State Water Resources Control Board

October 17, 2025

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 Updated Public Health Goal for N-Nitrosodimethylamine (NDMA) in Drinking Water

Dear Dr. Gettmann,

This letter is in response to the attached, revised 11 March 2025 request for external scientific peer review 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 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 submit to the CalEPA Peer Review Program for review, with their Curriculum Vitae. 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."

For each candidate judged to be free of conflict, the 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 18 June 2025, and all draft review reports were received by 22 July 2025. OEHHA staff conducted a sufficiency review of each report and found one of the three review reports to be incomplete. A subsequent review was initiated with a new reviewer on 28 August 2025, and the draft report was received on 11 September 2025. Upon receipt of the draft review reports, OEHHA staff conducted a sufficiency review of each 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. Joseph George, Ph.D.
   Professor, Kanazawa Medical University
   Department of Hepatology
   Uchinada, Ishikawa 920-0293, Japan

2. Catherine Metayer, MD, Ph.D.
   Adjunct Professor of Epidemiology, University of California, Berkeley
   School of Public Health

3. Yinsheng Wang, Ph.D.
   Distinguished Professor, University of California, Riverside
   Department of Chemistry

4. David A. Eastmond, Ph.D.
   Professor Emeritus, University of California, Riverside
   Department of Molecular, Cell, & Systems Biology

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

Sincerely,

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

Attachments:

(1) Revised 11 March 2025 by Kimberly Gettman, PhD, for Scientific Peer Review

(2) Letters to Reviewers Initiating the Review
   i. Joseph George, Ph.D.
   ii. Catherine Metayer, MD, Ph.D.
   iii. Yinsheng Wang, Ph.D.
   iv. David A. Eastmond, Ph.D.

(3) Guidance to Reviewers, posted at FTP site

(4) Curriculum Vitae
   i. Joseph George, Ph.D.
   ii. Catherine Metayer, MD, Ph.D.
   iii. Yinsheng Wang, Ph.D.
   iv. David A. Eastmond, Ph.D.

(5) Web Accessible Reviews
   i. Joseph George, Ph.D.
   ii. Catherine Metayer, MD, Ph.D.
   iii. Yinsheng Wang, Ph.D.
   iv. David A. Eastmond, Ph.D.

cc: Elaine Khan, Senior Toxicologist
Chief, Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

Christopher Banks, Senior Toxicologist
Chief, Water Toxicology Section
Office of Environmental Health Hazard Assessment

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Gavin Newsom, Governor
Yana Garcia, Secretary for Environmental Protection
David Edwards, Ph.D., Acting Director

M E M O R A N D U M

TO: Carol Perkins, Environmental Scientist
CalEPA Scientific Peer Review Program Lead
Office of Research, Planning, and Performance
California State Water Resources Control Board

FROM: Kimberly Gettmann, Ph.D. *Kimberly Gettmann*
Kimberly Gettmann (Mar 11, 2025 09:45 PDT)
Deputy Director for Scientific Programs

DATE: March 11, 2025

SUBJECT: REQUEST FOR EXTERNAL SCIENTIFIC PEER REVIEW OF THE SCIENTIFIC BASIS OF THE PROPOSED UPDATED PUBLIC HEALTH GOAL FOR N-NITROSODIMETHYLAMINE (NDMA) IN DRINKING WATER

Draft Public Health Goal for N-Nitrosodimethylamine (NDMA) in Drinking Water

This request is regarding the draft document titled, *Public Health Goal – N-Nitrosodimethylamine in Drinking Water*. This draft document represents the update of the Public Health Goal (PHG) for N-nitrosodimethylamine, or NDMA.

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. 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 updated PHG for NDMA.

When References will be Available at the FTP Site

February 04, 2025.

Requested Review Period

We request that scientific peer review be accomplished within 30 days once references become available.

Necessary Areas of Expertise for Reviewers

We estimate that two to three 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 NDMA 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 2 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 conclusions 1 and 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 the draft updated PHG value. 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 area of expertise pertains to conclusions 1 and 3 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.

cc: Chris Banks, Ph.D., Chief
Water Toxicology Section

Attachment 1: Plain English Summary

Under the California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365), the Office of Environmental Health Hazard Assessment (OEHHA) develops Public Health Goals (PHGs) for drinking water contaminants in California. A PHG is the level of a contaminant in drinking water at which adverse health effects are not expected to occur from a lifetime of exposure. PHGs are not regulatory and represent only non-mandatory goals for use by the State Water Resources Control Board in establishing primary drinking water standards (California Maximum Contaminant Levels, or MCLs). Whereas PHGs are based solely on public health considerations, MCLs take into consideration economic and technological feasibility. State law requires that MCLs be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health.

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. However, due to a lack of suitable noncancer toxicity studies, a noncancer HPC was not developed for N-nitrosodimethylamine (NDMA).

The proposed updated PHG of 0.0005 parts per billion (ppb), equivalent to 0.0005 micrograms per liter (µg/L), is based on bile duct, liver cell, and mesenchymal tumors in male rats following three and one half years of oral exposure and is set at a level where the cancer risk is one per one million persons exposed over a lifetime. The proposed PHG update is the result of a comprehensive analysis of information on the toxicology and toxicokinetics of NDMA published since the release of the original PHG in 2006, and includes consideration of sensitive populations, such as infants and children.

