March 31, 2023

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

Re: Proposed Amendments to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Part 7500, Part 7850, and Part 7860; Revisor's ID Number RD4587, OAH Docket No. 5-9000-38941

Dear Barbara Losey:

Thank you for your comments on the proposed Health Risk Limit for nonylphenol during the Health Risk Limits Rules Amendment pre-hearing comment period. MDH's responses are below after the points in the letter (numbered and *in italics*).

In a March 8, 2023, letter to the Minnesota Department of Health (MDH), APERC wrote that MDH developed guidance for nonylphenol on an effect (renal mineralization in male rats) that is not considered adverse, not replicated in other studies, and is inconsistent with other human risk assessments by other government agencies and peer-reviewed assessments. MDH thanks APERC for their interest in MDH guidance but disagrees with APERC on their assessment.

1) MDH disregarded a high-quality study by Tyl et al, 2006 in selecting a POD for pNP, with no credible basis; this study derived a clear NOAEL of 200 ppm pNP based on the absence of histopathological findings in rat kidneys at that dose, which is also supported by other studies.

MDH thoroughly assessed the three-generation dietary rat study by Tyl 2006[1]. This study was designed to confirm and extend the findings from Chapin 1999[2], MDH's critical study selection. In the three-generation dietary rat study of Chapin 1999, young male rats that had been exposed to nonylphenol in utero, through lactation, and then through young adulthood developed renal mineralization along with renal tubular degeneration. (All generations – adult, first generation, second generation, and third generation males – developed renal mineralization). MDH modeled renal mineralization from data in the second-generation males to produce a benchmark dose lower limit (BMDL) as the point-of-departure (POD). Although renal mineralization by itself may not be adverse as it can spontaneously occur in rats as they

age, the mineralization observed in three consecutive generations occurred in young males at the lowest dose tested - and that is the key.

Tyl 2006 repeated the study by feeding groups of rats a Purina 5002 diet and the NIH-07 diet. (Dietary composition affects the outcome of nonylphenol-induced results). Chapin fed the three generations of rats the NIH-07 diet. In the Tyl study, the NIH-07 diet was only supplied to rats at one dose – 650 ppm. At this dose, there was increased kidney weight in all generations, renal mineralization, and tubular nephropathy. Although single-dose experiments like the NIH-07 arm of the Tyl study are unfeasible to use for quantitative risk assessment, it is notable that these kidney effects were more severe in the NIH-07 diet relative to the Purina 5002 diet. It would have been ideal if Tyl 2006 had extended the NIH-07 arm of the study to include the lower doses that Chapin 1999 used so that a full comparison could be made, but the weight of evidence from these two studies supports that the observed kidney mineralization may be occurring in tandem with renal degeneration (discussed in greater detail below in #3).

2. Renal mineralization found at the lowest dose in the NTP, 1997\Chapin et al., 1999 study were not reproduced at that dose in other studies; the NOAEL for renal effects in rats in this study should be 200 ppm (approximately 13 mg/kg-bw/day).

MDH disagrees that the no-observed-adverse-effect-level (NOAEL) in the Chapin 1999 (also known as NTP 1997) study is 200 ppm (13 mg/kg-d administered dose or 3.8 mg/kg-d human equivalent dose - HED). Renal mineralization was observed in young male rats in all generations after nonylphenol exposure at 200 ppm (3.8 mg/kg-d_{HED}). The effects in these rats cannot be ignored because other studies, including Tyl, did not match the conditions used in this study, rendering a direct comparison impossible. In fact, Tyl did show increased renal mineralization in all generations at the only dose tested in the NIH-17 arm of the study, accompanied by increased incidence of tubular degeneration in two of the three generations. MDH considers this a LOAEL in the Tyl study.

MDH developed a POD using benchmark dose (BMD) modeling for the Chapin 1999 study rather than explicitly defining a NOAEL or LOAEL. MDH used a BMDL of 0.49 mg/kg-d_{HED} based on renal mineralization in the second generation of rats as the POD. In general, MDH preferentially develops PODs using BMD modeling rather than using a NOAEL/LOAEL (see Risk 101 attachment).

