Exhibit I. Written Comments

I1. Comments received during the Request for Comments period (January 19, 2021, to February 5, 2023) and MDH responses
Note that these comments are not officially part of the rulemaking record, but included for reference

I.1.a.i. Topic: Ethylene Glycol
Commenter: American Chemistry Council
Date: March 8, 2021

I.1.a.ii. Minnesota Department of Health's Response
Date: January 20, 2023

I.1.b.i. Topic: Per and Polyfluoroalkyl Substances (PFAS)
Commenter: Minnesota Center for Environmental Advocacy
Date: March 21, 2021

I.1.b.ii. Minnesota Department of Health's Response
Date: November 30, 2022

I.1.c.i. Topic: Nonylphenol
Commenter: Alkylphenols & Ethoxylates Research Council
Date: May 13, 2022

I.1.c.ii. Minnesota Department of Health's Response
Date: January 3, 2023

I2. Comments received during the Notice of Hearing Initial Comment Period (February 6, 2023, to March 8, 2023)

I.2.a.i. Topic: Nitrate and HRL Application and Enforcement -
Commenter: Jean Wagenius (Former State Representative)
Date: March 4, 2023

I.2.a.ii. Minnesota Department of Health's Response
Date: March 31, 2023

I.2.b.i. Topic: HRL Enforcement
Commenter: Jean Wagenius (Former State Representative)
Date: March 6, 2023

I.2.b.ii. Minnesota Department of Health's Response
Date: March 31, 2023

I.2.c.i. Topic: PFAS
Commenter: Steve Risotto, American Chemistry Council
Date: March 8, 2023

I.2.c.ii. Minnesota Department of Health's Response
March 31, 2023

I.2.d.i. Topic: Nonylphenol
Commenter: Barbara Losey, Alkylphenols & Ethoxylates Research Council
Date: March 8, 2023

I.2.d.ii. Minnesota Department of Health's Response
March 31, 2023

I.2.e.i. Topic: Imidacloprid
Commenter: William Reeves, Bayer Crop Science
Date: March 8, 2023

I.2.e.ii. Minnesota Department of Health's Response
March 31, 2023

I.2.f.i. Topic: Ethylene Glycol
Commenter: Bill Gulledge, American Chemistry Council Ethylene Glycol Panel
Date: March 8, 2023

I.2.f.ii. Minnesota Department of Health's Response
March 31, 2023

I.1.a. Written Comment: Request for Comments – Ethylene Glycol

I.1.a.i. Comment
Date: March 8, 2021
Chemical: Ethylene Glycol
Commenter: American Chemistry Council

I.1.a.ii. Minnesota Department of Health's Preliminary Response
Date: January 20, 2023

Via Email: nancy.rice@state.mn.us

March 8, 2021

Ms. Nancy Rice, MPH
Minnesota Department of Health
625 Robert Street North
P.O. Box 64975
Saint Paul, MN 55164-0975

Re: New Information on Ethylene Glycol (EG) For Determining More Accurate Ethylene Glycol Health Risk Limits in Groundwater

Dear Ms. Rice:

The Ethylene Glycols Panel (EGs Panel) of the American Chemistry Council (ACC) presents significant new information that should be considered in developing a regulatory risk assessment. The ACC EGs Panel represents the manufacturers of ethylene glycols in North America. ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier, and safer.

The Panel's comments identify an additional 14 peer-reviewed publications, not listed in the Minnesota Department of Health Toxicological Summary for Ethylene Glycol. Applying this new information would modify the derivation approaches of the health based value used by MDH and provide state of the science alternatives. These studies include new work on:

- Kinetics and Modeling
    - absorption,
    - distribution,
    - biotransformation
    - elimination
- Toxicodynamics,
- Mode and Mechanism of action

The EGs Panel believes this information will assist in developing a more up-to-date risk assessment. We would be glad to provide any of the references discussed in the comments below.

Background

The Minnesota Department of Health (MDH) requested (December 18, 2020) comments on amendments to the rules governing Health Risk Limits (HRLs) for Ethylene Glycol (EG) in groundwater. The proposed amendment for EG is to replace outdated HRL values in the existing Health Risk Limits Tables found in Minnesota Rules, parts 4717.7500 and 4717.7860. The EGs Panel understands it will have the opportunity to resubmit further comments after the rules are formally proposed.

The MDH August 2020 Toxicological Summary for Ethylene Glycol states that the Short-term Non-Cancer Health-based Value ($nHBV_{Short\text{-}term}$) is based on the results from the Neeper-Bradley et al., 1995 gavage study.

MDH's stated derivation is as follows:

Short-term Non-Cancer Health Risk Limits ($nHBV_{Short\text{-}term}$) = 2,000 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.33 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.038 L/kg-d)}}$$

= 1,736 rounded to 2,000 µg/L

Comments on MDH's $nHBV_{Short\text{-}term}$

Based on the considerable amount of research, the EGs Panel proposes that the science supports the following for Derivations of Short-term Non-Cancer Health-based Value ($nHBV_{Short\text{-}term}$) and differs from the one derived by MDH.

The mode of action (MOA) for EG-induced developmental toxicity has been described by an independent panel of developmental toxicity experts for NTP (CERHR, 2004. *U.S. Department of Health and Human Services, National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction (2004). CERHR Monograph on the potential human reproductive and developmental effects of ethylene glycol. Retrieved from ntp.niehs.nih.gov/ntp/ohat/egpg/ethylene/eg_monograph.pdf.)* and involves the formation of the metabolite, GA. Within this MOA, a key event that precedes and is required for the manifestation of developmental toxicity is the saturation of GA metabolism. The dose at which GA metabolism becomes saturated has been well characterized in rats (~500 mg/kg-d, non-bolus exposures) and humans (~150 mg/kg-d, non-bolus exposures) based on pharmacokinetic data and modeling (CERHR, 2004; Corley et al., 2011. *Corley, R.A., Saghir, S.A., Bartels, M.J. et al., 2011. Extension of a PBPK model for ethylene glycol and glycolic acid to include the competitive formation and clearance of metabolites associated with kidney toxicity in rats and humans.Toxicol. Appl. Pharmacol. 250, 229–244.).*

For bolus exposures, the saturating doses of EG are approximately 3-fold lower (e.g., ~150 mg/kg-d and ~50 mg/kg-d for rats and humans, respectively (Corley et al., 2011). Although a

PBPK model has not been developed for EG in mice, the pharmacokinetic data of Frantz et al. (*Frantz SW, Beskitt JL, Grosse CM, Tallant MJ, Dietz FK, Ballantyne B (1996a) Pharmacokinetics of ethylene glycol. I. Plasma disposition after single intravenous, peroral, or percutaneous doses in female Sprague-Dawley rats and CD-1 mice. Drug Metabolism and Distribution, 24:911-921; Frantz SW, Beskitt JL, Grosse CM, Tallant MJ, Dietz FK, Ballantyne B (1996b) Pharmacokinetics of ethylene glycol. II. Tissue distribution, dose-dependent elimination, and identification of urinary metabolites following single intravenous, peroral or percutaneous doses in female Sprague-Dawley rats and CD-1 mice. Xenobiotica, 26:1195–1220; Frantz SW, Beskitt JL, Tallant MJ, Zourelias LA, Ballantyne B (1996c) Pharmacokinetics of ethylene glycol. III. Plasma disposition and metabolic fate after single increasing intravenous, peroral, or percutaneous doses in the male Sprague-Dawley rat. Xenobiotica, 26:515–539)* clearly show that mice, like other species, also exhibit saturation of GA metabolism, and that this saturation occurs in mice at doses that are approximately 3-fold lower than observed in rats (see **Figure 1**).

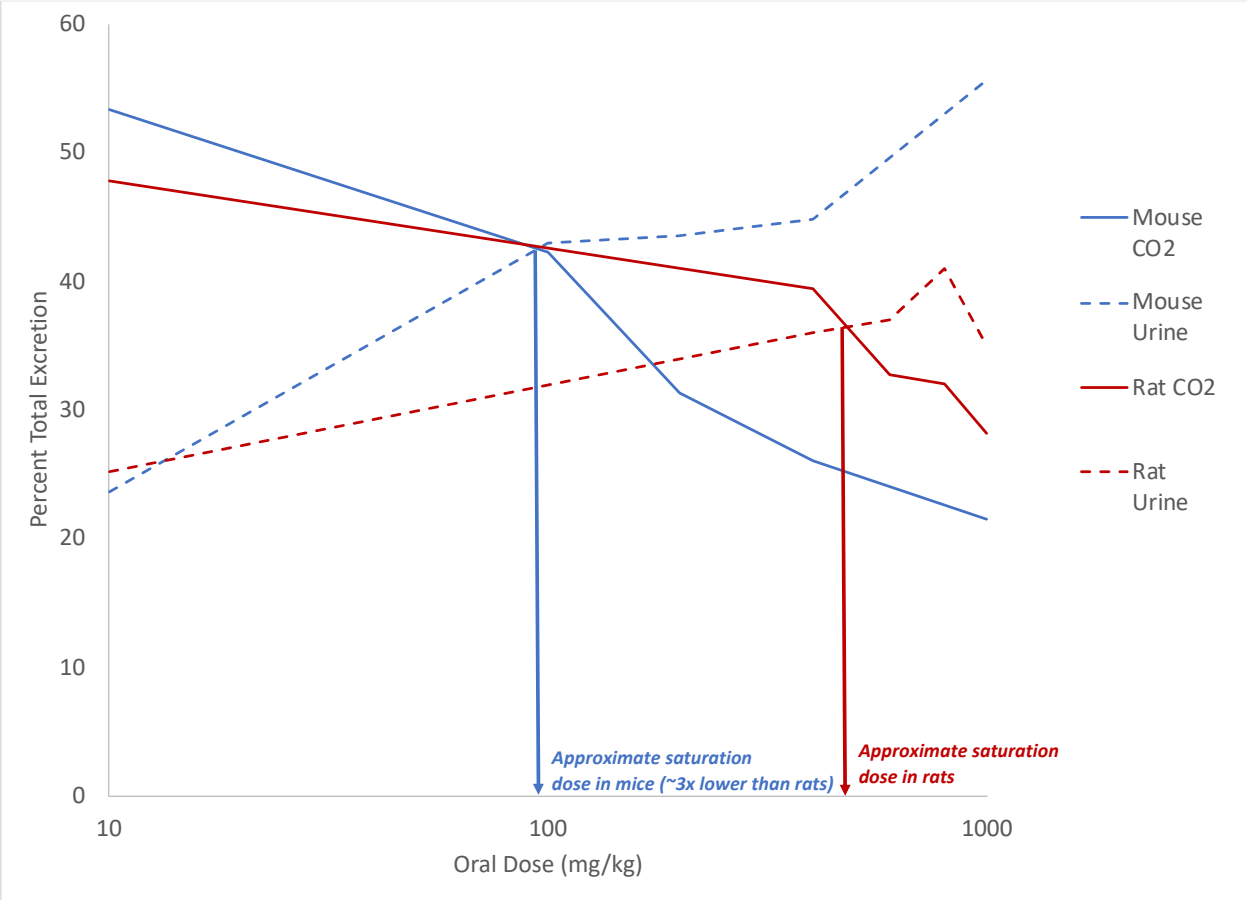

Figure 1. Dose-dependent excretion of radiolabel in rats and mice exposed to EG via gavage (Frantz et al., 1996c). Under linear toxicokinetics, excretion would not be dose-dependent (i.e., data would exhibit flat lines with zero slope). The dose-dependent changes in pathway contributions for EG is consistent with nonlinear toxicokinetics associated with saturation of metabolism. Using the dose at which the pathway contributions cross (urinary vs exhalation) as a crude indicator of the saturation dose, the dose at which metabolism becomes saturated appears lower in mice than in rats by a factor of approximately 3-fold.

It should be noted that allometric scaling practices, as used by MDH for interspecies extrapolation, do not perform well when doses fall within the nonlinear range associated with metabolic saturation (*Kirman CR, Sweeney LM, Meek ME, Gargas ML. Assessing the dose-dependency of allometric scaling performance using physiologically based pharmacokinetic modeling. Regul Toxicol Pharmacol. 2003 Dec;38(3):345-67*). Accordingly, the estimated dose of saturation in mice (~150 mg/kg-d) appears to be very similar to that estimated for humans and is not approximately 7.7-fold higher as would be predicted by default allometric scaling practices (i.e., use of a DAF of 0.13). The estimated saturation dose for mice (~150 mg/kg-d) is consistent with the mouse developmental toxicity data, falling intermediate of the NOAEL (50 mg/kg-d) and LOAEL (500 mg/kg-d) defined by Neeper-Bradley et al., 1995 (*Neeper-Bradley, T. L., Tyl, R. W., Fisher, L. C., Kubena, M. F., Vrbanic, M. A., and Losco, P. E., 1995. Determination of a no-observed-effect level for developmental toxicity of ethylene glycol administered by gavage to CD rats and CD-1 mice. Fundam. Appl. Toxicol. 27, 121–130*).
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Presented in **Table 1** are the EGs Panel suggested modified values used to determine the Short-term Non-cancer Health-based Value based on the Neeper-Bradley et al. (1995) study.

Table 1. Comparison of MDH 2020 Derivation to EGs Panel Derivation for Determining the Short-term Non-cancer Health-based Value ($nHBV_{Short\text{-}term}$) Using Neeper-Bradley et al., 1995 for the POD

	MDH Derivation 2020 Using the Neeper-Bradley et al. (1995)	**EGs Panel Derivation Using the Neeper-Bradley et al. (1995)**	**EGs Panel's Comments and Justification**
Point of Departure (POD)	75.6 mg/kg-d (BMDL10 based on ATSDR's BMD modeling of Neeper-Bradley et al., 1995)	75.6 mg/kg-d	The POD value is considered reasonable. A POD value that is approximately 2-fold lower could be supported based on more recent policy decisions regarding the use of a 5% response rate (i.e., BMDL05) for developmental effects. On the other hand, a POD value that is approximately 2-fold higher could be supported based on the mode of action (MOA) for EG developmental toxicity that involves saturation of GA metabolism. A human dose of 150 mg/kg-d has been estimated for this precursor key event (saturation of GA metabolism) based on human pharmacokinetic data and modeling (CERHR, 2004; Corley et al., 2011)
Dose Adjustment Factor (DAF)	0.13 (Allometric scaling	**1**	MDH (2017) identifies several situations in which allometric scaling may not be appropriate, one of which being "*when there is sufficient chemical-specific information*". In addition to the reasons

	from mice to humans)		identified, allometric scaling may not be appropriate when extrapolating doses at or above metabolic saturation (Kirman et al., 2003), as is evident for EG. Chemical-specific for EG indicate that the dose resulting in saturation of GA metabolism is approximately 500 mg/kg-d in rats and 150 mg/kg-d in humans (CERHR, 2004; Corley et al., 2011). In mice, saturation of metabolism is reached at doses that are approximately 3-fold lower than rats (Frantz et al., 1996a,b,c), which is similar to that estimated for humans (i.e., 150 mg/kg-d). Based upon the ratio of saturation doses in mice and humans (150 mg/kg-d: 150 mg/kg-d), chemical-specific information for EG support a DAF of approximately 1.
Human Equivalent Dose Adjustment (HED)	POD x DAF = 9.83 mg/kg-d	**POD x DAF = 75.6 mg/kg**-d	EGs Panel's proposal would result in modified HED of 75.6 mg/kg-d.
Uncertainty Factor (UF)	30	30	A factor of 10 is considered appropriate for a value based on human data and is comprised of a default factor of 10 for intraspecies variation (UFh). A modifying factor of 3 can be used to account for uncertainty in the exposure timing and intensity of drinking water events, since PBPK modeling predicts that bolus exposure reaches metabolic saturation at doses that are approximately 3-fold lower than corresponding non-bolus exposures to EG.
Reference Dose	9.83 / 30 = 0.33 mg/kg-d	**75.6 / 30 = 2.5 mg/kg-d**	
Relative Source Contribution	0.2	**0.5**	Per MDH administrative rules (4717.7820), the value for RSC is dependent upon chemical volatility. Based on a Henry's Law constant value of 6E-08 atm-m3/mol (PubChem. 2021; https://pubchem.ncbi.nlm.nih.gov/compound/1_2-Ethanediol#section=LogP), EG is considered to fall within in the nonvolatile range. For this reason, an RSC value 0.5 is supported for EG.
Short-term Intake Rate	0.038 L/kg-d	0.038 L/kg-d	

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$)	1,736 rounded to 2,000 µg/L	33,158 rounded to **30,000 µg/L**	

The MDH August 2020 Toxicological Summary for Ethylene Glycol states that the Subchronic Non-Cancer Health-based Value ($nHBV_{Subchronic}$) is based on the results from the Neeper-Bradley (1995) gavage study.

The MDH August 2020 states "The calculated Subchronic RfD (0.57 mg/kg-d) is higher than the Short-term RfD (0.33 mg/kg-d), which is based on developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH, 2008). Therefore, the Short-term RfD is used in place of the calculated subchronic RfD and the water intake rate for a pregnant woman is used."

EGs Panel believes that MDH should revert to their 2011 stated POD (from Cruzan et al., 2004) for determining Subchronic Non-cancer Health-based Value and not use the default derivation of the Short-term RfD from a gavage study.

In 2011, MDH document stated the derivation is as follows:

Subchronic Non-Cancer Health Risk Limits ($nHRL_{Subchronic}$) = 2,000 µg/L

$$\frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.715 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 1,857 rounded to 2,000 µg/L

Presented in **Table 2** are the EGs Panel suggested modified values used to determine the Subchronic Non-cancer Health-based Value based on the Cruzan et al. (2004) study.

