38941 Minnesota Department of Health Notice of Hearing (Initial Comment Period)

Closed Mar 08, 2023 · Discussion · 5 Participants · 1 Topics · 6 Answers · 0 Replies · 1 Votes

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“Other programs within MDH or other agencies may independently adopt these health-based values and incorporate them within enforceable requirements related to permitting or remediation activities.” SONAR p. 81-82.

MHD argues that no law tells it how to enforce HRL rules so it has no enforcement responsibility. But the law tells the commissioner to enforce standards. In this case, the standards the commissioner must enforce are HRLs that have been adopted into rule and new proposed HRLs once they have been adopted in this rulemaking. Minn. Stat. 144.0751 Health Standards does not provide for any exceptions that would give the commissioner discretion. Nor does the law give the commissioner the authority to tell other state agencies and others responsible for safe drinking water that they don’t have to follow rules that have the force and effect of law.

The OAH must determine, whether, given MDH’s stated intention to not enforce rules, this rulemaking should proceed.

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(1). https://www.ewg.org/interactive-maps/2020_nitrate_in_minnesota_drinking_water_from_groundwater_sources/
(2) https://minnesotareformer.com/2023/01/17/agriculture-pollutes-underground-drinking-water-in-minnesota-well-owners-pay-the-price/
(3) https://www.pca.state.mn.us/sites/default/files/wq-rule4-24c3.pdf

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Jean Wagenius · Citizen · (Postal Code: unknown) · Mar 06, 2023 7:35 pm
0 Votes

The comments that I submitted on March 4 need a correction. With the obvious exception of MDH, state agencies and others referred to in the SONAR that are not providing drinking water are not required to use or enforce HRLs. Other state agencies may adopt HRLs by reference but are not required to.

Steve Risotto · Citizen · (Postal Code: unknown) · Mar 08, 2023 2:22 pm
0 Votes

The comments of the American Chemistry Council on the proposed amendments to the rules governing health risk limits for groundwater are attached.

Barbara Losey · Citizen · (Postal Code: unknown) · Mar 08, 2023 2:25 pm
0 Votes

The Alkylphenols & Ethoxylates Research Council opposes the subchronic and chronic noncancer Health Risk Limits (HRL) for p-Nonylphenol (pNP) currently proposed under Ch. 4717.7860 Subpart 13a for the reasons explained in the attached comments.

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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
Initial Comment Period (Discussion 38941)

March 8, 2023

The Alkylphenols & Ethoxylates Research Council (APERC) submits these comments to oppose the Health Risk Lists (HRLs) proposed for p-Nonylphenol (4-Nonylphenol), CAS number 84852-15-3 under Ch. 4717.7860 Subp. 13a.

APERC is a North American organization whose mission is to promote the safe use of alkylphenols (APs), including p-Nonylphenol (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 NP and related compounds. The following comments relate to the proposed HRLs in the Proposed Rule under Ch. 4717.7860 Subp. 13a and the supporting data presented in the Minnesota Department of Health (MDH) Toxicological Summaries for pNP. [2, 3]

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 Point of Departure (POD) of 1.94 mg/kg-d (administered dose $BMDL_{10}$) from an effect (renal mineralization in male rats) that is not considered adverse, was not replicated in other high-quality and relevant studies and is inconsistent with No Observed Adverse Effect Levels (NOAELs) for kidney effects selected in other governmental and peer-reviewed human risk assessments for NP.

In short, MDH selected an incorrect POD and Critical Effect (CE) to calculate the pNP 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 high-quality follow-up rat

[1] APERC member companies include: The Dow Chemical Company, Dover Chemical Corporation, and SI Group, Inc.
[2] Minnesota Department of Health (MDH). (Nov. 1, 2022). Proposed Permanent Rules Relating to Health Risk Limits for Groundwater Standards Ch 4717.7860
[3] 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)

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 pNP based on the weight-of-evidence available for renal and other sensitive endpoints this compound should be used to derive revised subchronic non-cancer and chronic non-cancer RfDs and HRLs for pNP as shown in Table 1 below.

