April 26, 2023

Barbara Losey, Executive Director
The Alkylphenols & Ethoxylates Research Council (APERC)
1250 Connecticut Avenue, NW
Suite 700
Washington, DC 20036

Re: Comments of the Alkylphenols & Ethoxylates Research Council
In the Matter of the Proposed Amendments to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Ch. 4717.7860 Subpart 13a p-Nonylphenol (4-Nonylphenol) (Discussion 38941)

Dear Barbara Losey:

In an April 26, 2023, post-hearing letter to the Minnesota Department of Health (MDH), the Alkylphenols and Ethoxylates Research Council (APERC) reiterates that the health effect that MDH based their nonylphenol guidance on (renal mineralization reported in young male rats from Chapin 1999[1]) is not adverse and is inconsistent with assessments by other governmental agencies. APERC states that the renal mineralization was described as "slight to mild" by the study pathologist and provides graphs that visually support that description. APERC further asserts that by basing guidance on renal mineralization (a non-adverse effect according to APERC), MDH is acting contrary to our 2008 SONAR[2]. MDH sincerely appreciates the post-hearing comments from APERC on our nonylphenol guidance and respectfully disagrees with APERC that 1) renal mineralization in the Chapin 1999 study is not adverse; and that 2) MDH is not acting in accordance with our 2008 SONAR.

First, MDH emphasizes that the adverse effect, renal mineralization, is occurring in young male rats that were exposed to nonylphenol *in utero* and through lactation. The occurrence in young male rats is the key. This is a rare occurrence. Although renal mineralization was scored as "slight to mild" in the Chapin study, the incidence of this effect was observed in three different generations of rats at the lowest dose tested, and the incidence increased with increasing doses. Because this study was designed to capture developmental and early life health effects, the animals were not kept into adulthood. Renal mineralization is most often seen in adult animals as it can occur as part of normal aging in laboratory rodents. It is likely that if the animals were followed into adulthood, the level of renal mineralization would increase, indicating more severe kidney damage. Again, the fact that this effect was seen in young animals was concerning. In concordance with MDH, this effect was also identified as an adverse effect in a European Union risk assessment[3].

APERC is correct in that our 2008 SONAR does cite EPA's definition of an adverse effect as "a biochemical change, functional impairment, or pathological lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge".

However, our 2008 SONAR also states that "in order for an effect to serve as the basis for an MDH-derived HRL, it must be adverse, or a *precursor to an adverse effect*" (p27 MDH 2008, emphasis added). Therefore, whether renal mineralization is a marker for renal degeneration, as stated in the National Toxicology Program (NTP) Non-neoplastic Lesion Atlas[4], also cited by APERC, or whether a longer nonylphenol exposure would have produced a score more severe than "slight to mild" in these rats, both are considered adverse according to MDH's 2008 SONAR.

MDH respectfully concludes that renal mineralization is an adverse effect and follows the guidance in our 2008 SONAR.

Sincerely,

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References

[1]Chapin, RE *et al*. (1999). The Effects of 4-nonylphenol in Rats: A Multigeneration Reproduction Study. *Toxicol Sci*, 52(1), 80-91.

[2] Minnesota Department of Health Statement of Need and Reasonableness (SONAR). (2008). https://www.leg.mn.gov/archive/sonar/SONAR-03733.pdf#page=2

[3]European Chemicals Bureau (2002). European Union Risk Assessment Report for 4-nonylphenol (Branched) and Nonylphenol. https://echa.europa.eu/documents/10162/6c460d8a-9f18-475f-823c-b8941e18fa3a

[4]National Toxicology Program (NTP). Nonneoplastic Lesion Atlas. https://ntp.niehs.nih.gov/nnl/