The draft document was posted on December 6, 2024 on the OEHHA website https://oehha.ca.gov/sites/default/files/media/2025-01/ndmaphgdraft120624_0.pdf. OEHHA solicited comments from the public and interested stakeholders on the draft document during a 45-day comment period that opened on December 6, 2024, and closed on January 20, 2025. OEHHA also held a hybrid public workshop on January 24, 2025. Public comments received during the comment period or at the workshop may be viewed at our website after January 24, 2025: NDMA public comments or OEHHA can provide them to the 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

Reviewers are asked to determine whether the scientific work product is "based upon sound scientific knowledge, methods, and practices."

OEHHA requests that you make this determination for the chemical assessed in the draft document, *Public Health Goal – N-Nitrosodimethylamine in Drinking Water*. An explanatory statement is provided for the proposed updated PHG to focus the review.

NDMA is formed from both industrial and natural processes. It is a byproduct of water disinfection and can be created via reactions of dimethylamine and nitrate/nitrite in the human gastrointestinal tract. NDMA is a carcinogen and is listed on California's Proposition 65 list of known carcinogens. A risk/benefit analysis of the benefits of water disinfection versus the adverse health effects of disinfection byproducts is outside of the scope of the PHG and was not done by OEHHA.

The current PHG for NDMA is 0.003 parts per billion (ppb) or micrograms per liter (µg/L) in drinking water. This was based on the occurrence of bile duct tumors in female rats exposed to NDMA in drinking water for up to three and a half years (Peto et al., 1991a, b). A noncancer health-protective concentration (HPC) was not derived because no suitable studies of noncancer effects were identified. The proposed updated PHG of 0.0005 ppb is based on cancer effects.

Assumptions, Findings, and Conclusions

1. **Critical study and toxicity endpoints – The lifetime studies in rats from Peto et al. (1991a, b) are retained as the critical studies to develop the PHG update. Furthermore, cancer is retained as the most sensitive adverse health effect associated with exposure to NDMA.**

OEHHA conducted a literature search for studies that were published after the release of the original PHG in 2006. OEHHA did not identify any studies published since 2006 that would replace the critical studies in the original PHG. Therefore, the studies from Peto et al. (1991a, b) were retained as the critical studies for the proposed PHG update.

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

- Basis for the 2006 PHG (starting on pg. 6)
- Updated Toxicological Review (starting on pg. 7)
- Cancer Studies (starting on pg. 9).

2. **Noncancer health-protective concentration – OEHHA did not derive a health-**

protective concentration for noncancer endpoints.

OEHHA was unable to identify any suitable studies for derivation of a noncancer HPC, and thus a noncancer HPC was not developed for the PHG update. Similarly, no noncancer HPC was developed for the original PHG in 2006.

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

- Updated Toxicological Review (starting on pg. 7)
- Noncancer Studies (starting on pg. 8).

3. **Cancer potency determination – methodological updates. A multisite tumor analysis, incorporating the incidences of bile duct, liver cell, and mesenchymal tumors, was conducted with Benchmark Dose software. A body weight scaling adjustment was subsequently used to determine a human cancer potency from animal tumor data.**

The 2006 NDMA PHG was based on bile duct tumors reported in the studies by Peto et al. (1991a, b). For this PHG update, a multisite tumor analysis was conducted on the same studies, analyzing the incidences of bile duct, liver cell, and mesenchymal tumors in experimental animals. To derive the animal cancer potency, the data were modeled with Benchmark Dose (BMD) Software (BMDS; US EPA, version 3.3) using a benchmark response of 5% extra risk, which is OEHHA's policy as outlined in its peer reviewed guidelines (OEHHA, 2009). Additionally, several of the higher dose groups were removed in BMD modeling (eight (8) doses removed for bile duct and hepatocyte tumors in female rats; four (4) doses removed for bile duct, hepatocyte, and mesenchymal tumors in male rats) to achieve adequate model fit. The animal cancer potency was then converted to a corresponding human cancer potency using a body weight scaling adjustment.

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

- Dose-Response Assessment (starting on pg. 13)
- Appendix III (starting on pg. 28).

4. **Additional Considerations**

Reviewers are not limited to addressing only the specific topics presented above, and are asked to consider the following:

(a) For the proposed PHG, please comment on whether OEHHA has adequately addressed all important scientific issues relevant to the chemical and to the methods applied in the derivation of the proposed PHG. The proposed PHG is 0.0005 ppb, which is anticipated to result in an acceptable risk of one in one million extra cases

of cancer over a lifetime of exposure.

(b) For the chemical reviewed, please comment on whether a relevant study useful for assessing dose-response relationships (in experimental animals or humans) or otherwise informing the PHG development was missed.

(c) PHGs must be protective of known sensitive populations. Please comment on whether the PHG is adequately protective of sensitive populations. OEHHA used a time-weighted average drinking water intake rate over a 70-year lifetime which incorporates the higher water intake rates of infants and children. Age sensitivity factors were included to reflect the enhanced sensitivity of fetuses, infants, and children to carcinogens.

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 update for NDMA.