Table 2. Comparison of MDH 2011 Derivation to EGs Panel Derivation for Determining the Subchronic Non-cancer Health-based Value ($nHBV_{Subchronic}$) Using Cruzan et al., 2004 (*Cruzan, G., Corley, R.A., Hard, G.C. et al., 2004. Subchronic toxicity of ethylene glycol in Wistar and F 344 rats related to metabolism and clearance of metabolites. Toxicol. Sci. 81 (2), 502–511*) for the POD

	MDH Derivation 2011	**EGs Panel Derivation Using Cruzan et al. (2004)**	**EGs Panel's Comments and Justification**

	<u>Using the Cruzan et al. (2004)</u>		
Point of Departure (POD)	71.5 mg/kg-d (BMDL10 based on nephropathy by Cruzan, et al 2004. NOAEL/LOAEL were 150/500 mg/kg-d)	71.5 mg/kg-d	
Dose Adjustment Factor (DAF)	1	**0.6** (~1/1.6, rounded to 1 significant figure)	Chemical-specific information is available for EG based on PBPK modeling predictions. Based on PBPK modeling to estimate the internal dose associated with toxicity (cmax for total oxalate in rat and human kidney following dietary exposure), humans are expected to experience internal doses that are ~1.6-fold higher than rats (Snellings et al., 2013; **Figure 3. (***Snellings, W.M., Corley, R.A., McMartin, K.E., Kirman, C.R., Bobst, S.M., 2013. Oral Reference Dose for ethylene glycol based on oxalate crystal-induced renal tubule degeneration as the critical effect. Regul. Toxicol. Pharmacol. 65 (2), 229–241.)*
Human Equivalent Dose Adjustment (HED)	Insufficient data for adjustment	POD x DAF = 71.5 x 0.6 = **42.9 mg/kg-d**	As noted above, chemical-specific information is available from PBPK modeling for EG, which can be used to account for species differences between rats and humans in estimating the an HED.
Uncertainty Factor (UF)	100	**10** [1 for interspecies extrapolation and 10 for intraspecies variability]	By using PBPK modeling to estimate an HED, UFa should be reduced to 1, because humans are less sensitive than rats A default value for UFh (10) is considered appropriate for EG **<u>REDUCTION in UF</u>** For detailed justification of the reductions in uncertainty factors, refer to Table 7 in Snellings, et al., 2013 (*Snellings, W.M.,*

			Corley, R.A., McMartin, K.E., Kirman, C.R., Bobst, S.M., 2013. Oral Reference Dose for ethylene glycol based on oxalate crystal-induced renal tubule degeneration as the critical effect. Regul. Toxicol. Pharmacol. 65 (2), 229–241.) The justification for UF of 1 for interspecies extrapolation is as follows: There is a robust database to support this reduction because of the following toxicokinetics studies in rats and humans. <u>PHARMAKOKINETICS</u> a. *Corley, R.A., McMartin, K.E., 2005. Incorporation of therapeutic interventions in physiologically based pharmacokinetic modeling of human clinical case reports of accidental or intentional overdosing with ethylene glycol. Toxicol. Sci. 85 (1), 491–501*; b. *Corley, R.A., Bartels, M.J., Carney, E.W., et al., 2005a. Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic acid, in rats and humans. Toxicol. Sci. 85 (1), 476–490*; c. *Corley, R.A., Meek, M.E., Carney, E.W., 2005b. Mode of Action: oxalate crystal induced renal tubule degeneration and glycolic acid-induced dysmorphogenesis—renal and developmental effects of ethylene glycol. Crit. Rev. Toxicol. 35, 691–702*; d. *Corley, R.A., Saghir, S.A., Bartels, M.J., et al., 2011. Extension of a PBPK model for ethylene glycol and glycolic acid to include the competitive formation and clearance of metabolites associated with kidney toxicity in rats and humans.Toxicol. Appl. Pharmacol. 250, 229–244.*

			There is a robust database to support this reduction because of the following toxicodynamics studies. <u>TOXICODYNAMICS</u> *a) Guo, C., McMartin, K.E., 2005. The cytotoxicity oxalate, metabolite of ethylene glycol, is due to calcium oxalate monohydrate formation. Toxicology 208, 347–355.* *b) Guo, C., McMartin, K.E., 2007. Aluminum citrate inhibits cytotoxicity and aggregation of oxalate crystals. Toxicology 230, 117–125.* *c) Guo, C., Cenac, T.A., Li, Y., et al., 2007. Calcium oxalate, and not other metabolites, is responsible for the renal toxicity of ethylene glycol. Toxicol. Lett. 173, 8–16.* *d) Li, Y., McMartin, K.E., 2009. Strain differences in urinary factors that promote calcium oxalate crystal formation in the kidneys of ethylene glycol-treated rats. Am. J. Physiol. Renal Physiol. 296, F1080–F1087.* *e) Li, Y., McLaren, M.C., McMartin, K.E., 2010. Involvement of urinary proteins in the rat strain difference in sensitivity to ethylene glycol-induced renal toxicity. Am. J. Physiol. Renal Physiol. 299, F605–F615.* *f) McMartin, K.E., Wallace, K.B., 2005. Calcium oxalate monohydrate, a metabolite of ethylene glycol, is toxic for rat renal mitochondrial function. Toxicol. Sci. 84, 195–200.* A default value for UFh (10) is considered appropriate for EG (Snelling et al., 2013)
Reference Dose	71.5/100 = 0.715 mg/kg-d	42.9 / 10 = **4.29 mg/kg-d**	RfD is recalculated using the values supported above.
Relative Source Contribution	0.2	0.2	
Subchronic Intake Rate	0.077 L/kg-d	0.077 L/kg-d	

Subchronic Non-Cancer Health-based Value ($nHBV_{Subchronic}$)	1,857 rounded to 2,000 µg/L	11,143 rounded to **11,000 µg/L**	

Figure 3.

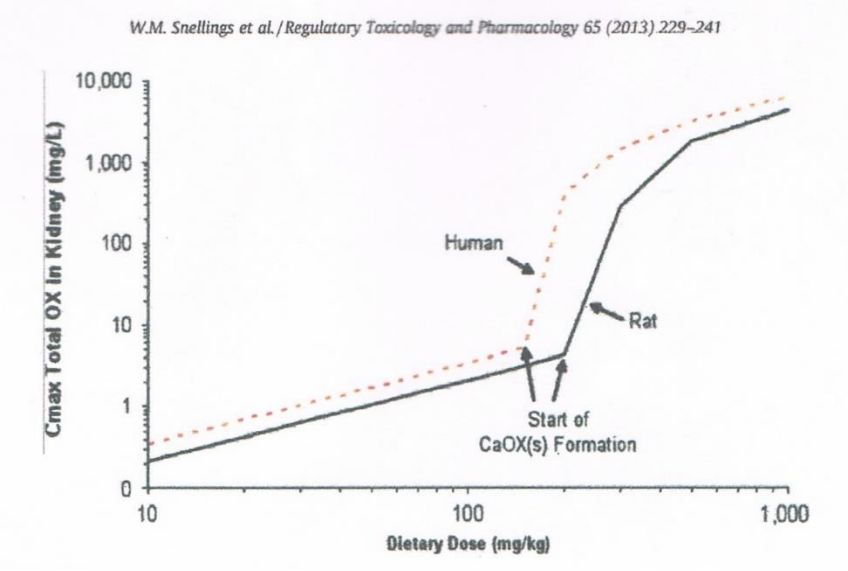

Figure. 3. PBPK predicted Cmax for total oxalate in kidney. Dose-response of internal dose surrogate Cmax for total oxalates in kidney following single day of dietary administration of EG in male Wistar rats and humans.

The MDH August 2020 Toxicological Summary for Ethylene Glycol states that the Chronic Non-Cancer Health-based Value ($nHBV_{Chronic}$) is based on the results from the Neeper-Bradley (1995) gavage study.

The MDH August 2020 document states "The calculated Chronic RfD (0.44 mg/kg-d) is higher than the Short-term RfD (0.33 mg/kg-d), which is based on developmental effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including short-term effects (MDH, 2008). Therefore, the Short-term RfD is used in place of the calculated Chronic RfD and the water intake rate for a pregnant woman is used. (Intake rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5). The calculated Chronic nHBV, before consideration of the Short-term RfD and HBV, resulted in the same water guidance value after rounding to one significant digit. Therefore, the chronic duration additivity endpoints of Male Reproductive system and Renal (kidney) system are added to Developmental. Additivity endpoints: Developmental, Male Reproductive system, Renal (kidney) system."

The EGs Panel believes that MDH should revert to their 2011 stated POD from Corley et al., 2008 (*Corley, R.A., Wilson, D.M., Hard, G.C., et al., 2008. Dosimetry considerations in the enhanced sensitivity of male Wistar rats to chronic ethylene glycol-induced nephrotoxicity. Toxicol. Appl. Pharmacol. 228,*

***165–178*) for determining Chronic Non-cancer Health-based Value and not use the default derivation of the Short-term RfD from a gavage study.**

In 2011, MDH stated the derivation is as follows:

$$\frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.5 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 2326 rounded to 2,000 µg/L

Presented in **Table 3** are the EGs Panel suggested modified values used to determine the Chronic Non-cancer Health-based Value based on the Corley et al., 2008 study.

Table 3. Comparison of MDH 2011 Derivation to EGs Panel Derivation for Determining the Chronic Non-cancer Health-based Value ($nHBV_{Chronic}$) Using Corley et al. (2008) for the POD

	MDH Derivation 2011 Using Corley, et al. (2008)	**EGs Panel Derivation using Corley, et al. (2008)**	**EGs Panel's Comments and Justification**
Critical effect	Critical effect(s): Decreased adult body weight; increased water intake resulting in lower urine specific gravities and higher urine volumes; increased kidney weight; gross and histological changes in kidney and bladder.	Rat kidney effects (Corley et al., 2008)	
Point of Departure (POD)	150 mg/kg-d (NOAEL based on kidney	**BMDL05 = 16 mg Eq OX/L**	Chemical-specific information (PBPK model for EG) supports characterizing the POD for nephrotoxicity in rats (Corley et al., 2008)

	changes reported by Corley et al., 2008. LOAEL was 300 mg/kg-d)	(PBPK-derived internal dose)	using internal dose as assessed in Snellings et al. (2013)
Dose Adjustment Factor (DAF)	NA	NA	Chemical-specific information (PBPK modeling) was used to estimate the human equivalent dose of EG instead of relying upon allometric scaling or dose equivalency assumptions
Human Equivalent Dose Adjustment (HED)	Insufficient data for adjustment	**150 mg/kg-d**	Chemical-specific information PBPK model was used to estimate HED
Uncertainty Factor (UF)	300 [10 for interspecies extrapolation, 10 for intraspecies variability, 3 for subchronic-to-chronic UF (comparison of the 16 week (Cruzan et al., 2004) and 12 month study (Corley, et al., 2008) suggests increased severity with increased duration, however, since the study is 12 months in length a factor of 3 rather than 10 was used]	**10** [1 for interspecies extrapolation, 10 for intraspecies variability, and no need for UF in duration]	**<u>CORLEY 12-MONTH STUDY DURATION</u>** The EGs Panel disagrees with the conclusion that the Corley 12-month study showed an increase in severity in comparison to the 16-weeks study. Increasing exposure length did not change the toxic findings or effect levels for EG when increasing testing duration from 16 weeks to 52 weeks. As Corley et al., 2008 (*Corley, R.A., Wilson, D.M., Hard, G.C., et al., 2008. Dosimetry considerations in the enhanced sensitivity of male Wistar rats to chronic ethylene glycol-induced nephrotoxicity. Toxicol. Appl. Pharmacol. 228, 165–178*) states, "the 12-month study recapitulated the results from the 16- week study…Comparison of these two studies also confirms that there is **no progressive or cumulative effect of ethylene glycol with increased duration of exposure** at dose levels that were non-toxic in short-term studies as was observed at higher dose levels causing toxicity….Identical NOAEL's of 150 mg/kg/d for the subchronic and chronic studies indicate that there is a threshold dose for renal toxicity below which

			exposure of any duration will not be expected to result in adverse renal effects." In addition, the Corley 12-month study is more than sufficient to satisfy the requirements of a well-established chronic study and is appropriate for human chronic oral toxicity risk assessment based on the following: 2. Extensive background of target organ knowledge from repetitive dosing studies in rodents a. *DePass, L.R., Garman, R.H., Woodside, M.D., et al., 1986a. Chronic toxicity and oncogenicity studies of ethylene glycol in rats and mice. Fundam. Appl. Toxicol. 7 (4), 547–565.* b. *DePass, L.R., Woodside, M.D., Maronpot, R.R., et al., 1986b. Three-generation reproduction and dominant lethal mutagenesis studies of ethylene glycol in the rat. Fundam. Appl. Toxicol. 7 (4), 566–572.* 3. Use of a more sensitive test strain and gender (male Wistar), which was confirmed in a comprehensive subchronic study. a. *Cruzan, G., Corley, R.A., Hard, G.C., et al., 2004. Subchronic toxicity of ethylene glycol in Wistar and F 344 rats related to metabolism and clearance of metabolites. Toxicol. Sci. 81 (2), 502–511.* 4. Use of a large number of animals/group (15) 5. Use of four dose groups plus a control over a narrow dose range (50-400 mg/kg-d) 6. Moreover, the use of a chronic exposure duration (12 months, 7 days/week) is acceptable length for different regulatory agencies including FDA* and Health Canada for chronic oral toxicity testing.

			REDUCTION in UF For detailed justification of the reductions in uncertainty factors, refer to Table 7 in Snellings et al., 2013 (*Snellings, W.M., Corley, R.A., McMartin, K.E., Kirman, C.R., Bobst, S.M., 2013. Oral Reference Dose for ethylene glycol based on oxalate crystal-induced renal tubule degeneration as the critical effect. Regul. Toxicol. Pharmacol. 65 (2), 229–241*.) The justification for UF of 1 for interspecies extrapolation is as follows: There is a robust database to support this reduction because of the following toxicokinetics studies in rats and humans. PHARMAKOKINETICS a. *Corley, R.A., McMartin, K.E., 2005. Incorporation of therapeutic interventions in physiologically based pharmacokinetic modeling of human clinical case reports of accidental or intentional overdosing with ethylene glycol. Toxicol. Sci. 85 (1), 491–501*; b. *Corley, R.A., Bartels, M.J., Carney, E.W., et al., 2005a. Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic acid, in rats and humans. Toxicol. Sci. 85 (1), 476–490*; c. *Corley, R.A., Meek, M.E., Carney, E.W., 2005b. Mode of Action: oxalate crystal induced renal tubule degeneration and glycolic acid-induced dysmorphogenesis—renal and developmental effects of ethylene glycol. Crit. Rev. Toxicol. 35, 691–702*; d. *Corley, R.A., Saghir, S.A., Bartels, M.J., et al., 2011. Extension of a PBPK model for ethylene glycol and glycolic acid to include the competitive formation and clearance of*

			metabolites associated with kidney toxicity in rats and humans.Toxicol. Appl. Pharmacol. 250, 229–244. There is a robust database to support this reduction because of the following toxicodynamics studies. <u>TOXICODYNAMICS</u> *g) Guo, C., McMartin, K.E., 2005. The cytotoxicity oxalate, metabolite of ethylene glycol, is due to calcium oxalate monohydrate formation. Toxicology 208, 347–355.* *h) Guo, C., McMartin, K.E., 2007. Aluminum citrate inhibits cytotoxicity and aggregation of oxalate crystals. Toxicology 230, 117–125.* *i) Guo, C., Cenac, T.A., Li, Y., et al., 2007. Calcium oxalate, and not other metabolites, is responsible for the renal toxicity of ethylene glycol. Toxicol. Lett. 173, 8–16.* *j) Li, Y., McMartin, K.E., 2009. Strain differences in urinary factors that promote calcium oxalate crystal formation in the kidneys of ethylene glycol-treated rats. Am. J. Physiol. Renal Physiol. 296, F1080–F1087.* *k) Li, Y., McLaren, M.C., McMartin, K.E., 2010. Involvement of urinary proteins in the rat strain difference in sensitivity to ethylene glycol-induced renal toxicity. Am. J. Physiol. Renal Physiol. 299, F605–F615.* *l) McMartin, K.E., Wallace, K.B., 2005. Calcium oxalate monohydrate, a metabolite of ethylene glycol, is toxic for rat renal mitochondrial function. Toxicol. Sci. 84, 195–200.* A default value for UFh (10) is considered appropriate for EG (Snelling et al., 2013) SUMMARY. By using PBPK modeling to estimate an HED, UFa should be reduced to 1, because humans are less sensitive than rats (as described in Snellings et al. (2013).

Reference Dose	Reference Dose / Concentration: 0.5 mg/kg-d (laboratory animal)	**15 mg/kg-d**	As assessed in Snellings et al. (2013). This value represents the more conservative of 2 RfD values derive (the other value being 47 mg/kg-d)
Relative Source Contribution	0.2	0.2	
Chronic Intake Rate	0.043 L/kg-d	0.043 L/kg-d	
Secondary effects	a. Decreased fetal/pup body weight; decreased embryo/fetal viability; b. Increased pre-implantation loss; c. Decreased adult body weight; d. Proteinurea; decreased testis weight and sperm count; increased incidence of renal lesions; and increased mortality		
Chronic Non-Cancer Health-based Value ($nHBV_{Chronic}$)	2326 rounded to 2,000 µg/L	69,767 rounded to 70,000 µg/L, but reduced to **11,000 µg/L**	The calculated Chronic RfD (15 mg/kg-d) is higher than the Subchronic RfD (4.29 mg/kg-d), which is also based on renal effects. Therefore, the nHBVsubchronic value of 11,000 µg/L calculated above is adopted here for the nHBVchronic value.

* July 2007, Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook 2000, Chapter IV.C.5.a. Chronic Toxicity Studies with Rodents. IV. Experimental Design, A. Duration of Testing: The test animal should be exposed to the test substance 7 days per week for at least 12 months (one year). (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivc5a-chronic-toxicity-studies-rodents)

<u>It should be noted that the EGs Panel is currently supporting the following:</u>

1. **Rodent developmental toxicity by gavage route of administration is probably not the best way for determining the point of departure in EG risk assessment.**
   - CERHR (2004) states there is negligible concern for adverse <u>human</u> developmental toxicity below 125 mg/kg
   - PBPK has been developed and predicts that human would only achieve the threshold for developmental effects at >350 mg/kg bd wt
   - Developmental toxicity in mice by gavage 500 mg/kg bd wt results in one skeletal variation (extra 14 rib; minor variation not considered significant by some researchers) and not until 750 mg/kg b dwt was there decrease in body weight and axial skeleton malformations.
   - Considerable research has been conducted on does-rate effects from EG treatments. Calculating the RfD using NOEL for gavage route of administration is not the best way to determine risks for drinking water.
   - Saturation (needed to increase glycolic acid above threshold) is expected to require much higher doses for slower dose-rate (non-bolus) exposures supports the renal toxicity is the critical effect of concern from oral exposure to EG
   - The NOEL for developmental toxicity is 150 mg/kg/b dwt. Chronic renal toxicity tests show that at 300 mg/kg bd wt there is death and the NOEL for any adverse effects on the kidney is 150 mg/kg. Both have the same NOEL, but the slope for renal toxicity is dramatically much greater.
   - Recent investigation demonstrated that GA uptake into the rat embryo occurs predominantly by a specific, pH-dependent, active uptake transporter protein, consistent with the proton-linked monocarboxylate transporters (MCT). Two isoforms of the MCT exist in the placenta, a high-affinity isoform (MCT1) and a low affinity isoform (MCT4). The published results indicate that polarity of these isoforms in the mouse and rat placenta syncytiotrophoblast is opposite to that in the rabbit and human placenta. In the rodent, MCT1 lies on the side of the maternal blood, while MCT4 lies on the side of the embryonic blood; in rabbits and humans MCT1 lies on the side of the embryonic blood while MCT4 lies on the side of the maternal blood (*Nigel P. Moore, Catherine A. Picut, Jeffrey H. Charlap, "Localisation of Lactate Transporters in Rat and Rabbit Placentae", International Journal of Cell Biology, vol. 2016, Article ID 2084252, 6 pages, 2016. https://doi.org/10.1155/2016/2084252*).
   - It is proposed that the rabbit, and not rat/mouse, is the appropriate species for the assessment of human relevance findings of the EG-induced developmental toxicity.

2. **Gavage is not the appropriate route of administration to determine human oral risks from ingesting EG contaminated drinking water**

   Dose-rate phenomenon must be considered.

   - Considerable toxicokinetic research has been conducted showing that EG is one of the best examples of the importance of dose-rate effects in determining the toxic response for certain chemicals. It is important to note, that dose rate (fast as in a gavage treatment) is paramount in understanding the mechanism of action for EG's

developmental toxicity. If EG is given as a non-bolus dosage (slow diet consumption), it is not a developmental toxicant, as it is when given at the same dose by gavage (fast bolus treatment).

