California Water Boards

Gavin Newsom
Governor

Yana Garcia
Secretary for
Environmental Protection

State Water Resources Control Board

May 28, 2026

Kimberly Gettmann, Ph.D.
Deputy Director for Scientific Programs
Office of Environmental Health Hazard Assessment

**SUBJECT: Final Response to the Request for External Scientific Peer Review of the Scientific Basis of the Proposed Public Health Goal for 1,4-Dioxane in Drinking Water**

Dear Kimberly,

This letter is in response to the attached, revised 16 January 2026 request for external scientific peer review in accordance with Health and Safety Code section 57004 for the subject noted above.

The review process is described below. All steps were conducted in confidence. Reviewers' identities were not disclosed.

To begin the process for selecting reviewers, the CalEPA External Scientific Peer Review Program (Peer Review Program) contacted the University of California, Berkeley (University) and requested recommendations for candidates considered qualified to perform the assignment. This service is supported through an Interagency Agreement co-signed by CalEPA and the University. The University was provided with the request letter and attachments. The University interviews each promising candidate.

Each candidate who was both qualified and available for the review period was asked to complete a Conflict of Interest (COI) Disclosure form and a Curriculum Vitae (CV) using a specified format and submit both documents to the Peer Review Program for review. The cover letter for the COI form describes the context for COI concerns that must be taken into consideration when completing the form: "As noted, staff will use this information to evaluate whether a reasonable member of the public would have a serious concern about [the candidate's] ability to provide a neutral and objective review of the work product." The Peer Review Program, including its legal advisors, review and retain the COI forms. The CV format was created to provide a balance of accessibility and brevity. The selection process uses a rigorous, single blind methodology in which the Peer Review Program and the University know the identity of the reviewer, and the requesting organization does not receive that information until the peer review process has been completed. The process is designed to identify peer reviewers who are

subject matter experts and are free from conflicts of interest related to this peer review.

For each candidate judged to be free of conflict, the Peer Review Program approved that person as reviewer, affirmed by an approval letter to initiate the review. These letters provided access instructions to a secure FTP site where all material to be reviewed was placed. Each reviewer was asked to address each conclusion for which they had previously agreed, as outlined in the initiation letters. Thirty days were provided for the review, unless a reviewer requested additional time. Guidance was provided to ensure confidentiality through the review process.

Reviewers' names, affiliations, curriculum vitae, initiating letters and reviews are being sent to you now with this letter. This information can be accessed easily through the bookmarks provided in this file.

The review commenced on 11 March 2026, and all draft review reports were received by 06 May 2026. Office of Environmental Health Hazard Assessment staff conducted a sufficiency review of each anonymized report and found the reviewers independently and collectively addressed all assumptions, conclusions, and findings under review. No clarification was sought from the reviewers. The review reports have since been brought into compliance with web accessibility standards. This letter includes those reports and concludes this peer review request.

**Approved reviewers**

1. Gary Ginsberg, Ph.D.
   Professor Adjunct of Epidemiology (Environmental Health)
   Yale School of Public Health
   60 College Street, New Haven, CT 06510

2. Joseph Wiemels, Ph.D.
   Professor of Population and Public Health Sciences
   University of Southern California
   1450 Biggy Street, Norris Research Tower 1506A, Los Angeles, CA 90033

3. Markus Brinkmann, Ph.D.
   Associate Professor and Director, Toxicology Centre
   University of Saskatchewan
   44 Campus Drive, Saskatoon SK, S7N 5B3 Canada

If you have any questions, please contact the CalEPA External Scientific Peer Review Program at this email address: ORPP-ExternalPeerReview@Waterboards.ca.gov.

Sincerely,

Paola Gonzalez
Senior Environmental Scientist Supervisor
CalEPA External Scientific Peer Review Program
Office of Research, Planning, and Performance
State Water Resources Control Board

**Attachments**

(1) Request Letter Revised 16 January 2026 by Kimberly Gettmann for Scientific Peer Review

(2) Web Accessible Letters to Reviewers Initiating the Review
   i. Gary Ginsberg, Ph.D.
   ii. Joseph Wiemels, Ph.D.
   iii. Markus Brinkmann, Ph.D.

(3) Web Accessible Guidance to Reviewers, posted at FTP site

(4) Web Accessible Curriculum Vitae
   i. Gary Ginsberg, Ph.D.
   ii. Joseph Wiemels, Ph.D.
   iii. Markus Brinkmann, Ph.D.

(5) Web Accessible Reviews
   i. Gary Ginsberg, Ph.D.
   ii. Joseph Wiemels, Ph.D.
   iii. Markus Brinkmann, Ph.D.

cc: Chris Banks, Ph.D.
Chief
Water Toxicology Section
Office of Environmental Health Hazard Assessment

Elaine Khan, Ph.D.
Chief
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

# MEMORANDUM

**TO:** Paola Gonzalez
Senior Environmental Scientist Supervisor
CalEPA External Scientific Peer Review Program
Office of Research, Planning, and Performance
California State Water Resources Control Board

**FROM:** Kimberly Gettmann, Ph.D.
Kimberly Gettmann (Jan 16, 2026 10:41:30 PST)
Deputy Director for Scientific Programs

**CC:** Chris Banks, Ph.D., Chief
Water Toxicology Section

Elaine Khan, Ph.D., Chief
Pesticide and Environmental Toxicology Branch

**DATE:** January 16, 2026

**SUBJECT:** REQUEST FOR EXTERNAL SCIENTIFIC PEER REVIEW OF THE SCIENTIFIC BASIS OF THE PROPOSED PUBLIC HEALTH GOAL FOR 1,4-DIOXANE IN DRINKING WATER

## Draft Public Health Goal for 1,4-Dioxane in Drinking Water

This request is regarding the draft document titled, *Public Health Goals – First Public Review Draft – 1,4-Dioxane in Drinking Water*. This technical support document describes the derivation of the proposed Public Health Goal (PHG) for 1,4-dioxane.

The Office of Environmental Health Hazard Assessment (OEHHA) staff requests that you initiate the process to identify external scientific peer reviewers for this draft PHG document, per the requirements of California Health and Safety Code section 57004.

## Purpose of Review

Under the California Safe Drinking Water Act of 1996 (Health and Safety Code Section 116365), OEHHA develops PHGs for drinking water contaminants in California. A PHG is the concentration of a contaminant in drinking water that is estimated to pose no significant health risk to individuals consuming the water over a lifetime. PHGs are based solely on health effects and are used to provide scientific guidance to the State Water Resources Control Board (SWRCB) in setting regulatory standards for drinking water. These standards, also known as Maximum Contaminant Levels (MCLs), must be set as close to the corresponding PHGs as is economically and technologically feasible. This document presents a proposed PHG for 1,4-dioxane.

**When References will be Available at the FTP Site**

The OEHHA staff anticipates submittal of the peer review package to CalEPA staff by January 16, 2026.