Section A. Office of Environmental Health Hazard Assessment Staff

Contributors:	Christopher Banks, Ph.D. Vanessa Cheng, Ph.D. Vincent Cogliano, Ph.D. Elaine Khan, Ph.D. Kannan Krishnan, Ph.D. Kate Li, Ph.D. Dan Qiao, Ph.D. Rose Schmitz, M.S. Craig Steinmaus, M.D. Meng Sun, Ph.D.
Acting Director:	David Edwards, 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:

OEHHA (2006). Public Health Goals for Chemicals in Drinking Water - N-Nitrosodimethylamine. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. December 22, 2006. Accessed at: https://oehha.ca.gov/media/downloads/water/chemicals/phg/122206ndmaphg.pdf

OEHHA (2009). Technical Support Document for Cancer Potency Factors: Methodologies for Derivation, Listing of Available Values, and Adjustments to Allow for Early Life Stage Exposures. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA. Accessed at: https://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009.

Peto R, Gray R, Brantom P, Grasso P (1991a). Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine. Cancer Res 51(23 Pt 2):6452-69.

Peto R, Gray R, Brantom P, Grasso P (1991b). Effects on 4080 rats of chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: a detailed dose-response study. Cancer Res 51(23 Pt 2):6415-51.

Joseph George
Professor
Department of Hepatology
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Japan

Dated: July 21, 2025

PEER REVIEW REPORT OF THE SCIENTIFIC BASIS OF PROPOSED PUBLIC HEALTH GOAL FOR N-NITROSODIMETHYLAMINE IN DRINKING WATER

A. General Mammalian Toxicology and Risk Assessment

B. Cancer Toxicology and Risk Assessment

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

1. Critical study and toxicity endpoints

N-Nitrosodimethylamine (NDMA) is a potent hepatotoxin, mutagen, and probable carcinogen (1). Activation and metabolic degradation of NDMA produce formaldehyde and methanol, and the alkylating intermediate reacts with nucleic acids and proteins and forms methylated macromolecules (2). NDMA is metabolized in the liver by cytochrome P-4502E1 (CYP2E1), and this process generates excessive amounts of reactive oxygen species (ROS), which can cause cellular impairment and a series of gene mutations that may end up in carcinogenesis (3). However, such a situation arises only after chronic ingestion of excessive amounts of NDMA, which results in a marked increase in the production of ROS that cannot be handled by the powerful antioxidant mechanisms present in the body. The incidence of cancer after chronic ingestion of very low levels of NDMA through drinking water is extremely remote, unless the situation coincides with another potent carcinogen such as ethanol. Both ethanol and NDMA are metabolized by CYP2E1, which results in a marked increase in the generation of ROS, leading to enhanced cellular oxidative stress and a series of gene mutations.

2. Noncancer health-protective concentration

Finding a noncancer health-protective concentration of NDMA in drinking water is very complicated and challenging, especially in terms of lifetime exposure. Cancer does not follow or develop as per the mathematical calculation. It is very hard to predict whether exposure to very low concentrations of NDMA through drinking water can develop cancer in humans. Aging induces gene mutations and is a major risk factor for the development of cancer. Therefore, if someone who is exposed to very low concentrations of NDMA develops cancer, it could be due to other reasons also. Anyone could develop cancer at any time, and it is practically difficult to find out the exact reason. The molecular mechanisms of the development of cancer in each individual might be significantly different, which also affects the virulence of the tumor cell. One of the major reasons for the pathogenesis of cancer is cellular oxidative stress from excessive production of free radicals and the subsequent molecular events that induce mutations in onco-suppressor genes or trigger oncogenes, leading to carcinogenesis.

Our studies were focused on the metabolism and toxicity of NDMA in rodent models. We induced liver injury in rats to elucidate the molecular and cellular mechanisms involved in the pathogenesis of hepatic fibrosis and early cirrhosis. During the span of 30 years, we have administered NDMA to over 1000 albino rats through intraperitoneal injections at a concentration of 10 mg/kg body weight on three consecutive days in a week for a period of maximum 4 weeks. On physical examination, we have never noticed a tumor on the liver tissue or any other organ of the animals exposed to NDMA. Furthermore, histopathological examination of the liver tissue of rats injected with NDMA did not show any tumor cells. We have noticed that the dose of 10 mg/kg body weight (diluted 1:100 with sterile saline) is very critical to induce hepatic fibrosis and accompanied changes. The animals cannot withstand higher doses with the same course (died due to massive hepatic necrosis and acute liver failure), and a lower dosage did not produce any significant pathological alterations in the liver. We did not expose animals to NDMA for more than 4 weeks or keep them for longer periods.

3. Cancer potency determination

Studies of Peto et al., 1991a (page 14, Table 4 in the Draft) demonstrated that NDMA produces tumors in the liver in a dose-dependent manner because NDMA is mostly metabolized in the liver by the enzyme CYP2E1. The metabolic degradation of NDMA generates extensive amounts of free radicals that induce a series of mutations leading to cancer development. It is also important to note that 10 out of 240 control animals without NDMA ingestion developed hepatic tumors. It strongly indicates that aging is an important factor for developing hepatocyte tumors since the animals were maintained up to 3.5 years, the lifespan of rats. Furthermore, the data suggest that a dosage up to 1.056 ppm or 0.044 mg/kg-day is not considered to be significant to develop tumors.

