anderson, J., Budinsky, R., Corey, L., Forsberg, N., Klapacz, J., & LeBaron, M. J. (2023). An integrated assessment of the 1,4-dioxane cancer mode of action and threshold response in rodents. *Regulatory Toxicology and Pharmacology: RTP*, *142*, 105428. https://doi.org/10.1016/j.yrtph.2023.105428
- 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*

[14] See for example https://pmc.ncbi.nlm.nih.gov/articles/PMC5903119/ and https://www.regulations.gov/document/EPA-HQ-OAR-2020-0044-0699.

Environmental Science and Health, *29*, 100389. https://doi.org/10.1016/j.coesh.2022.100389

- Webster, F., I. Lambert and C. Yauk (2021). *Adverse Outcome Pathway on Cyp2E1 activation leading to liver cancer* (OECD Series on Adverse Outcome Pathways No. 19). (2021). https://doi.org/10.1787/56e9bbf0-en
- Australian Government, Department of Health. (Jun. 30, 2022). *Evaluation statement: 1,4-Dioxane* (EVA00003).
- European Chemicals Bureau. (2002). *European Union Risk Assessment Report: 1,4-Dioxane* (Institute for Health and Consumer Protection).
- World Health Organization (WHO). (2005). *1,4-Dioxane in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality*.

All of these studies are relevant to development of the PHG, and all of them were published in the peer-reviewed literature or by authoritative bodies prior to August 2023, but none were mentioned in the draft PHG.

Study Selection

The female mice data from Kano et al. (2009), chosen for the point of departure (POD) and the PHG risk assessment, is of poor quality and not suitable for quantitative risk assessment purposes. Other rat and mouse liver tumors and nasal tumors offer a more reliable treatment-related cancer response for deriving a cancer slope factor.

The draft PHG document used the Kano et al. (2009) study as the basis for assessing cancer risks presumably because it was the most responsive to 1,4-DX exposure. However, this study has been controversial and remains an outlier among the numerous 1,4-DX cancer studies conducted to date. The quality and reliability of this study is suspect, which limits its utility for quantitative risk assessment purposes.

Kano et al. (2009) is a publication summarizing the results from the original cancer bioassay in rats and mice conducted in 1990 by the Japanese Bioassay Research Center (JBRC). As OEHHA acknowledges on page 58 of the draft PHG, there was significant mortality among female mice early in this study (before 85 weeks). Nearly half of the female mice in the control group died before week 85. Historical mortality for the Crj:BDF1 strain of mouse is about 16 percent at 78 weeks and only 34 percent at 104 weeks (Yamate et al., 1990). The high mortality in the Kano publication calls into question the health of the animal colony and animal care, which can bias results and reduces confidence in all the findings from the study.

In addition, there were unusually high background liver tumor rates. The combined hepatic adenoma and carcinoma in the control group female mice from this study was 22 percent. The BDF1 female mouse has been reported to naturally express an approximate 10 percent combined incidence of basophilic foci and combined hepatocellular adenomas and

carcinomas (Yamate et al., 1990). A separate study examining 499 female control BDF1 mice reported up to 6 percent basophilic foci and up to 8 percent hepatocellular adenomas and carcinomas (Katagiri et al., 1998). Furthermore, 70 percent of exposed female mice in the Kano publication developed tumors at the lowest dose (500 ppm or ~ 66 mg/kg/day), with only a modest increase at higher doses. This is substantially higher than that observed in other rodent studies, such as the NCI mouse study where the background hepatic adenoma and carcinoma incidence rate in female mice was zero with an incidence of 44 percent at an order of magnitude higher exposure (5,000 ppm, ~ 380 mg/kg/day). This calls into question the study design of Kano et al. (2009) since the steep dose-response increases uncertainty in the estimation of a point of departure and may simply be reflective of the high background of spontaneous liver tumors in the animals used in this study.

We also note that the tumor diagnostic criteria from Kano et al. (2009) are in question. They appear to have changed from the earlier report from the same study (JBRC, 1990, Yamazaki et al., 1994), but without clear documentation or supporting images.

> "*Diagnostic improvement from the hepatic hyperplasia in our preliminary report (Yamazaki et al., 1994) to the altered hepatocellular foci and hepatocellular adenomas in the present studies according to the current criteria (Mohr, 1997; Deschl et al., 2001) was found to increase the incidences of hepatocellular adenomas in the 1,4-dioxane-dosed groups, resulting in the definite dose-hepatocarcinogenic response relationships as compared with those in our preliminary report*." (pg. 2783, Kano et al., 2009)

This issue was also addressed by Dourson et al. (2017):

> "*The lack of liver noncancer histopathology in JBRC (1990s) is unexpected, especially since an increase in liver enzymes associated with cell damage is found in this same study. Also, the JBRC (1990b) 13-week study showed extensive liver noncancer histopathology at suitable adjusted-to-chronic doses. Unfortunately, this internal inconsistency is not resolvable because slides or pictures from a sufficient number of experimental animals are not available for the current reanalysis*." (pg. 53)

This causes uncertainty about whether non-cancerous liver lesions, such as altered hepatic foci, were misclassified as tumors, inflating the reported tumor rates. No altered hepatocellular foci (e.g., basophilic) were reported that could be used to evaluate the occurrence of proliferative pre-cancerous lesions. No histological pictures of the before-and-after assessments were provided to explain how the investigators changed their previous histopathology evaluation. Furthermore, if this study had employed Good Laboratory Practices (GLP), changing the histological diagnoses would require amendments to the protocol, which did not occur. In addition, the original tissue slides are unavailable for peer

review, so independent pathologists cannot verify the tumor diagnoses. This lack of transparency is a major limitation. As a result, it is uncertain whether the pathological assessment of the mouse findings inadvertently counted altered hepatic foci as tumors, which would artificially increase the number of liver tumors reported across the dose groups.