- Supporting research
  - LOEL developmental toxicity (decreased body weights, axial skeleton malformations and variations) reported in rats given EG by gavage was 1000 mg/kg-d. [*Neeper-Bradley TL. 1990. Developmental toxicity evaluation of ethylene glycol administered by gavage to CD (Sprague-Dawley) rats: Determination of a "no observed effect level" (NOEL). Bushy Run Research Center. CMA Project Report 52-656.*]
  - NOEL developmental toxicity reported in rats given EG in the diet was >1000 mg/kg-d. [*Maronpot RR, Zelenak JP, Weaver EV, et al. 1983. Teratogenicity study of ethylene glycol in rats. Drug Chem Toxicol 6(6):579-594.*]
  - Recent peer-reviewed publications show that saturation (needed to increase glycolic acid (GA), the proximate developmental toxicant, above threshold) is expected to require much higher doses for slower dose-rate (non-bolus) exposures as in drinking water ingestion.
  - Carney et al. in 2011 (*Toxicol Sci. 119:178-88*) published a pivotal study on EG. The title explains the importance of this study. "**The Impact of Dose Rate on Ethylene Glycol Developmental Toxicity and Pharmacokinetics in Pregnant CD Rats.**" Corley states that "this study exemplifies the tremendous disparities in pharmacokinetics that can occur following high-dose and high dose rate exposures relative to expected kinetic profiles at lower doses and dose rates. Increasingly, the wisdom of high-dose and high dose rate exposures, which run the risk of inducing shifts to nonlinear kinetics, is being questioned for the evaluation of chemicals present at low levels in the environment. For these types of chemicals, an alternative approach to the maximum-tolerated dose garnering support calls for setting the high-dose level based on the point of transition to nonlinear kinetics, supported by information on internal dose, so as to increase relevance of the data to humans….In the case of EG, we can see clearly that high-dose gavage studies cause a shift from linear to nonlinear GA kinetics, **which appears to be a prerequisite for EG-induced developmental toxicity**." However, most human exposures involve much lower doses, which are nonbolus. Given our understanding of GA kinetics from this publication, it is clear that gavage studies greatly overestimate the risk of typical environmental exposures that are characterized by low doses and/or low dose rates as in drinking water contamination.
  - For an excellent review of the studies linking developmental toxicity and kinetics, refer to Carney, 2011 (*Book chapter, Ethylene Glycol (Reproductive and Developmental Toxicology, Gupta editor, ISBN: 978-0-12-382032-7, 607-615.)* Briefly stated, several studies have been performed to show the relevance of dose-rate effects. Pharmacokinetics studies included Pottenger et al., 2001 (*Dose-dependent nonlinear pharmacokinetics of ethylene glycol metabolites*

in pregnant and nonpregnant Sprague-Dawley rats following oral administration of ethylene glycol. Toxicol. Sci. 62, 10–19) and Klug et al., 2001. (*Effects of ethylene glycol and metabolites on in vitro development of rat embryos during organogenesis. Toxicology in Vitro, Volume 15, Issue 6, Pages 635-642*), and a truly relevant discussion on dose rate is a study by Carney et al., 2011, (*The Impact of Dose-rate on Ethylene Glycol Developmental Toxicity and Pharmacokinetics in Pregnant CD Rats, Toxicol Sci. 119:178-88*). Carney (2011) in his book chapter states "…threshold values of 2mM GA in maternal blood and 4 mM GA in embryo were proposed….To test the validity of these proposed threshold values, a study was done to compare equivalent doses of EG given as a bolus (fast dose-rate) vs. as a slow continuous infusion (slow dose-rate) for their impact on kinetics and developmental outcome (Carney, 2011)….the fast dose-rate groups had peak maternal blood GA levels in excess of the putative 2 mM threshold and the fetuses from these dams showed significant increases in skeletal malformations and variations. In the slow dose-rate groups, GA levels remained below the putative threshold and there was no increase in the incidence of skeletal defects."

3. <u>Mouse and rat are not the appropriate species for developmental/reproductive risk assessment.</u>

Recent research is supporting that the rabbit is a better species to select for determining human oral risks.

- Supporting research
  - Carney et al., 2008, (*Species-specificity of ethylene glycol-induced developmental toxicity: toxicokinetic and whole embryo culture studies in the rabbit. Birth Defects Res B Dev Reprod Toxicol, 83: 573-81*) report "High-dose gavage exposure to ethylene glycol (EG) is teratogenic in rats, but not rabbits. To investigate the reason for this species difference, toxicokinetic and whole embryo culture (WEC) studies were conducted….The toxicokinetic profile suggested that the lower GA levels in rabbits were due to a slower rate of maternal metabolism of EG to GA, slow uptake of GA into the yolk sac cavity fluid which surrounds the embryo, and negligible transfer via the visceral yolk sac (VYS) placenta….Integration of these findings with published human data suggest that the rabbit is the more relevant model for human EG exposure,…"
  - Ellis-Hutchings et al., 2014, (*Disposition of glycolic acid into rat and rabbit embryos in vitro (Reprod Toxicol 46:46-55*) report that "This research explored the mechanisms of GA disposition into rat and rabbit conceptuses using whole embryo culture (WEC)….Results for this

research study suggest GA disposition into rat and rabbit embryos is energy- and pH-dependent, and carrier-mediated….These support and further refine an existing body of data indicating that the pregnant rat model is not relevant to humans due to fundamental differences in maternal metabolism coupled with qualitative differences in the direction of pH-dependent transport."

- Moore et al., 2016 (*Nigel P. Moore, Catherine A. Picut, Jeffrey H. Charlap, "Localisation of Lactate Transporters in Rat and Rabbit Placentae", International Journal of Cell Biology, vol. 2016, Article ID 2084252, 6 pages, 2016. https://doi.org/10.1155/2016/2084252*) report that the rabbit, and not rat/mouse, is the appropriate species for the assessment of human relevance findings of the EG-induced developmental toxicity. The mechanisms underlying molecular mechanisms and species differences in the developmental toxicity was discussed.

Should you have any questions regarding these comments, please contact me at (202) 249-6714 or bill_gulledge@americanchemistry.com .

Sincerely,

Bill Gulledge

Bill Gulledge

Senior Director, Chemical Products & Technology Division

January 20, 2023

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Via Electronic Mail: Bill_Gulledge@americanchemistry.com

Re: New Information on Ethylene Glycol (EG) For Determining More Accurate Ethylene Glycol Health Risk Limits in Groundwater

Dear Mr. Gulledge:

Thank you for submitting comments from the Ethylene Glycols Panel (EGs Panel) of the American Chemistry Council (ACC) on the proposed amendment to the Health Risk Limits Rule (HRL) for ethylene glycol dated March 8th, 2021.

In your letter you mentioned 14 peer-reviewed publications that were not explicitly called out in the reference section of our summary sheet for ethylene glycol, and while some of these publications were not individually cited, they are reviewed or summarized as part of larger reports like the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction's (CERHR) 2004 review. The list of sources at the end of our summary sheet includes the references that were impactful for water guidance development. It does not include the entire list of all references consulted as part of the review. The more specific comments in your letter regarding how this information might influence our assessment will now be addressed.

Minnesota Department of Health (MDH) risk assessors selected the Neeper-Bradley (1995) developmental mouse study as the critical study for the short-term duration guidance. Ethylene glycol is a known developmental toxicant for two different species of mammals (rodents). Although developmental toxicity has not been observed in accidental or occupational exposures, these do not represent a similar exposure as a person consuming ethylene glycol in their drinking water daily over a period of time. Our methods state that "It is assumed that humans are at least as sensitive as the most sensitive mammalian species for which there are toxicological data. Substantial evidence that the response seen in laboratory animals is due to a mechanism that does not exist in humans can overcome this assumption." The occupational and accidental exposures do not overcome the evidence in rodents (Statement of Need and Reasonableness, SONAR, 2009, page 27).

The lowest point of departure (POD) from Neeper-Bradley (1995) shows that a sensitive lifestage (i.e., developing fetuses) is affected. MDH identified an administered no observed adverse effect level (NOAEL) of 150 mg/kg-d and an administered lowest observed adverse effect level (LOAEL) of 500 mg/kg-d based on increased skeletal malformations. The selected POD from the critical study was the lower confidence limit of a benchmark dose corresponding to a 10% ($BMDL_{10\%}$) increase in skeletal malformations over control animals. The selection of this study and use of benchmark dose modeling to derive a POD is in accord with the guidance of our published methods laid out in our 2009 SONAR. Modeled results are often considered to be superior as modeling takes into account the entire dose response curve rather than a few discrete data points as does the LOAEL/NOAEL approach.

MDH risk assessors did not find the available toxicological and toxicokinetic information on ethylene glycol to be sufficient to develop chemical specific adjustment factors to extrapolate the dose from mice to humans. It appears that saturation of glycolic acid kinetics is likely needed to see the developmental effects captured in the various rodent studies, and in mice this threshold may indeed be near 150 mg/kg-d as you assert based on the Neeper-Bradley (1995) NOAEL and LOAELs. However, there is no *in vivo* human data that identifies the dose needed for glycolic acid metabolic saturation; therefore potential developmental effects could occur at a similar or even lower dose. Additionally, both the NTP and MDH identified the developmental NOAEL in the Neeper-Bradley (1995) study at 150 mg/kg-d, suggesting that kinetic saturation had not yet been reached at the lower POD, $BMDL_{10\%}$ of 76.5 mg/kg-d. Therefore, a body weight scaling based dosimetric adjustment factor (DAF) was used.

MDH follows the hierarchy that the EPA laid out in 2002 for applying HEDs. The preferred option is to use a chemical-specific physiologically based pharmacokinetic (PBPK) model. A PBPK model estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion. Constructing a PBPK model is an information intensive process that requires a significant quantity of chemical-specific data, including route-specific data. Such sophisticated data and models are usually available for only a small subset of chemicals that have extensive databases (SONAR, 2009). While the PBPK database for ethylene glycol may be rich for animal models, it is not complete enough to construct a realistic model for humans. Responses to chemicals are often incongruent between laboratory animals and humans. In the absence of strong evidence showing that the rodent PBPK is similar to humans, MDH defaults to developing an HED using a dosimetric adjustment factor (DAF) using body weight scaling (SONAR 2009).

MDH reviewed your comments in Table 1 of your letter on our guidance value derivation for the short-term duration. A benchmark response level (BMR) of 10%, which as stated by ATSDR in their 2010 assessment, is the lowest BMR that was supported by the data. Usually MDH would usually apply a BMR of 5% for a developmental critical effect because fetuses are more sensitive to chemicals, but it was not supported by the data. You also commented on MDH's choice of an appropriate relative source contribution factor (RSC). It is based on volatility as you noted, and MDH classified ethylene glycol as nonvolatile contaminant using the Henry's Law Constant. However, the critical endpoint occurred after *in utero* exposure, so a pregnant woman's intake rate was used because it represents the exposure of

concern, and therefore the default RSC for all other non-infant life stages (RSC= 0.2) for nonvolatile chemicals was used rather than the infant-based RSC of 0.5 (see SONAR, 2008, pg. 51). This is explained in the Toxicological Summary Sheet's footnote as well.

> The RfD is based on malformations that occur in utero, therefore, the intake rate for a pregnant woman is utilized rather than the default infant intake rate as described in the MDH 2008 SONAR (page 46). Effects relevant to post-natal development occurred at higher dose levels. As the short-term duration intake is based on pregnant women, not infants, a Relative Source Contribution of 0.2 is utilized. (MDH, 2020).

MDH acknowledges your comments on the subchronic and chronic duration guidance, namely that they should not be based on a gavage developmental study and that rodent studies evaluating renal effects as seen in the Corley et al. (2008) and Cruzan et al. (2004) studies are more appropriate. However, as per our methods, "the longer-duration HRLs must be protective of short exposures that may occur within the longer duration", therefore a developmental study would still be appropriate for a subchronic and chronic guidance as the short-term period of 2-30 days is also contained in those longer durations (SONAR 2009, p.23). This rulemaking does not address methods; the parameter specific comments laid out in Tables 2 and 3 will not be addressed further.

MDH reviewed the EGs Panel additional statements on 1) applicability of gavage route of administration in rodent developmental studies, 2) appropriateness of gavage route of administration for estimated risk from EG contaminated drinking water and dose-rate phenomenon, and 3) mouse and rat model versus the rabbit in developmental/reproductive risk assessment.

In choosing the critical study and POD for an assessment, MDH takes into consideration all available data from toxicology studies using oral routes of administration including gavage studies. It is true that many of the available animal toxicology studies utilize gavage (bolus) dosing and form the basis of assessments meant to estimate risk from lower, continuous exposures to the contaminant via water ingestion; this is not a new concern. Although our methods do not explicitly discuss bolus dosing versus continuous dosing, we carefully consider the limitations of all gavage studies we use in guidance development, and frequently choose to use them if they are the best available study in a sensitive species.

Your comments concerning the dose-rate phenomenon in rats for ethylene glycol and the inclusion of extensive comparison of effect levels taken from bolus vs non-bolus rat studies was helpful to MDH in examining this issue. We again reviewed the evidence and did not find the bolus dosing to be problematic. Additionally, our methods describe PODs as the lowest dose level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group; or the closest lower dose tested (the highest dose level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects) (SONAR, 2009). In addition to the NOAEL/LOAEL method for identifying a POD explained above, our methods also recommend Benchmark Dose (BMD) modeling as well. Although

we consider modeling to provide a higher quality POD, in some cases the data is not suitable to modeling and the other approach is used.

Neeper-Bradley (1995) was selected as the critical study because it provided the lowest POD in the most sensitive species identified, the mouse. The developmental and reproductive mouse studies that administered ethylene glycol via drinking water were not selected as the critical study because they used higher doses (Gulati et al., 1986; Morrissey et al., 1989, and Lamb et al., 1985 as discussed in NTP, 2004).

MDH also recognizes that there is evidence of species, strain, and sex differences in the metabolism and clearance of ethylene glycol. As the EG panel has pointed out, rabbits exposed *in utero* to ethylene glycol do not exhibit the same developmental effects as rodents do. The EGs Panel asserts that the mechanistic and toxicokinetic findings from Carney et al. (2008), Ellis-Hutchings et al. (2014), and Moore et al. (2016) conclude that rodents are inappropriate animal models for testing potential developmental effects following exposure to ethylene glycol and rabbits are more appropriate, however, MDH risk assessors do not agree and consider the findings preliminary.

Research by Ellis-Hutchings et al. 2014 used whole embryo cultures to explore the rat and rabbit's ability to concentrate ethylene glycol. Their findings suggest that the ability of the rat embryo to concentrate glycolic acid is pH dependent and may involve a protein transporter.

The expression of these transporters has been investigated in the rabbit and rat placenta by Moore et al., 2016, who concluded that the arrangement of transporters in the placenta of rats had an opposite polarity compared to the rabbit placenta, which they report is similar to the humans. There is no functional consequence reported.

It is also important to note that the time course for fetal development varies greatly between mammalian species. Processes that are observed at day 4 in mouse development likely do not appear in human fetuses on day 4. Additionally, the placenta is complex and dynamic during a pregnancy. Transporters that allow for the passage of nutrients and some chemicals across the placenta may be expressed differently at different times during a pregnancy.

While the studies cited above do provide some insight as to why there may be species differences in susceptibility to developmental effects due to differences in placental biology, they do not fully elucidate how these differences functionally change the processing of ethylene glycol. They also do not sufficiently demonstrate that the findings from the critical study in mice are irrelevant to human health risk assessment. As directed by our methods (SONAR 2009, p.27, also cited above) MDH selected a POD based on developmental effects from the most sensitive species, the mouse in this case, to derive the short-term guidance value.

It is MDH's mission to protect the health of all Minnesotans, including sensitive populations and the most vulnerable. The EGs Panel suggests using a higher DAF and RSC in the short-term guidance

derivation, and moreover that the route of administration and model species in the critical study were not appropriate. Applying these changes would result in a higher water guidance value that would not be protective of early life stages. Disregarding the developmental effects seen in fetal mice and reported in the Neeper-Bradley et al. (1995) study because of the route of administration and species sensitivity without more conclusive information would contradict MDH's mission to protect, maintain, and improve the health of all Minnesotans. Therefore, to be protective for all populations, MDH will retain the short-term proposed critical study, as well as the DAF and RSC without modification.

Sincerely,

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Cruzan G. RA Corley, GC Hard, JJWM Mertens, KE McMartin, WM Snellings, R Gingell, JA Deyo. 2004. Subchronic Toxicity of Ethylene Glycol in Wistar and F-344 Rats Related to Metabolism and Clearance of Metabolites. Tox Sci 81:502-511.

Neeper-Bradley, TL, RW Tyle, LC Fisher, MF Kubena, MA Vrbanic, PE Losco. 1995. Determination of a No-Observed-Effect Level for Developmental Toxicity of Ethylene Glycol Administered by Gavage to CD Rats and CD-1 Mice. Fund Appl Tox 27: 121-130.

NTP-CERHR 2004. NTP-CERHR Expert Panel report on the reproductive and developmental toxicity of ethylene glycol. Reproductive Toxicology 18:457-532.

I.1.b. Written Comment: Request for Comments- PFAS

I.1.b.i. Comment
Date: March 21, 2021
Chemicals: PFAS
Commenter: Minnesota Center for Environmental Advocacy

I.1.b.ii. Minnesota Department of Health's Preliminary Response
Date: November 30, 2022

Minnesota Center for Environmental Advocacy's Comments on the Minnesota Department of Health's "Possible Amendments to Rules Governing Health Risk Limits"

March 22, 2021

INTRODUCTION

Per- and Polyfluoroalkyl substances ("PFAS") "are a family of manmade chemicals that have been used for decades to make products that resist heat, oil, stains, grease, and water."[1] They are found in an array of products, including firefighting foam, food packaging, and non-stick cookware.[2] There are nearly 5,000 unique compounds that comprise the PFAS family, and more are currently in development.[3]

PFAS are problematic mainly because they are extremely toxic to human health and stable in the natural environment. PFAS molecules are composed of carbon-fluorine bonds, one of the strongest bonds in existence, meaning that "these chemicals do not degrade in the environment" and accumulate in humans over time.[4] Regulators consider some PFAS compounds to be hazardous to human health at shockingly small amounts, with safe levels measured in parts per trillion ("ppt"). For context, 1 part per trillion is "equivalent to a single drop of water in 20 olympic-

[1] *Conceptual Drinking Water Supply Plan*, Minn. Pollution Control Agency & Minn. Dep't of Natural Res. 21 (Sept. 2020), https://3msettlement.state.mn.us/sites/default/files/Draft_CDWSP_Chapters1_7.pdf.

[2] Geologic Society of America, *PFAS: These 'Forever Chemicals' are Highly Toxic, Under-Studied, and Largely Unregulated*, Science Daily (Oct. 29, 2020), https://www.sciencedaily.com/releases/2020/10/201029122943.htm.

[3] *Per and Polyfluoroalkyl Substances (PFAS)*, U.S. Food & Drug Admin., https://www.fda.gov/food/chemicals/and-polyfluoroalkyl-substances-pfas (last visited Dec. 4, 2020); *What are PFAS?*, U.S. Agency for Toxic Substances & Disease Registry, https://www.atsdr.cdc.gov/pfas/health-effects/overview.html (last visited Mar. 15, 2021).