It is stated that age sensitivity factors (ASFs) account for the increased susceptibility of infants and children to carcinogens (page 16, Table 7). Age sensitivity is not a significant factor because the probability of developing cancer is only during the concurrent ingestion of nitrosamines (NDMA) and ethanol. Since children below 16 years are not allowed to drink, the incidence of developing cancer in children due to NDMA is highly remote. However, it could be a serious risk if women consume alcohol during pregnancy.

Studies on albino rats demonstrated that alcoholic individuals may develop hepatocellular carcinoma even with small doses of NDMA ingestion (4). The authors first administered the rats a liquid diet containing ethanol for two weeks to induce the enzyme CYP2E1. Then they administered NDMA in drinking water to the ethanol-fed rats at two concentrations (1.5 ng/ml and 3.0 μg/ml) for 40 or 60 weeks along with the liquid diet containing ethanol. Unlike mice, rats do not drink water containing alcohol. Therefore, alcohol must be fed to rats mixed with a liquid diet. Since both ethanol and NDMA are metabolized by the same enzyme, CYP2E1, in order to avoid the competition for the metabolic degradation of ethanol and NDMA, the liquid diet containing ethanol was not provided to the rats during NDMA administration. They did not notice visible tumors or cancer-related histopathological changes in any group of rats at the end of 40 weeks. However, they noticed visible tumors in the livers of rats fed

with NDMA (both 1.5 ng/ml and 3.0 μg/ml groups) and ethanol at the end of 60 weeks. In contrast, tumors were not present in any rats fed with either NDMA or ethanol alone. These data suggest that long-term consumption of alcohol may induce the development of cancer in individuals exposed to even low concentrations of NDMA.

4. Additional Considerations

Compared to NDMA, N-nitrosomethylbenzylamine (NMBA) and N-nitrosodiethylamine (NDEA) are potent carcinogens. NMBA produces esophageal tumors after intraperitoneal injections at a dose of 0.1 mg/kg body weight twice a week for 10 weeks, which was promoted by ethanol (5). NDEA specifically induces hepatocellular carcinoma, and the NDEA-induced HCC model is widely used for liver cancer studies (6). Ethanol is classified as a carcinogen, and chronic ingestion of ethanol induces hepatocellular carcinoma without an additional agent in mice (7). The molecular mechanisms involved in alcohol-mediated carcinogenesis have been well established, and approximately 4% of cancers worldwide are caused by alcohol consumption (8, 9). Ethanol is metabolized by CYP2E1 in the liver, and the extensive amounts of free radicals formed during the metabolic detoxification of ethanol and the subsequent oxidative stress and genomic aberration lead to carcinogenesis. It is significant to note that NDMA is also metabolized in the liver by CYP2E1, and therefore concurrent intake of ethanol and even a low ingestion of NDMA through drinking water could be susceptible to the development of cancer.

The toxic effect of NDMA, especially on the hepatic tissue, is mainly due to the excessive generation of ROS and the subsequent cellular oxidative stress during the metabolic degradation of NDMA in the liver. Therefore, any powerful antioxidant could ameliorate or prevent the toxic effects of NDMA at lower concentrations. Multiple studies provided evidence that there is a marked decrease of antioxidant levels in the liver tissue during the metabolic degradation of NDMA (10, 11). Treatment with epigallocatechin-3-gallate (EGCG), a potent antioxidant present in green tea leaf extracts, prevents NDMA-induced hepatic fibrosis in rats by suppressing the oxidative stress (12).

Conclusion

Based on the studies with regard to liver toxicity and carcinogenesis, it is evident that NDMA alone is not a potent carcinogen at lower concentrations. The proposed updated public health goal (PHG) of 0.0005 ppb (equivalent to 0.5 ng per liter) in drinking water is a very low concentration to induce any type of tumor. Cancer can develop for anyone at any time without a particular reason or cause. Therefore, lifelong exposure to a very low dose of NDMA cannot be considered as a rationale to develop cancer. Chronic ingestion of alcohol (ethanol) would be more prone to developing cancer, and ethanol is a classified carcinogen. Cellular oxidative stress is a major risk factor for the development of cancer since it can induce a series of gene mutations leading to carcinogenesis.

References

1. George J, Rao KR, Stern R, Chandrakasan G. Dimethylnitrosamine-induced liver injury in rats: the early deposition of collagen. Toxicology 2001; 156(2-3):129-38. doi: 10.1016/s0300-483x(00)00352-8. PMID: 11164615.
2. George J, Tsuchishima M, Tsutsumi M. Metabolism of N-nitrosodimethylamine, methylation of macromolecules, and development of hepatic fibrosis in rodent models. J Mol Med (Berl) 2020; 98(9):1203-1213. doi: 10.1007/s00109-020-01950-7. PMID: 32666246.
3. George J, Tsuchishima M, Tsutsumi M. Molecular mechanisms in the pathogenesis of N-nitrosodimethylamine induced hepatic fibrosis. Cell Death Dis. 2019; 10(1):18. doi: 10.1038/s41419-018-1272-8. PMID: 30622238.
4. Tsutsumi M, Matsuda Y, Takada A. Role of ethanol-inducible cytochrome P-450 2E1 in the development of hepatocellular carcinoma by the chemical carcinogen, N-nitrosodimethylamine. Hepatology. 1993; 18(6):1483-1489. doi: 10.1002/hep.1840180630 PMID: 8244274.