There is also inconsistency in reporting of non-neoplastic lesions. In a report from the 13 week drinking water study by the same lab (Kano et al., 2008), there was significant non-neoplastic liver pathology. However, none of these lesions were included in the 2-year study report. Because the authors do not report hepatotoxicity relative to liver tumors in the chronic study, the reported liver tumor response to 1,4-DX exposures in Kano et al. (2009) is highly uncertain.

We also note that other regulatory agencies have considered and rejected Kano et al. (2009) because of the uncertainties in the reliability of this study. For example, Health Canada recently cited these various discrepancies as justification for rejecting Kano et al. (2009) as the basis for quantitative health risk assessment:

> "*The absence of non-cancer histopathological changes and the concomitant increase in liver enzymes in the JRBC studies despite the presence of both endpoints in the subchronic studies from the same group (described in sections 9.2.2.1 and 9.2.2.5) lend credence to the uncertainty surrounding the development of tumors at this low dose*." (pg. 30, Health Canada, 2018)

Given all of the uncertainties and disparities in the mouse data reported in Kano et al. (2009), the data from this study are not of suitable quality to be used to derive a PHG for 1,4-DX.

Mode Of Action (MOA)

The draft PHG uses a linear low-dose risk model to estimate cancer slope factors. We submit that this approach mischaracterizes the most likely mode of action (MOA) for 1,4-DX carcinogenesis and thus is not the appropriate model for assessing health risks from exposure to 1,4-DX. Rather, the weight of the evidence for 1,4-DX demonstrates a threshold MOA for carcinogenicity.

Identifying the most likely MOA for a carcinogen is essential for modeling the cancer risk from high-exposure rodent data and deriving a cancer toxicity value that is relevant to humans because it informs the proper selection of risk assessment methods. In general, a chemical either has (1) a direct DNA-acting MOA, or (2) a MOA that involves an uncontrolled increase in cellular proliferation such that there is clonal expansion of cells with mutations. The latter MOA may occur via dysregulation of various cellular processes, including but not limited to, cell signaling pathways, oxidative stress regulation, or cell-to-cell contact inhibition.

Several government agencies, including Health Canada, the WHO, and the European Chemicals Bureau have determined that 1,4-DX is a threshold carcinogen. Several peer-

reviewed publications have also presented proposed MOAs for 1,4-DX, including recent papers by Chen et al. (2022) and Kirman et al. (2026). OEHHA should incorporate these interpretations of the MOA data into their literature review and conduct a more thorough and transparent evaluation of the most likely MOA for carcinogenic effects.

Health Canada's 2018 assessment presents one of the most comprehensive and scientifically rigorous MOA evaluations for 1,4-DX, employing a well-established standard-of-practice framework – the modified Bradford Hill criteria for mode of action-human relevance – for evaluating mode of action information according to dose-response, temporal concordance, consistency and specificity, and biological plausibility (Meek et al., 2014). Based on this analysis, Health Canada concluded:

> *"[T]he genotoxic mode of action was not able to satisfy the conditions of dose concordance, consistency and specificity, and biological plausibility of the modified Bradford Hill criteria for a plausible MOA (Meek et al., 2014). This analysis indicates that the pattern of genotoxicity is inconsistent with a MOA where genotoxicity is an early and influential key event in the carcinogenic MOA. Similar conclusions were reached by the governments of Canada (Environment Canada and Health Canada, 2010) and Australia (NICNAS, 1998), by the European Union (European Commission, 2002), and by the U.S. EPA (2013)."*

Health Canada specifically rejected a genotoxic MOA in favor of a threshold MOA involving regenerative proliferation-induced carcinogenicity, citing the following conclusions:

> *"Dose and temporal concordance are evident upon consideration of multiple studies across different durations. Increased 1,4-dioxane doses were associated with increased tumour incidence in mice and rats, and the key events are observed at doses below or similar to those associated with cancer. The sequence of key events is logical, and the key events and adverse outcomes occur in an expected order. More specifically, histopathological changes indicative of hypertrophy and necrosis are observed following short-term studies and are further observed in chronic bioassays preceding the development of tumours. These key events have been observed in repeated chronic experiments in different laboratories (NCI, 1978; Kano et al., 2009) as evidence for consistency.... [S]upport for the proposed MOA is found by analogy to other solvents that cause liver tumours in both rats and mice. Moreover, all key events in the rodent MOA are concordant and plausible in humans, although limited data are available to provide support."*

Recently, an expert panel evaluated the potential MOAs for 1,4-DX in a blind assessment (modified delphi format) (Kirman et al., 2026). The panel concluded that metabolic saturation is an early key event, followed enzyme induction, oxidative stress, cytotoxicity, and

regenerative proliferation, and therefore, the non-linear extrapolation method for deriving human health toxicity values is the most scientifically valid approach.

The probable MOA for 1,4-DX-mediated cancer involves several threshold events - including metabolic saturation, which induces cellular proliferation from mitogenic stimulation likely resulting from dysregulation of oxidative stress. While there is strong evidence of this MOA for rat liver tumors, the same mechanism also explains the incidence of other tumor types observed in rodent studies. As noted above, this threshold mechanism has been used by authoritative bodies worldwide, including the WHO, to characterize carcinogenic risk from exposure to 1,4-DX.

