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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)

Submitted to the Office of Administrative Hearings under eComments
OAH Docket No. 5-9000-38941

April 26, 2023

The Alkylphenols & Ethoxylates Research Council (APERC) submits these post-hearing comments to oppose proposed amendments to rules governing Health Risk Limits (HRLs) for groundwater, Minnesota Rules, Ch. 4717.7860 Subpart 13a, p-Nonylphenol (pNP), also called 4-Nonylphenol (4NP). These comments are submitted under discussion 38941 to OAH Docket No. 5-9000-38941. Specifically, APERC opposes the proposed sub-chronic and chronic HRLs for pNP for the reasons discussed below.

Background

APERC is a North American organization whose mission is to promote the safe use of alkylphenols, including pNP through science-based research and outreach efforts, within the framework of responsible chemical management.[1] For more than thirty years, APERC and its member companies have been actively engaged in the conduct and review of studies on the toxicological effects of pNP and related compounds.

APERC submitted detailed written comments on March 8, 2023 to the docket in the matter of the proposed HRLs for pNP. Previous comments and a presentation that were provided as preregulatory information to the MN Department of Health (MDH) were included as attachments to those comments. Those comments primarily responded to MDH's focus on the selection of mineralization in male rat kidneys as the Critical Effect for the derivation of subchronic and chronic HRLs for pNP.

APERC thanks the MDH for the considerable time and effort they put into the development of the HRLs for pNP and for their professionalism accepting, carefully considering, and responding

[1] APERC member companies include: The Dow Chemical Company, Dover Chemical Corporation, and SI Group, Inc.

to our comments throughout this process. The topic of assessing renal effects observed in toxicology studies is complex and we appreciate the effort MDH undertook to do this with respect to pNP.

During the public administrative hearings on April 5th and 6th, 2023 Judge James Mortenson outlined the following three key issues under consideration during the public administrative hearing.

1. Does the Agency have legal authority to adopt the rules?
2. Has the Agency fulfilled all relevant legal and procedural requirements to promulgate the rules?
3. Has the Agency demonstrated the need and reasonableness of each portion of the proposed rules?

APERC's comments below assert that MDH has not sufficiently demonstrated reasonableness (item 3 above) in its selection of renal effects (mineralization) as the Critical Effect for derivation of the subchronic and chronic HRLs for pNP. The Minnesota Administrative Procedure Act (APA), Minnesota Statutes, chapter 14, requires MDH to justify the need to amend the existing HRL rules and the reasonableness of the amendments in a Statement of Need and Reasonableness (SONAR). (See Minn. Stat. § 14.131). For the subchronic and chronic HRLs for pNP, MDH has selected a Point of Departure (POD) based on their interpretation that renal mineralization seen in male rats in a study conducted by the National Toxicology Program (NTP) in 1997 and published by Chapin et al., 1999 is an "adverse" effect. [2,3] This interpretation is unreasonable for the reasons discussed in Section 1.0 below. APERC's recommended Critical Effect, POD and derivation of the HRL for pNP are provided in Section 2.0 below.

1.0 The evidence for adversity in the selection of renal mineralization in young male rats as the Critical Effect for pNP is weak and not consistent with the SONAR definition of "adverse"; therefore, selection of this as a Critical Effect for pNP is not reasonable.

The January 2023 SONAR related to this rulemaking to amend HRLs includes the following definitions in Appendix A "Glossary of Terms Used in Risk Assessment". [4]

- **Adverse Effect**: A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge.

[2] National Toxicology Program (NTP). (1997). Final Report on the Reproductive Toxicity of Nonylphenol (CAS #84852-15-3) (Vol. RACB No. 94-021, pp. 576): National Institute of Environmental Health Sciences
[3] Chapin, R. E., Delaney, J., Wang, Y., Lanning, L., Davis, B., Collins, B., Mintz, N., & Wolfe, G. (1999). The effects of 4-nonylphenol in rats: a multigeneration reproduction study. *Toxicol Sci*, **52**(1), 80-91. This is the peer-reviewed publication that summarizes the NTP study referenced above.
[4] Minnesota Department of Health (MDH) (2023, January 26) Statement of Need and Reasonableness (SONAR): Proposed Amendments to the Rules on Health Risk Limits for Groundwater (Minnesota Rules, Chapter 4717, Parts 7500, 7850, and 7860).