3. Renal mineralization in rats, as seen at [the] lowest dose in the NTP, 1997\Chapin et al, 1999 study, is common and not considered adverse in rat pathology; its occurrence at the lowest dose in this study was in isolation from other true adverse effects and should not be viewed as a

treatment-related adverse effect and should not be the critical effect from which a POD is calculated for pNP.

Renal tubular degeneration was present along with renal mineralization at the lowest nonylphenol dose in the young male rats in the Chapin 1999 study. As noted in the APERC comments citing the NTP Neoplastic Lesion Atlas[3] "…mineralization may also be seen as a consequence to degeneration and necrosis." Renal degeneration was observed in the Chapin study; therefore, it is plausible that the mineralization was occurring because of those effects, thereby indicating the mineralization observed at the lowest dose may be a marker of more severe effects and may also be considered adverse.

4. No other governmental assessment of the NTP, 1997/Chapin, 1999 study has interpreted the kidney lesion/mineralization seen at the lowest dose to be adverse; all have selected LOEL\LOAELs (kidney) of 200 ppm (12-13 mg/kg-bw per day) based on other adverse kidney effects.

MDH is confident that its analyses stand on their own merits, and neither MDH's methodology nor guiding legislation require that another agency come to the same conclusion to promulgate proposed HRLs. However, we will note that the European Union (EU) identified tubular mineralization as one of the predominant renal lesions in the Chapin 1999 study. The EU risk assessment report of 2002[4] concluded that 200 ppm is the LOAEL of the Chapin 1999 study based on histopathological changes – including mineralization – in the kidney, contradicting APERC's assertion.

5. No evidence suggests any predictive value of such renal mineralization\lesions seen in the lowest dose of the NTP, 1997\Chapin, 1999 study in rats with respect to human renal toxicity.

The kidney is one of the primary targets of nonylphenol toxicity. Accompanying the renal mineralization in young male rats was renal degeneration. The key, again, is that this occurred prematurely in young rats. There is no conclusive evidence that this effect isn't relevant to humans. Minnesota Statute 144.0751[5] states that Minnesota HRLs "include a reasonable margin of safety to adequately protect the health of infants, children, and adults". MDH's BMDL for renal mineralization accomplishes this.

6. A human risk assessment for NP published by Osimitz et al., 2015[6] conducted a review of the available toxicological data for NP and identified a NOAEL of 13 mg/kg-bw/day for systemic and reproductive toxicity effects found in multigeneration rat studies.

MDH thanks Thomas Osimitz for the nonylphenol risk assessment presentation to MDH. However, the toxicologists at MDH came to a different conclusion after analyzing the nonylphenol study database. MDH selected the three-generation rat study by Chapin 1999 as the critical study with renal mineralization as the critical adverse effect. The Chapin study is thorough, of high-quality, and performed by a highly reputable group – the National Toxicology Program (NTP), a division of the National Institutes of Health (NIH). The renal mineralization observed in this study is adverse because it is occurring prematurely in young male rats and might be associated with renal degeneration. These rats were exposed in utero, during lactation, and as young adults. Modeling the renal mineralization data from the second generation of young males produced a point-of-departure at the BMDL of 0.49 mg/kg-d_{HED}. As discussed in the Risk 101 document, BMDLs do not require defining a LOAEL or NOAEL, but instead uses the entire dataset to determine a dose where effects are unlikely to occur.

Summary

MDH is obligated to follow the risk assessment methodology laid out in our 2008 SONAR[7]. Our analysis, conducted within that methodological framework, resulted in a final guidance value based on renal mineralization in young male rats. Young males may be the most sensitive population to nonylphenol effects and selecting a higher POD would not protect younger animals that showed increased sensitivity. A subsequent 3-generation study by Tyl supports possible kidney effects at lower doses, however, the study did not assess lower doses and cannot be used to assess a POD. Therefore, in order to be protective for all human populations, MDH will retain the POD defined by BMD analysis without modification.