[4] *Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS)*, Nat'l Institute of Health, https://www.niehs.nih.gov/health/topics/agents/pfc/index.cfm (last visited Mar. 15, 2021).

sized swimming pools."[5] And once PFAS enter the natural environment, either through spills, industrial releases, or another pathway, they are extremely difficult to remediate. PFAS has created significant public health challenges for Minnesota. Unfortunately, these are statewide issues that have affected places like the East Metro,[6] Bemidji,[7] and close to 100 landfills, "stretching from the Northwest Angle nearly to the Iowa border."[8]

Fortunately, the State of Minnesota (the "State") has chosen to be a leader in the fight against PFAS pollution. From achieving a $850 million settlement in 2018,[9] to the recent rollout of the State's PFAS Blueprint,[10] the State clearly understands the extreme dangers PFAS present to human health.[11] In its PFAS Blueprint, the State has articulated an inter-agency approach to combating this problem.[12] This vision centers on the need to "[q]uantify[] PFAS risks to human health."[13] Establishing Health Risk Limits ("HRLs") for PFAS is crucial because, as the State has

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[5] *1 Part Per Trillion (ppt) is Equivalent to a Single Drop of Water in 20 Olympic-Sized Swimming Pools*, State of Michigan, https://www.michigan.gov/documents/pfasresponse/1ppt_is_Equal_to_1_Drop_of_Water_in_20_Olympic_Swimming_Pools_664966_7.pdf (last visited Mar. 15, 2021).
[6] *Minnesota 3M PFC Settlement*, Minn. Pollution Control Agency & Minn. Dep't of Natural Res., https://3msettlement.state.mn.us/ (last visited Mar. 15, 2021).
[7] Kristi Marohn, *'Forever' Chemicals Leave Costly Water Problem in Bemidji, Cities Across the Country*, MPR News (Feb. 14, 2019), https://www.mprnews.org/story/2019/02/14/pfas-leaves-costly-water-problem-in-bemidji-and-other-cities.
[8] Kristi Marohn, *'Forever Chemicals' Found in Groundwater at Dozens of Minn. Landfills*, MPR News (Mar. 18, 2021), https://www.mprnews.org/story/2021/03/18/forever-chemicals-found-in-groundwater-at-dozens-of-minn-landfills.
[9] *Minnesota 3M PFC Settlement*, Minn. Pollution Control Agency & Minn. Dep't of Natural Res., https://3msettlement.state.mn.us/ (last visited Mar. 15, 2021).
[10] *Minnesota's PFAS Blueprint*, Minn. Pollution Control Agency, https://www.pca.state.mn.us/waste/minnesotas-pfas-blueprint (last visited Mar. 15, 2021).
[11] Jennifer Bjorhus, *With PFAS Everywhere, Minnesota Calls for Big New Crackdown on the 'Forever Chemicals'*, Star Trib. (Feb. 10, 2021), https://www.startribune.com/with-pfas-everywhere-minnesota-calls-for-big-new-crackdown-on-the-forever-chemicals/600021420/?refresh=true.
[12] *See generally Minnesota's PFAS Blueprint*, Minn. Pollution Control Agency Feb. 2021), https://www.pca.state.mn.us/sites/default/files/p-gen1-22.pdf.
[13] *Id.* at 42.

noted, "[t]he scientific literature regarding PFAS toxicity and occurrence is evolving rapidly,"[14] and "new PFAS are being invented, used in industry and incorporated into commercial products, and released into the environment every day."[15]

In January 2021, the Minnesota Department of Health ("MDH") published a Request for Comments in the *Minnesota State Registrar* for "Possible Amendments to Rules Governing Health Risk Limits,"[16] which contemplate adopting new HRL values for thirty chemicals, including three PFAS compounds: Perfluorohexane Sulfonate ("PFBS"), Perflourobutane Sulfonate ("PFHxS"), and Perfluorooctane Sulfonate ("PFOS").[17] Under this rulemaking process, MDH will accept preliminary comments now before "[a]nother more formal comment period opens up later."[18]

In order to aid MDH's determination of HRL values for PFBS, PFHxS, and PFOS, MCEA is submitting this public comment to ensure that MDH sets aggressive and scientifically supported HRLs for these acutely toxic chemicals. MDH should follow the precautionary principle. The precautionary principle "encourages policies that protect human health and the environment in the face of uncertain risks."[19] The principle enables decision makers "to adopt precautionary measures

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[14] *Id.*

[15] Jennifer Bjorhus, *With PFAS Everywhere, Minnesota Calls for Big New Crackdown on the 'Forever Chemicals'*, Star Trib. (Feb. 10, 2021), https://www.startribune.com/with-pfas-everywhere-minnesota-calls-for-big-new-crackdown-on-the-forever-chemicals/600021420/?refresh=true.

[16] 45 29 Minn. Reg. 792 (Jan. 19, 2021), *available at* https://mn.gov/admin/assets/SR45_29%20-%20Accessible_tcm36-463399.pdf#page=8.

[17] Health Risk Limits Rules for Groundwater: Rules Amendments-Contaminants, Minn. Dep't of Health (Feb. 2021), https://www.health.state.mn.us/communities/environment/risk/rules/water/chemicals.html.

[18] Health Risk Limits Rules for Groundwater: Request for Comments, Minn. Dep't of Health (Jan. 2021), https://www.health.state.mn.us/communities/environment/risk/rules/water/reqcomments.html.

[19] Joel A. Tickner, *Guest Editorial: Precaution and Preventative Public Health Policy*, 117 Public Health Reports 493 (Nov. 2002), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1497489/pdf/12576528.pdf.

when scientific evidence about an environmental or human health hazard is uncertain and the stakes are high."[20] Following this principle, MDH should establish HRLs that are the most protective of human health under current scientific understanding, but building in a margin for safety that anticipates inevitable future scientific research demonstrating PFAS is toxic at lower levels than currently understood.

I. BACKGROUND ON PFAS HRL AMENDMENTS

A. Through This Rulemaking Process, The State Of Minnesota Has A Key Opportunity To Support Its Broader Vision For Addressing The Threats Of PFAS.

The State recently outlined its comprehensive vision for addressing PFAS, envisioning "a holistic and systematic approach."[21] In the PFAS Blueprint, the State identified "[t]en priorities to protect communities and families."[22] One of these priorities is "[q]uantifying PFAS risk to human health."[23] This is a critical step; assessing the risk of particular PFAS compounds will inform much of the State's future work on combatting PFAS pollution, such as limiting PFAS exposure from drinking water and food sources, remediating contaminated sites, and managing PFAS in waste.[24] Thus, it is vital for MDH use its regulatory power to set aggressive HRLs that are protective of human health. The State should seize this opportunity to be a leader in the fight against PFAS, especially since the federal government has been slow to react to this public health crisis.[25]

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[20] *The Precautionary Principle*, European Parliamentary Research Serv. (Dec. 2015), https://www.europarl.europa.eu/thinktank/en/document.html?reference=EPRS_IDA(2015)573876.

[21] *Minnesota's PFAS Blueprint*, Minn. Pollution Control Agency, https://www.pca.state.mn.us/waste/minnesotas-pfas-blueprint (last visited Mar. 15, 2021).

[22] *Id.*

[23] *Id.*

[24] *See generally Minnesota's PFAS Blueprint*, *supra* note 12.

[25] Paul Quackenbush, *A Persistent Problem: Applying RCRA's Citizen Suit Provision to PFAS*, Vermont L. Rev. (Online), https://lawreview.vermontlaw.edu/a-persistent-problem-applying-

MCEA is pleased to see MDH taking concerted action on some of the better understood PFAS compounds.[26] PFBS is a chemical that has been used "as a surfactant in industrial processes and in water-resistant or stain-resistant coatings on consumer products such as fabrics, carpets, and paper."[27] The HRL for PFBS was last updated in 2011.[28] PFHxS is a chemical that has been used "in stain-resistant fabrics, fire-fighting foams, food packaging, and as a surfactant in industrial processes."[29] Although MDH has not established an HRL for PFHxS, MDH recently set a Health-Based Value (HBV) in August 2020.[30] PFOS is one of the best understood PFAS chemicals,[31] and has been used "in stain-resistant fabrics, fire-fighting foams, food packaging, and as a surfactant

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rcras-citizen-suit-provision-to-pfas/#:~:text=Despite%20increased%20public%20scrutiny%2C%20the,been%20slow%20to%20regulate%20PFAS.&text=Yet%20few%20state%20regulations%20exist,from%20PFAS%20waste%20is%20widespread (last visited Mar. 22, 2021) ("Despite increased public scrutiny, the federal government has been slow to regulate PFAS. The Environmental Protection Agency (EPA) has not yet promulgated a legally enforceable standard for any of the more than 4,700 individual chemicals in the PFAS group, in part, due to the still incomplete understanding of the effects of PFAS on human health." (citations omitted))

[26] *Human Health-Based Water Guidance Table*, Minn. Dep't of Health, https://www.health.state.mn.us/communities/environment/risk/guidance/gw/table.html (last visited Mar. 15, 2021) (listing MDH's current health standards for PFBS, PFHxS, and PFOS).

[27] *PFBS and Drinking Water*, Minn. Dep't of Health (Dec. 2017), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbsinfo.pdf.

[28] *Toxicological Summary for Perflourobutane Sulfonate (PFBS),* Minn. Department of Health (Mar. 21, 2011), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbs.pdf.

[29] *PFHxS and Groundwater*, Minn. Dep't of Health (Apr. 2019), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxsinfo.pdf.

[30] *Toxicological Summary for Perflourohexane Sulfonate (PFHxS)*, Minn. Dep't of Health (Aug. 2020), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf.

[31] *Basic Information on PFAS*, U.S. Envtl. Protection Agency, https://www.epa.gov/pfas/basic-information-pfas#:~:text=The%20most%2Dstudied%20PFAS%20chemicals,have%20caused%20tumors%20in%20animals (last visited Mar. 15, 2021) ("PFOA and PFOS have been the most extensively produced and studied of these chemicals.").

in industrial processes."[32] The HRL for PFOS was last updated in 2009.[33] Updating the HRLs for PFBS, PFHxS, and PFOS presents a critical opportunity for mitigating PFAS; doing so is also necessary for MDH to fulfill its statutory obligations.

B. Regulating PFAS Through HRLs And MDH's Statutory Obligations.

HRLs are "a concentration of a substance or chemical adopted by rule of the commissioner of health that is a potential drinking water contaminant because of a systemic or carcinogenic toxicological result from consumption."[34] Pursuant to the Groundwater Protection Act of 1989, MDH is authorized to "adopt and revise health risks limits for substances degrading groundwater."[35] In this context, "[i]t is the goal of the state that groundwater be maintained in its natural condition, free from any degradation caused by human activities," and "where prevention is practicable, it is intended that it be achieved."[36] MDH has a statutory obligation to review adopted HRLs "at least every four years."[37]

For carcinogenic toxicants like PFAS, HRLs may be established only after the MDH Commissioner determines that the process has "undergone thorough scientific review."[38] Another statutory provision specifies additional requirements for establishing safe drinking water standards, such as those related to PFAS, and imposes requirements that HRLs: (1) "be based on

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[32] *PFOS and Groundwater*, Minn. Dep't of Health (Apr. 2019), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfosinfo.pdf.
[33] *Toxicological Summary for Perflourooctane Sulfonate (PFOS)*, Minn. Dep't of Health (May 5, 2009), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos2010.pdf.
[34] Minn. Stat. § 103H.005.
[35] 45 29 Minn. Reg. 792 (Jan. 19, 2021), *available at* https://mn.gov/admin/assets/SR45_29%20-%20Accessible_tcm36-463399.pdf#page=8.
[36] Minn. Stat. § 103H.001.
[37] Minn. Stat. § 103H.201, subd. 3(a).
[38] Minn. Stat. § 103H.201.

scientifically acceptable, peer-reviewed information," and (2) "include a reasonable margin of safety."[39]

MDH has previously regulated four PFAS compounds through the HRL process: PFOS (2009), PFBS (2011), PFBA (2018), and PFOA (2018).[40] With respect to the three PFAS compounds of concern for this rulemaking process, the HRLs for PFBS and PFOS are outdated, since the HRLs were last updated ten years ago and twelve years ago, respectively.[41] HRLs are developed for individual PFAS compounds, which contrasts with recent State of Washington legislation that "directs agencies to address classes of chemicals [including PFAS] and moves away from a chemical by chemical approach, which has historically resulted in companies switching to equally bad or worse substitutes."[42] Moving forward, setting HRLs for the whole PFAs class of chemicals in the same regulatory cycle would be beneficial, both in terms of efficiency and administrative consistency. In this way, MDH could revisit HRLs for all known PFAS compounds at the same time, enabling the public to be better involved in the process.[43]

C. The Importance Of Regulating PFAS Through HRLs.

HRLs are a vital regulatory tool for MDH to use in the fight against PFAS. Until an HRL exceedance occurs, the State lacks effective options to help remediate contamination in a water supply. Once an HRL is exceeded, however, the State must "promote implementation of best

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[39] Minn. Stat. § 144.0751.
[40] *Minnesota's PFAS Blueprint*, *supra* note 12, at 143. MCEA anticipates that MDH will revisit the 2018 HRLs for PFBA and PFOA in 2022, consistent with Minn. Stat. § 103H.201, subd. 3(a).
[41] Minn. Stat. § 103H.201, subd. 3(a).
[42] Erin Brockovich, *Plummeting Sperm Counts, Shrinking Penises: Toxic Chemical Threaten Humanity*, The Guardian (Mar. 18, 2021), https://www.theguardian.com/commentisfree/2021/mar/18/toxic-chemicals-health-humanity-erin-brokovich.
[43] *See Minnesota's PFAS Blueprint*, *supra* note 12, at 45 ("Costs for assessing the chronic or multi-generational toxicity can exceed several million dollars per chemical.").

management practices to prevent or minimize the source of pollution to the extent practicable."[44] Best management practices relate to activities such as restrictions of practices, management plans, treatment requirements, and other activities that cause groundwater degradation.[45] HRLs "specify a minimum level of quality for water used for human consumption,"[46] are related to developing Class 1 Water Quality Standards,[47] and are used by the U.S. Environmental Protection Agency ("EPA") and U.S. Department of Defense as "applicable or relevant and appropriate requirements" ("ARARs") in remediation efforts.[48] These ARARs could be critically important under federal superfund laws, particularly if the federal government continues to lag behind in regulating PFAS.[49]

Conversely, HBVs are "developed to provide water guidance between rule-making cycles for chemicals that may have been recently detected in the water or for which new health information has become available."[50] In the recent PFAS Blueprint, the State appeared to conflate HBVs with HRLs, citing an HRL statutory provision in a discussion of "health-based guidance values."[51]

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[44] Minn. Stat. § 103H.275.
[45] Minn. Stat. § 103H.005, subd. 4.
[46] Minn. R. 4717.7810.
[47] *Minnesota's PFAS Blueprint*, *supra* note 12, at 72, Minn. Pollution Control Agency (Feb. 2021), https://www.pca.state.mn.us/waste/minnesotas-pfas-blueprint.
[48] *Id.* at 130.
[49] *Applicable or Relevant and Appropriate Requirements (ARARs)*, U.S. Envtl. Protection Agency, https://www.epa.gov/superfund/applicable-or-relevant-and-appropriate-requirements-arars (last visited Mar. 18, 2021).
[50] *Conceptual Drinking Water Supply Plan*, *supra* note 1, at vi.
[51] *Minnesota's PFAS Blueprint*, *supra* note 12, at 45.

HBVs have no associated statutory criteria for adoption and, unlike HRLs, are only used in discretionary agency actions and as technical guidance,[52] such as setting limits for the State's remediation of the East Metro under the 2018 Settlement with 3M.[53] According to MDH's own statements, "if a chemical has been detected in water, MDH anticipates that HBVs for Minnesota's groundwater will become HRLs . . . at the time that MDH next amends the Health Risk Limits for Groundwater rule."[54] Given that PFBS, PFHxS, PFOS, PFBA and PFOA have all been detected in Minnesota water, the time is ripe for MDH to translate all its HBVs for PFAS to HRLs.

A related concept is Minnesota's Contaminants of Emerging Concern ("CEC") Initiative, whereby MDH strives to "take a proactive approach to the protection of drinking water."[55] Although this Initiative presumably allows MDH to examine chemicals that "have not been found in Minnesota, but have the potential to enter our waters," it is unclear what effect the CEC Initiative has.[56] For example, on October 14, 2020, MDH started a review of PFHxA under the CEC Initiative, providing for a 30 day public comment period.[57] However, PFHxA "has been detected in ambient groundwater and drinking water in Minnesota,"[58] which begs the question of why MDH

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[52] *Health-Based Values and Risk Assessment Advice for Water*, Minn. Dep't of Health, https://www.health.state.mn.us/communities/environment/risk/guidance/hbvraawater.html#hbv (last visited Mar. 19, 2021).
[53] Conceptual Drinking Water Supply Plan, *supra* note 1, at vi.
[54] *Health-Based Values and Risk Assessment Advice for Water*, Minn. Dep't of Health, https://www.health.state.mn.us/communities/environment/risk/guidance/hbvraawater.html#hbv (last visited Mar. 19, 2021).
[55] *Contaminants of Emerging Concern (CEC)*, Minn. Department of Health, https://www.health.state.mn.us/communities/environment/risk/guidance/dwec/index.html#cecnom (last visited Mar. 19, 2021).
[56] *Id.*
[57] *The Minnesota Department of Health has Started a Review of PFHxA*, PFAS Central (Oct. 14, 2020), https://pfascentral.org/policy/the-minnesota-department-of-health-has-started-a-review-of-pfhxa.
[58] *Id.*

is not examining PFHxA for an HRL, or an HBV at minimum. MCEA cannot identify the results of this review and wonders how MDH intends on using the CEC Initiative going forward.[59]

MDH's use of HRLs to regulate PFAS is a critical tool. Other statutes, such as the Minnesota Environmental Response and Liability Act, are not currently being used to provided needed regulatory teeth to respond to this public health crisis.[60] HRLs are therefore the primary vehicle to reduce PFAS in the environment to safe levels.

II. REGULATORY HISTORY AND TRENDS OF PFOS, PFBS, AND PFHxS

According to a senior official from the Centers for Disease Control and Prevention, the threat of PFAS in drinking water presents "one of the most seminal public health challenges for the next decades."[61] Unfortunately, PFAS regulation is still in its infancy. Governments and regulatory bodies, including Minnesota, are doing what they can to catch-up in their efforts to address PFAS contamination. Although PFAS were developed in the early 1900s, governments have only recently taken action to control releases into the environment and to establish guidance for safe ingestion levels.

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[59] Additionally, the MPCA recently announced site-specific water quality for PFOS in Lake Elmo and connected waterbodies, Bde Maka Ska, and Pool 2 of the Mississippi River. *MPCA Announces New Protective Water and Fish Values for PFAS*, Minn. Pollution Control Agency (Oct. 1, 2020), https://www.pca.state.mn.us/news/mpca-announces-new-protective-water-and-fish-values-pfas. MCEA is interested to know how establishing new HRLs for PFAS chemicals intersected with updating fish consumption values.

[60] Jennifer Bjorhus, *With PFAS Everywhere, Minnesota Calls for Big New Crackdown on the 'Forever Chemicals'*, Star Trib. (Feb. 10, 2021), https://www.startribune.com/with-pfas-everywhere-minnesota-calls-for-big-new-crackdown-on-the-forever-chemicals/600021420/?refresh=true (reporting that the PFAS blueprint "calls for clearly designating the entire class of man-made chemicals called PFAS as a 'hazardous substance' in state law. . . require[ing] companies to disclose any PFAS they use to regulators.").

[61] Pat Rizzuto, David Schultz, & Sylvia Carignan, *CDC Sounds Alarm on Chemical Contamination in Drinking Water*, Bloomberg Law (Oct. 17,\ 2017), https://www.bloomberglaw.com/document/X5939JJ0000000?bna_news_filter=environment-and-energy&jcsearch=BNA%25200000015f2adfd07fa35feeffe4d90000#jcite.

The response at the federal level has been slow, jeopardizing the safety of countless individuals and forcing states devise their own solutions.[62] Because the federal government does not "require toxicity research before compounds enter commerce," continual toxicity assessments are necessary.[63] The EPA recently announced its intent to establish drinking water standards for PFOA and PFOS,[64] which would represent—if successful—the federal government's first regulatory standards for PFAS.[65] Although some feel encouraged that we will now "see a different administration with respect to PFAS,"[66] time is of the essence and experience tells us that federal PFAS regulation is anything but a foregone conclusion.[67] In the absence of the federal government, states have entered the void, in varying degree, to regulate PFAS chemicals. Currently, there is a "patchwork of inadequate legislation" existing to regulate PFAS.[68] If we are to respond effectively to the challenges PFAS presents, it may need to be of our own accord.

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[62] *A Persistent Problem*, *supra* note 25.

[63] *Minnesota's PFAS Blueprint* at 45 Minn. Pollution Control Agency (Feb. 2021), https://www.pca.state.mn.us/waste/minnesotas-pfas-blueprint.

[64] *EPA Takes Action to Address PFAS in Drinking Water*, U.S. Envtl. Protection Agency (Feb. 22, 2021), https://www.epa.gov/newsreleases/epa-takes-action-address-pfas-drinking-water.