TABLE 1: APERC Recommended Revisions to pNP Subchronic and Chronic RfDs and HRLs

Recommended Reference Doses

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

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

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**

1.0 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 selected a POD for pNP from a study conducted by the National Toxicology Program in 1997 and published by Chapin et al, 1999 for the calculation of HRLs for pNP. [4] [,5] In a response to comments previously submitted by APERC to MDH the Department stated "A subsequent 3-generation study by Tyl supports possible kidney effects at lower doses, however, the study is incomplete and cannot be used to assess a POD."[6] However, no reasoning is provided to support the statement that Tyl et al, 2006 is incomplete.

Attachment I to these comments is a presentation that APERC provided to MDH on December 15, 2022.[7] The slides include a review of the three pivotal studies that address kidney effects of pNP in rats and their relevance to each other: NTP, 1997\Chapin, 1999, Cunny et al., 1997 and Tyl et al, 2006. [8] [, 9, 10, 11]The Tyl et al, 2006 study was conducted to reexamine the conflicting kidney findings seen in the two previous studies and to examine the effect of diet on mineralization in the kidney.

APERC is not aware of any authority that views the Tyl et al, 2006 study as "incomplete" or in any way deficient

MDH points out that the Chapin, 1997 study "is a thorough study performed by a highly reputable group."[12] APERC recognizes and respects the reputation of Dr. Chapin, formerly at the NTP, and the research of his group and we are not questioning the conduct of that study.

Similarly, APERC also recognizes and respects the reputation of Dr. Tyl who has over 100 peer-reviewed publications in developmental and reproductive toxicology over her 40+ year career. Prior to her retirement, she was director of the program in developmental and reproductive toxicology (DART) and a Senior RTI Fellow in DART at RTI International. She was Past President of the Society of Teratology and the Society of Toxicology's Reproductive and Developmental Toxicology Specialty Section.

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[4] 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
[5] 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
[6] Johnson, S.F. (2023, Jan. 3). MDH Response to APERC Regarding Nonylphenol Comments
[7] Osimitz, T.G. (2022, December 15). Nonylphenol – Critical Effect, Presentation to Minnesota Department of Health
[8] NTP. (1997).
[9] NTP. (1997).
[10] 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.
[11] 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
[12] Johnson, S.F. (2023, Jan. 4).

While the reputation of the researchers is one consideration, the question more relevant to selection of POD from a number of available studies relates to study quality and relevance within the context of the weight-of-evidence.

The Tyl et al, 2006 study was conducted by a reputable researcher in accord with EPA test guideline for reproduction and fertility effects. [13] The authors note, some endpoints required to meet full guideline compliance (e.g., vaginal patency determinations in pNP-treated animals) were not conducted because previous studies adequately defined the effects and doses for these responses. However, the study also exceeded the guideline requirements by conducting histopathology on the kidney, and including a third generation. In addition, all facets of the study were conducted in compliance with EPA Toxic Substances Control Act, Good Laboratory Practice Standards. [14] [U.S. EPA, 1989]

APERC questions MDH's statement that the Tyl et al, 2006 study is incomplete, particularly with regard to the examination of kidney effects in rats. We are also questioning MDH's focus on the Chapin et al, 1999 study in light of the weight-of-evidence on kidney histopathology and effects provided by other high-quality studies, including Tyl et al, 2006. Tyl et al, 2006 and Cunny et al, 1997 did not replicate the findings of kidney mineralization at the lowest doses in Chapin et al, 1999. 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]

Based on the absence of histopathological findings, a NOAEL of 200 ppm (15 mg/kg/d) was derived for kidney effects in Tyl et al, 2006. At higher concentrations this study verified renal toxicity in F0, F1, and F2 adult male (650 and 2000 ppm) resulting in a LOAEL of 650 ppm (approx. 50 mg/kg/d in males).[16] 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).[17]

Considering factors such as study quality and reproducibility APERC views the Tyl et al, 2006 study as most suitable to identify a CE and POD for pNP.