This package includes the draft document titled, *Public Health Goals – First Public Review Draft – 1,4-Dioxane in Drinking Water* and all references and appendices. OEHHA understands that the CalEPA External Scientific Peer Review Program staff, housed under the Office of Research, Planning, and Performance at the State Water Resources Control Board (State Water Board) has set up a secure File Transfer Protocol (FTP) site for posting documents for the peer reviewers. OEHHA will upload all the necessary documents for this review to the FTP site. OEHHA received comments from the public on the draft PHG document, and the comments can be found on OEHHA's website (https://oehha.ca.gov/water/comments/comment-submissions-proposed-public-health-goal-phg-14-dioxane-drinking-water). However, OEHHA is not asking for a review of the public comments.

## Requested Review Period

We request that scientific peer review be accomplished within 30 days.

## Requested Review Format

In accordance with CA AB 434 (California Government Code section 11546.7), OEHHA requests that documents submitted as part of this review are compliant with Web Content Accessibility Guidelines (WCAG) 2.2, Level AA.

## Necessary Areas of Expertise for Reviewers

We estimate that four reviewers will be adequate to cover the areas of expertise needed to review the conclusions detailed in Attachment 2. We request selection of reviewers with expertise in the following areas:

General mammalian toxicology and risk assessment. We are looking for expertise in the evaluation of mammalian toxicity studies for both cancer and noncancer effects, including test methods, histopathology, and dose-response analysis. This expertise is needed to evaluate our conclusions regarding the toxicity of 1,4-dioxane in animals and the adequacy of the database for developing a health-protective concentration (HPC), the level of a chemical contaminant in drinking water that does not pose a significant risk to health, for noncancer effects. This area of expertise pertains to conclusions 1 and 4 presented in Attachment 2.

Environmental epidemiology and biostatistics. Expertise in environmental epidemiology and biostatistics, with some knowledge of cancer epidemiology, is needed to evaluate whether our conclusions regarding the currently available epidemiologic studies are appropriate. This area of expertise pertains to conclusion 2 presented in Attachment 2.

Cancer toxicology and risk assessment. Expertise in cancer risk assessment is needed to evaluate our methods and conclusions in deriving an HPC for cancer. This expertise is also needed to evaluate if our methods for deriving the cancer potency, in particular the dose-response assessment (benchmark dose modeling, multisite tumor analysis), are suitable. This evaluation should also include an assessment of the modes of action that underlie carcinogenesis, and whether the methods selected to evaluate the cancer dose-response relationships are appropriate. This area of expertise pertains to conclusions 1, 3, and 4 presented in Attachment 2.

## Attachments

Attached please find:

1. Attachment 1: Plain English Summary.
2. Attachment 2: Scientific Assumptions, Findings, and Conclusions to Review.
3. Attachment 3: Individuals Who Participated in the Development of the Proposal.
4. Attachment 4: References Cited.

## Attachment 1: Plain English Summary

Public Health Goals (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, including use of OEHHA's peer-reviewed risk assessment guidelines. For known carcinogens, a health-protective concentration (HPC) is developed for both cancer and noncancer effects, and the lower of the two values is selected as the PHG. SWRCB must set the corresponding drinking water regulatory standard, or Maximum Contaminant Level (MCL), as close to the PHG as is economically and technologically feasible.

1,4-Dioxane is used as a solvent in multiple industrial applications, e.g., as a wetting and dispersing agent in textile processing, degreasing agent, polymerization catalyst and as a component in various paints, varnishes and related products. It is also found in various personal care products.

In 1998, the Drinking Water Program at the California Department of Public Health established a notification level (NL) of 3 ppb for 1,4-dioxane. NLs are non-regulatory health-based advisory levels for chemicals in drinking water that lack MCLs (SWRCB, 2021). In 2010, US EPA concluded a one-in-one-million cancer risk would correspond to a 1,4-dioxane drinking water concentration of 0.35 ppb and as a result, the NL was revised to 1 ppb. The NL was revised to 1 ppb instead of 0.35 ppb due to limitations in accurately quantifying 1,4-dioxane at levels below 1 ppb.

The proposed PHG of 0.04 parts per billion (ppb), equivalent to 0.04 micrograms per liter (µg/L), is based on liver tumors in female mice and multiple tumor types in male mice. The PHG concentration is set at a level where the extra cancer risk is one per one million persons exposed over a lifetime. The proposed PHG is the result of a comprehensive analysis of information on the toxicology and toxicokinetics of 1,4-dioxane, and includes consideration of sensitive populations, such as infants and children. The analysis details will be introduced in Attachment 2 and thoroughly covered in the technical draft document, *Public Health Goals – First Public Review Draft – 1,4-Dioxane in Drinking Water*.

The draft document was posted on September 26, 2025 on the OEHHA website. The American Chemistry Council requested an extension to the 45-day public comment period, and OEHHA granted an extension of 15 days. OEHHA received comments from the public and interested stakeholders on the draft document during a comment period that opened on September 26, 2025, and closed on November 25, 2025. OEHHA also held a hybrid public workshop on November 13, 2025. Public comments received during the comment period and at the workshop may be viewed at our website or OEHHA can provide them to peer reviewers if requested. OEHHA is not asking for review of those

comments. OEHHA will revise the draft as appropriate based on peer review and public comments. The document will then be posted on OEHHA's website for a second public comment period that will last for 30 days.

## Attachment 2: Scientific Assumptions, Findings, and Conclusions to Review

Following a review of available scientific literature, comprehensive evaluation of the human epidemiology research, potential carcinogenicity modes of action (MOAs), and modeling all the significant tumor incidences in the carcinogenicity studies of 1,4-dioxane, OEHHA developed a proposed PHG for 1,4-dioxane in drinking water and requests that this review focus on the following listed conclusions. The results of OEHHA's scientific literature review and research are presented in the draft document, *Public Health Goals – First Public Review Draft – 1,4-Dioxane in Drinking Water*. OEHHA requests that reviewers determine whether the scientific work product is "based upon sound scientific knowledge, methods, and practices." An explanatory statement is provided in Attachment 1 for the proposed PHG to focus the review.

In evaluating OEHHA's assumptions, findings, and conclusions, absolute scientific certainty is not required. Instead, the task for reviewers is to determine if there is adequate scientific basis supporting the proposed PHG.

### *Assumptions, Findings, and Conclusions*

1. **Critical studies and toxicity endpoints – The carcinogenicity studies in mice from Kano et al. (2009) and Kasai et al. (2009) for oral and inhalation exposures, respectively, were selected as the critical studies to develop the HPC for cancer. A noncancer HPC was derived from Kociba et al. (1974), based on liver and kidney toxicity in rats. Please comment on the comprehensiveness of the literature search for animal toxicity studies and the suitability of these critical studies and endpoints for PHG derivation.**

OEHHA conducted a systematic literature search for studies that were published after the NL was revised in 2010. The search included studies from January 2009 up to April 2019, and updated searches were conducted in August 2021 and August 2023. OEHHA screened 1,306 studies, and following title/abstract and full-text reviews, seven studies were identified. The Kano et al. (2009), Kasai et al. (2009), and Kociba et al. (1974) studies were considered to be of sufficient quality because they included multiple doses/concentrations, had large sample sizes, used appropriate routes of exposure (drinking water and inhalation), and were of sufficient duration (2 years). Dose-response analyses, using benchmark dose modeling where appropriate, provided points of departure for noncancer effects, and cancer slope factors for cancer effects. The study associated with the largest cancer slope factor for each route (oral and inhalation) was selected as a critical study for cancer effects. The liver and kidney toxicity reported in Kociba et al. (1974) were the most sensitive noncancer endpoints, thus this study was selected as the critical noncancer study.