OEHHA's statement in the first paragraph of Appendix F that " ... there are no specific mechanistic data to suggest deviation from the standard assumptions, including low dose linearity ..."[15] is incorrect. Rather, there is both well-established evidence cited in the above-noted assessments, and more recent publications such as Chen et al. (2022) and Kirman et al. (2026), that support the following MOA for 1,4-DX.

1. **Metabolic saturation:** The accumulated evidence for 1,4-DX demonstrates that the MOA for tumor formation is best characterized by a sequence of responses resulting from exposures that overwhelm the ability of animals to metabolically eliminate the absorbed 1,4-DX. This metabolic clearance becomes rate-limiting at high exposure levels, which is the threshold for subsequent events that can lead to tumor formation. Moreover, numerous *in vitro* and *in vivo* studies have reported no effects on genotoxic endpoints, except at doses exceeding the estimated metabolic threshold. The majority of the absorbed 1,4-DX is biotransformed to β-hydroxyethoxyacetic acid (HEAA) and excreted in the urine (Braun and Young, 1977; Göen et al., 2016; Take et al., 2012; Young et al., 1978). The cytochrome P450 enzyme system, particularly Cyp2B1/2 and Cyp2E1, is associated with the biotransformation of absorbed 1,4-DX to HEAA (Braun and Young, 1977; Nannelli et al., 2005). At low exposure levels, metabolism is a linear process in which the rate of metabolism and elimination is proportional to dose. However, at higher exposures there is evidence of saturation (Göen et al., 2016; Sweeney et al., 2008; Young et al., 1978). Saturation occurs because there are no longer enough cytochrome P450 enzymes available to hydroxylate the 1,4-DX molecules. Therefore, 1,4-DX builds up in the body and is able to circulate, untransformed.

2. **Dysregulation of oxidative stress and cytotoxicity:** Recent research has identified oxidative stress as a key event in the 1,4-DX cancer MOA (Charkoftaki et al., 2021; Chen et al., 2022). Oxidative stress likely plays a role in the development of 1,4-DX mediated cytotoxicity and subsequent events leading to tumors. Up-regulation of

[15] Office of Environmental Health Hazard Assessment, Public Health Goals, First Public Review Draft, 1,4-Dioxane in Drinking Water, September 2025, page 148.

Cyp2E1 has been reported following 1,4-DX exposure (Chen et al., 2022). An increase in Cyp2E1 activity is a recently identified pathway leading to liver carcinogenesis (Webster et al., 2021). The reactive oxygen species generated by Cyp2E1 causes cellular damage and a regenerative proliferative response. OEHHA's section on oxidative stress (page 46) is missing some additional key references, including Mnaa et al. (2016) and Qiu et al. (2019) which included several doses in their analysis and show that dysregulation of the cellular redox balance only occurred at high doses that exceeded the estimated metabolic thresholds (see also Totsuka et al., 2020).

3. **Increased cellular proliferation:** Several studies have identified indications of increased cellular proliferation following 1,4-DX exposure preceding or concomitant with tumors, including target tissue cell hypertrophy and increased cellular proliferation. Liver histopathology including lesions, centrilobular swelling, hyperplasia, and necrosis have been shown to occur following high dose exposure (doses above the metabolic saturation level). Examples include Dourson et al., 2014 and 2017; Kano et al., 2008 and 2009; Kasai et al., 2009; Kociba et al., 1974; and Stott et al., 1981. Increased DNA synthesis has been specifically observed in some rodent studies following high doses of 1,4-DX (e.g., Lafranconi et al., 2021; Miyagawa et al., 1999; Stott et al., 1981). In male rats, signs of regenerative-repair induced cellular proliferation were significantly increased following inhalation exposures of 1250 ppm, but not 250 ppm (Kasai et al., 2009). A similar increase in indications of cell-damage-mediated proliferation was reported in male and female rats after two years of ingesting 5,000 ppm 1,4-DX, but not at the next lower water concentration of 1,000 ppm (Kano et al., 2009).

Results from Lafranconi et al. (2021) with follow-up by Chappell et al. (2021) provide additional information and data on 1,4-DX's MOA, however, OEHHA only included the Lafranconi study in their evaluation of sub-chronic effects. In this study, female mice were given drinking water at concentrations of 0, 40, 200, 600, 2000, or 6000 mg/L (parts per million) 1,4-DX over a 90-day period. The mice were analyzed for treatment-related liver effects and concomitant proliferation, apoptosis, and liver transcriptomic changes, among the standard suite of clinical observations and clinical chemistry analyses. Blood concentrations of 1,4-DX and its primary metabolite, HEAA, were also evaluated. The results indicate that when 1,4-DX is administered via drinking water at various doses, a clear time- and dose-dependent threshold for hepatic effects in female mice is observed. These data clearly indicate metabolic saturation and accumulation of 1,4-DX in the blood, with subsequent increases in hepatocellular proliferation from a mitogenic, non-genotoxic mechanism (Lafranconi et al., 2021). In addition, the evaluation of genomic signals from this study by Chappell et al. (2021) also demonstrated a threshold response at exposures above 600 ppm (~360 mg/kg/day). The targeted analyses for DNA damage/repair gene sets and high-

throughput screening (HTS) assays for genotoxicity showed no evidence of a mutagenic response.

These studies provide the additional scientific basis necessary to rule out a linear, non-threshold, low-dose, genotoxic MOA in favor of a non-linear, threshold, low-dose cytotoxic MOA for 1,4-DX exposure.

