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Submitted via email: Health.Risk@state.mn.us

Subject: Comments on Minnesota Department of Health Proposed Health Risk Limits for *p*-Nonylphenol, branched isomers

Dear Ms. Rice,

The Alkylphenols & Ethoxylates Research Council (APERC) appreciates this opportunity to provide comments on the Minnesota Department of Health's (MDH's) proposed Health Risk Limit (HRL) Rule for *p*-nonylphenol, branched isomers (NP).[1, 2, 3]

APERC is a North American organization whose mission is to promote the safe use of alkylphenols (APs), alkylphenol ethoxylates (APEs), including NP through science-based research and outreach efforts, within the framework of responsible chemical management.[4] For more than thirty years, APERC and its member companies have been actively engaged in the conduct and review of studies on the environmental fate, occurrence and toxicological effects of NP and related compounds. The following comments relate to the proposed HRLs and the supporting data presented in the MDH Toxicological Summaries for NP. [5]

[1] Minnesota Department of Health (MDH) (2022, February 2). Slides from the Health Risk Limits Rules Public Meeting. 2022 Health Risk Limits Rules Amendments Public Meeting slides February 2, 2022
[2] Minnesota Department of Health (MDH). (2021, January) Request for Comments: Health Risk Limits Rules for Groundwater. Health Risk Limits Rules Amendments - Overview and Links - EH: Minnesota Department of Health (state.mn.us)
[3] Minnesota Department of Health (MDH). (2021/2022). Health Risk Limit Proposed Rules Amendments, Revisor's ID Number 4396 Narrative Description Proposed Rules: Health Risk Limits 2021 Minnesota Department of Health (state.mn.us)
[4] APERC member companies include: The Dow Chemical Company, Dover Chemical Corporation, and SI Group, Inc.
[5] Minnesota Department of Health (MDH). (2020, September). Toxicological Summary for p-Nonylphenol, branched isomers, CAS 84852-15-3. p-Nonylphenol Toxicological Summary Minnesota Department of Health September 2020 (state.mn.us)

In short, MDH selected an incorrect Point of Departure (POD) for the NP HRLs for subchronic non-cancer and chronic non-cancer effects and did not consider the weight-of-evidence and the perspective gained from consideration of other follow-up rat studies that further evaluated the renal effects that were the basis for the POD selected. For the reasons discussed below, a POD of 13 mg/kg-bw/day for NP based on the weight-of-evidence available for renal and other sensitive endpoints this compound should be used to derive HRLs for subchronic non-cancer and chronic non-cancer effects for NP. [6]

Comments on Proposed HRLs for NP

The MDH Toxicological Summary for NP indicates that MN DOH calculated a subchronic non-cancer Health Based Values ($nHBV_{subchronic}$ = 40µg/L) and a chronic non-cancer HBV (nHBV chronic = 20µg/L) for NP based a POD of 1.94 mg/kg-d (administered dose $BMDL_{10}$) from an effect (renal mineralization in male rats) that was not considered adverse and/or was not replicated in other relevant studies and is inconsistent with No Observed Adverse Effect Levels (NOAELs) selected in other governmental and peer-reviewed human risk assessments for NP.

1.0 The NOAEL for renal effects in rats in the study conducted by the National Toxicology Program (NTP, 1997\Chapin et al., 1999) should be 200 ppm (approximately 13 mg/kg-bw/day).

MDH selected renal mineralization seen in a three-generation study with male rats conducted by the National Toxicology Program (NTP) in 1997 and published by Chapin *et al,* 1999 as the POD for subchronic non-cancer and chronic non-cancer HBV for NP. [7, 8] However, since NTP, 1997\Chapin *et a*l., 1999 did not report a NOAEL for this effect, the MDH conducted a Benchmark Dose evaluation ($BMDL_{10}$) to calculate a POD of 1.94 mg/kg-day. While APERC generally agrees with the use of benchmark doses when starting with a Lowest Observed Adverse Effect Level (LOAEL), rather than a NOAEL, we disagree with the selection of the low dose from NTP, 1997\Chapin, *et al*. 1999 as an adverse effect.

The NTP, 1997\Chapin, *et al*. 1999 study described renal effects at all doses, however convincing dose-response relationships were not always evident for these effects. Moreover, at the lowest dose, the effects seen can be considered non-adverse due to being minimal in severity without accompanying inflammation or significant changes in kidney weights or body

[6] Osimitz, T.G., Droege, W. and Driver, J.H. (2015): Human Risk Assessment for Nonylphenol, *Human and Ecological Risk Assessment*. . 21:1903-1919
[7] 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
[8] 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

weights. Thus, the NOAEL for this effect in this study should be considered to be 200 ppm (approximately 13 mg/kg-bw/day).

The Canadian government's 2001 risk assessment of NP also considered the relevance of kidney effects see in Chapin *et al.*, 1999 in its selection of a NOAEL. [9] The Canadian assessment notes that "although secondary sources were used to identify many of the available data, the original reports for toxicological studies (except for acute toxicity and genotoxicity) identified in the reviews were acquired in order to confirm results." [10] Following is the Canadian assessment of the renal effects seen in Chapin *et al.*, 1999 and its conclusion regarding NOAEL selection for screening assessment:

> "The renal lesions identified in the [Chapin *et al*] multigeneration study were described as being of minimal to mild severity, even at the higher dose levels, and were interpreted by the authors as a slight acceleration of the tubular nephropathy normally seen in this strain of rats (Chapin *et al* 1999). There was also no effect on serum urea nitrogen or creatinine at this dose in the subchronic study (Cunny *et al* 1997), suggesting that renal function was not affected (though urinalysis was not conducted in any study, and plasma urea concentration is not a sensitive marker of nephropathy). Based on these considerations, it seems likely that the LOEL of 12 mg/kg-bw per day is close to a No-Observed-Adverse-Effect-Level (NOAEL) for effects on the kidney, and, therefore, this effect level is considered appropriate for use in determining the margin of exposure in the screening assessment" [11, 12]

2.0 In other similar rat studies with NP, including a study designed to confirm and extend the findings of Cunny *et al.*, 1997 and Chapin *et al.*, 1999 for adult male kidney toxicity resulting from continued exposure to NP over multiple generations, kidney effects were either not observed, or were observed with a NOAEL approximately 13 mg/kg-bw/day.