The sections of the draft document that pertain to this conclusion include:

- Animal toxicity studies (starting on pg. 26)
- Dose-response assessment (starting on pg. 51)
- Appendix I – Literature search strategies (starting on pg. 81).

2. **Human epidemiology evaluation – OEHHA determined that the available human epidemiology studies of 1,4-dioxane were not suitable for hazard identification or derivation of HPCs. Please comment on the comprehensiveness of the literature search for human studies and whether the rationale provided supports this conclusion.**

OEHHA conducted a comprehensive evaluation of the human epidemiology research on 1,4-dioxane presented in the US Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile published in 2012. ATSDR (2012) reported that two occupational studies showed no increases in death, cancer, or biochemical markers of liver, kidney, or hematologic disease. However, sample sizes were small, and data on potential confounders and co-exposures were incomplete. Other identified studies were acute in duration, and therefore not suitable for HPC derivation.

OEHHA also identified seven additional human epidemiology studies published after 2011, from its own systematic literature search. These studies examined potential association of 1,4-dioxane exposure and adverse health outcomes, including breast cancer (2 studies, no association), autism spectrum disorder (2 studies, one identified a potential association), reduced telomere length (1 study, potential association), and irritation/inflammation (2 studies, inconclusive). The studies contained weaknesses which limited their usefulness in this assessment, including uncertain exposure estimates and the use of unvalidated models. Because of these weaknesses and the absence of strong, consistent associations with specific adverse endpoints, human data were not considered for HPC development.

The sections of the product that pertain to this conclusion include:

- Human epidemiology studies (starting on pg. 23).

3. **Cancer potency determination – OEHHA determined that the cancer mode of action (MOA) evidence does not conclusively support one predominant MOA for carcinogenesis. Because of this, and because a genotoxic MOA cannot be ruled out, OEHHA used linear extrapolation (as opposed to a threshold approach) to derive cancer slope factors for 1,4-dioxane. Please comment on whether OEHHA has provided adequate evidence to support this approach.**

OEHHA evaluated the potential carcinogenicity modes of action (MOAs) of 1,4-dioxane. OEHHA presented the mechanistic data using a framework based on the key

characteristics of carcinogens. OEHHA also evaluated studies examining metabolic saturation, cytotoxicity, changes in gene expression, and tumor promotion.

OEHHA identified eight studies reporting positive genotoxicity results in animal studies. However, OEHHA also identified four studies reporting negative genotoxicity results, and 1,4-dioxane does not appear to be mutagenic in the majority of in vitro systems tested. Even though these results are mixed, OEHHA could not rule out genotoxicity as a potential MOA of carcinogenesis because of the positive studies.

Multiple studies reported that 1,4-dioxane induced oxidative stress in exposed animals, including oxidative DNA damage. However, results were inconsistent across studies, with some studies reporting the absence of oxidative biomarkers in the liver of exposed rodents. It is likely that 1,4-dioxane does induce oxidative stress, but it is unclear whether this is the primary driver of carcinogenesis.

Metabolic saturation, followed by cytotoxicity and regenerative hyperplasia have also been proposed as key events in 1,4-dioxane carcinogenesis. OEHHA identified multiple studies that show an increase in DNA synthesis in the liver. However, there are also inconsistent data for this proposed MOA, with multiple studies showing cytotoxicity and cellular necrosis at doses below those that lead to tumor formation. Additionally, tumors were observed at doses without reported cytotoxicity and necrosis. It is unclear whether this proposed MOA is significant.

OEHHA concluded that there are multiple potential MOAs for 1,4-dioxane carcinogenicity. The oxidative stress and metabolic saturation MOAs support the use of a cancer threshold for dose-response analysis. Conversely, genotoxic chemicals do not have cancer thresholds, and linear extrapolation is used to derive a cancer slope factor. Because the evidence does not definitively support a predominant MOA for carcinogenesis, and because genotoxicity could not be ruled out as a potential MOA, OEHHA took the health-protective approach and used linear extrapolation to derive cancer slope factors. This approach is consistent with US EPA's cancer assessment guidelines and US EPA's most recent assessment of 1,4-dioxane (US EPA, 2024).

The sections of the product that pertain to this conclusion include:

- Cancer studies in animals (starting on pg. 38)
- Mode of action and mechanistic considerations (starting on pg. 44).

4. **Public Health Goal derivation – OEHHA conducted benchmark dose modeling of tumor data from Kano et al. (2009) and Kasai et al. (2009). The oral cancer slope factor was derived from liver tumors in female mice (Kano et al., 2009). The inhalation cancer slope factor was derived from a multisite tumor analysis in male mice (Kasai et al., 2009). Daily water intake was determined using**

**lifetime weighted average drinking water rates, and a multimedia exposure model to determine the relative contribution from inhalation and dermal exposure. Please comment on the appropriateness of this approach and whether all important relevant scientific issues have been addressed.**

OEHHA modeled all the significant tumor incidences in the carcinogenicity studies of 1,4-dioxane: NCI (1978); Kano et al. (2009); and Kasai et al. (2009). OEHHA conducted multisite analyses when multiple tumor types were present in the same cohort. OEHHA derived cancer slope factors from all the modeled tumor data and selected the largest slope factor for each route of exposure, as it was the most health-protective option.

PHGs must be protective of known sensitive populations. OEHHA used a 70-year lifetime weighted average drinking water rate, which incorporates the higher water intake rates of infants and children, reported in OEHHA (2012) for PHG derivation. Additionally, age sensitivity factors were included to reflect the enhanced sensitivity of fetuses, infants, and children to carcinogens.

To determine the relative contributions of inhalation and dermal exposure from general uses of tap water, OEHHA used the CalTOX 4.0 multimedia exposure model developed by the Lawrence Berkeley National Laboratory. The modeling indicated that oral intake is the predominant route of exposure, and that inhalation exposure is around 9-17% of the total daily exposure (depending on life stage). Dermal exposure was negligible.

The sections of the product that pertain to this conclusion include:

- Cancer studies in animals (starting on pg. 38)
- Dose-response assessment – cancer (starting on pg. 53)
- Health-Protective Drinking Water Concentrations (starting on pg. 64)

## Attachment 3: Individuals Who Participated in the Development of the Proposal

For the sake of completeness, OEHHA has taken a special effort to identify all staff involved in the process of developing the proposed PHG for 1,4-dioxane.