OEHHA should employ the available MOA and adverse outcome pathway frameworks, which constitute "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"[16] to critically and thoroughly evaluate which of the possible MOAs, including the above-noted threshold MOA, is best supported by the weight of evidence. This approach would be far more transparent and scientifically rigorous than the current draft, and would be consistent with the United States Environmental Protection Agency (US EPA) 2005 Guidelines for Carcinogen Risk Assessment (Guidelines), which allow for evaluation of alternative approaches "with significant biological support."[17] Moreover, as this section and the following section demonstrate, the alternative MOA for 1,4-DX has stronger biological support than the default approach initially selected by OEHHA, and therefore, at a minimum, the alternative approach should be evaluated in OEHHA's assessment and directly compared to the default approach.

Genotoxicity

The draft PHG fails to systematically consider the available evidence regarding genotoxicity associated with 1,4-DX exposure or the role of oxidative stress, cytotoxicity, and sustained proliferation at exposures above metabolic saturation (the Molecular Initiating Event in the cancer MOA for 1,4-DX) in genotoxic outcomes. OEHHA concludes that "[t]aken together, a genotoxic MOA for 1,4-dioxane cannot be ruled out … ,"[18] but this conclusion disregards recent peer-reviewed publications, including but not limited to Lafranconi et al. (2023) and Kirman et al. (2026), that address the contribution of genotoxicity to the cancer MOA for 1,4-DX. The latter involves a critical review of the dataset by six distinguished experts in the field of MOA analysis. These experts agree that the weight of evidence indicates a very low (negative) confidence rating for tumor induction via a direct genotoxic MOA. Furthermore, OEHHA's conclusions on the genotoxic potential of 1,4-DX contradict the findings of every other US and global agency that has evaluated the relevant dataset, all of which concluded

[16] Health and Safety Code §116365(c).
[17] US EPA's Guidelines for Carcinogen Risk Assessment (2005) allow assessments to present results based on more than one approach "where alternative approaches with significant biological support are available for the same tumor response and no scientific consensus favors a single approach …"
[18] Office of Environmental Health Hazard Assessment, Public Health Goals, First Public Review Draft, 1,4-Dioxane in Drinking Water, September 2025, page 67.

that 1,4-DX is not likely to be mutagenic and is only weakly genotoxic.[19] Critically, OEHHA's conclusions also contradict the conclusions in US EPA's 2020 Toxic Substances Control Act (TSCA) assessment, which OEHHA cites in support of its decision to use the default linearized multistage dose response model[20]:

> "[b]ased on the weight of scientific evidence, EPA concluded that 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."[21]

The draft PHG also fails to distinguish between direct and indirect mutagenic and genotoxic properties of 1,4-DX in the draft PHG. This is another critical departure from US EPA's Guidelines, which establish that a genotoxic MOA may involve either mutagenic or clastogenic events. A mutagenic MOA would typically be initiated by the formation of pro-mutagenic DNA lesions, such as alkylation caused by the electrophilic parent or its metabolites at prominent nucleophilic DNA sites (such as *N7* or O^6 positions of dG). These lesions could be fixed into mutations during DNA replication if not properly repaired, or if repair is overwhelmed or delayed. However, no alkylating DNA adducts have been identified following 1,4-DX exposure, indicating that a direct mutagenic MOA is unlikely.

As noted above, numerous peer-reviewed and authoritative body assessments have concluded that 1,4-DX does not exhibit direct mutagenicity. Further, the available evidence does not indicate that mutation is an early key event in the cancer MOA for 1,4-DX, particularly at low exposure levels but that the cancer etiology for the substance is underlined by threshold pathophysiological mechanisms of oxidative stress, cytotoxicity, and/or, as OEHHA argues, inflammation. Mutations observed following subchronic exposures exceeding 1,000 ppm, such as in Gi et al. (2018), have been linked to genotoxic outcomes from oxidative DNA damage, including strand breaks and repair intermediates, in conjunction with cytotoxicity and mitotic regeneration, and these events are more likely than direct genotoxicity.

With regard to DNA adducts, the draft PHG fails to state that 1,4-DX does not cause direct DNA damage, which was reported as early as 1981 by Stott et al. Since these studies were done *in vivo* and utilized radioactive material, findings would also have included any potential

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[19] European Chemicals Agency (ECHA), Committee for Risk Assessment (RAC), 2022; Health Canada, 2021; and US EPA, 2020.

[20] US EPA did not change this approach in the 2024 Final Revised Risk Determination for 1,4-Dioxane. (See 2024 Final Revised Risk Determination for 1,4-Dioxane, available at https://www.epa.gov/system/files/documents/2024-11/2.-1-4-dioxane-.-revised-risk-determination-.-public-release-.-hero-.-nov-2024.pdf; 2024 Supplement to the 2020 Risk Evaluation for 2,4-Dioxane, available at https://www.epa.gov/system/files/documents/2024-11/1.-1-4-dioxane-.-supplement-to-the-risk-evaluation-.-public-release-.-hero.-nov-2024.pdf.)

[21] United States Environmental Protection Agency, Final Toxic Substances Control Act Risk Evaluation for 1,4-Dioxane, December 2020: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-14-dioxane.

DNA-reactive metabolites. The absence of such metabolites in the published literature stands in stark contrast to OEHHA's statement that "[i]t is possible that metabolites of 1,4-dioxane are mutagenic."[22] OEHHA further states that even though the *in vitro* studies largely indicated a lack of genotoxic potential, the experimental systems could have lacked full metabolic capabilities. However, the Stott et al. (1981) 11-week study results, coupled with the more recent Totsuka et al. (2020) investigation, undermine that claim.