[65] *A Persistent Problem*, *supra* note 25.

[66] Michelle Stocker, *Wisconsin Environmental Experts Expect Different Approach to PFAS Under Biden*, The Capital Times (Feb. 25, 2021), https://madison.com/ct/news/local/govt-and-politics/wisconsin-environmental-experts-expect-different-approach-to-pfas-under-biden/article_c5645ceb-3136-535e-ae5f-5757dd6e6471.html.

[67] *See* Glenn G. Lammi, *Consequences Must be Carefully Assessed Before PFAS are Pushed into the Superfund Quagmire*, Forbes (Sept. 26, 2019), https://www.forbes.com/sites/wlf/2019/09/26/consequences-must-be-carefully-assessed-before-pfas-is-pushed-into-the-superfund-quagmire/?sh=624c8d316c37.

[68] Erin Brockovich, *Plummeting Sperm Counts, Shrinking Penises: Toxic Chemical Threaten Humanity*, The Guardian (Mar. 18, 2021), https://www.theguardian.com/commentisfree/2021/mar/18/toxic-chemicals-health-humanity-erin-brokovich.

A. Minnesota's PFAS Regulatory History.

Minnesota's historical use of using HRLs and HBVs is outlined in the charts and discussion below. The use of HBVs is indicted in red text, while the use of HRLs is indicated in green text.

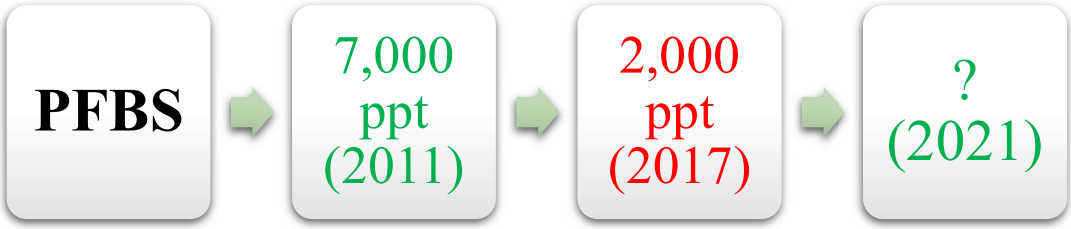
1. PFOS.

Minnesota first began regulating PFOS in drinking water in 2002 when MDH established an HBV of 1,000 ppt.[69] In setting this level, MDH necessarily relied upon the peer reviewed data available at the time, which was rather undeveloped. Seven years later, MDH established a much lower HRL of 300 ppt.[70] MDH revisited its assessment in 2017, when it lowered the HBV to 27 ppt.[71] Finally, in 2018, MDH set the existing HBV of 15 ppt, which represents a 99% decrease from the first HBV MDH set less than two decades earlier.[72] This extreme adjustment is illustrative of how rapidly the science has evolved. Outside of a 2020 "re-evaluation that used three recent

[69] *Toxicological Summary for Perflourooctane Sulfonate (PFOS)*, Minn. Dep't of Health (Aug. 2020), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf.
[70] *Toxicological Summary for Perflourooctane Sulfonate (PFOS)*, Minn. Dep't of Health (May 5, 2009), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos2010.pdf.
[71] *Id.*
[72] *Id.*

state and federal comprehensive reviews" that did not change the HBV value nor the HRL value, MDH has not revised its HRL for PFOS since 2009, nor its HBV for PFOS since 2018.[73] PFOS has been detected in public drinking water sources at levels up to 1400 ppt and in the Mississippi River at levels up to 15 ppt. [74] It has also been detected in drinking water supplies throughout the East Metro.[75]

2. PFBS.



MDH first began regulating PFBS in 2011, when it established an HRL of 7,000 ppt.[76] In 2017, MDH dramatically lowered its toxicity assessment, using an HBV, rather than an HRL, setting a level of 2,000 ppt after incorporating recently published toxicological studies for short-

[73] *Id.*; *Toxicological Summary for Perflourooctane Sulfonate (PFOS)*, Minn. Dep't\ of Health (Aug. 2020), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf.
[74] *PFOS and Groundwater*, Minn. Dep't of Health (Apr. 2019), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfosinfo.pdf.
[75] James Kelly & Karla Peterson, *Perfluorochemicals (PFCs) in the East Metro*, Minn. Dep't of Health 11-12 (Aug. 21-22, 2018), https://3msettlement.state.mn.us/sites/default/files/PFCs%20in%20the%20East%20Metro.pdf.
[76] *Toxicological Summary for Perflourobutane Sulfonate (PFBS)*, Minn. Dep't of Health (Mar. 21, 2011), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbs.pdf.

term guidance derivation.[77] PFBS has been detected in public drinking water sources at levels up to 300 ppt.[78]

3. PFHxS.

MDH established the current HBV of 47 ppt for PFHxS in 2019 a decade after it determined "there was insufficient data" at that point to establish a health value.[79] PFHxS has been detected in public drinking water sources at levels up to 570 ppt and Twin Cities metro area lakes at levels up to 150 ppt.[80]

4. Takeaways from MDH's previous regulation of PFAS.

There are two main takeaways from MDH's previous PFAs regulation. First, MDH has consistently and significantly reduced its toxicity assessments for PFAS chemicals, setting levels

[77] *Toxicological Summary for Perflourobutane Sulfonate (PFBS)*, Minn. Dep't of Health (Aug. 2020), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbssummary.pdf.
[78] *PFBS and Drinking Water*, Minn. Dep't of Health (Dec. 2017), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbsinfo.pdf.
[79] *Toxicological Summary for Perflourohexane Sulfonate (PFHxS)*, Minn. Dep't of Health (Aug. 2020), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf.
[80] *PFHxS and Groundwater*, Minn. Dep't of Health (Apr. 2019), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxsinfo.pdf.

more protective that reflect the developing science that continues to show PFAS is dangerous at extremely low levels. Second, MDH has relied upon HBVs in place of HRLs for several years, despite the fact that they are statutorily obligated to reassess HRLs every four years.[81] This overreliance on HBVs is problematic because "MDH does not use guidance values to regulate water quality"[82] and HBVs are intended to be used "between rule-making cycles,"[83] rather than ten or more years. Additionally, an exceedance does not trigger any regulatory action. Unless an agency decides to step in, drinking water supplies that exceed an HBV may continue to be used. Further, the HBVs are presently set at much lower levels than HRLs, which is a tacit admission that the existing HRLs are inadequate.

B. Other States Have Similarly Reacted To Developing Science By Continually Lowering Their Tolerance Limits For PFAS.

The downward trajectory of PFAS toxicity assessments is not unique to Minnesota. Over the past decade, several states have also continued to update their health standards for various PFAS compounds. In examining the current leading health standards across the country, it is clear that Minnesota has room to improve, particularly as it relates to PFBS, PFHxS, and PFOS. MDH cannot continue its previous trend of overreliance on HBVs; incorporating new studies and evidence only in HBVs does a disservice to Minnesota and Minn. Stat. § 103H.201, subd. 3(a). Since MDH last established HRLs for PFBS and PFOS more than ten years ago, the science has rapidly developed. Here, Minnesota has the opportunity to be a leader and a responsibility to protect its citizens.

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[81] Minn. Stat. § 103H.201, subd. 3(a).

[82] *PFOS and Groundwater*, Minn. Dep't of Health (Apr. 2019), https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfosinfo.pdf.

[83] Conceptual Drinking Water Supply Plan, *supra* note 1, at vi.

In August 2020, Michigan adopted a regulatory limit for PFBS at 420 ppt, less than ¼ of the current HRL in Minnesota.[84] Although it does not appear any other states have established limits for PFBS, in establishing Michigan's standard, state agencies "conducted a year-long review of current scientific and health data about PFAS and consulted several academic, environmental and business stakeholders."[85] Of particular concern, research from Michigan demonstrates that "PFBS is expected to travel faster and further than other PFAS released from a particular source."[86]

With respect to PFHxS, at least three states have more protective standards than Minnesota: Massachusetts, New Hampshire, and Vermont.[87] All three states have standards less than ½ of the current HRL in Minnesota. The Massachusetts and Vermont standards were established as coordinated efforts, setting limits that factor in the composition of various PFAS compounds to set a total PFAS limit.[88] On the other hand, New Hampshire developed a specific standard for PFHxS which is the most protective in the country.[89] In announcing this standard, New Hampshire pointed out that their limits were adopted "[u]sing the most recent and best science available."[90] Notably,

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[84] *Michigan Adopts Strict PFAS in Drinking Water Standards*, State of Michigan (July 22, 2020), https://www.michigan.gov/som/0,4669,7-192-47796-534660--,00.html.
[85] *Id.*
[86] *Perfulorobutane Sulfonic Acid (PFBS) Chemistry, Production, Used, and Environmental Fate in Michigan,* AECOM (Sept. 23, 2019), https://www.michigan.gov/documents/pfasresponse/Perfluorobutane_Sulfonic_Acid_PFBS_Chemistry_Production_Uses_and_Environmental_Fate_704238_7.pdf.
[87] *Per- and Polyfluoroalkyl Substances (PFAS)*, ASDWA, https://www.asdwa.org/pfas/ (last visited Mar. 18, 2021).
[88] *Final PFAS Maximum Contaminant Level (MCL) and Updates*, Mass. Dep't of Envtl. Protection (Sept. 24, 2020), https://www.mass.gov/doc/final-pfas-maximum-contaminant-level-mcl-and-updates/download; *Per and Polyfluoroalkyl Substances (PFAS)*, Vt. Dep't of Envtl. Conservation, https://dec.vermont.gov/water/drinking-water/water-quality-monitoring/pfas (last visited Mar. 18, 2021).
[89] *NHDES Submits Final Rulemaking Proposal for PFOA, PFOS, PFHxS, and PFNA*, N.H. Dep't of Envtl. Servs. (June 28, 2019), https://www4.des.state.nh.us/nh-pfas-investigation/?p=1044.
[90] *Id.*

all three of these PFHxS standards were adopted within the last two years, indicating that they better reflect where recent research stands.

As previously mentioned, PFOS is one of the better understood PFAS compounds. Minnesota's current HRL of 300 ppt is severely behind its own HBV developments and the other states that have established standards for PFOS. Minnesota's most recent PFOS HBV of 15 ppt is similar to where other states have established regulatory limits.[91] In July 2020, New York announced a standard of 10 ppt, the most protective in the country.[92] This standard was promoted by New York's Drinking Water Quality Council, "comprised of academic scientists, engineers, public water system professionals, and experts from the New York State Departments of Health and Environmental Conservation," who "followed the available science regarding potential health impacts.[93] Similarly, in June 2020, New Jersey released a PFOS standard of 13 ppt, after several water quality expects "reviewed numerous health studies."[94]

Many states, including Minnesota, have continued to make their PFAS standards more protective, and of the states who have acted recently, it is clear that they are establishing even more protective limits. Establishing significantly more protective HRLs for PFBS, PFHxS, and PFOS

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[91] *Per- and Polyfluoroalkyl Substances (PFAS)*, ASDWA, https://www.asdwa.org/pfas/ (last visited Mar. 18, 2021) (noting the following state limits: New York (10 ppt), New Jersey (13 ppt), New Hampshire (15 ppt), Michigan (16 ppt), Massachusetts (20 ppt), Vermont (20 ppt).

[92] *Governor Cuomo Announces First in the Nation Drinking Water Standard for Emerging Contaminant 1,4-Dioxane*, State of New York (July 30, 2020), https://www.governor.ny.gov/news/governor-cuomo-announces-first-nation-drinking-water-standard-emerging-contaminant-14-dioxane.

[93] *Id.*

[94] *Affirming National Leadership Role, New Jersey Publishes Formal Stringent Drinking Water Standards for PFOA and PFOS*, N.J. Dep't of Envtl. Protection (June 1, 2020), https://www.nj.gov/dep/newsrel/2020/20_0025.htm#:~:text=In%202018%2C%20New%20Jersey%20became,for%20perfluorononanoic%20acid%2C%20or%20PFNA.&text=To%20date%2C%20New%20Hampshire%20and,drinking%20water%20standards%20for%20PFAS.

would be both consistent with the approach of other states and reflective of the rapidly developing science.

III. DEVELOPING SCIENTIFIC RESEARCH ON PFBS, PFHxS, AND PFOS

The science is still developing on the human health risks associated with consuming PFAS.[95] This is unsurprising, as most academic research of PFASs did not commence until the early 2000s.[96] But what we do know is startling. The battery of known health complications linked to PFAS consumption include thyroid disease,[97] kidney cancer,[98] hypercholesterolemia,[99] and more.[100] Minnesota's own risk assessments for PFAS demonstrate "many toxic effects, impacting multiple organ systems.[101] Sensitive populations are especially at risk. High prenatal exposure to PFAS via the placenta is associated with low birth weight.[102] PFAS exposure in children is

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[95] *Minnesota's PFAS Blueprint*, supra note 12, at 42 ("The scientific literature regarding PFAS toxicity and occurrence is evolving rapidly; MDH is conducting ongoing literature searches to identify if new data warrant revising existing risk assessments. This is a significant effort."). Notably, in 2017 the Environmental Protection Agency identified PFOS and PFOA, two of the most researched PFAS compounds, as an "emerging concern," further evincing how little we truly understand the impact these chemicals have on human health. *Technical Fact Sheet – PFOS and* PFOA, U.S. Envtl. Protection Agency (Nov. 2017), https://www.epa.gov/sites/production/files/2017-12/documents/ffrrofactsheet_contaminants_pfos_pfoa_11-20-17_508_0.pdf.

[96] Elsie M. Sunderland et al., *A Review of the Pathways of Human Exposure to Poly- and Perfluoroalkyl Substances and Present Understanding of Health Effects*, 29(2) J. Expo. Sci. Envtl. Epidemiology 131-47 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6380916/.

[97] Bevin E. Blake et al., *Associations Between Longitudinal Serum Perfluoroalkyl Substance (PFAS) Levels and Measures of Thyroid Hormone, Kidney Function, and Body Mass Index in the Fernald Community Cohort*, 242(A) Envtl. Pollution 894-904 (Nov. 2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6309414/.

[98] *Probable Link Evaluation for Chronic Kidney Disease*, C8 Sci. Panel (Oct. 29, 2012), http://www.c8sciencepanel.org/pdfs/Probable_Link_C8_Kidney_29Oct2012.pdf.

[99] *Probable Link Evaluation for heath disease*, C8 Sci. Panel (Oct. 29, 2012), http://www.c8sciencepanel.org/pdfs/Probable_Link_C8_Heart_Disease_29Oct2012.pdf.

[100] *Toxicological Profile for Perfluoroalkyls: Draft for Public Comment Chapter 2* at 5, U.S. Agency for Toxic Substances and Disease Registry (May 2009), https://www.atsdr.cdc.gov/toxprofiles/tp200-c2.pdf.

[101] *Minnesota's PFAS Blueprint*, *supra* note 12, at 42.

[102] Eleni Papadopoulou et al., *Exposure of Norwegian Toddlers to Perfluoroalkyl Substances*, Envtl. Int'l (July 2016), https://www.researchgate.net/profile/Eleni_Lila_Papadopoulou/publicati

associated with lower bone mineral density.[103] And PFAS consumption is associated with elevated incidence of developmental, autoimmune, and kidney disorders among children under eighteen years of age.[104]

Moreover, many PFAS bioaccumulate in humans, meaning "they have a long residence time in living things and can be transferred through food chains."[105] Exposure to these chemicals is irreversible, and as individuals continue ingesting PFAS, even in trace amounts, "the level of PFAS in their bodies may increase to the point where they suffer from adverse health effects."[106] The established science is clear: PFAS contamination is a public health crisis that deserves a robust response.

There are many recent publications documenting new or developed understandings of the toxicity of PFAS as it relates to immune system dysfunction.[107] Just this week, it was reported that

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on/305624668_Exposure_of_Norwegian_toddlers_to_perfluoroalkyl_substances_PFAS_The_association_with_breastfeeding_and_maternal_PFAS_concentrations/links/59c0c482a6fdcca8e572b0ad/Exposure-of-Norwegian-toddlers-to-perfluoroalkyl-substances-PFAS-The-association-with-breastfeeding-and-maternal-PFAS-concentrations.pdf.

[103] Charles W. Schmidt, *Reduced Bone Mineral Density in Children*, 128(4) Envtl. Health Perspectives (Apr. 2020), https://ehp.niehs.nih.gov/doi/pdf/10.1289/EHP6519.

[104] Bindu Panikkar et al., *Making the Invisible Visible*, Environmental Health (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6717361/.

[105] Jacob Hildebrand, Noelle-Nadia Filali, & Sydney Widell, *Proactive Prediction: Mapping PFAS Risk in Dane County*, Univ. of Wis. Undergraduate Colloquium (Dec. 16, 2019), https://minds.wisconsin.edu/bitstream/handle/1793/80359/Hildebrand%20Filali%20Widell.pdf?sequence=1.

[106] *Basic Information on PFAS*, U.S. Envtl. Protection Agency, https://www.epa.gov/pfas/basic-information-pfas (last visited Dec. 4, 2020).

[107] CM Bulka et al., *Associations of Exposure to Perfluoroalkyl Substances Individually and in Mixtures with Persistent Infections: Recent Findings from NHANES 1999-2016*, Envtl. Pollution (Jan. 29, 2021), https://europepmc.org/article/med/33578314; Phillipe Grandjean et al., *Severity of COVID-19 at Elevated Exposure to Perfluroinated Alkylates*, PLoS One 15(12), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0244815.

chemicals like PFAS may forebode the loss of humanity's ability to reproduce.[108] There is also new evidence on DNA methylation that suggestions effects on prenatal programming.[109] Recent studies on PFOS suggest that PFOS has significantly negative impacts on learning and memory[110] and heart development.[111] A recent study on PFBS and PFHxS demonstrates that they disrupt stem cell development.[112] A recent study on PFHxS analyzed its effects on brain development.[113]

Although there is certainly much we do not yet know about PFAS, what we do know is alarming. Further, as more research continues, it will likely reveal that PFAS are more dangerous than previously understood, as experience has demonstrated. Setting new and significantly more protective HRLs for PFBS, PFHxS, and PFOS will provide a substantial improvement to the health and well-being of all Minnesotans; however, the science is rapidly progressing, and Minnesota will necessarily have to reassess the toxicity for all PFAS moving forward. We simply do not know

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[108] Erin Brockovich, *Plummeting Sperm Counts, Shrinking Penises: Toxic Chemical Threaten Humanity*, The Guardian (Mar. 18, 2021), https://www.theguardian.com/commentisfree/2021/mar/18/toxic-chemicals-health-humanity-erin-brokovich.

[109] Sonia L. Robinson et al., *Perfluorooctanoic Acid (PFOA) or Perflourooctane Sulfonate (PFOS) and DNA Methylation in Newborn Dried Blood Spots in the Upstate KIDS Cohort*, Envtl. Research (Mar. 2021), https://pubmed.ncbi.nlm.nih.gov/33387539/; Anne P. Starling et al., *Prenatal Exposure to Per- and Polyfluoroalkyl Substances, Umbilical Cord Blood DNA Methylation and Cardio-Metabolic Indicators in Newborns: The Healthy Start Study*, Envtl. Health Perspectives (Dec. 2020), https://pubmed.ncbi.nlm.nih.gov/33356526/.

[110] Abdallah Mshaty et al., *Neurotoxic Effects of Lactational Exposure to Perfluorooctane Sulfonate on Learning and Memory in Adult Male Mouse*, 145 Food & Chem. Toxicology (Nov. 2020), https://www.sciencedirect.com/science/article/abs/pii/S0278691520306001.