**Section A. Office of Environmental Health Hazard Assessment Staff**

| | |
|---|---|
| Contributors: | Christopher Banks, Ph.D.<br>Vanessa Cheng, Ph.D,<br>David Edwards, Ph.D.<br>Ida Flores-Avila, Ph.D.<br>Kimberly Gettmann, Ph.D.<br>Elaine Khan, Ph.D.<br>Kannan Krishnan, Ph.D.<br>Martha Sandy, Ph.D.<br>Anatoly Soshilov, Ph.D.<br>Craig Steinmaus, M.D. |
| Director: | Kristina Thayer, Ph.D. |

# Attachment 4: References Cited

## References

All references cited in the draft PHG update document will be provided to reviewers at a file transfer protocol site.

Critical studies and guidance documents used in the derivation of the PHG update are as follows:

Kano H, Umeda Y, Kasai T, Sasaki T, Matsumoto M, Yamazaki K, Nagano K, Arito H, Fukushima S (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.

Kasai T, Kano H, Umeda Y, Sasaki T, Ikawa N, Nishizawa T, Nagano K, Arito H, Nagashima H, Fukushima S (2009). Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. Inhal Toxicol 21(11): 889-897.

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.

NCI (1978). Bioassay of 1,4-dioxane for possible carcinogenicity. National Cancer Institute Carcinogenesis Technical Report Series No. 80. Bethesda, MD. 80: 1-123.

OEHHA (2012). Air toxics hot spots program risk assessment guidelines: technical support document for exposure assessment and stochastic analysis. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA

US EPA (2024). Supplement to the Risk Evaluation for 1,4-Dioxane. CASRN 123-91-1. United States Environmental Protection Agency, Washington DC.

**Subject: Gary Ginsberg Comments for the Peer Review of OEHHA's Proposed Public Health Goal For 1,4-Dioxane in Drinking Water**

**Date: April 10, 2026**

*Conclusion # 1*
*Critical studies and toxicity endpoints – Please comment on the comprehensiveness of the literature search for animal toxicity studies and the suitability of these critical studies and endpoints for PHG derivation.*

***Response: The draft PHG document identifies the key animal toxicity studies showing the most sensitive endpoints and dose response profiles that I am aware of. The long-term hazard and dose response studies were conducted primarily before 2010 while more recent animal studies have focused upon mechanistic endpoints in liver, primarily at high dose. The PHG document does a good job of summarizing the mechanistic information although a number of in vivo studies are not presented (e.g., Wang, et al. 2024: https://pmc.ncbi.nlm.nih.gov/articles/PMC11500436/ ; Honda et al. 2026: https://pubmed.ncbi.nlm.nih.gov/41308846/ ; Toyoda et al. 2023: https://pubmed.ncbi.nlm.nih.gov/37258237/ ). I don't believe these additional studies would change the hazard or dose response assessment, or even the analysis of mechanism of action, but I recommend they be evaluated by Cal OEHHA for this purpose. Along these lines CalOEHHA should also be aware of Kirman et al. 2026 (https://pubmed.ncbi.nlm.nih.gov/41015149/).***

***Regarding developmental outcomes, a new study in zebrafish is available (https://pubmed.ncbi.nlm.nih.gov/40323311/) which should be evaluated with respect to whether it has any impact on the need for the uncertainty factor used in this analysis for datagaps.***

*Conclusion # 2:*
*Human epidemiology evaluation – Please comment on the comprehensiveness of the literature search for human studies and whether the rationale provided supports OEHHA's determination that the available human epidemiology studies of 1,4-dioxane were not suitable for hazard identification or derivation of HPCs.*

***Response: I agree that the draft PHG summary of the epidemiology literature is complete and is justified in reaching the conclusion that it is insufficient to inform hazard identification or dose response assessment and thus also not suitable for the derivation of HPCs.***

*Conclusion # 3*
*Cancer potency determination – Please comment on whether adequate evidence has been provided to support use of linear extrapolation (as opposed to a threshold approach) to derive cancer slope factors for 1,4-dioxane.*
***Response: The carcinogenic mechanism for 1,4-dioxane is an active area of research that has thus far not identified a clear mechanism(s) or adverse outcome pathway. Thus we still don't know whether parent compound or active metabolite is required, what effects may extend from high dose to low dose given that most of the mechanism information is at high dose, or whether a particular vulnerability***

***exists. Without further clarification on mechanism it is difficult to evaluate the potential for thresholds to occur either from a toxicokinetic or toxicodynamic perspective.***

***However, the draft document could do a more comprehensive assessment of the potential for thresholds to impact dose response as TK evidence for metabolic saturation exists and it is important to consider whether this type of saturation could create a non-linearity in dose response for carcinogenesis. Ginsberg et al. 2022 (https://pubmed.ncbi.nlm.nih.gov/37091947/ )summarize evidence that metabolic saturation has been documented after single dose or short-term studies but may not occur under chronic exposure regimens given that 1,4-dioxane induces its own metabolism. Similarly cytotoxicity and cell proliferation do occur after relatively high doses and this could contribute to the number of tumors seen after high dose. The PHG synthesis of mechanistic data with respect to the potential for these types of high dose effects to create non-linearities could be more completely discussed. A key finding of the draft PHG which I agree with is that tumor increases have been found in female mice at doses below which there was evidence for cytotoxicity which decreases the likelihood that cytotoxicity is a necessary and essential element for carcinogenicity by this chemical. Further there is evidence for a mutagenic effect in rat liver at in vivo doses that were not cytotoxic (92 mg/kg/d) (Gi et al. 2018) further supporting a role for DNA damage in the cancer mechanism. As an aside the description of this study on Page 45 implies that it may have been of value to test WT rats as well. This is not needed and a misleading statement implying that there is some deficiency in this study. The gpt delta transgenic F344 system is a reporter gene assay which is not believed to be any more vulnerable to mutation than WT animals; finding mutations in WT animals is more difficult and a less sensitive approach and would not be expected to be a part of the design, as opposed to toxicity studies involving a susceptibility transgene where comparison to WT is important. I recommend removing that part of the sentence.***

*Conclusion # 4*
*Public Health Goal derivation – Please comment on the appropriateness of the described approach and whether all important relevant scientific issues have been addressed.*

***The PHG was derived based upon standard approaches, sound science and appears to be accurately constructed. It is abundantly conservative given that it applies both low dose linearity and childhood ASFs for a carcinogen of unknown mechanism. This degree of precaution may be appropriate policy for the derivation of a goal (e.g., the federal MCLG for carcinogens is set at 0) that is non-regulatory in nature.***

*Other Comments:*

***Table 18 lists a wide range of drinking water guidelines and regulatory standards for 1,4-dioxane in drinking water but is missing the NYS MCL of 1 ug/L established in 2020***
*(https://www.health.ny.gov/environmental/water/drinking/emerging_pfas_publicwater.htm#:~:text=New%20York%27s%20drinking%20water%20standards,for%201%2C4%2Ddioxane.).*

