

June 14, 2017

Gerald W. Bowes, PhD
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Office of Research, Planning and Performance
State Water Resources Control Board
1001 "I" Street, MS – 16-B
Sacramento, CA 95814

**RE: External peer review of the Office of Environmental Health Hazard Assessment
Draft Updated Public Health goals for Nitrate and Nitrite in Drinking Water**

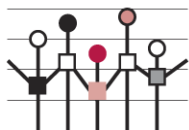
Description of Scientific Assumptions, Findings, and Conclusions to be Addressed by the Peer Reviewers.

Reviewers are asked to determine whether the scientific work product is “based upon sound scientific knowledge, methods, and practices.” We request that you make this determination for the chemicals reviewed in OEHHA’s document, “Proposed Updated Public Health Goals for Nitrate/Nitrite in Drinking Water.” An explanatory statement is provided for each proposed updated PHG to focus the review.

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

- (a) For each PHG update, please comment on whether OEHHA has adequately addressed all important scientific issues relevant to each chemical and to the methods applied in deriving the PHG.
- (b) For each chemical reviewed, please comment on whether a relevant study useful for assessing dose-response relationship or otherwise informing the PHG development was missed.
- (c) PHGs must be protective of known sensitive subpopulations. Please comment on whether each PHG is health protective.

Reviewers should also note that some proposed actions may rely on professional judgment where available scientific data are not as extensive as desired to support the statutory requirement for absolute scientific rigor. In these situations, the proposed course of action is favored over no action.



1. Nitrate

“After reviewing the literature on nitrate since the publication of the PHG in 1997, OEHHA concludes that methemoglobinemia remains the primary adverse health effect associated with human exposure to this chemical. OEHHA is retaining this critical endpoint and its supporting studies for PHG derivation. Infants under the age of 3 months are especially vulnerable to methemoglobinemia. OEHHA is using the lowest-observed-adverse-effect level/no-observed-adverse-effect level (LOAEL/NOAEL) approach for point of departure (POD) determination from studies of children exposed to nitrate in drinking water.”

2. Nitrite

“Nitrite is not frequently detected in drinking water; it has not been detected in public water supply wells in California at levels above its MCL of 1 mg/L in the last three years. However, nitrite may be formed due to microbial reduction of nitrates in hygienically poor quality well water. In the body, nitrate can be converted to nitrite, and it is nitrite that causes the oxidation of normal hemoglobin to methemoglobin. Methemoglobinemia, therefore, remains the primary adverse health effect associated with human exposure to this chemical and the proposed PHG derivation for nitrite is linked to that for nitrate.”

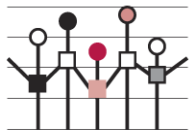
3. Nitrate/Nitrite

“The current joint nitrate/nitrite PHG of 10 mg/L (10 ppm, expressed as nitrogen) derived in 1997, which accounts for the additive toxicity of nitrate and nitrite, is also retained for the proposed PHG. It does not replace the individual values, and the maximum contribution from nitrite should not exceed 1 ppm nitrite-nitrogen.”

I have completed a careful review of the document as well as the supporting materials. It was also useful to review the 1997 PHG support document as a starting point for my review. I have read a subset of the key references to verify that they have been accurately described and utilized. After my review, I have come to the same conclusion as OEHHA, that despite the many new epidemiologic studies, animal toxicology, advances in understanding of the pathophysiology of nitrate/nitrite human health effects and the pharmacokinetics of nitrate and nitrite interaction, the current PHG should be retained. The scientific work product I reviewed is based upon sound scientific knowledge, methods, and practices consistent with current state-of-the-art risk assessment approaches and those found in the current USEPA risk assessment guidance.

The document is scientifically robust, comprehensive, well organized and follows a logical order. I am quite familiar with the nitrate/nitrite literature and cannot think of a critical study missed that might have altered the choice of key studies, adverse effects or most vulnerable sensitive sub-populations to protect.

The document could be strengthened.

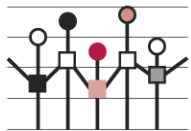


I would suggest the work product would benefit from some process additions. The document is missing a detailed “methods” section. The literature review is quite comprehensive but no explanation is given for how the authors went about locating the published literature (key words searched for and in which data systems etc.). I have no doubt they used a systematic approach but that needs to be described. Knowing the process would be useful so someone could replicate the search if they wished. It would also be helpful so one could determine if some useful search criteria or data sources were missed. It is easier to identify possible missing articles from search criteria than expert’s memory – or at least my memory. I don’t think anything significant was overlooked but knowing the search words would help assure a comprehensive and systematic review was performed. Providing a description of how many papers were found during what years since 1997 and how they were prioritized would help. Next, as part of the methods section, the criteria used to determine which articles to review and summarize should be mentioned. Was there a hierarchy ranking used? Most of the articles are post the 1997 initial PHG.

The methemoglobinemia section needs to have a definition of “clinically significant methemoglobinemia”. It is mentioned that symptoms can occur at a level of 10% but the “normal” concentration is 2-3%. An increase in methemoglobin may be an “effect” but at what point does it become an “adverse effect”? Does OEHHA consider the separation between effect and adverse effect to be 10%. OEHHA needs to indicate when methemoglobinemia becomes an “adverse effect” as part of their determination of the NOAEL they use. It needs to be made clearer that it is not just elevated methemoglobin levels above normal that are the issue but clinically significant increased levels. Some of the literature summarized use of methemoglobin % as a marker of exposure and explore the association between increasing nitrate in water and an increasing methemoglobin level. It is important to be explicit that the endpoint the PHG is using and looking for in publications is an elevation percent that is considered clinically significant.

Because the USEPA MCL and the CalEPA MCL are based on infant methemoglobinemia it is often perceived by private well owners that nitrate in well water over the standard is safe for adults if they do not have infants in their households. The extensive literature review in the document on possible thyroid adverse effects as well as other organ system effects is strong secondary data in support of the PHG as relevant to everyone. It would be useful in the summary introduction paragraph to add that the PHG’s protect against infant methemoglobinemia as well as other toxic effects observed in adults – or some other mention that the health concern goes beyond just infant exposure.

It is totally appropriate for OEHHA to place emphasis on use of human epidemiologic data as a preference over laboratory animal studies. In the animal study section tables are provided which indicate NOELs, NOAELs etc. It is possible to use these figures as PODs and go through the exercise of calculating what PHG would result. Frequently in the document the point is made that there are considerable differences between the animal systems and humans which supports why human data use provides greater confidence.



In the summary, there is a very definitive statement that there are no new studies that support a change. There certainly are a lot of new data and health endpoints not discussed in the 1997 PHGs document that are discussed as potential for PHG development. After consideration, these were not considered sufficiently robust to replace the infant methemoglobin study data and thus do not qualify as primary in the PHG determination. These alternative data are not ignored but are determined to be supportive but not the key endpoints.

The document does an excellent job of outlining the complexity and challenges of performing a risk assessment. The decisions made are logical and scientifically appropriate.

It needs to be stressed that because the PHG does not change does not mean scientific understanding of nitrate/nitrate exposure impacts has not advanced considerably. The Updated Public Health goals for Nitrate and Nitrite in Drinking Water document will provide greater public confidence in the updated PHGs when finalized.

Sincerely,

A handwritten signature in black ink that reads "Henry A. Anderson, MD". The signature is fluid and cursive.

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