2.0 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).

[13] U.S. Environmental Protection Agency (U.S. EPA).(1998). Office of Prevention, Pesticides, and Toxic Substances (OPPTS), Health Effects Test Guidelines, OPPTS 870.3800, Reproduction and Fertility Effects
[14] U.S. Environmental Protection Agency (U.S. EPA) (1989). Toxic Substances Control Act, EPA (TSCA); Good Laboratory Practice Standards; Final Rule. Fed. Regist. 54, 34034–34050
[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 et al, 2006
[17] Nagao, T., et al (2001) .

MDH selected renal mineralization seen in the three-generation study with male rats conducted by the NTP in 1997 and published by Chapin *et al*, in 1999 as the POD for subchronic non-cancer and chronic non-cancer HBV for NP. [18, 19] 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 for pNP. 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 weights. *This is discussed more completely in section3.0 of these comments below*.

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

3.0 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.

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 NTP, 1997\Chapin et al, 1999 rat study should not be considered an adverse effect and should not serve as the critical effect from which to calculate a POD for HRLs.

We have extracted some relevant excerpts of pertinent publications below that address the prevalence of renal mineralization in the rat.

3.1 Seely et al. (2018) in Boorman's Pathology of the Rat (2nd Edition) summarizes the topic well:

"Renal mineralization is usually seen in female rats fed a semisynthetic diet but is also seen with regular laboratory feed. Imbalances of calcium, phosphorus (excessive phosphorus in the diet), chloride, magnesium, protein, and lipid have been incriminated or been shown to cause renal mineralization. The severity of mineralization is both sex and strain dependent; ovariectomy prevents renal mineralization, whereas gonadectomized males and females receiving estradiol benzoate develop renal

[18] Chapin, R.E., et al (1999).
[19] NTP. (1997).

mineralization quickly. Mineralization may be observed with other forms of renal disease including hyaline droplet nephropathy, dystrophic calcification, and end-stage CPN disease.

Mineralization can occur in any segment of the nephron but is most commonly seen at the junction of the outer and inner stripes of outer medulla in female rats *(this is the location of the effect in the nonyl phenol studies)*, where it is associated with an imbalance of the Ca 21 /PO4 ratio in diet. On rare occasions, chemical treatment can exacerbate this change in female rats and/or induce it in male rats. Mineralization is occasionally seen in the cortical proximal tubules in accompaniment with chemically induced tubule necrosis." [20]

3.2 The citation below from the National Toxicology Program, Neoplastic Lesion Atlas, provides additional perspective:

"Mineralization is commonly observed in the area of the outer stripe and inner stripe of the outer medulla." *(This is the location of the effect seen with nonylphenol.)*

"Comment: Mineralization is more commonly associated with spontaneous and minute background findings of basophilic deposits in the renal cortex, medulla, or papilla of rats and mice. In general, these deposits have no pathologic significance. However, mineralization may also be seen as a consequence to degeneration and necrosis. "[21]

"Recommendation: Mineralization should be diagnosed and graded. If small deposits of focal mineralization are recognized as a spontaneous background finding, they need not be diagnosed and the pathologist should use his or her judgment in deciding whether or not they are prominent enough to warrant diagnosis. When diagnosed, the pattern of the mineralization (e.g., linear papillary mineralization, focal medullary mineralization) should be described in the pathology narrative."[22]

Note: no evidence of renal necrosis is present in the nonylphenol studies.

3.3 Frazier et al. (2012) in their comprehensive article "Proliferative and Nonproliferative Lesions of the Rat and Mouse Urinary System" likewise describe the features of the mineralization:

"Mineralization: Medullary Collecting Ducts; Corticomedullary Junction; Proximal or Distal Tubules, Renal Pelvis.