5. Tsutsumi M, George J, Ishizawa K, Fukumura A, Takase S. Effect of chronic dietary ethanol in the promotion of N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in rats. J Gastroenterol Hepatol. 2006; 21(5):805-13. doi: 10.1111/j.1440-1746.2005.04040.x. PMID: 16704527.

6. Li X, Zhou X, Guan Y, Wang YX, Scutt D, Gong QY. N-nitrosodiethylamine-induced pig liver hepatocellular carcinoma model: radiological and histopathological studies. Cardiovasc Intervent Radiol. 2006; 29(3):420-428. doi: 10.1007/s00270-005-0099-8. PMID: 16502159.

7. Tsuchishima M, George J, Shiroeda H, Arisawa T, Takegami T, Tsutsumi M. Chronic ingestion of ethanol induces hepatocellular carcinoma in mice without additional hepatic insult. Dig Dis Sci. 2013; 58(7):1923-33. doi: 10.1007/s10620-013-2574-4. PMID: 23371017.

8. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer. 2007; 7(8):599-612. doi: 10.1038/nrc2191. PMID: 17646865.

9. Rumgay H, Murphy N, Ferrari P, Soerjomataram I. Alcohol and Cancer: Epidemiology and Biological Mechanisms. Nutrients. 2021; 13(9):3173. doi: 10.3390/nu13093173. PMID: 34579050.

10. George J. Ascorbic acid concentrations in dimethylnitrosamine-induced hepatic fibrosis in rats. Clin Chim Acta. 2003 Sep;335(1-2):39-47. doi: 10.1016/s0009-8981(03)00285-7. PMID: 12927683.

11. George J. Determination of selenium during pathogenesis of hepatic fibrosis employing hydride generation and inductively coupled plasma mass spectrometry. Biol Chem. 2018; 399(5):499-509. doi: 10.1515/hsz-2017-0260. PMID: 29408794.

12. George J, Tsuchishima M, Tsutsumi M. Epigallocatechin-3-gallate inhibits osteopontin expression and prevents experimentally induced hepatic fibrosis. Biomed Pharmacother. 2022; 151:113111. doi: 10.1016/j.biopha.2022.113111. PMID: 35594711.

07-15-2025

Catherine Metayer, MD, PhD

Adjunct Professor of Epidemiology

School of Public Health, University of California, Berkeley

SUBJECT: Peer Review Regarding the Scientific Basis of the Proposed Updated Public Health Goal (PHG) For N-nitrosodimethylamine (NDMA) in Drinking Water

To Whom it may Concern,

Based on my expertise and experience, I am reviewing the findings, assumptions, or conclusions # 1 and #3, and I agreed I could review with confidence.

Review of Conclusion # 1 (Critical study and toxicity endpoints – The lifetime studies in rats from Peto et al. (1991a, b) are retained as the critical studies to develop the PHG update. Furthermore, cancer is retained as the most sensitive adverse health effect associated with exposure to NDMA.)

The methodology of the systematic review aimed to identify new relevant publications regarding NDMA since the previous PHG report in 2006 is sound, with use of the PECO framework, queries of the main open literature databases, inclusive search terms, additional manual search, use of independent reviewers, and recent updates up to March 2024. Strict requirements were set forth to retain studies, including robust study design with sufficient sample size, detailed exposure data of NDMA in drinking water (note that dietary sources of NDMA are outside the scope of this report), and assessment of confounders. This search did not seem to have missed important studies.

The conclusion of the report stating that the lifetime studies in rats from Peto et al. (1991a, b) remained the only critical studies to develop the 2024 PHG update for cancer endpoints, is appropriate. Specifically, none of the epidemiological studies conducted in humans directly assessed the health effect of water intake of NDMA, but instead mostly used questionnaires to estimate NDMA levels from dietary intake. Animal studies were rare, and the only study discussed in the report did not directly assess the health effect of water intake of NDMA, but instead assessed the impact of other products/molecules on NDMA carcinogenicity (endpoints were pulmonary adenomas and carcinomas). In contrast, the studies by Peto et al. (1991a, b) directly assessed NDMA in drinking water, had sufficient sample size and length of follow-up to assess liver tumors (from four cell types: hepatocyte, bile duct, mesenchyme, and Kupffer cell), and conducted detailed dose-response analyses.

Regarding non-cancer studies, the 2024 PHG report is based on the conclusions from the 2007 US EPA publication on *Provisional Peer Reviewed Toxicity Values for N-Nitrosodimethylamine*,

and the review of new studies since 2005. No human studies were identified, and likewise cancer studies, animal studies did not directly assess the health effect of water intake of NDMA, but instead assessed the impact of other products/ molecules on NDMA toxicity. Most studies also lacked robust design.