- **Benchmark Dose (BMD**): Dose or concentration that produces a predetermined change in the response rate of an adverse or biologically meaningful effect.
- **Critical effect(s):** The health effect or health effects from which a non-cancer toxicity value is derived; usually the first adverse effect that occurs to the most sensitive population as the dose increases.

Based on these definitions, both the Critical Effect and the Benchmark Dose should be based on adverse effects, which are defined as "affecting the performance of the whole organism or reducing an organism's ability to respond to an additional environmental challenge".

The July 2008 MDH SONAR for HRLs, which describes the process for derivation of HRLs provides the following additional clarification for what constitutes "adverse":

> "…for the purpose of the MDH-derived HRLs, an adverse health effect is identified as the organ, tissue, or system in which the effect is manifested or as the occurrence of cancer" and "in order to constitute a toxic effect, several criteria must be satisfied" one of which is that "the effect observed must be either adverse or biologically meaningful."[5]

> 1.1 pNP does not exhibit a constellation of kidney effects that together indicate an adverse impact; or framed under the SONOR definition, a constellation of effects that "affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge."

The focus of MDH's efforts for pNP has been on understanding and applying data related to potential kidney effects. Assessment of toxicity in kidney is a multifaceted topic. Rodent (rat and mouse) toxicology studies feature many endpoints, not all of which are necessarily adverse individually, which can provide insight into toxicity. These endpoints include:

> *Kidney weights* – organ weights often are the most sensitive endpoint associated with toxicity. Although they may not indicate a specific mechanism, they are a good indicator that something may be amiss. Modest changes in kidney weights may occur in toxicology studies without histopathological evidence of cellular damage. It is uncommon that this is the only change noted in the presence of true kidney toxicity. Kidney weights were determined in almost all studies with pNP and with one exception of a ~10% increase in kidney weights in a study by Tyl, 2006, no treatment-dependent changes in weights were noted at the lowest dose in any of the studies. [6]

[5] Minnesota Department of Health (MDH). (2008, July 11). Statement of Need and Reasonableness (SONAR): Proposed Amendment to Rules Governing Health Risk Limits for Groundwater, Minnesota Rules, 4717.7810 *et seq.*
[6] Tyl, R.W., Myers, C.B., Marr, M.C., Castillo, N.P., Seely, J.C., Sloan, C.S., Veselica, M.M., Joiner, R.L., Van Miller, J.P., & Simon, G.S. (2006). Three-generation evaluation of dietary para-nonylphenol in CD (Sprague Dawley) rats. *Toxicological Sciences*, 92, 295-310

Clinical pathology – this refers to data that one obtains by analyzing components of blood, most commonly blood urea nitrogen (BUN) and serum creatinine. Elevations in either or both often point to alterations in kidney function.

Although the Chapin, 1999 study on pNP did not assess these parameters, a 90-day pNP study by Cunny et al., 1997 did and reported no treatment-related changes either BUN or serum creatinine.[7, 8]

Histopathology – The careful examination of tissue slides prepared from animals exposed and not exposed to the chemical of interest is an important factor. In addition to the incidence of effects (the number of animals exhibiting a change in renal histopathology) it's important to consider the severity of such results in determining when an observed endpoint is adverse. In the NTP study on pNP reported by Chapin,1999, essentially all the histopathological changes, regardless of dose, were described in by the authors as being "slight to mild."