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[20] Seely, J.C., G.C. Hard, and B. Blankenship, *Chapter 11 - Kidney*, in *Boorman's Pathology of the Rat (Second Edition)*, A.W. Suttie, Editor. 2018, Academic Press: Boston. p. 125-166

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

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

Species: rat, mouse Synonyms: calcification, nephrocalcinosis, multilamellar bodies
Pathogenesis/cell of origin

• Can occur either as dystrophic calcification specifically in the renal tubules and collecting ducts or as metastatic calcification as a result of systemic calcium/phosphorus imbalance
• Both types are common and occur spontaneously in laboratory animals or as a consequence of drug treatment
• Occur with dietary imbalance of calcium/phosphorus ratio, particularly in female rats; this can include calcium or Vitamin D administration, oxalates, parathyroid hormone-like hormones compounds or with drugs which modify urinary pH, as well as many other types of drugs and agents (Ritskes-Hoitinga and Beynen 1992)
• Typically composed of calcium (and much less commonly magnesium) salts, phosphorus, and glycoprotein
• One common spontaneous form of mineralization is thought to be derived from shedding of microvilli and microvesicles from S1 proximal tubules and accumulation in the outer stripe of the medulla where this debris subsequently undergoes mineralization (Nguyen and Woodard 1980)
• May be visible macroscopically as white stippling on cut surface or microscopically as densely basophilic granular deposits
• In rats, there can be a much higher prevalence of mineralization in the outer stripe of the outer medulla in females due to a dietary imbalance of calcium:phosphorus ratio and incidence and severity increase with age (Clapp, Wade, and Samuels 1982; Ritskes-Hoitinga and Beynen 1992)" [23]

3.4 Lord and Newberne (1990) Renal Mineralization- a ubiquitous lesion in chronic rat studies also addresses this issue.

"Renal mineralization occurs more frequently in rats than in any other species, and females appear to be more susceptible to cortico-medullary mineralization than males (Cousins and Geary, 1966; Feron et al., 1975)." [24]

"One manifestation of altered mineral metabolism is an increase in urinary calcium excretion and the development of renal mineralization. Some of the factors that may predispose to altered mineral metabolism include changes in the microbial population, changes in the levels and profiles of enzymes present in the gut, changes in intestinal pH and urinary electrolyte balance, alterations in water transport and an improper Ca/P ratio in the diet."[25]

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[23] Frazier, K.S., et al.,(2012), *Proliferative and nonproliferative lesions of the rat and mouse urinary system.* Toxicol Pathol, **40**(4 Suppl): p. 14s-86s

[24] Lord, G.H. and P.M. Newberne,(1990). *Renal mineralization--a ubiquitous lesion in chronic rat studies.* Food Chem Toxicol, **28**(6): p. 449-55.

[25] Lord, G.H. and P.M. Newberne, (1990).

3.5 Mineralization seen in the rat kidney at the lowest dose in the NTP, 1997\Chapin et al, 1999 rat study should not be considered an adverse effect and should not serve as the effect from which a POD for HRLs are calculated.

Determining whether an observation in a toxicology study represents an adverse or not adverse effect is one of the most important considerations when establishing a POD for risk assessment or to set regulatory limits. This is particularly difficult in cases of organs such as the kidney where many attributes can be assessed in a single study. Perhaps the most successful attempt at organizing an approach of looking at determining the adversity of an effect was reported by Lewis at al. (2002).[26] Criteria are used to differentiate a non-adverse effect of a treatment from an adverse effect. We applied this framework to the question of mineralization observed in the rat kidney. Lewis et al. detail several discriminating factors. We list those below and comment (in italics) with respect to the mineralization observed in the rat kidney.