OEHHA also discusses strand breaks, including γH2AX biomarker of double-stranded breaks and increased chromosomal outcomes in the ranges of single 900-3500 mg/kg or repeat 1000-3000 mg/kg/d dosages.[23] While strand breakage has been unequivocally associated with 1,4-DX treatment, it can result from a range of cellular processes that have not been demonstrated to follow from exposure to 1,4-DX, such as DNA reactivity,[24] intermediates of DNA repair processes,[25] programmed cell death/apoptosis,[26] replication stress,[27] enzymatic activities,[28] and high transcriptional activity[29]. Chappell et al. (2021) identified a dose-responsive trend in the expression of Rad51 after 90 days of high dosage (1063 mg 1,4-DX/kg/d treatment) in mouse livers. In humans, Rad51 plays a role in homologous recombination repair of double-stranded breaks, DNA damage response, and in DNA replication and processing of stalled replication forks (reviewed in Lafranconi et al. (2023)). These outcomes are consistent with published findings for 1,4-DX and, taken together, indicate indirect genotoxic effects such as bone marrow, peripheral blood, or hepatocyte micronuclei.

The draft PHG refers to DNA adducts associated with 1,4-DX exposures seen above metabolic saturation, but fails to acknowledge that, when measured, these are various signatures of oxidative stress, especially the most known and studied 8-OHdG biomarker adduct. OEHHA offers several arguments to diminish the contribution of oxidative stress to the MOA for 1,4-DX, each of which is lacking scientific evidence:

1. Gi et al. (2018) initially concluded that 1,4-DX associated mutations were not caused by oxidative stress in their 16-week oral drinking study, which arrived at no-observed genotoxic effect level (NOGEL) values of 92 mg/kg/d for *gpt* delta mutation frequency (MF) and A-to-G transitions (with lowest observed genotoxic effect level or LOGEL of

[22] Office of Environmental Health Hazard Assessment, Public Health Goals, First Public Review Draft, 1,4-Dioxane in Drinking Water, September 2025, page 45.
[23] Id., page 45.
[24] Not proven for 1,4-DX.
[25] This process should be relevant due to excision repair of oxidative lesions indirectly induced by 1,4-DX. However, the various representative transcripts of excision repair pathway genes were not upregulated in the Gi et al., 2018 study and DNA repair is mostly regulated by posttranscriptional modifications as even small upregulation can cause DNA repair imbalances resulting in increased mutations.
[26] Dose-dependent increases have been observed following 1,4-DX treatment.
[27] Should be relevant for 1,4-DX based on Rad51 finding.
[28] Such as Topoisomerases and Nucleases, which are not known to be relevant for 1,4-DX.
[29] Not known to be relevant for 1,4-DX.

about 440 mg/kg/d or 5000 ppm). The A-to-T transversions were reportedly significantly increased at 1000 ppm or about 92 mg/kg/d (LOGEL) mid-dose group of Experiment 1.[30] However, the percentage of MF were very similar between low and high dose groups (12.5 percent vs. 13.6 percent, respectively, with 18.9 percent of A-to-T mutations at mid-dose). Furthermore, the follow up investigation by Totsuka et al. (2020) of 1,4-DX-induced adductome from the same study did in fact report that 8-OHdG lesion was the most abundant adduct detected and that there was an "apparent threshold" in 1,4-DX treatment-related adductome between the low and the middle- and high-treatment groups. Totsuka et al. (2020) further concluded that the detected biomarker adducts "may not require direct binding action with DNA," which OEHHA does not acknowledge (see page 45).

2. OEHHA claims that the investigations evaluating plausible MOAs report conflicting results with respect to the role of oxidative stress.[31] This is due to inconsistencies in changes of some markers, especially the lack of change in the expression of the 4-hydroxynonenal (4-HNE) biomarker while changes were noted in glutathione-mediated detoxification and nuclear factor erythroid 2-related factor 2 (NRF2)-mediated oxidative stress response genes.[32] The 4-HNE biomarker is more accurately characterized as a reactive aldehyde that is formed as a product of lipid peroxidation and as a secondary signaling molecule underpinning the pathophysiology of several disease processes. 1,4-DX treatment may not necessarily change the expression of 4-HNE. Furthermore, while lipid peroxidation is associated with oxidative stress, even as a result of 1,4-DX treatment (as seen for example in the upregulation of MGMT repair protein), there are many other and better-known key oxidative stress biomarkers, including: production and concentration of the Reactive Oxygen/Nitrogen Species (RNOS); decrease in reduced glutathione (GHS) and GSH:GSSG ratio, which has been observed following exposure to 1,4-DX; increased superoxide dismutase and catalase enzymatic activities to neutralize RNOS as the first-line antioxidant defense system, which should be relevant for 1,4-DX; advanced oxidation protein products, which are not known to be relevant for 1,4-DX; and direct DNA/RNA oxidation biomarkers such as 8-OHdG. The latter has been repeatedly identified following 1,4-DX treatment and is the most widely used marker of oxidative DNA damage. The 8-OHdG oxidative lesion, while most abundant and best studied, is found in combination with more than 100

[30] Gi et al., 2018, reported 3 dose-response experiments in their publication, with first 2 being conducted in *gpt* delta transgenic F344 rats. In Experiment 1, 1,4-DX was administered at 0, 200, 1000 and 5000 ppm in drinking water where investigators were able to assess *gpt* MF and mutational spectra (data described above). In Experiment 2, the investigators saw no significant differences in *gpt* MF or mutation spectra between groups administered 0.2–20 ppm 1,4-DX. Experiment 3 was conducted in wild-type F344 rats and did not involve genetic toxicity endpoints.