It should be noted that non-cancer studies presented in the 2024 report encompass heterogeneous health endpoints (such as weight, blood cell counts, hormone levels, free radicals/antioxidant enzymes, etc.). The study by Peto (1991b) assessed nonneoplastic liver abnormalities (e.g., hyperplastic nodules or shrinkage of hepatocytes), and even though the study design was deemed robust, the study was not retained to assess noncancer endpoints. It may be useful to explain this decision.

Overall assessment: the scientific portion of the proposed rule for cancer endpoints is based upon sound scientific knowledge, methods, and practices. While this is mostly true for noncancer endpoints, clarification of why the study by Peto (1991b) was not retained is needed.

Review of Conclusion # 3 (Cancer potency determination – methodological updates. A multisite tumor analysis, incorporating the incidences of bile duct, liver cell, and mesenchymal tumors, was conducted with Benchmark Dose software. A body weight scaling adjustment was subsequently used to determine a human cancer potency from animal tumor data).

As stated in Conclusion #1, the animal studies by Peto (1991a, b) were retained to determine cancer potency because of their robust design. Since the 2006 report, several additions were made to strengthen the method used to assess cancer potency, including (1) a multisite tumor analysis (bile duct, liver cell, and mesenchymal tumors), (2) data modeling using the validated USEPA-based Benchmark Dose Software, (3) updated age-specific estimates for water ingestion of NDMA, and (4) adjustment with body weight scaling/age sensitive factor to account for age-sensitive populations such as children. A new physiologically based pharmacokinetic model developed for NDMA in rats (Kang et al. 2024) examined both intravenous and oral doses and incorporated multiple organ compartments; however, it was not used since external validation of the model was lacking. The report does not mention whether this new method had the potential to substantially or marginally improve data modeling.

Data for high-dose groups were excluded to fit a monotonic dose-response relationship for certain tumors and sex groups. For clarity, it would be useful to provide the rationale for only modelling monotonic dose-response relationships when estimating cancer potency, and for transparency, to also provide the shape of the dose-relationship curves using all data (even if all data were ultimately not used in the final analysis).

Overall assessment: The scientific portion of the proposed rule to update the PHG for NDMA to 0.0005 parts per billion, is based upon sound scientific knowledge, methods, and practices.

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July 22, 2025

Public Health Goal – N-Nitrosodimethylamine in Drinking Water

Based on my expertise and experience, I am reviewing the following two conclusions that I agreed I could review with confidence:

Conclusion #1 (Critical study and toxicity endpoints – The lifetime studies in rats from Peto et al. (1991a, b) are retained as the critical studies to develop the PHG update. Furthermore, cancer is retained as the most sensitive adverse health effect associated with exposure to NDMA).

Conclusion #3 (Cancer potency determination – methodological updates. A multisite tumor analysis, incorporating the incidences of bile duct, liver cell, and mesenchymal tumors, was conducted with Benchmark Dose software. A body weight scaling adjustment was subsequently used to determine a human cancer potency from animal tumor data).

Evaluation and Questions
Based on my review, I agree with Conclusion #1, i.e., Critical study and toxicity endpoints – The lifetime studies in rats from Peto et al. (1991a, b) are retained as the critical studies to develop the PHG update. The focus on cancer outcome is justified based on the fact no systematic, dose-dependent studies have been conducted focusing on non-cancer outcomes emanating from NDMA exposure. Thus, I also concur that cancer is retained as the most sensitive adverse health effect associated with exposure to NDMA.

Compared to an earlier version of the document, which was based on the development of bile duct cancer alone, the current updated document took into account the development of cancer at multiple sites, including bile duct, mesenchymal, and hepatocyte in male rats, as well as bile duct and hepatocyte in female rats. The authors also applied scaling based on body weight differences between rats and humans, and considered age sensitivity factors: 10 for *in utero* exposure in the last trimester and during infant (i.e., years 0-2), 3 for child (ages 2-16), and 1 for adult (ages 16-70). With respect to Conclusion #3, appropriate models are used for determining the updated PHG; nevertheless, I have several comments that require clarifications and corrections:

I wonder why they calculated the NDMA in drinking water from ppm to mg/kg-day, the data for male and female rats differ by almost a factor of 2. Do the authors assume that male and female rats drink the same volume of water? The daily water consumption by female rats is larger than male rats on a per kg basis, but the difference is rather small compared to the body weight difference (0.24 vs. 0.4 kg for female and male rats) (see reference: McGivern, R. F. et al. *Physiology & Behavior*, 1996, 59, 653-658).

The draft document stated that the data presented in Table 4 and Table 5 were compiled from Table 7 of Peto et al., 1991a. This does not seem to be correct. My review of the Peto study showed that the data were extracted from Tables 6 and 7.

In the study by Peto et al., 1991a, a good number of liver neoplasm arising from Kupffer cells were reported (a total of 10 for male rats and 8 for female rats). It is unclear why neoplasm from Kupffer cells was not considered.

In Table 1 of the draft, while the duration and age sensitivity factors were outlined, 3rd trimester was only considered for prenatal exposure. Please clarify why potential exposure to NMDA during the 1st and 2nd trimesters was not included.