An effect is less likely to be adverse if:

1. There is no alteration in the general function of the test organism or of the organ/tissue affected – *Other than mineralization, no other evidence of kidney toxicity is evident at the lower doses in the relevant studies.*
2. It is an adaptive response – *No data to suggest this*
3. It is transient – *No data to suggest this.*
4. The severity is limited, below thresholds of concern – *The effects were at a low incidence at the low dose and of low severity (the highest having a score of 1 or 2 out of 4 in Chapin et al, as reported by Hard).*
5. The effect is isolated or independent. Changes in other parameters usually associated with the effect of concern are not observed – *True with nonylphenol.*
6. The effect is not a precursor. The effect is not part of a continuum of changes known to progress with time to an established adverse effect – *True with nonylphenol.*
7. It is secondary to other adverse effect (s) - *No data to suggest this*
8. It is a consequence of the experimental model – *True with nonylphenol. Below we cite numerous studies indicating the rat-specific nature of this effect and its lack of relevance to humans.*

In conclusion, a close consideration of the above criteria leads us to conclude that the isolated effect of mineralization in the kidney should not be considered an adverse effect and should not serve as the effect from which a POD for pNP is established to derived HRLs.

3.6 Mineralization seen at the low dose in the NTP, 1997\Chapin et al, 1999, which occurred in isolation from other true adverse effects to the kidneys, should not be viewed as a treatment-related adverse effect and should not serve as the POD or CE for development of HRLs for pNP.

[26] Lewis, R.W., et al., (2002).*Recognition of adverse and nonadverse effects in toxicity studies.* Toxicol Pathol, **30**(1): p. 66-74

The rat kidney is prone to various spontaneous renal effects, some of which have no definitive cause. In some cases, drugs have been shown to induce them. Diet is a common cause. Since the mineralization seen at the lowest dose of the NTP, 1997\Chapin et al, 1999 study, was seen in isolation from other true toxic effects, the mineralization in the pNP studies should not be viewed as treatment-related adverse effects and thus it should not serve as the effect from which a POD or CE is selected for risk assessment or derivation of HRLs.

4.0 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.

4.1 Denmark

The Danish government (Nielsen et al, 2000) concluded a "LOEL for repeated exposure of 15 mg/kd-day pNP and noted "since renal tubular degeneration and/or dilation are common findings in untreated rats, and as they were not accompanied by other related signs or symptoms in the affected rats, they are not considered signs of severe toxicity by the rapporteur." [27]

4.2 U.S. Environmental Protection Agency (U.S. EPA)

U.S. EPA (2009, Sept) concluded "A treatment-related increase in the incidence of renal tubular degeneration/dilation was seen in the 2000 ppm females from the F1, F2, and F3 generations and in the 200 and 650 ppm females in the F3 generation" and specifically did not include mineralization seen in the lowest dose in the critical effect determination. [28]

4.3 U.S. Department of Agriculture, Forest Service

A U.S. Forest Service assessment in 2003concluded "The decision by Environment Canada (2001) to utilize the 12 mg/kg/day figure as a NOAEL is further reinforced by the results of Nagao et al 2001 and a recent study by Latendresse et al 2001, in which kidney effects (polycystic kidney disease) were seen in Sprague Dawley rats fed NP at doses at or above 1,000 ppm in soy- free feed. Latendresse et al determined a NOAEL for this kidney effect at 500 ppm, which is similar to what was determined in Cunny et al 1997 (a NOEL of 650 ppm based on kidney effects). An interesting side note to Latendresse et al 2001 is that it appeared that the soy-

[27]Nielsen, E. et al (2000). Toxicological Evaluation and Limit Values for Nonylphenol, Nonylphenol Ethoxylates, Tricresyl, Phosphates and Benzoic Acid. The Institute of Food Safety and Toxicology. Report No. 512
[28] 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

free diet exacerbated the kidney effects, and the authors surmise that soy in the diet could act to ameliorate these effects."[29]

