Toxicological Basis for Nitrate and Nitrite USEPA RfDs Lack Scientific Merit: Submission to USEPA in Response to Call for Comments on Revisions to Nitrate and Nitrite Reference Dos…

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Errata – Corrections included to: RESPONSE TO USEPA ON RFD ANNOUNCEMENT FINAL 12/11/2023

December 18, 2023

Mr. Wayne Cascio
Center for Public Health & Environmental Assessment
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Docket Number: EPA–HQ–ORD–2017–0496 for nitrate/nitrite

Dear Director Cascio:

USEPA recently announced that the IRIS toxicological basis for nitrate and nitrite RfDs is under review. USEPA does not intend to review the hematological basis for the RfDs.

"Given input received during scoping, the IRIS assessment will include evaluation of noncancer and cancer human health hazards associated with ingested nitrate and nitrite. Although all health effects will be considered for hazard identification, the assessment will take a different approach for hematological outcomes. A hematological hazard has already been established through the known association between methemoglobinemia and nitrate/nitrite (Ward et al., 2005; Walton, 1951). Therefore, EPA will not re-consider the hematological domain during hazard identification. Instead, any new studies identified for methemoglobinemia and supporting hematological endpoints will be examined for information on the quantitative relationship with nitrate/nitrite and the potential to support dose-response analysis." EPA-HQ-ORD-2017-0496-0010

Research for our upcoming contracted book with CRC Press (in preparation), currently titled *Nitrate and Nitrite Impacts on Groundwater, Drinking Water, and Public Health, Deriving New Health Protective Standards*, finds that errors, omissions and misrepresentations by USEPA of the cited basis for the RfDs negate USEPA's claims to fully understand the hematological basis of Infant Acquired Methemoglobinemia (IAM).

1. Selection of LOAELs is incorrect. USEPA apparently performed a limited literature review of IAM case statistics available in the peer review literature. Numerous other papers exist that demonstrate that the LOAEL range is much lower than USEPA acknowledges.
2. Walton (1951), the cited basis for the RfDs, leads to other papers from the United States that demonstrate LOAELs as low as 0.4 ppm nitrate-N from likely the best laboratory for such residue analysis in the United States during the 1940s.
3. USEPA eliminated IAM cases below 11 ppm nitrate-N for arbitrary reasons. One reason appears to be that USEPA mistranslated German language papers demonstrating IAM cases below 11 ppm nitrate-N (USEPA claims no such translations exist). Another

reason is concern that less than 11 ppm nitrate-N IAM cases were influenced by other nitrate exposures that were common around the world at that time and still occur today. USEPA's flawed conceptual model assumes that infants only ingest nitrate via contaminated infant formula. In reality, the historical international literature demonstrates that infant nitrate exposures via ingestion of supplemental water and feeding of vegetable broths was common around the world and in the United States and is still the case. Rather than additional nitrate exposures being uncommon and a concern for defining exposure concentrations leading to infant cyanosis, such exposures occur via normal feeding practices. This means that IAM cases under 11 ppm nitrate-N, discarded for these reasons, can now be included in the LOAEL distribution leading to RfD calculation. Thus, overwhelming evidence demonstrates that the RfD range should start at 0.4 ppm nitrate-N not 11 ppm nitrate-N.

4. That the majority of IAM cases are above 0.4 ppm nitrate-N is irrelevant to selecting the lowest valid IAM case concentration to serve as the LOAEL for RfD calculation. Thus, 0.4 ppm nitrate-N is the correct value for calculating the RfD for nitrate and nitrite.
5. Uncertainty is improperly addressed in the current RfD derivations. USEPA uses no intraspecies uncertainty factor for nitrate or nitrite. There is no scientific justification to assume that all infants are the same in their response to nitrate ingestion exposure from contaminated milk formula or any other liquid food. USEPA could ask any parent or physician, much less toxicologist, to determine that a UF=1 for intraspecies uncertainty is absurd on its face.
6. Data quality is impossible to determine for the cited principal studies. Walton (1951) and Bosch et al. (1950) are not peer reviewed studies according to the publishers of these papers. Data cited in these papers is not part of any epidemiological study according to the authors. The data in Walton (1951) is derived mostly from another paper that itself is based on a questionnaire. There is no way to address the data using USEPA data quality guidelines to verify and validate the data. Rather than there being no uncertainty in these two studies (much of Bosch et al. is included in the Walton paper), the data in these papers is highly uncertain, perhaps of unbounded uncertainty, and there can be no confidence in the papers themselves because they lack materials and methods and there is no possible way to verify the reliability of the data sets used in calculating the nitrate RfD, LOAEL or NOAEL, or derived nitrite values. USEPA has failed to apply its own data quality requirements to these papers thus creating RfDs that lack scientific merit and are scientifically indefensible.
7. USEPA's mechanistic basis for the RfDs (e.g., infant gastrointestinal tracts produce insufficient acid secretions that allow nitrosating bacteria to grow, produce nitrite, and cause IAM case induction) is based on outdated science and is likely obtained from non-peer reviewed papers. In fact, any paper before 1975-1980 is suspected of not being peer reviewed. USEPA's stable of RfDs have many chemical files that are constituted on papers that are not proven peer reviewed and may in fact be based on outdated science from non-peer reviewed papers. USEPA and the regulated community will need to review this problem to determine if these chemicals require rewriting of their basis to meet modern data quality standards and actual peer reviewed science.
8. USEPA's use of uncertainty factors (UFs) and modifying factors (MFs) for nitrate and nitrite RfDs appears to be designed to negate any acknowledgement that uncertainties