In considering the constellation of possible kidney effects from pNP in the Chapin, 1999 study, as well as other studies: no treatment related effects were seen in clinical pathology; essentially all the histopathological changes in the Chapin, 1999 study are of "slight to mild" severity; and with one exception, no treatment-dependent changes in kidney weights were noted at the lowest dose in any of the other studies on pNP. Therefore, with possible exception of effects at the higher doses, pNP is *unlikely* to induce adverse effects, as defined by the SONAR for HRLs, that would affect the performance of the whole organism (in this case the rat) or reduces an organism's ability to respond to an additional environmental challenge.

1.2 MDH's interpretation of kidney effects in the Chapin, 1999 study is unreasonable as it is inconsistent with scientific guidance on the relevance of the mineralization findings for pNP in rats, and does not fit the SONAR definition of "adverse".

APERC's previous comments noted that "the renal mineralization in rats, as seen at 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". [9] Furthermore, the comments provided significant expert citations from pertinent publications that explain that rats are widely known to have a high rate of various spontaneous kidney lesions, including mineralization. Mineralization seen in the rat kidney at the lowest dose in the Chapin, 1999 rat study should not be considered

[7] Chapin, (1999).
[8] Cunny, H.C., Mayes, B.A., Rosica, K.A., Trutter, J.A., & Van Miller, J.P. (1997). Subchronic toxicity (90-day) study with para-nonylphenol in rats. Regulatory Toxicology and Pharmacology, 26 (2), 172-178.
[9] Alkylphenols & Ethoxylates Research Council (2023, March 8). Comments in the Matter of the Proposed Amendments to rules Governing Health Risk Limits for Groundwater, Minnesota Rules, Ch. 1717.7860 Subpart 13a. Initial Comment Period. Discussion 38941.

an adverse effect and should not serve as the Critical Effect from which to calculate a POD for HRLs.

In its response to APERC's comments, MDH explained its view that "Renal mineralization observed in Chapin 1999 is adverse because it is occurring prematurely in young male rats and *might* be associated with renal degeneration" and "Mineralization observed at the lowest dose *may* be a marker of more severe effects and *may* also be considered adverse". [10] (Emphasis added). It is worth noting that expert guidance for toxicologic pathology in the rat kidney advises that "mineralization occurs more often in female than male rats because of its relationship with estrogen levels, but is found in both very young and old animals." [11]

It is APERC's view that MDH's interpretation of kidney effects reported by Chapin, 1999 is not a reasonable interpretation of "adverse" as it is inconsistent with scientific guidance on the relevance of the mineralization findings for pNP in rats, is inconsistent with the findings in the cited source study, and does not fit the SONAR definition of "adverse". [12, 13] SONAR defines "adverse effect" as "a biochemical change, functional impairment, or pathologic lesion that *affects* the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge. It does not say that effects that "*might* be associated" with another effect or "*may* be considered a marker" are adverse. Most important, the National Toxicology Program's (NTP's) Atlas to the Kidney states that: "In general, these deposits have no pathologic significance" in reference to renal mineralization lesions. [14]

1.2.1 Slight to mild histopathological findings, related to kidney lesions in young male rats as described in Chapin, 1999, which are generally viewed to have no pathologic significance, do not meet the level of "adverse" as defined in the SONARs for HRLs. [15, 16]