Comments on “FIRST PUBLIC REVIEW DRAFT of 1,4-Dioxane in Drinking Water”

My name is Joseph Wiemels, and I am a professor in the Department of Population and Public Health Sciences at University of Southern California. I review here the FIRST PUBLIC REVIEW DRAFT of 1,4-Dioxane in Drinking Water September 2025 in early 2026, Based on my expertise and experience, I am reviewing the findings, assumptions, or conclusions I agreed I could review with confidence:

*Conclusion # 2:*
*Human epidemiology evaluation – Please comment on the comprehensiveness of the literature search for human studies and whether the rationale provided supports OEHHA’s determination that the available human epidemiology studies of 1,4-dioxane were not suitable for hazard identification or derivation of HPCs.*

*Conclusion # 3*
*Cancer potency determination – Please comment on whether adequate evidence has been provided to support use of linear extrapolation (as opposed to a threshold approach) to derive cancer slope factors for 1,4-dioxane.*

And to consider whether you conclude the proposed rule, taken as a whole, is based on sound scientific knowledge, methods, and practices.

First of all, a short biography of Dr. Wiemels expertise on these matters. Dr. Wiemels has training in toxicology, epidemiology, and molecular genetics from his doctorate at UC Berkeley (1997), post-doctorate work at the Institute of Cancer Research (UK) (1997-1999), and 26-year faculty career at UCSF and USC. In his time at faculty he has long taught molecular and genetic epidemiology, conducted etiologic research on childhood and adult cancers, and is considered an expert in environmental health and childhood cancers, particularly leukemia and brain cancer. Dr. Wiemels currently runs the PhD program in epidemiology at USC and is an associate director of the Norris Comprehensive Cancer Center, and also runs the core laboratory of the Southern

California Environmental Health Sciences Center. Dr. Wiemels has long studied specific organic solvents and cancer, including his doctoral thesis on benzene and butadiene toxicology and carcinogenicity, and he has participated in reviews of formaldehyde and ethylene oxide for NAS/EPA. Much of his research is based on molecular mechanisms of carcinogenesis and the public's risks as defined interindividual vulnerabilities defined by genetics and interactions of genes with the environment.

1,4 dioxane is used both industrially as a solvent and incorporated within various consumer products – for these not as an "active ingredient" but a by-product of the synthesis of other ingredients, or a solvent or stabilizer. The chemical is classified as a class 2B "possibly carcinogenic in humans" carcinogen by IARC based largely on its capacity to induce nasal and liver tumors in animals. California Proposition 65 also classifies this chemical as a carcinogen. Concerns about 1,4 dioxane in the current setting appear to be primarily focused on benchmark regulatory levels in drinking water, where pervasive, population-level exposures require a Public Health Goal (PHG) lifetime exposure level in drinking water – this exposure level would be driven by cancer risk, the most sensitive human endpoint. Intermittent use by consumers of products containing 1,4 dioxane is less of a concern than the accumulation of waste 1,4 dioxane that contaminates groundwater and other effluents that end up in drinking water. The document leans heavily on animal data to negotiate the drinking water level, in part since the epidemiology studies yield insufficient or questionable quality data with largely negative or inconclusive studies. These studies historically are occupation-based, where studies are underpowered to detect anything but extremely strong carcinogenic impacts. As 1,4 dioxane is not a particularly strong mutagen or carcinogen, it has escaped calls for banning or intensive regulation and indeed has not evaluated extensively in human populations leading to a wide range of MCL's at the state and regional regulatory agencies. To the small extent that they were available, limited larger population-based studies were included in the Draft document when appropriate – and will form the basis of my review for "Conclusion 2" stated above.

<u>Epidemiology of 1,4 dioxane</u>

The Draft document describes literature research of over 1700 papers, dual abstract review, and the choice of 7 studies for more intensive investigation and the basis for hazard identification. These seven studies did not provide clear or convincing evidence of a health impact from 1,4 dioxane exposure – and while some significant results were indicated for autism as an outcome, co-exposures and multiple comparisons statistical issues obscure any possible interpretation. Historic case reports suggest acute toxic impacts do not include cancer, and short-term controlled studies of lower doses in humans do not indicate long lasting effects. These studies therefore did not provide definitive evidence for long-term health impacts of 1,4 dioxane, and are therefore cannot contribute meaningful perspective on a PHG for drinking water exposures. A thorough review of the strengths and weaknesses of these studies will not be presented here; such critiques are brief but substantive and honest within the DRAFT itself. Notwithstanding most of the epidemiology studies examine modeled airway exposures rather than drinking water exposures, so are less relevant.

*Thoroughness of review*: The review leans heavily on the ATSDR 2012 for older literature, and EPA reviews. This is appropriate as the legacy research is well covered in these reviews. Much of the older literature is less applicable anyway since it is based on occupational exposures, where intermittent high exposures on limited numbers of workers are not adequate for estimating risks of pervasive low dose exposures as a long term risk of adverse health effects. The more modern research reports (post-2012) were reviewed with multiple databases, PECO framework, and dual-person abstract screening which meets current standards of practice. Undoubtedly documents such as this Draft will be slightly out of date based on the timing of searches – and research will continue to improve as larger population-based studies with refined assessments of environmental exposure are incorporated. Saying this, I could not find any newer research that should be included (last searched in April 2026). An study on actual tested drinking water concentrations of 1,4 dioxane in New York was interesting, showing that the relevant concentrations discussed in this DRAFT apply in a real world (though not California) setting – and imply possible future study designs (PMID: 41824932). Such studies that then could include active exposure monitoring (sampling) connected with spatial estimations would exposure modelling over a population large enough to detect

the 1 in one million health events desired to be captured by OEHHA as an agency tasked with protecting public health. Multiple studies report 1,4 dioxane levels in crucial consumer items such as diapers, cosmetics, hygiene products, etc; it is clear that a drinking water standard may have implications on the levels of 1,4 dioxane on such products, but quality studies on 1,4 dioxane in drinking water and epidemiology of human health outcomes do not exist. Such a lack of studies has impelled the authors of this Draft to nearly entirely dismiss human epidemiology data in the formulation of this PHG and lean on other data from animal studies.

Could the Draft include more human epidemiologic considerations? Certainly there might be additional studies included, though several barriers exist.  First, most human studies are based on inhalation, which is less relevant to a drinking water standard. Second, the existing human data suffers from either small size (the occupation studies, underpowered for cancer) or poor exposure assessment, confounding (mixture and co-exposure studies). Third and perhaps most importantly, the studies that are included are the highest quality that exist; though they suffer from multiple exposures, unreliable exposure metrics, and the wrong route of exposure. Diminishing returns will be added with additional studies, which is therefore not recommended.