4.4 Canada

Environment Canada and Health Canada (2001) concluded "The renal lesions identified in the [Chapin et al., 1999] 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. 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…" [30]

Another assessment in Canada conducted by the provincial ministers in 2002 to develop Environmental Quality Guidelines also did not consider mineralization in the rat kidney in the critical effect determination for human health. [31]

4.5 European Chemicals Agency (ECHA)

An assessment of the NTP, 1997\Chapin, 1999 study by the European Chemicals Agency (ECHA, 2014) concluded "Although increased absolute and relative kidney weights were observed in F1 males at 200 ppm NP (Purina 5002), 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 the lowest concentration (200 ppm) NP. Based on the absence of histopathological findings at this concentration a NOAEL of 200 ppm (15 mg/kg/d) was derived. At higher concentrations this study verified renal toxicity in F0, F1, and F2 adult male (650 and 2000 ppm) resulting in a LOAEL of 650 ppm (approx. 50 mg/kg/d in males)." [32]

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[29] 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

[30] 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

[31] 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-of-aquatic-life-en.pdf Accessed March 2023

[32] European Chemicals Agency (ECHA) Committee for Risk Assessment (RAC) and Committee for Socio-economic 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-11892e1fdc39

5.0 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.

It is important to consider whether the observations of mineralization such as seen in some of the pNP studies, are relevant to, or predictive of, such effects in humans. Mineralization, often resulting in kidney stones in humans, has been well studied. The texts cited below discuss the onset and development of such lesions in humans. To the best of our knowledge none of the steps and ultimate outcome described for humans are related to the observations seen in the mineralization in the rat kidney.

5.1 Kidney stones in humans:

> "Kidney stones (calculi) are mineral concretions in the renal calyces and pelvis that are found free or attached to the renal papillae. By contrast, diffuse renal parenchymal calcification is called nephrocalcinosis. Stones that develop in the urinary tract (known as nephrolithiasis or urolithiasis) form when the urine becomes excessively supersaturated with respect to a mineral, leading to crystal formation, growth, aggregation and retention within the kidneys. Globally, approximately 80% of kidney stones are composed of calcium oxalate (CaOx) mixed with calcium phosphate (CaP). Stones composed of uric acid, struvite and cystine are also common and account for approximately 9%, 10% and 1% of stones, respectively3. Urine can also become supersaturated with certain relatively insoluble drugs or their metabolites, leading to crystallization in the renal collecting ducts (iatrogenic stones)."[33]

5.2 From Matlaga et al. (2003):

> "Urinary calculi may be induced by a number of medications used to treat a variety of conditions. These medications may lead to metabolic abnormalities that facilitate the formation of stones. Drugs that induce metabolic calculi include loop diuretics; carbonic anhydrase inhibitors; and laxatives, when abused. Correcting the metabolic abnormality may eliminate or dramatically attenuate stone activity. Urinary calculi can also be induced by medications when the drugs crystallize and become the primary component of the stones. In this case, urinary supersaturation of the agent may promote formation of the calculi. Drugs that induce calculi via this process include magnesium trisilicate; ciprofloxacin; sulfa medications; triamterene; indinavir; and ephedrine, alone or in combination with guaifenesin."[34]

Note: Nonylphenol is chemically distinct from the drugs cited above known to produce kidney stones in humans.

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[33] Khan, S.R., et al., *Kidney stones.* Nat Rev Dis Primers, 2016. **2**: p. 16008.
[34] Matlaga, B.R. et al., (2003). Drug-Induced urinary calculi. *Rev Urol*., 5(4) p.227-31

5.3 Rat models have been developed to mimic the formation of kidney stones in humans. The chemical chosen (ethylene glycol) is metabolized to chemicals such as calcium oxalate.