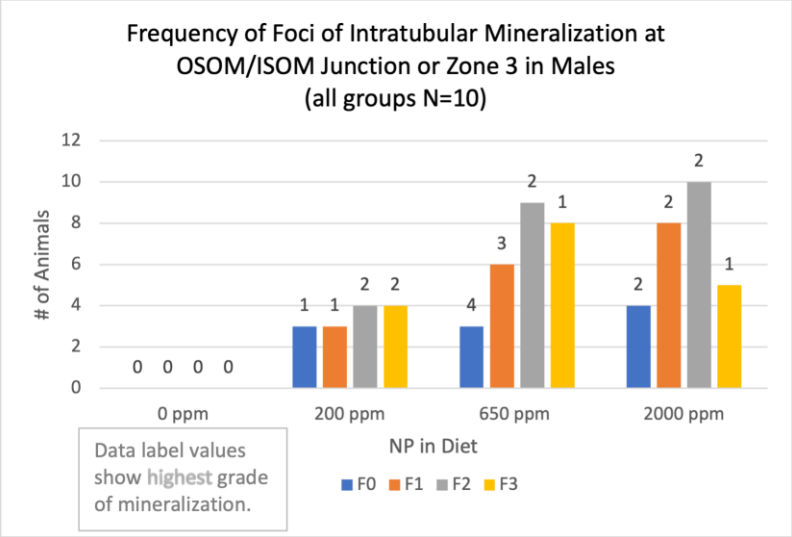
The text in Chapin, 1999 provided qualitative descriptions of "slight to mild" for the kidney mineralization effects seen from pNP in rats. However, no numerical score were provided in this study. Nonetheless an expert review of the histopathology slides from the NTP 1997\Chapin,

[10] Minnesota Department of Health (MDH) (2023, March 31) Letter to Alkylphenols & Ethoxylates Research Council in Response to Comments.
[11] Hard, G.C., Alden, C.L, Bruner, RH.G., Frith, C.H., Lewis, R.M. Owen, R.A., Krieg, K and Durchfeld-Meyer, B. (1999). Non-proliferative lesions of the kidney and lower urinary tract in the rat, URG-1. Guides for Toxicologic Pathology. STP/ARP/AFIP, Washington, DC
[12] MDH. (2008, July 11).
[13] MDH. (2023, January 26).
[14]Schmidt CW. National Toxicology Program (NTP). (2014). Non-Neoplastic Lesion Atlas: a new tool for toxicologic pathology. *Environ Health Perspect.* 122(3): A76-9. doi: 10.1289/ehp.122-A76. PMID: 24583717; PMCID: PMC3948027.
[15] MDH. (2008, July 11).
[16] MDH. (2023, January 26).

1999 study by Dr. Gordon Hard produced numeric scores, which are presented in Figures 1 and 2 below.[17]

Figures 1 and 2 summarize the severity of kidney mineralization in male and female rats in the NTP\Chapin, 1999 study as scored by expert review in Hard, 1998. The highest mineralization score (i.e., 1-4) is noted above the bar for each test group.

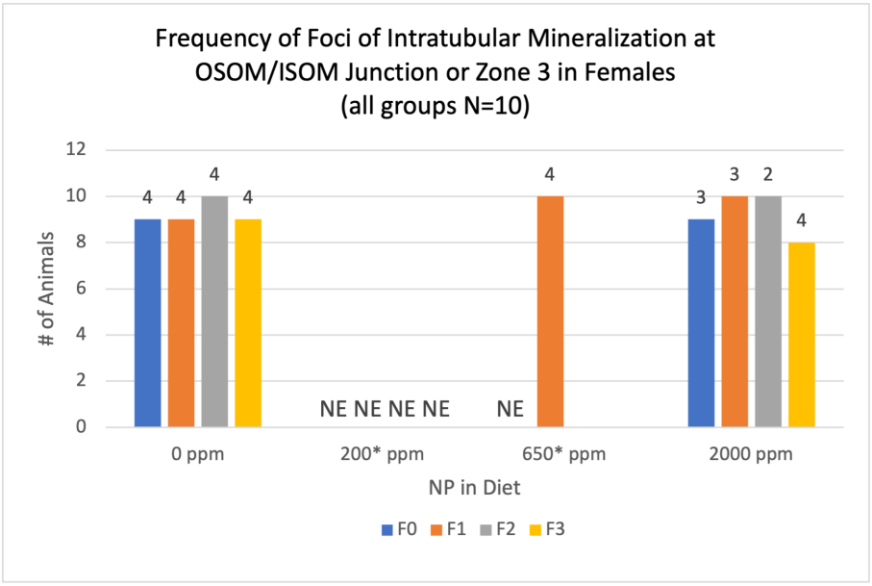
Figure 1: Kidney mineralization scores in male rats based on expert review by Hard



(1) Scores represent the highest score in each group. Scores for individual animals were not available.