Essential to the epidemiology research process is the identification of exposures that are hazardous to human health and the provision of definitive research results to allow action on prevention or regulation. In regulatory environments this corresponds to identification of a dose minimizing hazards to the scale of 1 to 10^6. The generalized epidemiologic process is somewhat blunt (even large studies are impaired by co-exposures, low exposures, confounding and bias), and those conventional epidemiology studies for which 1,4 dioxane has been assessed certainly fall within these issues. The discipline of “molecular epidemiology” combines genetic and environmental epidemiology to permit more definitive results by helping to identify those in the population at most genetic risk of environmental exposure. Such vulnerable persons are the individuals that respond with a toxic endpoint to an offending chemical due to genetic susceptibility. To his knowledge, not a single human study has investigated 1,4 dioxane risks in concert with known polymorphisms in enzymes critical for 1,4 dioxane

metabolism, notably for the known polymorphic enzyme CYP2E1, representing a potential gap in knowledge that might lead to a better understanding of individuals carrying genetic liabilities to exposure. CYP2E1 is a crucial primary enzyme in the breakdown of 1,4 dioxane to excretable metabolites, but it is just one of many polymorphic enzymes or traits that can yield interindividual differences in susceptibility to chemicals such as 1,4 dioxane. Without this type of research available, a more precautionary approach is appropriate – which brings this review to cancer potency determination.

Cancer potency determination

While quality and informative human data is desirable, the decision not to use animal data exclusively for current calculations in the Draft is appropriate. This data included multiple studies on genetic toxicology, reproductive health and developmental toxicology, long term studies of kidney function, cancer, body weight and other relevant endpoints. The authors examine 1,4 dioxane in relation to the “key characteristics” establishing the genotoxicity, oxidative stress, inflammation, cell proliferation. Metabolic saturation is shown not to be a requirement for carcinogenicity, therefore low dose considerations are relevant, as considered for this PHG. This key point (low dose activity not dependent on saturation) is a one of the most important points on choice of low dose modelling, arguing for a linear approach. Dose-response results from oral-exposure studies support this as well. A careful review of the mode of action yields a myriad of mechanisms including formation of cytogenetic aberrations (micronuclei), oxidative stress, inflammation and promotion of cell proliferation. I agree that these characteristics are suggestive of a “complete carcinogen” which again leads to precautionary or linear low dose extrapolation, particularly since there is not a single or dominant mode of action for which to base a threshold approach.

While the linear approach is appropriate, the best data available for a quantitative approach was chosen from select rodent oral exposure manuscripts. I did not deeply review the quality of data or presentation of these manuscripts apart from a review of consistency of experimentation and results. The rodent experiments included high doses at which saturation may occur, although they do metabolize more efficiently than

humans. This metabolism is qualitatively similar suggesting that toxicological endpoints and cancer would echo such similarities as well.

While a linear approach is deemed scientifically valid, rodent experiments do tend to overpredict human cancer risks, and this overprediction will be exaggerated once uncertainty factors are applied. In the effort to come to one standard which applies universally to the population, without consideration of those with genetic vulnerabilities, these precautionary steps are however highly justified. Therefore, it is my opinion that a PHG should be conservatively set on the best available science as set forth in the DRAFT. The current EPA mark (0.35 ppb) and California notification level (1 ppb) are based on a negotiation between good science and detection limits of testing apparatus. That the PHG is an order of magnitude lower than these other marks can serve as a guide for product formulation and use, wastewater and drinking water treatments, and the formulation of regulatory goals that protect the consumer and those most vulnerable in our society. The linear extrapolation of this PHG from higher exposures is justified, and additional conservative assumptions drive the PHG lower. Those conservative assumptions, particularly the “300” uncertainty factor, while conventional, could be reconsidered or justified more strongly. An actual MCL at the level of 0.04 ppb is likely unreasonable with current technology for testing and purification. Finally, the uncertainty contained within this PHG goal should be communicated within the DRAFT document itself more thoroughly as well as its goal at pointing towards regulatory goals rather than establishing this mark as a final standard.

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April 10, 2026

## External Scientific Peer Review of the Scientific Basis of the Proposed Public Health Goal for 1,4-Dioxane in Drinking Water

Based on my expertise and experience, I am reviewing the findings, assumptions, or conclusions I agreed I could review with confidence:

- ***Conclusion # 1: Critical studies and toxicity endpoints*** *– Please comment on the comprehensiveness of the literature search for animal toxicity studies and the suitability of these critical studies and endpoints for PHG derivation.*
- ***Conclusion # 2: Human epidemiology evaluation*** *– Please comment on the comprehensiveness of the literature search for human studies and whether the rationale provided supports OEHHA's determination that the available human epidemiology studies of 1,4-dioxane were not suitable for hazard identification or derivation of HPCs.*
- ***Conclusion # 4: Public Health Goal derivation*** *– Please comment on the appropriateness of the described approach and whether all important relevant scientific issues have been addressed.*

This review will be structured as follows: First, I will provide some general observations on the proposed Public Health Goal; then, I will provide overarching comments regarding my review of conclusions 1, 2, and 4 and the supporting text, as well as detailed comments on the First Public Review Draft of the Proposed Public Health Goal for 1,4-Dioxane in Drinking Water.

## General Observations

I want to begin by commending OEHHA for creating a compelling, comprehensive, and balanced draft of the proposed Public Health Goal for 1,4-Dioxane in Drinking Water that provides a solid basis for deriving such a Public Health Goal. Based on my thorough review of the provided materials (as outlined in the March 11, 2026, Commencement Letter), I conclude that the scientific portion of the proposed rule is based on sound scientific knowledge, methods, and practices.

Any suggestions and comments provided below are submitted to OEHHA to further streamline the Conclusions and the proposed Public Health Goal draft document.

## Overarching Comments Regarding the Scientific Assumptions, Findings, and Conclusions to Review

Comments in this section are provided in an itemized format, with the original text in Attachment 2, Scientific Assumptions, Findings, and Conclusions to Review, followed by my comments in italicized formatting.

**Conclusion #1: Critical studies and toxicity endpoints – The carcinogenicity studies in mice from Kano et al. (2009) and Kasai et al. (2009) for oral and inhalation exposures, respectively, were selected as the critical studies to develop the HPC for cancer. A noncancer HPC was derived from Kociba et al. (1974), based on liver and kidney toxicity in rats. Please comment on the comprehensiveness of the literature search for animal toxicity studies and the suitability of these critical studies and endpoints for PHG derivation.**

OEHHA conducted a systematic literature search for studies that were published after the NL was revised in 2010. The search included studies from January 2009 up to April 2019, and updated searches were conducted in August 2021 and August 2023. OEHHA screened 1,306 studies, and following title/abstract and full-text reviews, seven studies were identified.

> *Overall, the literature search appears comprehensive and appropriately targeted toward identifying animal toxicity studies relevant to chronic exposure and PHG derivation. The combination of a post-2009 systematic search with targeted consideration of earlier foundational carcinogenicity studies (e.g., NCI, Kociba et al.) is scientifically appropriate and minimizes the likelihood that critical studies were overlooked.*

The Kano et al. (2009), Kasai et al. (2009), and Kociba et al. (1974) studies were considered to be of sufficient quality because they included multiple doses/concentrations, had large sample sizes, used appropriate routes of exposure (drinking water and inhalation), and were of sufficient duration (2 years).