Sincerely,

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References

[1]Tyl, RW *et al*. (2006). Three-generation Evaluation of Dietary Para-nonylphenol in CD (Sprague-Dawley) Rats. *Toxicol Sci*, 92(1), 295-310.

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

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

[4]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

[5]Minnesota Statutes. (2022). Health Standards. 144.0751. https://www.revisor.mn.gov/statutes/cite/144.0751

[6]Osimitz, TG et al. (2015). Human Risk Assessment for Nonylphenol. Human and Ecological Risk Assessment: An International Journal. (21) 1903-1919.

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

ATTACHMENT A "Risk 101"

Risk Assessment Methodology for Health Risk Limits Derivation, Summarized from 2023 SONAR[1]

The Minnesota Department of Health (MDH) derives Health Risk Limits (HRLs) based on United States Environmental Protection Agency (EPA) risk assessment methods and guidelines. Risk assessment methods require that MDH determine: the health effects associated with a chemical and the lowest dose at which an adverse effect may arise; an evaluation of human exposure; and an integration of these and other considerations that may contribute to human health risk. The following is a brief step-wise description of the approach MDH's scientists use to calculate the HRLs.

An MDH-derived HRL is the concentration of a chemical in drinking water that is likely to pose little or no health risk to humans, including vulnerable subpopulations, based on current levels of scientific understanding. Vulnerable populations vary depending on the chemical of interest, but may include: fetuses, infants, pregnant women, prepubescent childrenn, and others. The HRL concentration is a function of how toxic a chemical is (that is, the minimum quantity that will cause health effects), the duration of exposure, and the amount of water individuals drink during the exposure period. In addition, a HRL value incorporates several adjustment factors to account for uncertainty in our understanding of a chemical's health risks.

1) Toxicity Evaluation – Noncancer Effects

Rather than wait until health effects are evident in humans, the accepted method for assessing potential toxicity to humans is through controlled laboratory studies using mammals (the term "animal" shall be used throughout to describe mammalian species). In toxicity testing, animals are divided into groups and each group is administered one of several doses of a chemical, usually daily, over a set period of time. Testing has two goals: (1.) to identify the hazard or toxic effects caused by the chemical, and; (2.) to evaluate the relationship between the dose and the animal's response. The dose-response relationship may vary depending on when (e.g., the life stage) during the life stage and for how long (duration) the exposure occurred.

In evaluating the dose and the response for noncancer health effects, researchers seek to determine the lowest dose where adverse effects related to dosing are observed (the "lowest observed adverse effect level," or LOAEL) and the highest dose where no adverse effects related to dosing are observed (the "no observed adverse effect level," or NOAEL). By definition, LOAELs and NOAELs can only be a dose used in the study of interest. A newer analysis method, benchmark dose (BMD) modeling, uses statistical modeling to evaluate a dose-response dataset using a pre-determined effect level. Modeling assesses the shape of the dose response relationship and allows scientists to calculate a dose where a given response level (e.g., 10% change in organ weight) is expected to be seen. While not all datasets are compatible with BMD modeling, when feasible, it is preferable to a NOAEL/LOAEL approach because it considers the entire dose-response curve rather than relying on discrete dose points. BMD modeling is now a standard risk assessment practice that is used by many state, federal, and international regulatory agencies; indeed, the US EPA developed and maintains a free-to-use BMD modeling software that is employed by MDH and other states to evaluate appropriate datasets.

The dose resulting from dose-response evaluation (also referred to as a point of departure (POD) dose) serves as the starting point for deriving health-protective concentrations for environmental media.