Review of the Proposed Public Health Goal for N-Nitrosodimethylamine in Drinking Water document

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Sept. 11, 2025

General comments:

The draft Proposed Public Health Goal for N-Nitrosodimethylamine in Drinking Water document is a brief and well-written overview of the approach used by OEHHA to develop the proposed public health goal (PHG). The document builds upon and updates a PHG value with its associated document that was published by OEHHA in 2006. The authors conducted an updated review of the toxicological literature and have used some updated methods, but since the majority of the key studies on NDMA were performed 30+ years ago, the critical studies are quite similar to those used in the earlier 2006 OEHHA PHG document. The proposed PHG is lower, largely because of some changes in dose modeling, a change in the water ingestion rate, and the use of additional adjustment factors.

The document is at times quite brief but, in most cases, this is appropriate given the large number of studies and amount of information available on this model mutagen and carcinogen. However, in some areas I consider it to be overly brief and does not convey important background information (see examples below). In spite of the large number of studies, a considerable number of data gaps and study limitations remain that make it difficult to confidently evaluate all important health endpoints and establish reliable health-based guidance values. These will be discussed in more detail below when addressing the major conclusions of the proposed PHG document.

1. Critical cancer study and toxicity endpoints.

NDMA has been shown to be tumorigenic in a range of mammal species (mouse, rat, rabbit, hamster, guinea pig, and mink), inducing tumors in multiple tissues and by different routes of administration (IARC, 1978; NTP, 2021; ATSDR, 2023). In spite of this large number of studies, almost all of them were conducted prior to the establishment of Good Laboratory Practices, and the methods and information reported for most studies are inadequate for the basis of establishing a PHG. The best of these early studies are the lifetime studies in rats conducted by Peto et al. (1991a, b), and these have been retained by OEHHA as the critical studies to develop the PHG update. Cancer has also been retained as the most sensitive adverse health effect associated with exposure to NDMA.

In my opinion, these choices are warranted but there are a few aspects of the Peto studies (Peto et al., 1991a,b) that should be noted. These studies were unusually large with 60 male and 60 female rats being treated in 15 different treatment groups. There were also 240 male and 240 female rats in the control groups. The animals were administered NDMA in the drinking water for their lifetimes which was over 3 years for some of the rats in the low treatment groups. This is considerably longer than the duration of a standard rat cancer bioassay. Ten percent of the animals were sacrificed

at 12 months and another 10% at 18 months. It is not clear how the analyses were adjusted, if at all, to account for the early sacrifices. There was also high cancer-related mortality among the animals receiving the higher doses of NDMA with all animals at the highest dose living less than one year.

In part because of the effects of NDMA on survival, much of the data in the studies was adjusted during the analyses and in its presentation. The articles describing the study results are fairly comprehensive, but also complicated and difficult to follow. Suggestive positive trends were reportedly seen at some sites other than the liver but the actual data are not presented. For all sites, the raw summary data and data on the individual animals are no longer available (as mentioned in OEHHA, 2006) so it is not possible to reconstruct the analyses and confirm the results. This also makes it hard to derive health-based guidance values for non-cancer endpoints. I might mention that the Peto (1991a,b) studies comprised a major part of Paul Brantom's doctoral dissertation, and summarized tumor data for the 192 control animals and the 48 animals in each treatment group that were followed until the end of the study can be found in his dissertation (Brantom, 1983). This may allow additional analyses to be performed if desired.

As described in the Peto et al. (1991a) article, the combination of low control mortality, large sample sizes, and the lifetime study design, makes the study highly sensitive for detecting NDMA's carcinogenic effects, particularly in the low dose region. The Peto studies are thought to be considerably more sensitive than studies conducted using the standard rat 2-year cancer bioassay. As a result, the derived PHG may be more health-protective than those derived from other rodent bioassays.

It should be noted that the authors and research laboratories who conducted the study are well regarded and the data are widely accepted as being reliable. In addition to the evaluations by OEHHA, the Peto et al. (1991a,b) studies have been used by the EPA, the WHO, the European Medicines Agency, Health Canada, and other agencies and groups in assessing the carcinogenic risks of NDMA.

As indicated above, I believe that the Peto et al. (1991a,b) studies are of sufficient quality to derive the cancer-based PHG but there are clearly some ambiguities about the assay performance, the analyses and the results.

2. Noncancer health-protective concentration

OEHHA decided not to derive a health-protective concentration for noncancer endpoints concluding that the relevant studies had significant limitations that did not allow them to be used to derive a reliable noncancer PHG. Similar conclusions have been reached by the USEPA (as described in OEHHA, 2006) and the ATSDR (2023). I agree with OEHHA's decision. I am not aware of any subchronic or chronic study on NDMA of sufficient quality that would be suitable for use in deriving a noncancer PHG. I might note that some noncancer effects were reported in the chronic studies by Peto et al. (1991b) but the presentation of the results as well as the inability to access the original data do not allow reliable risk estimates to be performed.

3. Cancer potency determination – methodological updates

In this update, OEHHA conducted a multisite tumor analysis, incorporating the incidences of bile duct, liver cell, and mesenchymal tumors, using Benchmark Dose

software. A standard body weight scaling adjustment was also used to calculate a human cancer potency value from the animal tumor data. The analysis raised a few questions in my mind.