[17] Hard, G.C. (1998). Expert Report on Renal Histopathologic Changes in Rat Dietary Studies with Nonylphenol Goldens Bridge NY, USA. Prepared for the Alkylphenols & Ethoxylates Research Council, Washington, DC, USA

Figure 2; Kidney mineralization scores in female rats based on expert review by Hard 1999 [(1), (2)]



(1) Scores represent the highest score in each group. Scores for individual animals were not available
(2) NTP 1997\Chapin, 1999 did not evaluate females the 200 ppm group and at 650 ppm only F1 was evaluated.

NE = not evaluated for mineralization as histopathologic slides were not prepared by NTP.

As illustrated in Figure 2 essentially all the histopathological changes in the kidney in male rats in the Chapin study, have been described as "slight to mild" with no indication of adversity as defined in the SONAR guidance. The exception was a score of 4 seen in the F0 650 ppm dose male group, which represents a very high dose of pNP. Also of particular note, is that the highest kidney mineralization scores in the female rats were all 4 for the female control group. Even with a high score of 4 for kidney mineralization, no adverse effects were noted in the control female rats, indicating that the mineralization did not affect the performance of the whole organism or reduce the organism's ability to respond to an additional environmental challenge.

Considering this, and that no functional changes in the kidney were seen in another 90-day rat toxicology study, and that no kidney weight changes were noted at the low doses in any of the studies, APERC's conclusion is that the kidney effects seen in male rats, in the Chapin, 1999 study, and the pNP dataset more broadly, are not adverse as defined in the SONARs for HRLs (2008, 2023).[18, 19]

In summary, it is important to keep in mind that all renal effects in young male rats in Chapin, 1999 were reported as slight to mild. [20]. Slight to mild histopathological findings related to

[18] Cunny. (1997).
[19] Chapin. (1999).
[20] Chapin. (1999).

kidney lesions in rats, which are generally viewed to have no pathologic significance, do not meet the level of "adverse" as defined in the SONARs for HRLs. [21, 22]

1.2.2 Renal mineralization in the Chapin, 1999 study was not accompanied by any other dose-related renal changes in the F2 male group, which was the group used by MDH to derive the POD for pNP.

In its response to APERC's comments on the subchronic and chronic HRLs for pNP, MDH justified its selection of renal mineralization as adverse because it "*might* be associated with renal degeneration" and "mineralization observed at the lowest dose *may* be a marker of more severe effects and *may* also be considered adverse."[23]

Table 1 shows the histopathology finding in the kidneys from male rats in the Chapin, 1999. All four generations of animals and the corresponding dose levels (ppm pNP in the diet) are presented. Although mineralization was present in males in all generations at the lowest dose, it was not accompanied by any other dose-related changes renal changes in the F2 male group, which was used in the BMDL modeling by MDH.

Table 1 Renal Effects in Generations of Male Rats (n=10, Table shows number of animals affected)

	F0				F1				F2				F3			
ppm	0	200	650	2000	0	200	650	2000	0	200	650	2000	0	200	650	2000
Renal Tubular Mineralization	0	3	3	4	1	4	7	7	0	5	9	10	0	4	9	6
Renal Tubular Casts	0	0	0	0	0	0	3	4	0	0	3	4	0	0	0	0
Renal Tubular Hydronephrosis	0	0	0	0	1	1	3	6	0	0	0	0	0	0	3	4
Renal Tubular Dilatation	0	0	0	0	0	0	0	0	1	2	1	7	1	5	10	8
Renal Tubular Cysts	0	0	0	0	0	0	0	0	1	2	1	5	1	4	10	8

No dose-related increase vs. controls
Dose-related increase vs. controls
Apparent increase vs. controls with problemmatic dose-response

1.3 MDH derived a POD for pNP based on an unreasonable interpretation of kidney mineralization in Chapin, 1999 as an adverse effect, this point-of-view is inconsistent with other governmental assessments of the same effect in the same study.