[111] Ren Zhou et al., *Combined Effects of BPA and PFOS on Fetal Cardiac Development: In Vitro and In Vivo Experiments*, 80 Envtl. Toxicology & Pharmacology (Nov. 2020), https://www.sciencedirect.com/science/article/pii/S1382668920301101.

[112] Shuyu Liu, *The Short-Chain Perfluorinated Compounds PFBS, PFHxS, PFBA, and PFHxA Disrupt Human Mesenchymal Stem Cell Self-Renewal and Adipogenic Differentiation*, 88 J. Envtl. Sciences 187-99 (Feb. 2020), https://www.sciencedirect.com/science/article/abs/pii/S1001074219307314.

[113] Louise Ramhoj et al., *Evaluating Thyroid Hormone Disruption: Investigations of Long-Term Neurodevelopmental Effects in Rats After Perinatal Exposure to Perfluorohexane Sulfonate (PFHxS)*, Scientific Reports (Feb. 14, 2020), https://www.nature.com/articles/s41598-020-59354-z.

what we do not know, and any toxicity assessment must strategically build in measures for precaution.

CONCLUSION

PFAS pose a fundamental threat to human health. Action is needed now to ensure this growing public health crisis does not overwhelm Minnesota's drinking water supplies in the coming years. MCEA appreciates MDH's effort to make current HRLs for three PFAS compounds; this is a vital step towards ensuring the state's drinking water supplies remain safe to consume. But more work needs to be done. MDH should take this opportunity to revisit its guidance levels for all currently known PFAS, and follow its statutory obligation to update PFAS HRLs every four years. Minnesotans demand its state agencies react swiftly and strongly to contaminants threatening our drinking water. MCEA expects MDH—and all other state regulators—to allocate the money and expertise needed to solve this problem. MCEA looks forward to continued engagement with MDH as it advances towards establishing updated HRLs.

Respectfully submitted,

/s/Jay Eidsness
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November 30, 2022

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RE: MCEA's Response to Request for Comments submitted March 22, 2021.

Dear Jay Eidsness and Sam Brower:

The Minnesota Department of Health (MDH) has a long history regarding development of human health-based guidance (HBG) for per- and polyfluoroalkyl substances (PFAS). In 2002 MDH was among the first states to derive HBG for PFOA and PFOS and has repeatedly revised the values as new toxicity information has become available. MDH currently has HBG for six PFAS compounds (PFBA, PFHxA, PFOA, PFBS, PFHxS, and PFOS). MDH re-evaluates HBG values when significant new scientific information becomes available. The guidance values for each of these PFAS includes a database uncertainty factor, which is intended to address the potential that additional toxicity data could result in a lower point of departure.

In addition to the individual HBG for each PFAS, MDH under the Health Risk Limit (HRL) rules requires an additivity assessment when contaminants that affect the same health endpoint occur in mixtures. PFAS virtually always occur in mixtures and therefore the combined risk must be assessed by calculating a Health Risk Index (HRI). For each PFAS a ratio is calculated by comparing the water concentration to the HBG for that chemical and then summing the ratios to calculate an HRI. Even if the individual ratios do not exceed 1 the combined ratios may exceed 1. MDH calculates and makes decisions based on the combined HRI. For example, see the Interactive Dashboard for PFAS Testing in Drinking Water webpage for how this is implemented.

MDH has also been a leader for protecting the most sensitive and most highly exposed individuals by publishing and freely sharing new methods for incorporating placental and breastmilk transfer of PFAS compounds to infants (Goeden et al 2019).

MDH has promulgated new or revised HRL values on a regular basis since 2008/2009 (rules updated 2010/2011, 2012/2013, 2014/2015, and 2016/2018). MDH had intended to propose rules in early 2020, but unfortunately all staff who derive HBG were reassigned to COVID activities, several through the fall of 2021. As a result, there was a delay in revision of the HRL rules as well as any chemicals under review. For example, the review of PFHxA was announced in October 2020 but was not completed until December of 2021 due to staff COVID reassignments. PFBS, PFHxA, and PFHxS are included in the

proposed HRL rules revision. A complete list of contaminants currently included in the rules revision can be found at: Health Risk Limits Rules Amendments - Contaminants - EH: Minnesota Department of Health. The proposed values for PFOA and PFOS were recently withdrawn from the proposed rules (GovDelivery notice sent July 20, 2022) and a re-evaluation, focusing on epidemiology data, has been initiated (GovDelivery notice sent September 29, 2022). To keep abreast of MDH's activities it is recommended that interested parties subscribe to the free GovDelivery service. Subscribing can be done by going to MDH's Human Health-Based Water Guidance webpage and entering an email address in the box near the "Get email updates" text at the bottom of the page.

Under the Groundwater Protection Act of 1989, MDH is authorized to derive HRLs using US Environmental Protection Agency (US EPA) risk assessment methods. These standard methods require sufficient relevant mammalian toxicity data. As discussed at the 2022 annual Contaminants for Emerging Concern (CEC) meeting, over 40 PFAS compounds have been nominated to MDH's CEC Initiative, however, more than 80% do not have sufficient *in vivo* mammalian toxicity data to derive HBG utilizing standard risk assessment methodology. PFAS are a very large group of diverse substances and treating them as a single group is not scientifically supportable. As presented at the 2022 annual meeting, MDH is partnering with US EPA to explore the use of recently released *in vitro* bioassay data for several of the PFAS of concern in Minnesota that do not have sufficient *in vivo* data. US EPA and MDH staff will review and determine whether the *in vitro* information can be used to group and identify surrogates and/or to derive relative potency factors so that risk context for additional PFAS compounds can be provided. MDH has previously utilized surrogates until sufficient chemical specific data becomes available. Identifying and utilizing a surrogate does require information regarding chemical similarity. For example, based on structural, toxicokinetic, and limited toxicity data PFOS was used as a surrogate for PFHxS from 2013 until 2017. A copy of the annual meeting slides and accompanying narrative as well as a summary of questions and answers can be found on MDH's Contaminants of Emerging Concern webpage.

Since its inception in 2010 MDH's CEC initiative has completed screening and prioritization of over a hundred contaminants as well as completed full reviews and guidance derivation for nearly 50 unique contaminants. A full list of the contaminants that have been nominated and evaluated by the CEC initiative can be found at: Updated Nominated Status Table December 2021 (PDF).

The Health Risk Limit rules are not regulatory in nature and do not include or mandate use of the guidance values. MDH's Drinking Water Program implements the federal Safe Drinking Water Act (SDWA). Under the SDWA Maximum Contaminant Levels are enforceable standards, MDH's HRLs are not enforceable standards. Because PFAS are not currently regulated under the SDWA, MDH works with local water suppliers to reduce health risks but cannot require that action be taken.

Health-Based Values (HBVs) represent MDH's recommended guidance value and are the values incorporated into the Additivity Calculator (Excel) for assessing potential individual as well as combined risks. HBVs as well as HRLs can be referenced in rules promulgated by other state agencies for regulatory purposes. Some regulatory programs have referenced both the HRLs and HBVs in regulatory documents

such as consent decrees or permits. MDH is committed to promulgating HBVs for contaminants that have been found in Minnesota's groundwater in a timely manner as its resources allow.

Thank you again for submitting your comments regarding the HBVs being considered for adoption into HRL rules. We encourage you to subscribe to our email updates on this topic if you have not already done so.

If you have additional questions or concerns we invite you to contact us at health.risk@state.mn.us or 651-201-4899 to arrange a continued discussion.

Sincerely,

/s/ Sarah Johnson

Sarah Fossen Johnson, Supervisor

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Resources:

Additivity Calculator (Excel)
(https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/guidance.xlsx)

Contaminants of Emerging Concern
(https://www.health.state.mn.us/communities/environment/risk/guidance/dwec/index.html)

Goeden, H. M., Greene, C. W., & Jacobus, J. A. (2019). A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. *Journal of exposure science & environmental epidemiology*, *29*(2), 183-195. (https://pubmed.ncbi.nlm.nih.gov/30631142/)

"Get Email Updates" on Health-Based Water Guidance
(https://public.govdelivery.com/accounts/MNMDH/subscriber/new?topic_id=MNMDH_39)

Health Risk Limits Rules Amendments - Contaminants - EH: Minnesota Department of Health
(https://www.health.state.mn.us/communities/environment/risk/rules/water/chemicals.html)

Human Health-Based Water Guidance webpage
(https://www.health.state.mn.us/communities/environment/risk/guidance/gw/table.html)

Interactive Dashboard for PFAS Testing in Drinking Water webpage
(https://www.health.state.mn.us/communities/environment/water/pfasmap.html)

Nominated Contaminant Status and Information (PDF)
(https://www.health.state.mn.us/communities/environment/risk/docs/guidance/dwec/chemstatus.pdf)

I.1.c. Written Comment: Request for Comments- Nonylphenol

I.1.c.i. Comment
Date: March 13, 2022
Chemicals: Nonylphenol
Commenter: Alkylphenols and Ethoxylates Research Council (APERC)

I.1.c.ii. Minnesota Department of Health's Preliminary Response
Date: January 3, 2023

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May 13, 2022

Nancy Rice
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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

Barbara S. Losey
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)

Nonylphenol – Critical Effect

Meeting with Minnesota Department of Health

December 15, 2022

Thomas G. Osimitz, PhD, DABT

Alkylphenols and Ethoxylates Research Council (APERC)

Agenda

- Introductions
- Purpose of Meeting
  - Selection of Critical Effects
- Scientific overview
  - Review of histopathology
  - Adverse? Renal toxicity - weight of evidence
- Regulatory overview
  - Comparative assessments
- Recommendations
- Discussion

Preview – Conclusions

- Renal mineralization seen at some dose(s) in all three pivotal studies
  - It was low incidence and low severity
  - No other renal effects accompany the mineralization
- Mineralization is a frequent finding in rat studies
  - Possible mineral imbalance, gut flora, etc.
- Mineralization alone at the low dose in a single study should not be considered a critical effect

Present MDH Assessment

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 20 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0049 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 21.7 rounded to **20 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.485/100 = 0.0049 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	1.94 mg/kg-d (administered dose $BMDL_{10}$, NTP 1997/Chapin 1999, subchronic exposure)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.94 mg/kg-d x 0.25 = 0.485 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability and 3 for subchronic to chronic extrapolation
Critical effect(s):	Renal mineralization in male rats

Present MDH Assessment

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 40 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

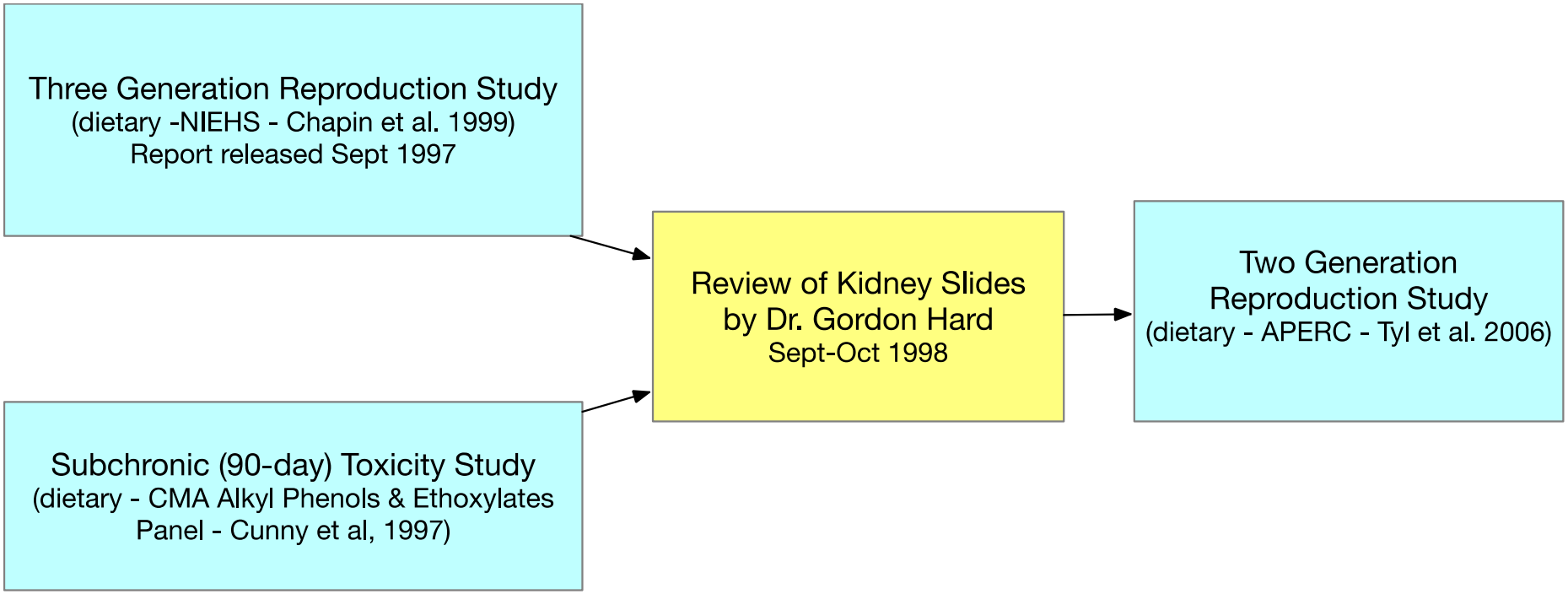
$$= \frac{\text{(0.016 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 43.2 rounded to **40 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.485/30 = 0.016 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	1.94 mg/kg-d (administered dose $BMDL_{10}$, NTP 1997/Chapin 1999)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.94 mg/kg-d x 0.25 = 0.485 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Renal mineralization in male rats
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Focus - Pivotal Studies



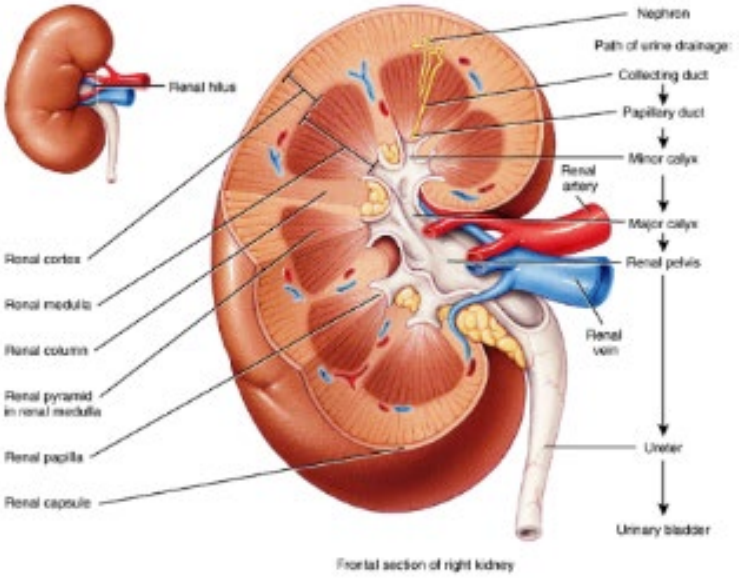
Review of Cunny et al. and Chapin et al.

- Conducted by Gordon Hard, BVSc, PhD, DSc, FRC Pat, FRCVS, FATS (noted renal pathologist)
- Goal: review kidney tissue using same pathologist, criteria, and nomenclature

Renal Mineralization

- Nature of the effect
  - Renal anatomy and pathology
- NP association – study data
- Causes
  - Chemical and non-chemical
- Gauging Adversity
  - LOAEL or LOEL

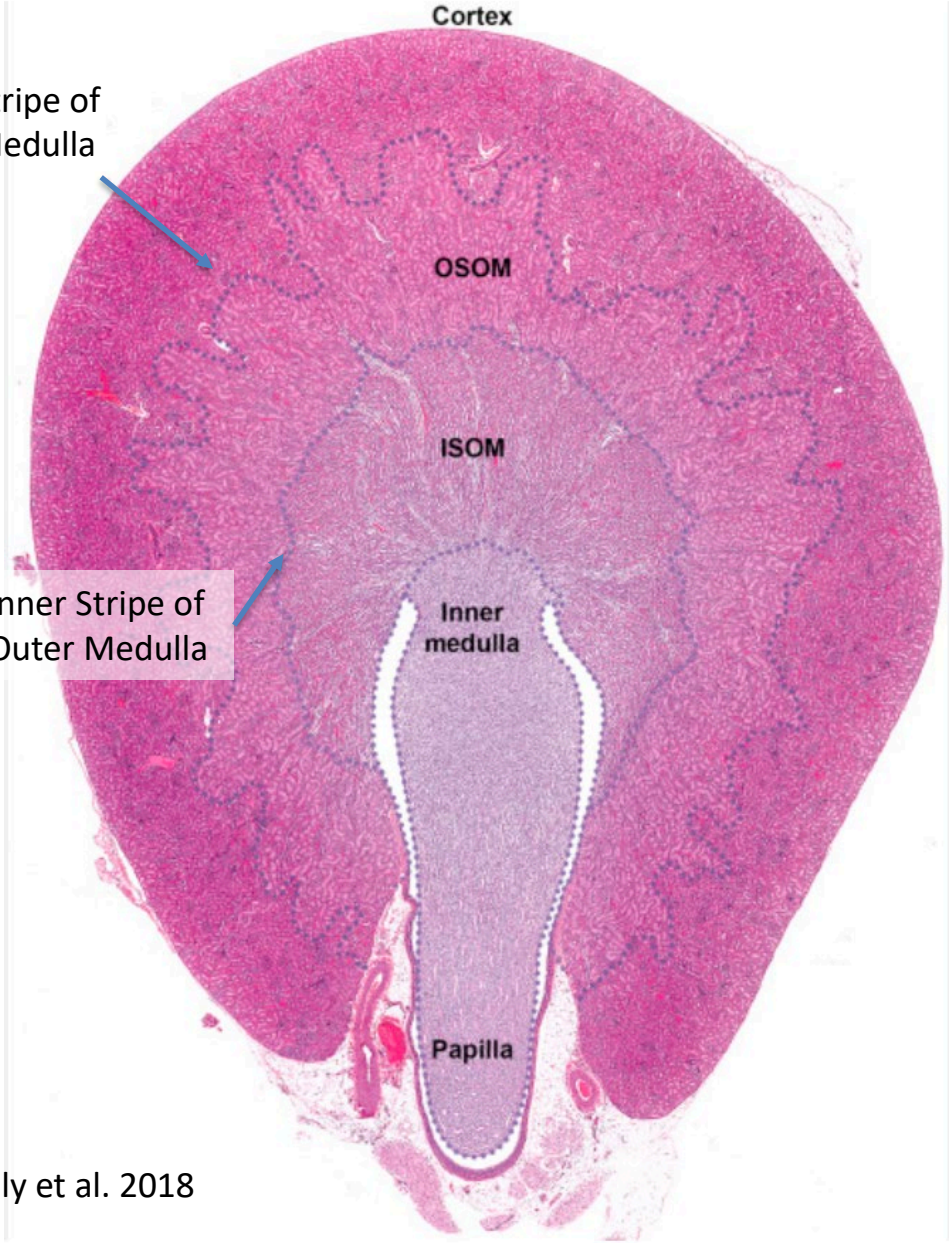
Renal Orientation



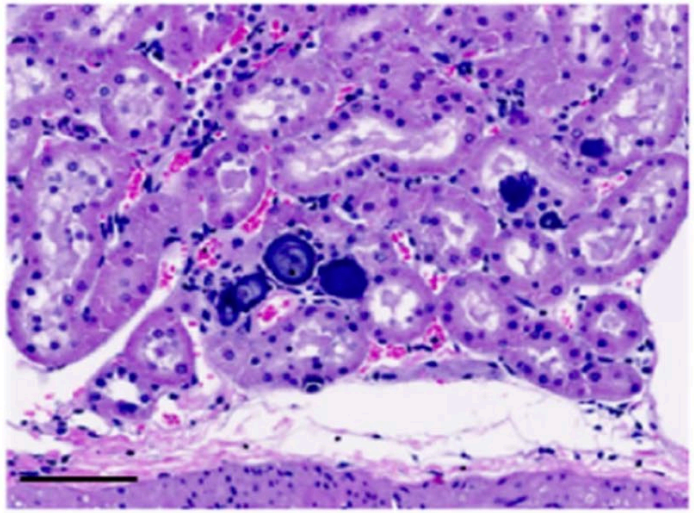
Maurya et al. 2018

Outer Stripe of Outer Medulla

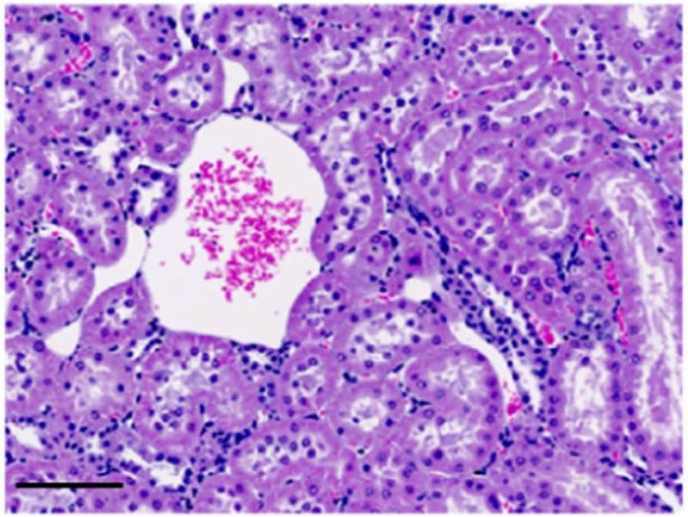
Inner Stripe of Outer Medulla



Seely et al. 2018



Mineralization (tubular)