1. After eliminating multiple high dose groups, OEHHA used various multistage models to model the bile duct, hepatocyte and mesenchymal tumors in the male rats and bile duct, hepatocyte tumors in the female rats. The dose response information for each tumor type is then combined using the Multi-site Cancer model to estimate the probability of cancer occurring at any of the sites. I can understand the rationale for combining the male tumor types but I cannot understand why the model of liver tumor in the female rats where a dose-related increase was not seen across the modeled range was combined with that of the bile duct tumors. This may significantly increase the variability when combining the models and could possibly result in an unjustifiably low BMDL. I conducted both the Cochran-Armitage and the Mantel-Haenszel tests for trend on the female liver tumor data over the modeled dose range and neither were statistically significant.

In Appendix III OEHHA provides a brief but valuable overview of the approach that was used to perform the multisite analysis. However, it is not clear how the models were combined, how the confidence intervals of the combined model were determined, and their interpretation. I recommend that the description be expanded to cover these points and to ensure that the variability used to derive the confidence limits is appropriate.

4. Protection of known sensitive populations.

OEHHA used age sensitivity factors to reflect the enhanced sensitivity of fetuses, infants, and children to carcinogens. This follows OEHHA's policy and is similar to that used by the USEPA with the exception that the USEPA does not apply an extra age sensitivity factor for fetuses. I believe that OEHHA's approach is justified. One might argue that CYP2E1, the enzyme involved in the bioactivation of NDMA into a DNA-damaging methylating agent, is not present at significant levels prior to birth (Ginsberg et al., 2004; Robinson et al., 2020) and that the highly reactive metabolites formed in the mother would be unlikely to reach the fetus in significant quantities. However, there is enough evidence from animal studies showing that *in utero* exposure to NDMA confers increased cancer risks later in life (ATSDR, 2023) to justify adding the age sensitivity factor during the 3rd trimester of the fetal period.

OEHHA also used a total lifetime daily exposure rate of 0.130 L/kg-day over a 70-year lifetime which incorporates higher water intake rates of infants and children. The total lifetime daily exposure of 0.130 L/kg-day also includes adjustments for the age sensitivity factors and fractional durations. The inclusion of these two factors into the description of the 0.130 L/kg-day number on page 17 needs to be clearly indicated, otherwise the intake rate appears to be a significant 3-fold overestimate of lifetime drinking water intake (such as that recommended by the USEPA (2019)).

The expression of CYP2E1 varies among individuals and is also inducible. This suggests that those with elevated CPY2E1 levels [such as obese individuals (Emery et al., 2003), moderate to heavy alcohol consumers (Neafsey et al., 2009), and diabetics (Wang et al., 2003)] may be at an increased risk of cancer or other adverse effects when exposed to NDMA. Tobacco smoke, chloramine-treated water, NDMA-, nitrate-

and nitrite-containing foods, selected medicines and personal care products, as well as alcoholic beverages are all sources of NDMA exposure or can be converted to NDMA in the body (Hrudley et al., 2013; NTP, 2021; ATSDR, 2023). Individuals exposed to high levels of any of these or that consume large amounts of water (e.g. those working or exercising strenuously under hot conditions) would be at higher risk of NDMA-induced adverse effects. While these all confer elevated risks, it is not clear to me what OEHHA should do about them. Some of these are water-related and others are not.

5. Additional comments:

a) Page 1. The presence of NDMA in tobacco smoke should also be included in the Introduction as it is a major source of human exposure (ATSDR, 2023).
b) Page 8. The document states that the current literature search did not find relevant human studies for noncancer endpoints. While this may be true, it is misleading as earlier studies have reported that NDMA was hepatotoxic in poisoned humans and in several cases, led to the individuals' deaths (ATSDR, 2023). This is an example of where the document is overly brief. A brief summary of this information should be added.
c) Page 10. The authors may want to include a description of Hidajat et al. studies (described in ATSDR, 2023). These are large multi-year studies of the cancer and noncancer effects in NDMA-exposed rubber workers.
d) Page 11. The short summary of the results of the animal cancer studies performed prior to 2006 should be added. In addition, the authors might want to include the results of the liver pathology studies that were performed by Lynch et al. (2024) following oral administration of NDMA. There were multiple studies conducted, one of which lasted for 28 days. Histopathological effects appearing 10 weeks after treatment of mice with 2 ip injections of NDMA were also reported by Armijo et al. (2023).
e) Page 12. There is a new quantitative mutagenesis article on NDMA (You et al., 2025) that the authors may consider including.
f) Tables 4 and 5 (pages 14-15) The ppm values in the Peto studies and the draft PHG document are quite unusual and are presented as volume/volume rather than the more common weight/volume. Although the differences are minor, I recommend that the units be specified and the conversion factor included in the Table footnotes of the PHG document, or preferably, the values be presented in the more common form (mg/L form). Based on a few sample calculations, the mg/kg-day values in the Peto studies (and also presented in the draft PHG) were calculated by first converting the ppm (v/v) values to ppm (mg/L) values and then to mg/kg-day values.
g) Footnote c in Table 5 (page 15) indicates that the trend test on the first 8 dose groups in the "Animals with hepatocyte tumors" column was highly significant ($p < 0.0001$). This is incorrect based on a visual inspection and using the trend tests mentioned above. This should be corrected.
h) Page 17. Combined should be inserted between "based on" and "liver tumors."

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