MDH has interpreted as "adverse" renal mineralization, a phenomenon that is widely recognized as common in rats. Background on this point was provided above and in APERC's previous comments.

[21] MDH. (2008, July 11).
[22] MDH. (2023, January 26).
[23] MDH. (2023, March 31)

Minnesota Statutes, section 144.0751, subdivision a, requires MDH to use "scientifically acceptable, peer-reviewed information" in deriving HRLs. Peer review ensures that the design and performance of the study meet scientific and technical standards and allows for a thorough critique of the study. The statute recognizes that governmental agencies also assemble and critically evaluate studies for the purpose of deriving a toxicity value such as a reference dose or slope factor. Once a governmental agency has derived a toxicity value from available data, the value is subject to review and constructive criticism by the scientific and risk assessment communities.

While APERC recognizes and respects the fact that MDH is not required to come to the same conclusions as other agencies, it is notable that five other authorities did not view the kidney effects in MDH's key study by NTP, 1997\Chapin, 1999 as adverse, especially at low doses. This was summarized in section 2.0 of the comments submitted by APERC on March 8th. The authorities cited were: US EPA (2009), US Dept of Agriculture, Forest Service (2003), Demark (2000), Environment and Health Canada (2001), and the European Chemicals Agency (ECHA), (2014). [24, 25, 26, 27,28]

In APERC's view MDH's conclusions regarding the kidney effects in rats diverges from the other authorities due to its unreasonable and singular misinterpretation of what signifies "adverse" in rat kidney studies.

> 1.4 It is APERC's view that MDH has not provided a reasonable justification for its interpretation of kidney mineralization as an "adverse" effect; MDH's conclusions regarding kidney mineralization are inconsistent with scientific guidance on the relevance of the mineralization in rats as well as the findings in the cited source study, and are not consistent with the SONAR definition of "adverse".

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[24] U.S. Environmental Protection Agency (US EPA), (2009, September) Screening Level Hazard Characterization Document: Alkylphenols Category. Developed under the High Production Volume Chemical Challenge. Link to Alkylphenols Summary Document

[25] Bakke, D. USDA Forest Service (2003, May). Human and Ecological Risk Assessment of Nonylphenol Polyethoxylate-based (NPE) Surfactants in Forest Service Herbicide Applications. https://www.fs.usda.gov/Internet/FSE_DOCUMENTS/stelprdb5346866.pdf Accessed March 2023

[26] Environment Canada and Health Canada (EC and HC). (2001). Priority substances list assessment report for nonylphenol and its ethoxylates. ISBN: 0-662-29248-0. http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/nonylphenol/index-eng.php

[27] Canadian Council of the Ministers of the Environment (CCME) (2002) Canadian water quality guidelines for the Protection of Aquatic Life. Nonylphenol and its ethoxylates. https://ccme.ca/en/res/nonylphenol-and-its-ethoxylates-canadian-sediment-quality-guidelines-for-the-protection-ofaquatic-life-en.pdf Accessed March 2023

[28] European Chemicals Agency (ECHA) Committee for Risk Assessment (RAC) and Committee for Socioeconomic Analysis (SEAC). (2014, May 14), Background document to the Opinion on the Annex XV dossier proposing restrictions on Nonylphenol Ethoxylate. ECHA/RAC/ RES-O-0000005317-74-01/F 2014; Available from: https://www.echa.europa.eu/documents/10162/92b9634c-8d8e-4866-b9fe-11892e1fdc3

MDH has not demonstrated reasonableness for its reliance on an end point (kidney mineralization effects in male rats) as adverse for the selection of a Critical Effect for pNP. There is scientific consensus that rats are prone to have a high rate of these spontaneous kidney lesions. This was addressed in the presentation that Dr. Osimitz provided to MDH on Dec. 15, 2022. Furthermore, MDH has stretched the definition of "adverse" beyond what is defined in the SONAR guidance for deriving HRLs.