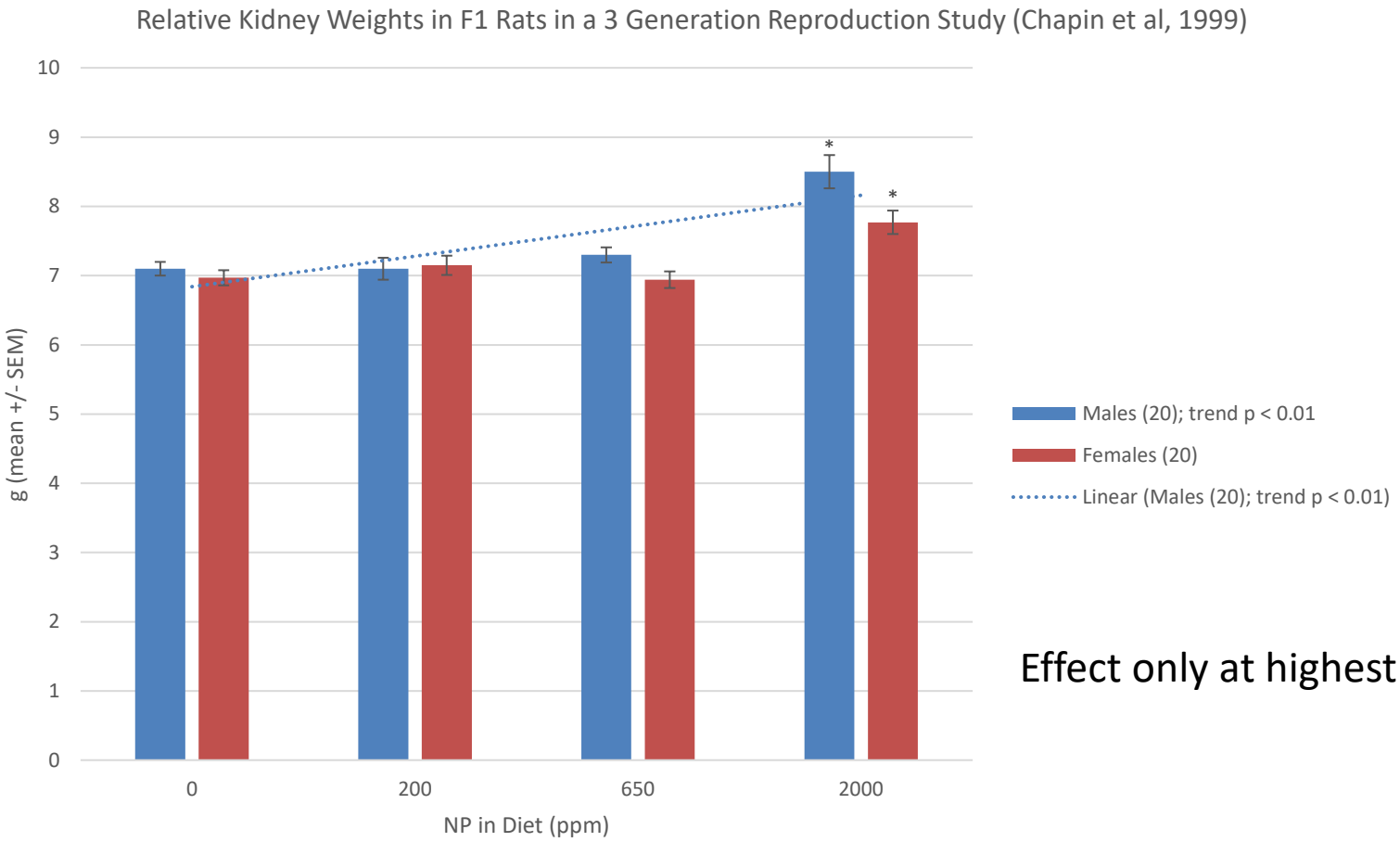


Normal tubular histology

Byun et al. (2022)

Chapin et al. – Closer Look

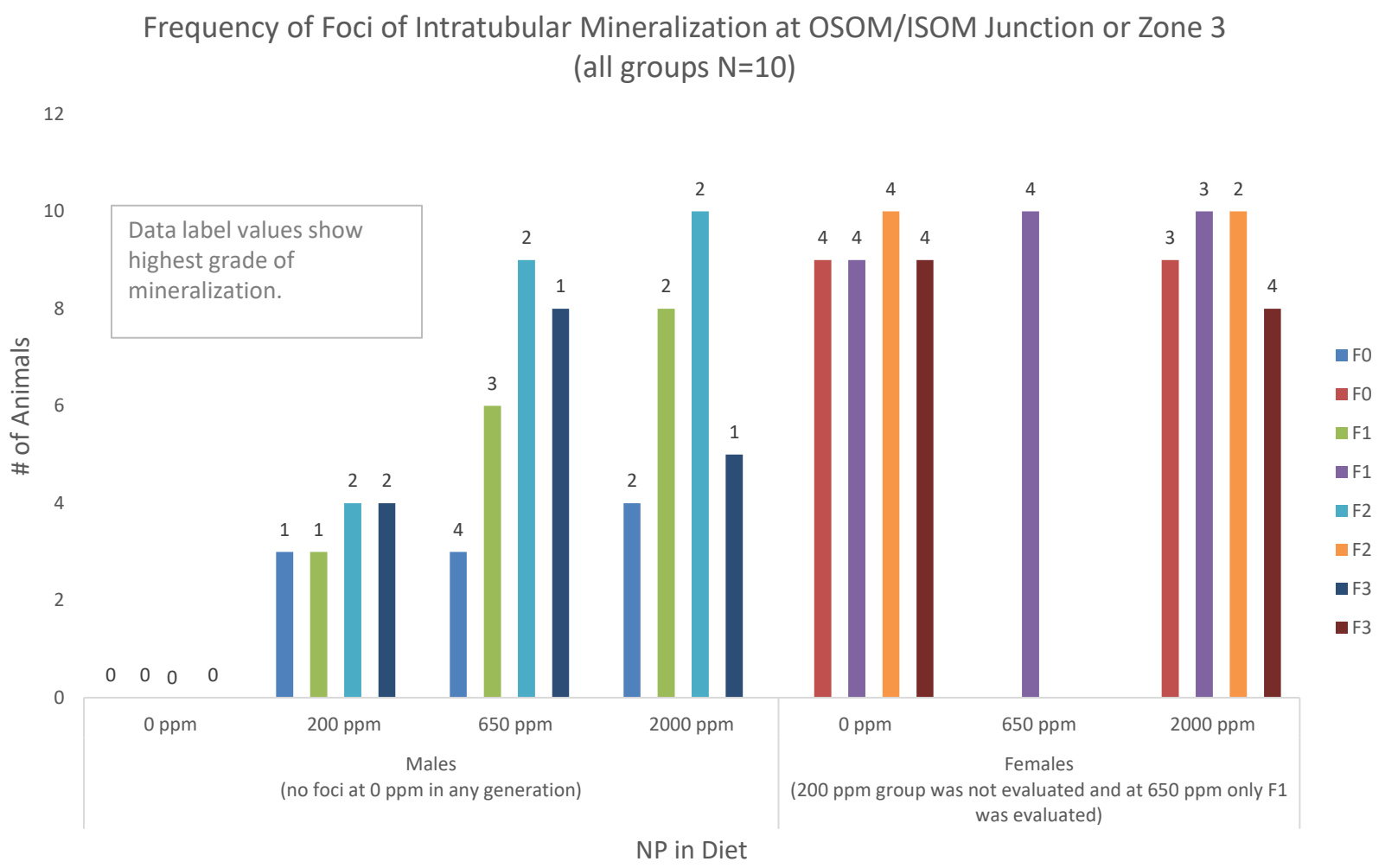
(From Hard, 1998)



Effect only at highest dose

Chapin et al. – Closer Look

(From Hard, 1998)



Mineralization at low grade and low incidence in males at 200 ppm

Chapin et al. – Closer Look

(From Hard, 1998)

Other changes which showed an association with treatment in high-dose (and sometimes mid-dose) rats of the F1, F2 and F3 generations (but not in the 90-day study or F0 generation) were cystic tubules and/or fibrotic areas, scattered or sporadic dilated tubules, granular or cellular casts, and foci of mononuclear cell inflammation, all at the OSOM/ISOM junction or in zone 3. In addition, some treated animals in the F2 and F3 generations had tubular involvement suggestive of pyelonephritis. The PWG identified hydronephrosis above control levels in the males of the F1, F2 and F3 generations, which was generally confirmed during this review. However, the PWG did not consider the observed hydronephrosis to have a definitive treatment relationship. Nevertheless, this condition can reflect chronic inflammation or obstruction in the lower urinary tract (Hard et al., 1998), and possibly may be a further indication of some intercurrent process superimposed on the treatment.

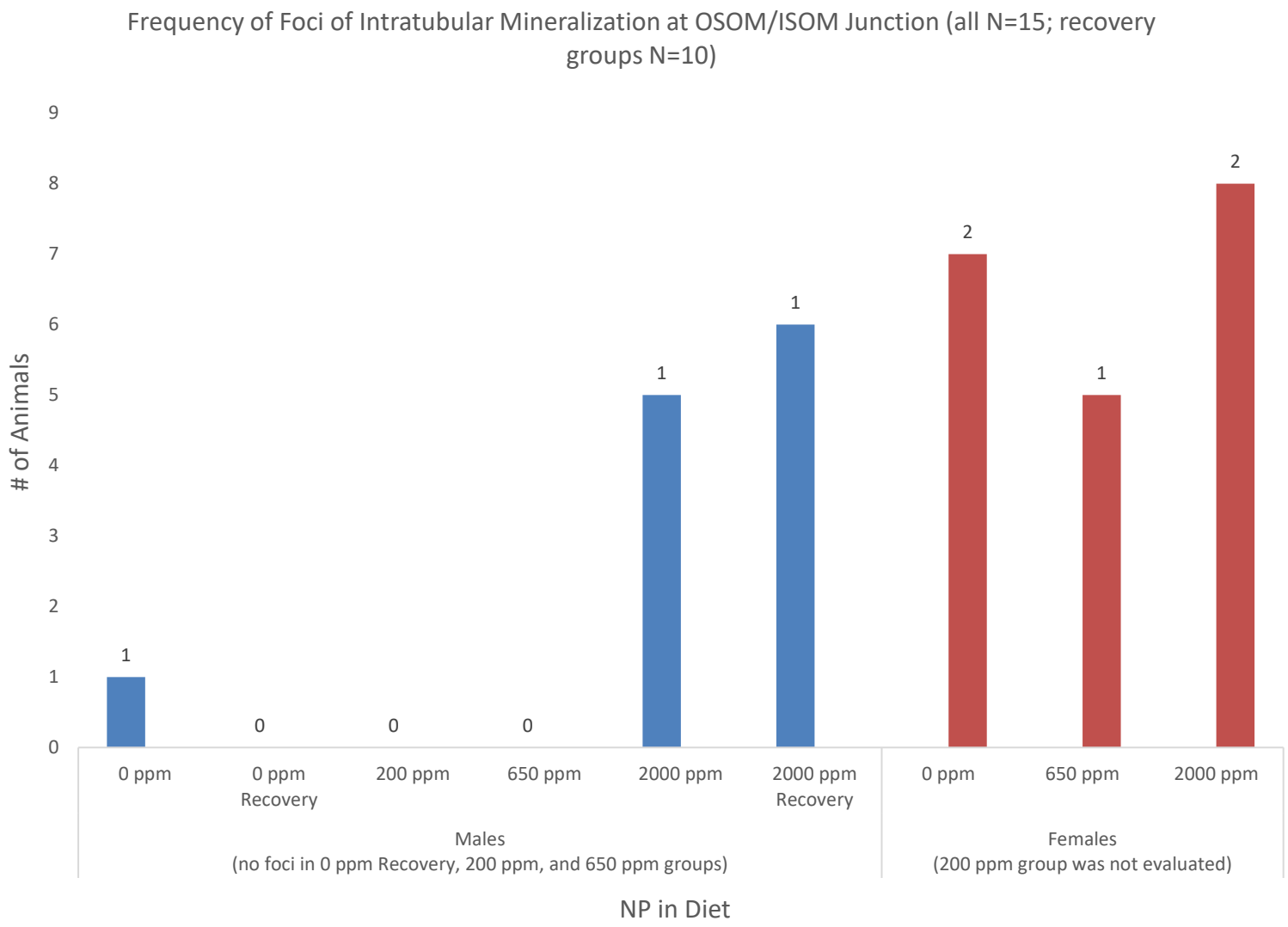
Cunny et al. – Closer Look

(from Hard, 1998)

- "The only treatment-related pathological effect observed was an increase in the frequency of deposits of intratubular mineralization in the P3 (straight) of the proximal tubule at the OSOM/ISOM junction in the high does males. In this group, 11 of 25 rats had such mineral deposits compared to none in the lower dose groups and 1 of 25 control rats. A similar treatment related effect not observed in female rats because foci of intratubular mineralization in all groups, controls were comparable."

Cunny et al. – Closer Look

(from Hard, 1998)



Mineralization in all female dose groups, but only high dose in males

Cunny et al. – Closer Look

(from Hard, 1998)

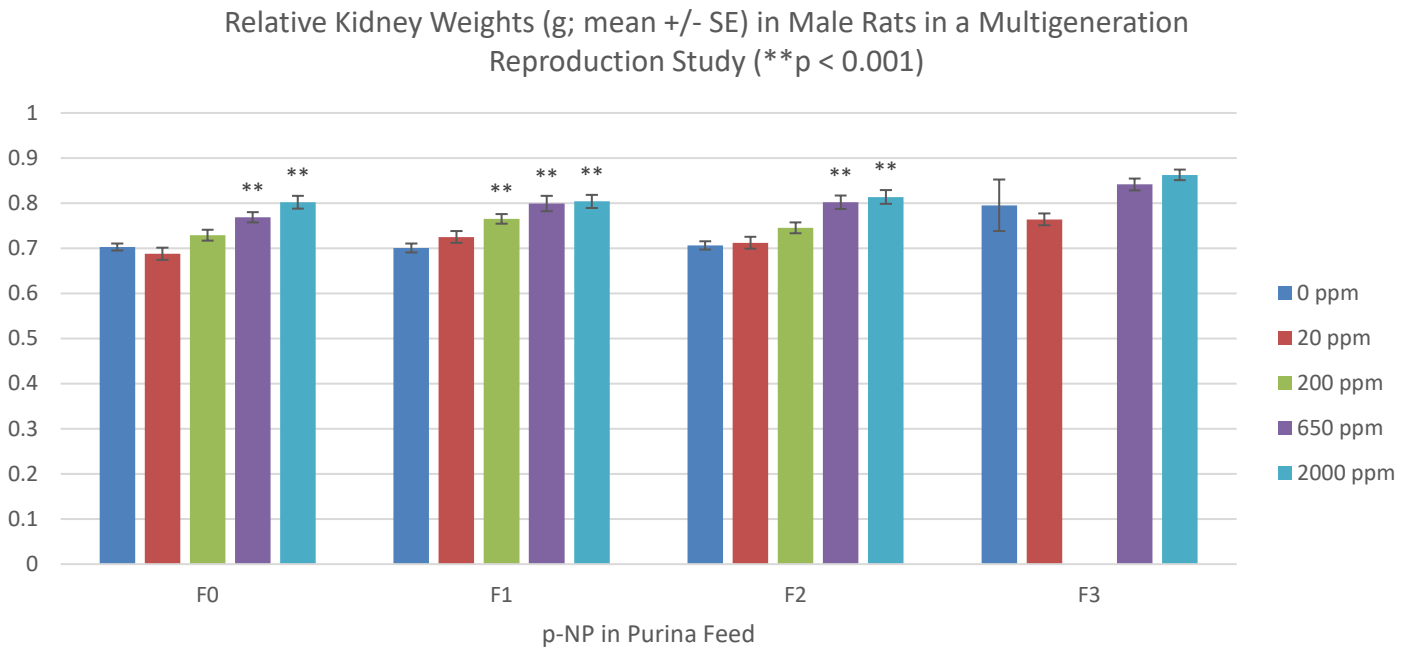
- Mineralization may represent calcium phosphate formation - frequently associated with a decrease in the dietary calcium/phosphorus ratio below 1.0. The rat is considered less able than other species to cope with disturbance in calcium homeostasis, with female rats more prone to renal tubular mineralization than male rats, “as estrogen levels may play a role in the process” (Hard, 1998; p. 8).