> *I concur with OEHHA's assessment of study quality and suitability. These studies represent the most robust long-term toxicity datasets available for 1,4-dioxane, and*

*their consistent findings across species, exposure routes, and target organs provide a strong and internally consistent basis for identifying critical effects relevant to human health protection.*

Dose-response analyses, using benchmark dose modeling where appropriate, provided points of departure for noncancer effects, and cancer slope factors for cancer effects.

*The application of benchmark dose modelling, rather than reliance on NOAELs alone, is scientifically justified and consistent with current best practices in quantitative risk assessment. OEHHA's transparent discussion of model fit, uncertainty, and selection criteria strengthens confidence in the resulting points of departure. While a complete mathematical reanalysis of the results provided here was beyond the scope of my review, the model fits provided in the Appendix appear solid and based on the best available science.*

The study associated with the largest cancer slope factor for each route (oral and inhalation) was selected as a critical study for cancer effects.

*Selecting the cancer slope factor that yields the greatest potency for each exposure route is a conservative and health-protective approach, consistent with OEHHA guidance and the mandate of PHG development. This approach appropriately addresses uncertainties in tumour site relevance and interspecies extrapolation. Based on my read of the provided data, I arrived at the same conclusion as OEHHA.*

The liver and kidney toxicity reported in Kociba et al. (1974) were the most sensitive noncancer endpoints, thus this study was selected as the critical noncancer study.

*Although Kociba et al. (1974) predates current guideline expectations, the study remains scientifically sound and informative, particularly given its chronic duration, drinking-water exposure route, and detailed histopathological evaluation, which support their selection as critical noncancer endpoints.*

The sections of the draft document pertaining to this conclusion that I reviewed in detail included:

- Animal toxicity studies (starting on pg. 26)
- Dose-response assessment (starting on pg. 51)
- Appendix I – Literature search strategies (starting on pg. 81).

**Conclusion #2: Human epidemiology evaluation – OEHHA determined that the available human epidemiology studies of 1,4-dioxane were not suitable for hazard identification or derivation of HPCs. Please comment on the comprehensiveness of the literature search for human studies and whether the rationale provided supports this conclusion.**

OEHHA conducted a comprehensive evaluation of the human epidemiology research on 1,4-dioxane presented in the US Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile published in 2012. ATSDR (2012) reported that two occupational studies showed no increases in death, cancer, or biochemical markers of liver, kidney, or hematologic disease. However, sample sizes were small, and data on potential confounders and co-exposures were incomplete. Other identified studies were acute in duration, and therefore not suitable for HPC derivation.

> *The reliance on the ATSDR (2012) synthesis is appropriate, as it represents the most comprehensive evaluation of occupational and clinical human data available prior to OEHHA's updated search timeframe. Given the exposure routes, durations, and outcome measures of these studies, their limited utility for chronic risk characterization is adequately justified.*

OEHHA also identified seven additional human epidemiology studies published after 2011, from its own systematic literature search. These studies examined potential association of 1,4-dioxane exposure and adverse health outcomes, including breast cancer (2 studies, no association), autism spectrum disorder (2 studies, one identified a potential association), reduced telomere length (1 study, potential association), and irritation/inflammation (2 studies, inconclusive).

> *OEHHA's identification and evaluation of post-2011 epidemiological studies demonstrates due diligence and confirms that newer studies do not materially alter the overall weight of evidence. While some studies reported suggestive associations, these findings lacked consistency across studies and health endpoints. The respective section in the document eloquently outlines the findings and shortcomings of the various human epidemiological studies. In particular, the widespread use of exposure models in these studies, which are associated with uncertainties and potentially narrow exposure ranges, poses challenges to relying on them for hazard identification or HPC derivation.*

The studies contained weaknesses which limited their usefulness in this assessment, including uncertain exposure estimates and the use of unvalidated models. Because of

these weaknesses and the absence of strong, consistent associations with specific adverse endpoints, human data were not considered for HPC development.

*I agree with OEHHA's conclusion that the available human epidemiology data are insufficient for hazard identification or quantitative derivation of HPCs. In particular, the pervasive reliance on model-based exposure estimates, limited exposure contrast, and lack of validation data substantially weaken causal inference and preclude their use in dose-response assessment.*

The sections of the draft document pertaining to this conclusion that I reviewed in detail included:

- Human epidemiology studies (starting on pg. 23).

**Conclusion #4: Public Health Goal derivation – OEHHA conducted benchmark dose modeling of tumor data from Kano et al. (2009) and Kasai et al. (2009). The oral cancer slope factor was derived from liver tumors in female mice (Kano et al., 2009). The inhalation cancer slope factor was derived from a multisite tumor analysis in male mice (Kasai et al., 2009). Daily water intake was determined using lifetime weighted average drinking water rates, and a multimedia exposure model to determine the relative contribution from inhalation and dermal exposure. Please comment on the appropriateness of this approach and whether all important relevant scientific issues have been addressed.**

OEHHA modeled all the significant tumor incidences in the carcinogenicity studies of 1,4-dioxane: NCI (1978); Kano et al. (2009); and Kasai et al. (2009). OEHHA conducted multisite analyses when multiple tumor types were present in the same cohort. OEHHA derived cancer slope factors from all the modeled tumor data and selected the largest slope factor for each route of exposure, as it was the most health-protective option.

*This approach is methodologically sound and appropriately conservative. Modelling multiple tumour endpoints and employing multisite analyses where warranted ensures that the full carcinogenic potential of 1,4-Dioxane is captured, rather than focusing narrowly on a single tumour site or study.*

PHGs must be protective of known sensitive populations. OEHHA used a 70-year lifetime weighted average drinking water rate, which incorporates the higher water intake rates of infants and children, reported in OEHHA (2012) for PHG derivation.

Additionally, age sensitivity factors were included to reflect the enhanced sensitivity of fetuses, infants, and children to carcinogens.

> *The use of lifetime-weighted average drinking water intake rates, combined with age sensitivity factors, represents a scientifically robust and consistent approach. This methodology explicitly accounts for life-stage-specific differences in exposure and susceptibility, thereby strengthening the public health protectiveness of the derived PHG.*

To determine the relative contributions of inhalation and dermal exposure from general uses of tap water, OEHHA used the CalTOX 4.0 multimedia exposure model developed by the Lawrence Berkeley National Laboratory. The modeling indicated that oral intake is the predominant route of exposure, and that inhalation exposure is around 9-17% of the total daily exposure (depending on life stage). Dermal exposure was negligible.

> *The application of CalTOX 4.0 to evaluate multi-route exposure appears appropriate for a volatile, water-miscible compound such as 1,4-Dioxane. The conclusion that oral exposure dominates overall intake is consistent with the physicochemical properties of 1,4-Dioxane and supports using the oral cancer slope factor as the primary driver of the PHG.*

The sections of the draft document pertaining to this conclusion that I reviewed in detail included:

- Cancer studies in animals (starting on pg. 38)
- Dose-response assessment – cancer (starting on pg. 53)
- Health-Protective Drinking Water Concentrations (starting on pg. 64).