[31] Office of Environmental Health Hazard Assessment, Public Health Goals, First Public Review Draft, 1,4-Dioxane in Drinking Water, September 2025, page 51.

[32] Id., page 46.

DNA oxidative lesions and could be relevant for 1,4-DX, as other DNA lesions were reported in the Totsuka et al. (2020) investigation. DNA strand breaks, detected via comet assay, are directly relevant to the 1,4-DX MOA, whereas increased levels of apurinic/apyrimidinic (AP) sites are not yet known to be relevant to the 1,4-DX MOA.

3. OEHHA identifies DNA–protein crosslinks as a notable biomarker of oxidative stress, but this type of DNA modification is much less frequent than 8-OHdG or other oxidative DNA damage, including DNA strand breaks caused directly (by RNOS) or indirectly (as a result of DNA excision repair) during oxidative stress. DNA–protein crosslinks have not been detected following 1,4-DX treatment. Furthermore, OEHHA does not evaluate the mechanism(s) for these DNA strand breaks observed in the *in vivo* genotoxicity assays conducted with 1,4-DX, listed in Table 3 of the draft PHG. However, as discussed above, Lafranconi et al. (2023) did carefully consider these mechanisms and anchored their conclusions regarding a threshold MOA for liver cancer in the two relevant Adverse Outcome Pathways (AOPs) developed by respected experts in the field of genetic toxicology: (1) AOP 220 (Cyp2E1 Activation Leading to Liver Cancer that involves oxidative stress, authored by Health Canada experts Webster, Lambert and Yauk (2021) and reviewed by the Organisation of Economic Co-operation and Development (OECD) Secretariat in 2024); and (2) AOP 296 (Oxidative DNA damage leading to chromosomal aberrations and mutations (cited in Cho et al., 2022, and Huliganga et al., 2025)).

4. OEHHA states that the single gavage exposure to 2,550 mg 1,4-DX/kg "showed DNA single strand breaks in the absence of cytotoxicity (Kitchin and Brown, 1990)."[33] Although cytotoxicity was not measured and a small but significant increase in DNA strand breaks has been reported in rat hepatocytes after two oral doses of 2550 mg 1,4-DX/kg administered within the same day, Lafranconi et al. (2023) report that the highest dose of 4200 mg/kg was the LD50 value. It is likely that dosages approximating LD50 and LD25 values caused tissue and cell damage that resulted in the various cellular outcomes described above that led to the observed DNA strand breaks.

There is no evidence supporting the conclusion that exposure to 1,4-DX causes direct mutagenicity. Overall, OEHHA's statements in the draft PHG regarding genotoxic MOA contributions to 1,4-DX tumorigenicity are inconsistent with other evaluations and lack the careful consideration consistent with a weight of evidence approach. Such broad generalizations result in science policy choices that overstate the health risk from exposure to 1,4-DX and if left unchanged are likely to result in the cascade of unintended negative consequences noted in our cover letter.

[33] Id., page 45.

Toxicokinetics

The draft PHG comments on the metabolic saturation properties of 1,4-DX but there are nuances about the interpretation of the available data that don't appear to be considered in the draft PHG. In particular, the information reviewed for the pharmacokinetics (toxicokinetics) section is not utilized in the final risk assessment. This is an unfortunate omission because the toxicokinetic information for 1,4-DX has substantial relevance to the cancer risk assessment.

Metabolic Saturation – Michaelis-Menton Kinetics: The draft PHG dismisses the metabolic saturation concept for risk assessment purposes. As the draft PHG acknowledges, studies conducted in rodents and humans demonstrate that 1,4-DX is readily absorbed, distributed and metabolized after ingestion or inhalation. By either route, or when 1,4-DX is administered directly into systemic circulation by intravenous injection, the majority of the absorbed 1,4-DX is biotransformed by cytochrome P450 systems to β-hydroxyethoxyacetic acid (HEAA) and excreted in the urine (Goen et al., 2016, Young et al., 1978, Woo et al., 1977). At low levels of exposure metabolism is a linear first-order process in which the rate of metabolism and elimination is proportional to dose. However, at higher exposures the kinetics shift and show characteristics of saturation (Young et al., 1978; Sweeney et al., 2008). The dose at which this transition occurs is important to the risk assessment because exceeding it leads to an accumulation of unmetabolized 1,4-DX and subsequent pre-neoplastic and tumorigenic effects (Dourson et al., 2014 and 2017; Health Canada, 2021; Lafranconi et al., 2023).

Species Sensitivity: In addition, information from toxicokinetic studies can inform the observed differences in species sensitivities, which is another important consideration for risk assessment. *In vitro* methods have demonstrated differences in the biotransformation kinetics of 1,4-DX across rat, mouse, and human hepatocytes (Sweeney et al., 2008). There was a marked difference in the maximal rate (V_{max}) of metabolism of 1,4-DX to HEAA. Rat hepatocytes generated the lowest V_{max} and human hepatocytes generated the highest values. The calculated relative affinity of 1,4-DX for the biotransformation enzymes, determined by the K_m (see Table 1 below), was judged by the authors to be the same for rat and mouse but higher for human hepatocytes.

From these findings it is likely the biotransformation capacity, and subsequent metabolic threshold, would be higher in humans than in rodents, thus making rodents more susceptible to metabolic saturation than humans.