The dose level selected from the dose-response evaluation of the animal study(s) is identified as a point of departure dose (POD). The dose to the laboratory animal is converted to a human equivalent dose (HED) by adjusting for differences in how these species handle the chemical in the body. An HED represents the dose to humans that would result in the same internal dose as the dose administered to the laboratory animal species, assuming that the toxic response is similar in the two species.

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[1] MDH. 2023 Statement of Need and Reasonableness (SONAR), as cited in MDH 2023 SONAR. (https://www.health.state.mn.us/communities/environment/risk/docs/rules/hrlsonar23full.pdf).

The HED is then reduced by variability and uncertainty factors (UFs) to account for what is not known about a chemical's toxicity to a human population. The factors account for:

- UF_A - uncertainty in extrapolating from animal data to humans (e.g., it may not be known whether humans are more or less sensitive than the test animal);
- UF_H - variation in sensitivity among human individuals (e.g., variability in internal dose levels or sensitivity to the toxicological effects);
- UF_S - uncertainty in extrapolating from effects observed in a short-term study to potential effects from a longer exposure;
- UF_L - uncertainty associated with using a study in which health effects were found at all doses tested (lowest dose was a LOAEL and no NOAEL was identified); and
- UF_{DB} - deficiencies (data gaps) in available data.

In the absence of chemical-specific information, each of the five factors is typically assigned a value between 1 and 10. Values of 1, $10^{0.5}$ and 10 are most common. Values assigned to all factors are multiplied to determine the overall uncertainty factor. By convention, half-power values (e.g., $10^{0.5}$) are factored as whole numbers when they occur singly but as powers or logs when they occur in tandem. For example, individual UFs of 3 and 10 would be expressed as 30 (3×10^1), whereas individual UFs of 3 and 3 would be expressed as 10 ($10^{0.5} \times 10^{0.5} = 10^1$).

The HED is divided by the product of the uncertainty and variability factors to calculate a reference dose (RfD). An RfD is expressed in milligrams of chemical per kilogram of body weight per day (mg/kg-day) and is defined as an estimate of a dose level that is likely to be without an appreciable risk of adverse effects.

2) Exposure

HRLs must be protective against adverse health effects from short-term as well as long-term exposures to contaminants in drinking water. MDH considers sensitive life stages and subpopulations as well as the magnitude and duration of exposure necessary to elicit a toxic effect. Intake rate is expressed as the quantity of water consumed per kilogram of body weight per day (L/kg-day). Studies of water consumption indicate that infants and young children drink more water for their body weight than do adults. Newborns derive all, or nearly all, their nutrition from liquid. Intake rates fall rapidly with age; by age seven, intake rates are nearly the same as those of adults.

MDH uses water intake rates that are recommended by US EPA Exposures Factor Handbook (EPA 2019). These rates are based on data collected from individuals across the US as part of the US Department of Agriculture's Continuing Survey of Food Intake by Individuals (CSFII) survey.

3) Risk Characterization

An RfD incorporates information about the toxicity of a single chemical associated with a given dose. Exposure to a chemical may result from multiple sources. The Groundwater Protection Act requires that MDH use a "relative source contribution" (RSC) factor when deriving HRLs for noncancer effects. The RSC allocates only a portion of the RfD to exposure from ingestion of water, and reserves the remainder of the RfD for other water-related exposures (e.g., inhalation of volatilized chemicals, dermal absorption) as well as exposures via other contaminated media such as food, air, and soil. MDH has relied upon EPA's Exposure Decision Tree approach (EPA 2000) to facilitate determining appropriate default RSC values.

MDH combines the above information into an equation for noncancer health effects:

$$\text{Noncancer HRL } (\mu g/L) = \frac{\text{RfD (mg/kg-d) x RSC x 1,000 } \mu g/mg}{\text{Intake Rate (L/kg-d)}}$$

References:

Minnesota Department of Health 2023. Statement of Need and Reasonableness in the Matter of Proposed Rules Relating to Health Risk Limits for Groundwater. Available online: https://www.health.state.mn.us/communities/environment/risk/docs/rules/hrlsonar23full.pdf