## Reviewed Literature

I reviewed the critical studies and guidance documents listed below, copies of which were provided to me through the File Transfer Protocol (FTP) site, in addition to other references as appropriate:

Kano H, Umeda Y, Kasai T, Sasaki T, Matsumoto M, Yamazaki K, Nagano K, Arito H, Fukushima S (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.

Kasai T, Kano H, Umeda Y, Sasaki T, Ikawa N, Nishizawa T, Nagano K, Arito H, Nagashima H, Fukushima S (2009). Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. *Inhal Toxicol* 21(11): 889-897.

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.
NCI (1978). Bioassay of 1,4-dioxane for possible carcinogenicity. *National Cancer Institute Carcinogenesis Technical Report Series No. 80*. Bethesda, MD. 80: 1-123.
OEHHA (2012). Air toxics hot spots program risk assessment guidelines: technical support document for exposure assessment and stochastic analysis. Office of Environmental Health Hazard Assessment, *California Environmental Protection Agency*, Sacramento, CA
US EPA (2024). Supplement to the Risk Evaluation for 1,4-Dioxane. CASRN 123-91-1. *United States Environmental Protection Agency*, Washington DC.

## Specific Comments on the Draft of the Public Health Goal for 1,4-Dioxane in Drinking Water

Comments in this section are provided in an itemized format, providing the page and paragraph number (due to the absence of line numbers) for reference. Commentary and/or suggested changes are indicated below.

- Page ii, section “Preface”: This section provides a succinct background for the need to derive a Public Health Goal (PHG) for 1,4-Dioxane.
- Page 5, section “Summary”: This section is very well done and provides a comprehensive, yet succinct summary of the Public Health Goal document.
- Page 5, section “Summary”, first paragraph: While the proposed PHG is provided in both µg/L and ppb, the noncancer health-protective concentration (HPC) is only provided in ppb. I suggest harmonizing the reporting here.
- Page 6, Table 6: While references are provided for all other physico-chemical properties, no references are required for either the molecular weight or the physical state at ambient temperature.
- Page 7, section “PHG Derivation”: I believe it would be helpful here to explain whether dose-response relationships were always modelled by OEHHA based on raw data extracted from the publication, or if, in some instances, author-reported values were used.
- Page 7 and following: These sections, outlining critical concepts for deriving Health-Protective Concentrations for Noncancer Effects, including the sections on Point of Departure (POD), Acceptable Daily Dose (ADD), Uncertainty and Variability Factors (UF), Daily Water Intake Equivalent (DWI), Relative Source Contribution (RSC), and Derivation of the Health-Protective Concentration, are extremely well-written. The

same pertains to the sections on critical concepts for deriving Health-Protective Concentrations for Cancer Effects, including the sections on Cancer Dose-Response Analyses and Cancer Potency Derivation, Method of Calculating Cancer Potency, calculating Average Daily Dose, Dose-Response Model, Adjusting for Early Mortality in Experimental Animals, Adjusting for Experimental Duration, Adjusting for Human-Animal Differences, Accounting for Increased Susceptibility During Early-in-Life Exposures, and Derivation of the Health-Protective Concentration.

- Page 15 and following: While this section is generally well-written, it omits the critical importance of the presence of 1,4-Dioxane as an impurity in personal care and cleaning products to the environmental levels found in surface and groundwater in California and elsewhere. Through incomplete removal of this persistent, mobile, and toxic (PMT) chemical in wastewater treatment plants, 1,4-Dioxane can widely contaminate source waters for drinking water generation. The Product-Chemical Profile for Personal Care and Cleaning Products Containing 1,4-Dioxane (Profile), which forms part of the recently initiated rulemaking by the California DTSC on 1,4-Dioxane, outlines these sources very eloquently. I would suggest using some of this background information to help inform revisions to this section.
- Page 16, section “Absorption”: While I generally concur that the reproduction of the wording used by Young et al. (1977) is accurate, the intended meaning is not. Figure 1 in Young et al. is semilogarithmic, i.e., it has a linear x-axis and a logarithmic y-axis. That means the plasma concentration decreased log-linearly (i.e., following first-order kinetics, not linearly (as indicated in the Proposed PHG text), which would suggest zero-order kinetics, i.e., a capacity-limited elimination or saturation kinetics. Please correct, as the current wording is misleading.
- Page 19, section “Metabolism”, last paragraph: This paragraph lacks clarity and would benefit from some careful editing. What is the intended takeaway?
- Page 20, section “Physiologically-Based Pharmacokinetic Models”: This section is extremely well-written, and I commend the OEHHA for a very thorough review of these models, which, in summary, provide a solid justification for not using these models in their dose-response analysis.
- Page 23, section “Human Epidemiology Studies”: This section is also very well done, and outlines the findings and shortcomings of the various human epidemiological studies. In particular, the widespread use of exposure models in these studies, which are associated with uncertainties and potentially narrow exposure ranges, presents challenges to relying on these studies for hazard identification or derivation of HPCs. As outlined in the section pertaining to Conclusion #2 above, I concur with OEHHA’s determination that these studies are unsuitable for this purpose.

- Page 31, section “Genetic toxicity”, bottom of page: I feel that the discussion of the perceived inconsistencies between Sweeney et al. (2008) and Takano et al. (2010) is not complete. Sweeney et al. describe in their publication that “[…] the high 1,4-dioxane substrate concentrations may have resulted in solubilization of the artificial (endoplasmic reticulum) microsomal membranes, alternatively, the limited incubation time was not sufficient to produce HEAA concentrations at levels above our analytical detection limit.” While the authors did not mention the initial substrate concentration in their publication, Takano et al. (2010), who were able to generate a useful microsome dataset, used a concentration of 50 µM in the presence of an NADPH-generating system, which is best practice. I would suggest revising this paragraph to avoid overemphasizing the perceived discrepancies between the two studies.
- Page 44 and following, section “Mode of action and mechanistic considerations”: I found this section very well-developed and a thorough depiction of the poorly understood carcinogenic mode of action of 1,4-Dioxane. As such, a threshold-based approach for the derivation of cancer risk would be inappropriate, and a linear low-dose extrapolation is more appropriate for dose-response analysis.
- Page 51 and following, section “Dose-response Assessment”: I went through this entire section and double-checked all relevant calculations that I could, based on the available information. Where model outputs were involved, I was unable to verify those.
- Page 64 and following, section “Health-Protective Drinking Water Concentrations”: I went through this entire section and double-checked all relevant calculations that I could, based on the available information. Where model outputs were involved, I was unable to verify those.
- Page 81 and following, Appendices: I thoroughly reviewed the provided appendices. While conducting a formal reanalysis of the provided literature search and mathematical modelling results was beyond the scope of my review, the results appear logical and are based on the best available science.