TABLE 1: Toxicokinetic Modelling Predictions of Metabolic Capability for Biotransformation of 1,4-DX by Species from Sweeney et al. (2008)

Source of Hepatocytes	**V_{max}[a] (mg/h $Kg^{0.7}$)**	**K_m[b] (mg/L)**
Rat	7.5, 12.7	21
Mouse	39, 46	21
Human	54 - 192	29 - 147

[a]Values for rat and mouse represent maximal rates generated by hepatocytes from uninduced and phenobarbital-induced hepatocytes. Values for human hepatocytes represent the range of V_{max} from three sources of human hepatocytes.

[b]Km is the Michaelis-Menten constant and represents the blood concentration at half the Vmax. It is an indication of the affinity of the substrate for the enzyme system.

Inhalation: The PHG draft cites results from a 13-week inhalation study of 1,4-DX (Kassai et al., 2008) to conclude that "metabolic saturation does not appear to be evident." This is based on the dose-dependent linear increase in plasma concentrations of 1,4-DX at exposure levels of 400 ppm and greater. This interpretation is confounded because this finding was obtained from a single point in time (one hour after cessation of exposure on week 12) without the benefit of time-course sampling to enable detection of the threshold-response kinetics. The plasma levels of 1,4-DX could simply reflect redistribution of absorbed 1,4-DX from other tissue compartments. This study also did not include analysis of plasma or urine measurements of HEAA which is the primary signal from the metabolism of 1,4-DX. In addition, we note that Young et al. (1978) demonstrated that blood levels of 100 mg/ml in male rats represented the metabolic threshold. The plasma levels reported in the 13-week inhalation study by Kasai et al. (2008) achieved average values of 48 and 80 mg/ml at the lowest exposure level of 400 ppm for males and females respectively. The other exposures used in this study, 800, 1600, and 3200 ppm, all generated blood levels of 1,4-DX which would presumably exceed the metabolic threshold.

The draft PHG also notes that a threshold was not detected in the study by Young et al. (1977) in which human volunteers were exposed to 50 ppm of 1,4-DX vapor for 6 hours. This is not surprising since exposure to 50 ppm (180 mg 1,4-DX /m^3) for six hours generated peak plasma levels in the volunteers of less than 20 mg/ml, and the high ratio of HEAA to 1,4-DX in the urine of volunteers from this study supported the conclusion that metabolic saturation was not achieved by inhalation of 50 ppm 1,4-DX.

PBPK Models: We agree that the physiologically-based pharmacokinetic (PBPK) models developed to date (Leung and Paustenbach, 1990); Sweeney et al., 2008;

Takano et al., 2010), are imperfect, like all models, and are likely to under-predict systemic exposure in humans. However, they do provide a solid framework for predicting rodent blood levels and, as such, are useful as tools for comparing predicted systemic exposures in rodent studies with development of apical endpoints such as liver tumors.

Epidemiology

We agree with OEHHA's decision to refrain from drawing conclusions regarding alleged associations between exposure to 1,4-DX and Autism Spectrum Disorder (ASD) or telomere length. These endpoints are based on limited studies of questionable quality and lack any proposed biological plausibility. Accordingly, we recommend they be omitted from future draft PHGs unless additional scientific data is published that warrants their inclusion.

Exposure Assessment

The cancer risk estimate in the draft PHG is a case study on the cumulative effect of over-reliance on default assumptions in risk assessment. OEHHA starts with a point of departure (POD) based on a highly improbable MOA that overstates cancer risk and then magnifies the impact of the POD in the PHG calculation by using equally improbable exposure assumptions. The result is a cancer risk estimate that in all probability substantially overstates health risk from exposure to 1,4-DX in drinking water relative to what a weight-of-evidence-based analysis would likely yield. Furthermore, OEHHA's failure to include an alternative PHG calculation using a threshold-based POD and reasonable worst-case exposure inputs masks the magnitude of this effect.

Age Sensitivity Factor: The Age Sensitivity Factor (ASF) is a default value introduced by OEHHA in 2009.[34] The ASF was developed in response to SB 25 (Escutia, 1999). OEHHA's 2009 Technical Support Document for Cancer Potency Factors states: "Under SB 25, OEHHA is mandated to consider infants and children specifically, where data permit, in evaluating the health effects of Toxic Air Contaminants (TACs)."[35] However, in this case, the available data do not support the use of the default ASF.

The ASF decreases the Health Protective Concentration (HPC) without scientific support and use of the ASF disregards the extreme conservatism already embedded in the cancer risk assessment process in the interest of public health protection. OEHHA's approach for all PHG cancer risk assessments relies on a *de minimis* 1 in 1,000,000 excess cancer risk. This approach is made more conservative for 1,4-DX by OEHHA's choice to use a linear non-

[34] Office of Environmental Health Hazard Assessment, Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures, 2009.
[35] Office of Environmental Health Hazard Assessment, Technical Support Document for Cancer Potency Factors, May 2009, page 32.

threshold approach. This approach already assumes lifetime exposures, so additional weighting without justification is unwarranted. More importantly, OEHHA fails to provide scientific support for the proposed ASF. Rather, the draft PHG states that "These default factors are applied regardless of the mechanism of action, **unless chemical specific data exist to better guide the risk assessment** (emphasis added)." This statement implies that OEHHA has determined that there is no such data available for 1,4-DX, but there is no information in the draft PHG describing OEHHA's investigation or how it concluded that the available evidence fails to support a chemical-specific approach. OEHHA does acknowledge that the choice of ASF-10 for third-trimester fetus to 2 years of age and ASF-3 for ages 2 to16 is a policy decision,[36] but it fails to disclose that the assessment used to determine the weighting factors was based on limited studies with high variability and uncertainty.