It is APERC's view that MDH did not provide a reasonable interpretation of "adverse" regarding renal mineralization in rats as it is inconsistent with scientific guidance on the relevance of the mineralization findings for pNP in rats, is inconsistent with the findings in the cited source study, and is not consistent with the SONAR definition of "adverse". [29, 30] SONAR defines "adverse effect" as "a biochemical change, functional impairment, or pathologic lesion that *affects* the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge." It does not say that effects that "*might* be associated" with another effect or "*may* be considered a marker" are adverse.

2.0 APERC Recommended Revisions to pNP subchronic and chronic, POD, RFDs and HRLs.

It is APERC's view that renal mineralization in male rats as seen in the Chapin, 1999 study does not meet the definition of an "adverse effect" as defined under in the SONARs for HRLs and it is therefore unreasonable to use this endpoint as the POD in calculating the subchronic and chronic HRLs for pNP. Rather, APERC recommends that MDH use the No Observable Adverse Effect Level (NOAEL) for acceleration of vaginal opening in female rats from the same study as the Critical Effect and POD in calculating the subchronic and chronic HRLs for pNP. Acceleration of vaginal opening is recognized as an adverse effect, a clear NOAEL is available for this endpoint in the Chapin, 1999 study and five other governmental authorities have selected this effect from the same study as the Critical Effect or POD for risk assessments.

TABLE 2: APERC Recommended Revisions to pNP Subchronic and Chronic RfDs and HRLs based on NOAEL for acceleration of vaginal opening in female rats in Chapin, 1999.

Recommended Reference Doses
Reference Dose/Concentration = HED/Total Uncertainty Factor (UF)

	Subchronic	**Chronic**
POD (mg/kg) (developmental\reproductive)	13	13
Dose Adjustment Factor (DAF)	0.25	0.25

[29] MDH. (2008, July 11).
[30] MDH. (2023, January 16).

Human Equivalent Dose (HED): POD x DAF (mg/kg)	**3.25**	**3.25**
Interspecies UF (TD)	3	3
Intraspecies UF	10	10
Subchronic to Chronic		3
Total uncertainty factor (UF)	**30**	**100**
Reference Dose (mg/kg)	0.108	0.0325

Recommended Health Based Values

Health Based Value = (Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor) (Subchronic Intake Rate, L/kg-d)

	Subchronic	**Chronic**
Reference Dose (mg/kg/day)	0.108	0.0325
Relative Source Contribution	0.2	0.2
Conversion Factor (1000 µg/mg)	1000	1000
Intake rate - L/kg/day	0.074	0.045
Health Based Value (µg/L)	**293**	**144**

Recognizing that MDL has discretion to use a Benchmark Dose (BMD) approach rather than a NOAEL to derive a POD for derivation of HRLs, APERC ran US EPA's BMD software (ver. 3.3.0) for the accelerated vaginal opening endpoint results seen in Chapin, 1999. [31] The LogProbit model was recommended as the best fitting model in the BMD output, since it had the lowest AIC [32] value of all of the models. The LogProbit gave a BMDL result of 224.468 ppm, which is equivalent to approximately 16 mg/kg-d. This modeled POD is slightly higher than the NOAEL of 200 ppm (13 mg/kg-d) pNP and would result in a higher HRL.

[31] U.S. EPA (2023, March 14) Benchmark Dose Software online. Version 3.3.0.. https://www.epa.gov/bmds/bmds-online

[32] The Akaike information Criterion (AIC) is most often used for model selection. By calculating and comparing the AIC scores of several possible models, you can choose the one that is the best fit for the data. The EPA states that "The model with the lowest AIC may be used to calculate the BMDL for the Point of Departure for risk assessment. This criterion is intended to help arrive at a single BMDL value in an objective, reproducible manner."