exist. The assertion that all human epidemiology morbidity and mortality data are without blemish is unsupportable and refuted by the aldicarb human study.

9. USEPA has never produced a scientifically defensible dose-response curve that provides any predictability for IAM case induction and, if induced, the severity of the IAM case. These are basic toxicological outputs that, if not possible to create, clearly indicate a lack of USEPA's most fundamental understandings of the cause/effect relationship and dose-response relationship of the chemical(s) under review. Given USEPA's spurious claim that it essentially has perfect institutional knowledge of the IAM paradigm (e.g., by use of a cumulative UF equal to 1), it should be able to produce these relationships. It cannot. In fact, our findings indicate that USEPA's knowledge of the hematological basis for the RfDs is broken and cannot be fixed by trying to rehabilitate its non-peer reviewed cited principal studies whose data cannot be verified and validated by applying the spackle of supporting studies that themselves have unverified and unvalidated data and may not be peer reviewed. Thus, no uncertainty becomes high uncertainty and perhaps unbounded uncertainty. High confidence in the studies becomes no confidence in the studies. UF = 1 becomes cumulative UFs of as high as 1,000X. No data gaps for modifying factors becomes 10X. In fact, there are not enough UF and MF categories to describe and compensate for all the problems with the papers and data used by USEPA to calculate its nitrate and nitrite RfDs. Of course, this means that any MCLs based on any RfDs citing to the current principal studies are also fatally flawed and must be immediately reduced in concentration to account for data problems with the source documents or withdrawn.
10. USEPA leaves no margin of safety between the 11 ppm nitrate-N lowest LOAEL and the selected 10 ppm nitrate-N NOAEL. This implies a steep dose-response curve akin to a cliff. At 10 ppm nitrate-N, infants are safe and at 11 ppm nitrate-N infants are at acute toxic risk. If USEPA is correct that there is no intraspecies variation, then all infants are at equal risk of IAM induction. Yet, the IAM case data doesn't bear this out. USEPA has yet to explain this phenomenon that would, in part, be explained by intraspecies variability in the infant population. It would appear that a 10X intraspecies variability factor is needed.
11. Using drinking water source nitrate concentrations as the delivered dose/concentration to infants is mathematically incorrect. Infants displaying nitrate induced cyanosis ingested diluted source water containing some fraction of the contaminated source water nitrate concentration. A correction factor is needed to reduce the equivalent delivered concentration for use in RfD calculation that would reduce the RfD (and MCL) 10-fold at most. This correction needs to be done immediately as this critical error demonstrates that nitrate is far more toxic than previously admitted by USEPA.
12. USEPA has an incorrect conceptual model of IAM induction. International literature demonstrates that IAM induction likely is the result of nutrient/microbial ingestion from contaminated water and not just nitrate. This means that mixture risk assessment is required, not just single chemical risk assessment evaluations. USEPA's chemical mixtures guidelines demonstrate that USEPA understands that mixtures pose different risks than single chemical exposures. IAM is the result of chemical/biological mixtures. Therefore, sole use of nitrate as a surrogate for the mixture that leads to nitrite toxicosis is toxicologically untenable and does not rise to the level of risk assessment science that models real world exposures rather than hypothetical assumption-based exposures.