The compound-related kidney effects observed in the NTP, 1997\Chapin *et al*,1999 study were not observed in a subchronic study in the same strain of rats administered the same dose levels of NP in the diet and similar exposure duration (90 days in Cunny *et al*., 1997 and 105 days in F0 in

[9] Environment Canada and Health Canada (EC and HC). (2001). Priority substances list assessment report for nonylphenol and its ethoxylates. ISBN: 0-662-29248-0
[10] EC and HC. (2001)
[11] EC and HC. (2001)
[12] 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.

Chapin et al., 1999). [13, 14] Moreover, another multigeneration study by Nagao *et al*. (2001) reported no kidney effects at similar doses (the midrange dose was 10 mg/kg/day) as used in Chapin *et al*. (1999).[15]

Finally, a 3-generation rat study by Tyl *et al.*, 2006 was designed to define a NOAEL for the kidney toxicity identified in the Chapin *et al*., 1999 and Cunny *et al.*, 1997, as well as for potential reproductive toxicity, resulting from continued exposure to NP over multiple generations.[16] This study also examined the influence of diet on kidney and reproductive effects. Tyl *et al*., 2006 "verified renal toxicity in F0 adult males at 650 and 2000 ppm (Cunny *et al*., 1997) and in F1 and F2 adult male offspring at these dietary concentrations (Chapin *et al*., 1999) but not the limited effects observed in some animals at 200 ppm in the Chapin *et al*., study". Although increased absolute and relative kidney weights were observed in F1 males at 200 ppm NP, they were "not associated with increased incidence of the two microscopic findings (medullary cysts and mineralization at the cortico-medullary junction) and there were no renal effects (organ weights or histopathology) in F0 or F2 males at 200 ppm NP".[17] In this study, the NOAEL for adult male renal toxicity, based on absence of histopathology at 200 ppm NP, was 200 ppm NP (~ 15 mg/kg/day) in the diet.[18] Tyl *et al.*, 2006 also demonstrated a lack of transgenerational effects (effects in the second generation that did not occur in the first) on epididymal sperm counts or on any other reproductive endpoints and confirms the conclusions of Chapin *et al*., 1999 and Nagao *et al*., 2001 that NP is not a selective reproductive toxicant with a reproductive toxicity NOAEL of > 2000 ppm (>~ 150 mg/kg/day) in the diet.

3.0 A human risk assessment for NP published by Osimitz *et al.*, 2015 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.[19]

Osimitz *et al.*, 2015 conducted a risk assessment for human exposure to NP.[20] These authors reviewed the available toxicological data for NP, including all of the studies summarized above, and identified the acceleration of vaginal opening in females (Chapin *et al*., 1999), and

[13] Cunny, H.C. *et al.*, (1997)
[14] Chapin, R.E. *et al*., (1999)
[15] Nagao, T., Wada, K., Marumo, H., Yoshimura, S., & Ono, H. 2001. Reproductive effects of nonylphenol in rats after gavage administration: A two-generation study. *Reproductive Toxicology*, 15 (3), 293-315
[16] 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
[17] Tyl, R.W. *et a*l., (2006)
[18] Tyl, R.W. *et al*., (2006)
[19] Osimitz, T.G *et al*., (2015)
[20] Osimitz, T.G *et al*., (2015)

toxicologically significant changes in the kidney from males (Chapin *et al*., 1999; Nagao *et al.*, 2001; Tyl *et al*., 2006), both of which occurred at doses of >200 ppm (~13 mg/kg bw/day) as the most conservative value for use in risk assessment. [21,22, 23, 24]

Based on the weight-of-evidence discussed above and summarized in Osimitz *et al.*, 2015, a POD of 13 mg/kg-bw/day for NP should be used to derive the MDH HRLs for subchronic non-cancer and chronic non-cancer effects for NP.[25]

It is also relevant to note that Osimitz *et al.*, 2015 conducted critical reviews of two categories of exposure data: environmental monitoring and biomonitoring from exposed individuals. Environmental monitoring data included the measurement of NP in food, water, air, and dust. From these data and estimates of human intake rates for the sources and exposures were estimated from each source and source-specific Margins of Exposure (MOEs) calculated. Aggregate exposure to NP was also derived from human biomonitoring studies. The MOEs were all greater than 1000 for drinking water (ranging from 2.7×10^3 to 8.125×10^{10}) and in aggregate based on biomonitoring (ranging from 2.863×10^3 to 8.4×10^7) indicating reasonable certainty of no harm.

Respectfully,

Barbara S. Losey

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Executive Director

[21] Osimitz, T.G *et al*., (2015)
[22] Chapin, R.E. *et al*., (1999)
[23] Nagao, T. *et al*., (2001)
[24] Tyl, R.W. *et al*., (2006)
[25] Osimitz, T.G *et al*., (2015)