The drinking water rates used by OEHHA are also unrealistically high. For example, OEHHA assumes a third trimester fetus drinks 0.047 L/kg-d of tap water. Assuming the average fetus weighs 3.4 kg (US EPA, 2011), this ingestion rate for the fetus (not the pregnant woman) is equivalent to 0.16 L/d. OEHHA further assumes that a 0 to 2 year old infant drinks 0.196 L/kg-d. Based on an average body weight of 11.4 kg this ingestion rate is equivalent to 2.2 L of tap water every day.

Exposure Sources: The Environmental Occurrence and Human Exposure section does not provide sufficient information about sources of exposure in the general population related to the occurrence of 1,4-DX in products and the environment.

Specifically, in its discussion of Consumer Products,[37] OEHHA should identify concentrations of 1,4-DX reported in recent literature. The draft document states that residue in consumer products "is a significant source of human exposure" but provides no reference for this citation and provides no concentration data. Many consumer products no longer include detectable 1,4-DX. OEHHA should provide a scientific basis for this assertion or remove it from the draft PHG and reconsider the exposure assumptions in the PHG calculation.

This section also fails to mention the Centers for Disease Control National Health and Nutrition Examination Survey results for 1,4-DX. Blood collected from a geographically diverse population of U.S. adult residents (approximately 3,000 individuals for each sampling period) found no 1,4-DX above the methodology's limit of detection (LOD: 0.5 ng/mL) for 2009-2010, 2011-2012, 2013-2014, and 2015-2016 (CDC, 2019). This study indicates that despite the potential for human exposure to 1,4-DX from various sources, including consumer products or impacted sources of public drinking water, persistent or continuous exposure in the general population is negligible.

[36] Id., page 49: "… the size of the weighting factors used to weight risk by age at exposure is a policy decision."
[37] Id., page 16.

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Attachment B

Recommended Areas of Expertise and Charge Questions for External Peer Reviewers of OEHHA's First Public Review Draft PHG for 1,4-Dioxane in Drinking Water

November 25, 2025

Independent and trustworthy external scientific peer review is a legally-required and essential part of the PHG development process, providing a trusted form of scientific collaboration that is a hallmark of scientific work.[38] It ensures that the scientific basis underlying the agency decision "meet[s] accepted standards and [to] prevent[] influence on rulemakings stemming from irrelevant findings, unwarranted claims, unacceptable interpretations, and personal views."[39] SWRCB administers the CalEPA Peer Review Program to implement Health and Safety Code section 57004, which requires "highly-qualified external experts to perform impartial, independent peer reviews."[40]

For external peer review of the draft 1,4-DX PHG to meet these requirements, it is critical that OEHHA: (1) identify each scientific question raised in the draft PHG in its charge questions to the peer reviewers; and (2) request external peer reviewers who have expertise in all relevant scientific disciplines needed to address these questions.

Relevant Charge Questions to External Peer Reviewers

Based on our evaluation of the scientific questions posed in the draft PHG, which are discussed in detail in Attachment A, we recommend that OEHHA pose the following charge questions to the external scientific peer reviewers:

1. Does the draft PHG systematically and objectively consider the full weight of evidence regarding the genotoxicity of 1,4-DX, biomarker dataset interpretation and mutagenic mode of action?
2. Does the draft PHG adequately evaluate the role of oxidative stress as a key event in the genotoxic and carcinogenic mode of action for 1,4-DX?
3. Does the draft PHG adequately distinguish between indirect genotoxicity and direct DNA-reactive mechanisms in its evaluation of 1,4-DX mode of action?
4. Does the available information lead you to the conclusion that 1,4-DX is mutagenic?
5. Is the Kano et al. (2009) study of sufficient quality to be used in assessing cancer risks to humans?

[38] See Health & Saf. Code, § 57004.
[39] SWRCB, External Scientific Peer Review, available at https://www.waterboards.ca.gov/resources/peer_review/.
[40] *Id.*

6. Is there sufficient data available for 1,4-DX to support the application of OEHHA's default Age Sensitivity Factor?
7. Does the available information best support a linear-low dose or a threshold cancer mode of action for 1,4-DX?
8. Has OEHHA adequately characterized uncertainty in assessing the cancer and non-cancer risks and establishing the PHG for 1,4-DX?

For each of the above recommended charge questions, we recommend that OEHHA ask the external scientific peer reviewers to provide a rationale and justification for their answers.

Critical Areas of Expertise for External Peer Reviewers

We appreciate and agree with OEHHA's proposal to request external peer reviewers with expertise in toxicology and risk assessment. To fully address the scientific questions raised by the draft PHG, we recommend that OEHHA also request that the external scientific peer review panel include the following scientific expertise:

- Cancer biology and cancer mode of action
- Oxidative stress
- Metabolism and toxicokinetics
- Pathobiology

Expertise in cancer biology and mode of action is essential because of the complexity of the cancer development process and the essential role the mode of action analysis has in this PHG assessment of 1,4-DX. Expertise in oxidative stress is necessary to resolve the outstanding questions of the role of oxidative stress on the genotoxicity outcomes and subsequent cellular responses to 1,4-DX exposures. Expertise in metabolism and toxicokinetics is needed due to the central role these concepts play in evaluating the threshold mode of action. Finally, expertise in pathobiology is needed for evaluating the impact of the changes in diagnostic criteria used in the Kano/JBRC tumor incidence reporting.