13. There are logical reasons to increase or decrease the RfDs and any MCLs based on their use, regardless of source (e.g., USEPA's nitrate and nitrite MCLs are based on Office of Drinking water unique RfDs that are different from the IRIS RfDs either in narrative or numerical basis (see Nitrate/Nitrite Criteria Document for details and to compare with current IRIS nitrate and nitrite RfDs). Increases or decreases in numerical values are currently impossible because USEPA denies the existence of errors, omissions, and misrepresentations in nitrate and nitrite RfDs (and MCLs) even though the author of this submission has provided this information to USEPA over the last two years in various forms. Thus, it would appear that USEPA is disingenuously putting forth the discredited notion that the current hematological basis for the RfDs is understood and need not be revisited in an attempt to bury this new knowledge that has been presented to them concerning the lack of scientific basis of their current RfDs. Because of this position, there is really no way to know if any population or subpopulation of humans is adequately protected by the RfDs when linked to MCLs and whether the enormous regulatory burdens linked back to the RfDs are justified. All communities need USEPA to formulate nitrate and nitrite RfDs that represent good science and not stealth risk management decisions that have no place in RfD formulation or represent just plain bad risk analysis products.
14. In the 1970s and again in the 1980s, USEPA Assistant Administrator Kimm noted in official USEPA documents that USEPA frequently did not know the actual exposure concentrations associated with IAM cases. Furthermore, USEPA has never identified which, if any, IAM exposure concentrations are reliable. Assistant Administrator Kimm impeached USEPA's principal studies and likely supporting studies a decade or so before the first IRIS nutrient RfD was written. This means that USEPA knew or should have known the data sets were unreliable. USEPA needs to use maximalized UFs and MFs to account for data unreliability. Not knowing which, if any, of the cited principal studies' IAM case statistics are usable means that the current UF of 1 is untenable and, perhaps, the RfDs should be withdrawn.
15. USEPA states that nitrite is an acute toxicant. IAM cases follow days, weeks, or months of intermittent or continuous exposure to nutrient contaminants in source drinking water. The RfDs do not explain how an acute toxicant turns into a longer-term exposure toxicant without accumulating and/or causing long term subclinical hypoxia and anoxia and potentially associated developmental effects. This is a critical question that might explain developmental effects in infants yet to be linked with a cause. Without opening up the hematological basis for the RfDs, USEPA will not investigate the potential links between developmental disorders and hematological toxicity of nitrate and nitrite and mixtures of nutrients and microbes linked to IAM cases.
16. "Through the IRIS Program, EPA provides high quality science-based human health assessments to support the Agency's regulatory activities and decisions to protect public health." Given the evidence presented in this submission, it appears that for nitrate and nitrite RfDs USEPA has never provided "...high quality science-based human health assessments to support the Agency's regulatory activities and decisions to protect public health." This assertion is proven if even one of the claims in this submission is found scientifically valid. For example, the admissions of Mr. Kimm support this assertion.

17. USEPA has opened the door to inclusion of the historical hematological basis for the IRIS nitrate and nitrite RfDs by referring back to the principal studies in narrative and tables in previous six-year reviews. Therefore, it seems too late to close the door now.
18. Given that the nitrate and nitrite MCLs are not linked to the IRIS RfDs (according to the USEPA Nitrate/Nitrite Criteria Document), what is the point of this review?

It should be noted that USEPA was invited to peer review work product for the book in preparation but curtly refused to agree to any interactions with the authors except via PIO requests for information that were unproductive. Despite USEPA's desire to remain ignorant of our interim book findings, the Agency was apprised of these findings via multiple communications.

USEPA's unprofessional approach to having their science products reviewed in a collegial manner was a great disappointment that culminated with ignoring our findings and moving forward with a nitrate and nitrite RfD review process that excludes the fatally flawed IRIS RfD explanation for the hematological processes that result in a case of IAM.

For all these reasons and more that will be presented in our book, USEPA needs to reopen the hematological basis for the nitrate and nitrite RfDs. USEPA's nitrate and nitrite RfDs have been demonstrated to lack scientific and procedural rigor. Their narrative basis is flawed because much of it is based on assumptions that do not match real world exposures or modern science that replaced outdated or disproven science.

USEPA needs to move its RfDs from dalliances with past papers and hypotheses, starting as early as the 1920s for the mechanistic basis of IAM and infant physiology and biochemistry to the third decade of the 21st century. It needs to replace the musings and hypotheses turned into paradigm (starting in the 1940s and coalesced into doctrine in the 1970s) to instead practice modern peer review science and assure data quality.

In closing, I would like to thank USEPA for training me in the writing and reviewing of RfDs, MCLs and risk assessment products during and after my time as Wisconsin's State Toxicologist and State Groundwater Toxicologist.

This document and USEPA's response will serve, in part, as USEPA peer review previously denied. USEPA is again invited to participate in the peer review of our book chapters as they become available.

Thank you for the opportunity to comment on your FR notice.

Dr. David A. Belluck
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