"Calcium oxalate (CaOx) crystallization and oxidative stress are essential for kidney stone diseases. The kidney stone model in a rat was established by using ethylene glycol to affect the oxalic acid metabolism." [35]

5.4 The formation of kidney stones in humans begins with the formation of mineral deposits along the surface of the renal papillae. In contrast, in rats "Mineralization is commonly observed in the area of the outer stripe and inner stripe of the outer medulla. " (Sherer et al., 2018). This is the case with nonylphenol.

"Regarding the formation of nephrolithiasis[36] has become axiomatic in the study of nephrolithiasis that particle retention must occur prior to stone formation. Randall's plaques (RP), first identified in 1937, are interstitial calcium phosphate deposits near the tips of renal papillae found in ~20% of kidneys. RP act as an anchor of outward growth for most calcium-based stones without involving tubular lumens. Many stones exhibit a concavity matching the contour of the papillary surface. Along the concave portion of isolated stones, a dense protuberance of calcium phosphate (herein referred to as the stone's "stem") was often found that was similar in appearance and composition to that found in the interstitial plaque. Over the ensuing decades, others have subsequently detected calcium phosphate footprints of RP along concavities of calcium-based stones on stems, believed to have formed in response to emerging RP coming into contact with the uriniferous space. Endoscopic observations confirm the frequent presence of mineral deposits along the surface of renal papillae, especially in calcium-based stone formers."[37]

"Taken together, proximal intratubular calcifications, distal interstitial calcifications, and stones with stems showing both patent tubules within calcium phosphate stems suggest a stepwise progression of events from nephrocalcinosis to nephrolithiasis (Figure 5). As the proximal tubules become occluded with the plate-like calcium-composed debris, resultant changes in fluid dynamics and diverted fluid flow will induce changes in the interstitial physiology in the distal papilla. CNPs will steadily accumulate, through an as yet uncharacterized mechanism resulting in a growing deposit of apatite. When these calcifications erode through the subsurface layers of the papillary epithelium into the renal collecting system, it makes itself visible to the endoscope, and clinically is termed as Randall's Plaque (RP). Urine continues to trickle through patent tubules of the calcified interstitium and promote the nucleation and growth of a calcium oxalate interface between stone and 'stem' which is a part and parcel of RP".[38]

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[35] Li, Z. et al (2021). Modulation of Rat Kidney Stone Crystallization and the Relative Oxidative Stress Pathway by Green Tea Polyphenol. ACS Omega, 2021 **6** 2): p1725-1731
[36] Nephrolithiasis is another term often used for kidney stones.
[37] Sherer, B.A. et al. (2018) A Continuum of mineralization from human renal pyramid to stones on stems. Acta Biomater. **71**: p72-82
[38] Sherer, B.A. et al (2018)

5.5 Conclusions:

Renal mineralization in the rat as observed from pNP occurs at a different anatomical site and has a different etiology and progression than the most common mineralization seen in humans (kidney stones). Moreover, no evidence suggests any predictive value of such renal lesions in rats with respect to human renal toxicity.

6.0 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.[39]

Osimitz *et al.*, 2015 conducted a risk assessment for human exposure to NP.[40] 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 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. [41,42, 43, 44]

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.[45]

ATTACHMENTS

I. Osimitz, T.G. (2022, December 15). Nonylphenol-Critical Effect. Presentation to MN Dept, Of Health

II. Alkylphenols & Ethoxylates Research Council (2022, May 13). Comments on Minnesota Department of Health Proposed Health Risk Limits for p-Nonylphenol, branched isomers

[39] Osimitz, T.G., Droege, W. and Driver, J.H. (2015): Human Risk Assessment for Nonylphenol, Human and Ecological Risk Assessment. . 21:1903-1919
[40] Osimitz, T.G *et al*., (2015)
[41] Osimitz, T.G *et al*., (2015)
[42] Chapin, R.E. *et al*., (1999)
[43] Nagao, T. *et al*., (2001)
[44] Tyl, R.W. *et al*., (2006)
[45] Osimitz, T.G *et al*., (2015)