Tyl et al. – Another Look

- This study evaluated the potential for dietary para-nonylphenol (NP; CAS No. 84852-15-3) to affect parental fertility and growth and development of three offspring generations in CD (SpragueDawley [SD]) rats, including sperm counts across generations to determine the validity of equivocal reductions observed in the F2 generation by R. E. Chapin et al. (1999, Toxicol. Sci. 52, 80–91). Male rat kidney toxicity was also examined based on inconsistent observations in NP-exposed rats at 2000 ppm but not at 200 or 650 ppm in Purina 5002 (H. C. Cunny et al., 1997, Regul. Toxicol. Pharmacol. 26, 172–178) and at all of these NP concentrations in NIH-07 diet

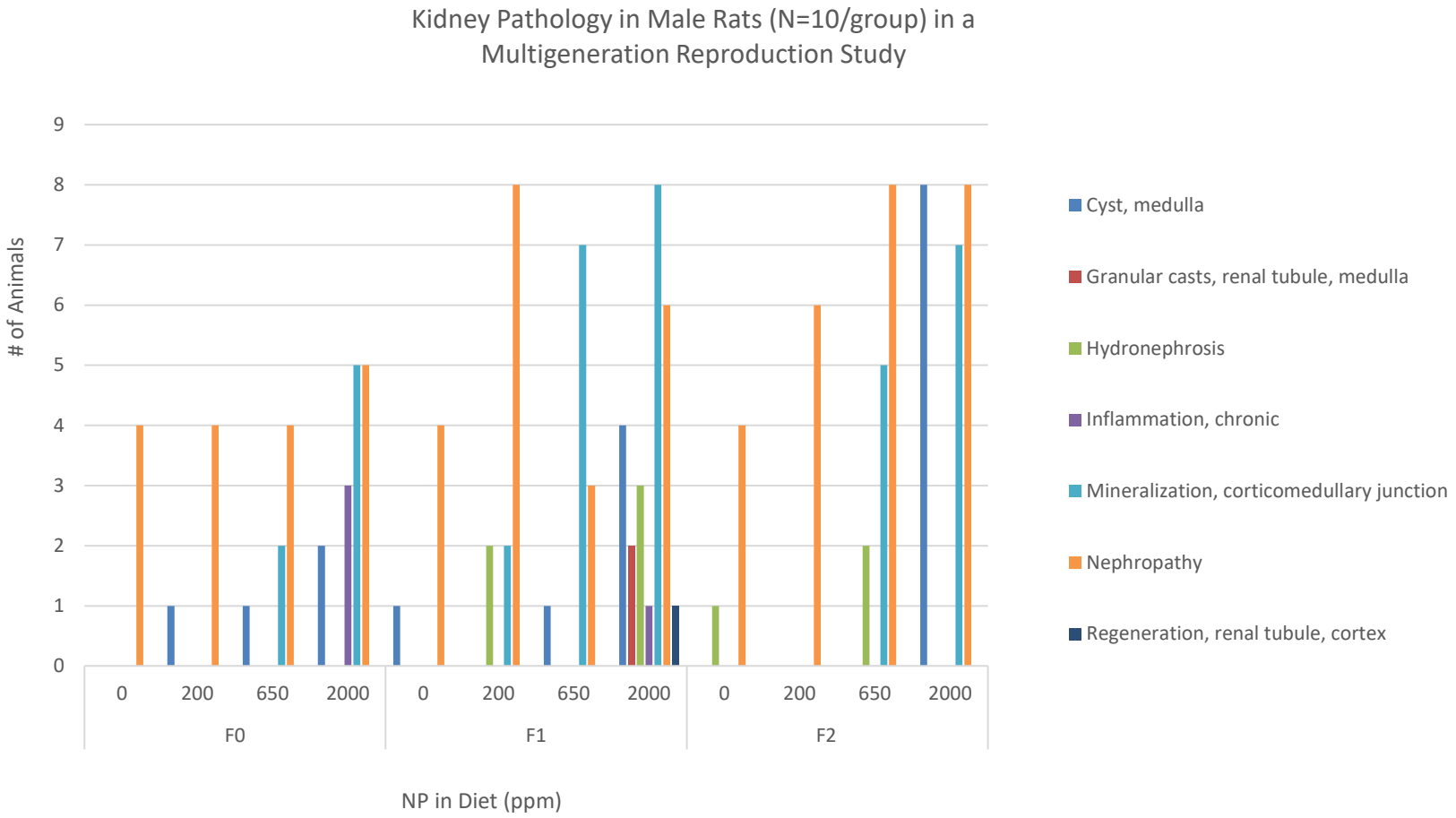
- Kidney toxicity (histopathology) occurred at 650 and 2000 ppm with no clear difference for the two diets.

Tyl et al. – Another Look



Effects if any only at highest 2 or 3 doses

Tyl et al. – Another Look



No mineralization at low dose (200 ppm) in F0, F2, and only 2/10 males in F1

Perspectives on Mineralization

Perspectives on Mineralization

“Renal mineralization is usually seen in female rats fed a semisynthetic diet but is also seen with regular laboratory feed (Figure 11.38). 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 mineralization quickly. Mineralization may be observed with other forms of renal disease including hyaline droplet nephropathy, dystrophic calcification, and end-stage CPN disease.”

Seely et al. 2018

Perspectives on Mineralization

"Mineralization is commonly observed in the area of the outer stripe and inner stripe of the outer medulla."

"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*. Mineralization may be induced by chemicals, hormones, or diet."

"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."

*No evidence for this in NP studies

NTP Non-neoplastic lesion atlas

Perspectives on Renal Effects (including mineralization) in Rats

"Comparing previous studies with this one (where the dose and route of exposure of NP are the same, but the diet is not),the striking difference in the severity of Polycystic Kidney Disease (PKD) observed leads to the conclusion that the renal toxicity of NP is highly dependent on the diet on which the animals are maintained. Furthermore, there appear to be some protective effects associated with soy-meal supplementation, although the dietary factors responsible are unknown.

Because of the reported weak estrogenic activity of NP, it is possible that the minimal mineralization observed in the 3 male groups exposed to the highest doses was an "estrogenic" effect of NP on kidney tubules. This seems more plausible than the possibility that it was a sequela of tubular epithelial necrosis associated with the toxicity of the NP-dietary interaction (e.g., PKD), because severe PKD occurred in 100% of the 2000-ppm group, but mineralization was observed in only 40% of the same group. Furthermore, mineralization was present the 500-ppm group that, like the control and the 3 other lower-dose groups, did not have PKD."

Laterdresse et al. 2001

Regulatory Perspectives

- Danish Environmental Protection Agency (Nielsen, et al. 2000)
- Environment Canada (2001,2002)
- US Forest Service (2003)
- USEPA (2009)

Denmark (Nielsen)

- Nielsen, et al. (2000) conclude with regards to Chapin et al. (1999):

  "Consequently, the conclusion has been drawn from this study that there is a **LOEL** (emphasis added) for repeated exposure of 15 mg/kg/day, based on histopathological changes in the kidneys. Since renal tubular degeneration and/or dilatation 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."

USEPA

- Hazard Characterization Document – September 2009

  "Toxicity was manifested as reductions in terminal body weights at 650 ppm in F2 males (8%) and F1 females (7%) and on post-natal days 55-58 in F3 females (10%) and at 2000 ppm in F1 female (9%), F2 (7%), and post-natal day 55-58 F3 (7%) males and F0 (9%), F1 (12%), F2 (10%), and post-natal day 55-58 F3 (11%) females. Increased relative kidney weights were observed at 650 ppm and/or 2000 ppm in adult males from the F0, F1, and F2 generations and in the F1 2000 ppm adult females. A treatment-related increase in the incidence of renal tubular degeneration/dilatation was seen in the 200, 650, and 2000 ppm males from all generations and in the 2000 ppm females from the F1, F2, and F3 generations and in the 200 and 650 ppm females in the F3 generation."

- Mineralization not included in critical effect determination

Environment Canada (2001)

- “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…”

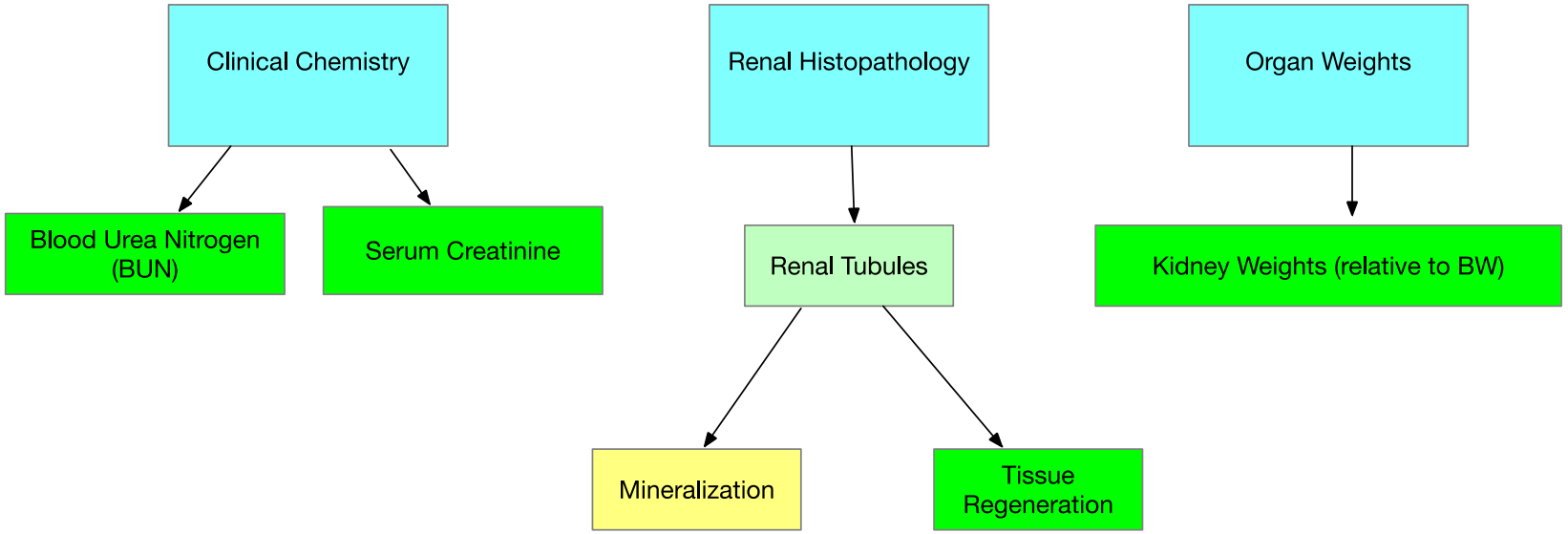
Environment Canada (2002) Canadian Environmental Quality Guidelines for PA & Ethoxylates

- In a multigenerational study, Chapin et al. (1999) examined the effects of nonylphenol administered through dosed food on Sprague Dawley rats (Rattus norvegicus). At a diet concentration of 650 mg·kg -1 (i.e., a dose of 30-108 mg·kg -1 body weight) vaginal opening at an earlier age was observed in the F1 generation. Significant effects observed at a diet concentration of 2000 mg·kg -1 (i.e., a dose of 100-360 mg·kg -1 body weight) included increased relative kidney weights and decreased adult ovary weights in the F1 generation, and increased estrous cycle length in both the F1 and F2 generations.
- Mineralization not included in critical effect determination

US Forest Service

- “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- free diet exacerbated the kidney effects, and the authors surmise that soy in the diet could act to ameliorate these effects.”

Elements of Weight of Evidence Assessment



Overall Weight of Evidence Mineralization

- Renal mineralization seen at some dose(s) in all three pivotal studies
  - It was low incidence and low severity
  - No other renal effects accompany the mineralization
- Mineralization is a frequent finding in rat studies – (mineral imbalance, gut flora, etc.)
- Finding alone (without other indications of renal toxicity should not be considered a critical effect)

Recommendations

- The critical effects in the multi-generation reproduction studies
  - Acceleration of vaginal opening in females (Chapin et al. 1999)
  - Toxicologically significant changes in the kidney from males (Chapin et al. 1999; Nagao et al. 2001; NCTR 2009; Tyl et al. 2006), both of which occurred at doses of >200 ppm.
- Note: no vaginal effects were observed in a five-generation study at doses up to and including 750 ppm (the highest dose tested), whereas kidney effects were seen only at 750 ppm (NCTR 2009).
- Point of Departure = 200 ppm in the diet, equating to approximately 13 mg/kg bodyweight/day

January 3, 2023

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

MDH RESPONSE TO APERC REGARDING NONYLPHENOL COMMENTS

Dear Ms. Losey:

We thank the Alkylphenols & Ethoxylates Research Council (APERC) for their comments on nonylphenol and for sharing their expertise with us. In their comments from May 13, 2022 and virtual presentation to the Minnesota Department of Health (MDH) on December 15, 2022, APERC disagreed with MDH's point-of-departure (POD) for subchronic and chronic critical noncancer effects upon nonylphenol exposure. MDH selected a 3-generation rat study by the National Toxicology Program (NTP) 1997 that was reported by Chapin 1999 as the critical subchronic and chronic study with renal mineralization in young male rats as the critical effect. It is a thorough study performed by a highly reputable group (NTP). NTP reported a dose response for renal mineralization in not only the male parental rats, but also in the 1st generation male progeny, and the 2nd generation male progeny. Usually, renal mineralization in young male rats is a rare effect, however, this effect was a nonylphenol-induced effect observed at the lowest dose tested. Although, the effect was reportedly minimal at this dose, there were other renal effects occurring at this dose including renal degeneration, which indicates a true treatment induced effect on the kidneys. APERC suggests identifying the lowest dose tested as the NOAEL of the study (13 mg/kg-d).

MDH's published risk assessment methods direct risk assessors to use a benchmark dose (BMD) approach to evaluate critical effects when possible. EPA supports the use of BMD modeling and wrote technical guidance for BMD modeling in 2012. BMD modeling uses the entire range of doses in a study and corresponding data from all of these doses to calculate a lower BMD (BMDL) confidence limit for a dose associated with a predefined effect level (example, a 10% change). This approach uses all of the data to derive a POD instead of using a study-selected NOAEL or LOAEL. The dose response for the F1 males was modellable and produced a $BMDL_{HED10\%}$ = 0.49 mg/kg-d and a $BMD_{HED10\%}$ = 1.1 mg/kg-d. The BMD/BMDL are lower than the

lowest dose used in the study (13 mg/kg-d), suggesting that nonylphenol-induce effects are likely occurring at doses below those used in the study. MDH used the BMDL as the POD in accordance with EPA 2012 technical guidance.

It is MDH's mission to protect the health of all Minnesotans, including sensitive populations and the most vulnerable. Although APERC suggests a higher POD using weight-of-evidence from other animal studies and a 2001 Health Canada Report, discounting the young male rat data and MDH modeling produced from the NTP 1997 study because effects occur at a lower dose than other studies contradict MDH's mission. 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 is incomplete and cannot be used to assess a POD. Therefore, in order to be protective for all populations, MDH will retain the POD defined by BMD analysis without modification.

Sincerely,

/s/ Sarah Johnson

Sarah Fossen Johnson, PhD
Supervisor, Health Risk Assessment Unit
Minnesota Department of Health

www.health.state.mn.us
Phone: 651-201-4899
Email: Health.risk@state.mn.us

I.2.a. Written Comment: Pre-Hearing Comment

I.2.a.i. Comment
Date: March 4, 2023
Chemical: Nitrate and HRL Rules Application and Enforcement
Commenter: Jean Wagenius

I.2.a.ii. Minnesota Department of Health's Preliminary Response
Date: March 31, 2023

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

5	1	6	0	1
PARTICIPANTS	TOPICS	ANSWERS	REPLIES	VOTES

SUMMARY OF TOPICS

SUBMIT A COMMENT

6 Answers · 0 Replies

Important: All comments will be made available to the public. Please only submit information that you wish to make available publicly. The Office of Administrative Hearings does not edit or delete submissions that include personal information. We reserve the right to remove any comments we deem offensive, intimidating, belligerent, harassing, or bullying, or that contain any other inappropriate or aggressive behavior without prior notification.

Jean Wagenius · Citizen · (Postal Code: unknown) · Mar 04, 2023 7:33 pm

0 Votes

In the Matter of the 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 4587

OAH Docket No. 5-9000-38941

I appreciate the opportunity to comment on the Minnesota Department of Health's (MDH) proposed rules cited above. Two issues must be addressed before the rules are adopted.

One, MDH did not include a needed update of the nitrate rule even though MDH says in its Statement of Need and Reasonableness (SONAR) that MDH ensures that its health risk limits (HRLs) reflect the most up-to-date toxicity information.

Two, MDH is promulgating rules that will have the force and effect of law but in the SONAR MDH says that it will not be enforcing the HRLs and that the HRLs are not binding on other state agencies or "risk managers."

NITRATE/NITROGEN:

MDH proposes to adopt new standards for 17 contaminants and to update 19 other existing standards. These standards are called health risk limits. See Minn. Stat. 144.0751 reproduced below. MDH defines an HRL as a "concentration of a groundwater contaminant, or a mixture of contaminants that is likely to pose little or no health risk to

humans, including vulnerable populations, and has been adopted into rule." SONAR p. 6. "HRLs specify a minimum level of quality for water used for human consumption…."SONAR p. 6-7. "An HRL can be used to determine if groundwater is acceptable to drink." SONAR p. 1. HRLs are critical for the health of Minnesotans because "(g)roundwater provides about 75 percent of Minnesota's drinking water…." SONAR p. 1.

MDH cites the Groundwater Protection Act of 1989 as authority to adopt HRLs: "(i)f groundwater quality monitoring results show that there is a degradation of groundwater, the commissioner of health may promulgate health risk limits under subdivision 2." SONAR p. 2

The Department also cites Minn. Stat. 144.0751 which provides the criteria that an HRL must meet.

144.0751 HEALTH STANDARDS.

(a) Safe drinking water or air quality standards established or revised by the commissioner of health must:

(1) be based on scientifically acceptable, peer-reviewed information; and

(2) include a reasonable margin of safety to adequately protect the health of infants, children, and adults by taking into consideration risks to each of the following health outcomes: reproductive development and function, respiratory function, immunologic suppression or hypersensitization, development of the brain and nervous system, endocrine (hormonal) function, cancer, general infant and child development, and any other important health outcomes identified by the commissioner.

(b) For purposes of this section, "peer-reviewed" means a scientifically based review conducted by individuals with substantial knowledge and experience in toxicology, health risk assessment, or other related fields as determined by the commissioner.

MDH updates HRLs every two to four years "to ensure the HRL values reflect the most up-to-date toxicity information." SONAR p. 77. "MDH rejects the possibility of leaving the proposed chemicals in their outdated or HBV status." SONAR p. 78. "A failure to revise the rules would ignore legislative directives and leave an outdated set of standards in place, providing only limited options for protecting some segments of the population." SONAR p. 79.

Yet, the list of chemicals to be updated in this rule making does not include updating the nitrogen/nitrate standard. There are many reasons that it must be included:

1. State agencies are well aware that a large number of private wells and a smaller but significant number of municipal wells in Minnesota are contaminated with nitrogen. (1) Many private well owners are not aware that their well is contaminated; others are aware but don't have the resources to purchase the necessary filtering equipment. (2) MDH declines any responsibly for protecting private drinking water wells even though the groundwater that supplies the wells was likely contaminated by someone other than the owner of the well. (1) However, since there is a nitrate standard, MDH must update the current limit that was set in 1962 to guard against blue baby syndrome. (1) MDH's standard for nitrate must be up-to-date since it informs private well owners when their well water should not be used for drinking. Similarly public facility operators need the

updated standard to know when their facility needs to be upgraded.

2. The Environmental Working Group reports that newer research indicates that drinking water with significantly lower levels of nitrate than the current standard are associated with higher risks of colorectal cancer and adverse birth outcomes. (1 p.6) Similarly the Minnesota Center for Environmental Advocacy cites recent health studies supporting a more protective standard and urges that MDH update the nitrate standard. (3 p. 3)

3. The maximum contaminant level (MCL) for nitrate was adopted by reference as a HRL in 2009. SONAR p. 4. MCLs are federal standards that "consider the costs required to reduce contaminant concentrations to a given level and the technological feasibility of reaching that level…most MCLs were developed using outdated methods based only on adult intakes and body weight." SONAR p. 80. In contrast "HRL values are based strictly on human health." SONAR p. 79. A MCL does not meet the health standards in Minn. Stat. 144.0751 that require "a reasonable margin of safety to adequately protect the health of infants, children…."

4. For this rule making, MDH is using "the most recent intake rates from the EPA Exposure Factors Handbook. Water intake values were updated in 2019." SONAR p. 12. These current updated water intake rates were not used when the nitrate MCL, now the HRL in use, was created.

Each one of these four factors more than justifies an update of the nitrate HRL. Taken together, they require an update.

ENFORCEMENT OF HRLs

This MDH rule making process will, if completed, will establish rules that "shall have the force and effect of law." Minn. Stat. 14.38.

Yet, in the SONAR, MDH says repeatedly that it will not enforce the new HRLs in the rules and that state agencies and others can use the HRLs as guidance but that they need not enforce them.

In effect, MDH used the health standards law to justify the need for a rule making, but by refusing to enforce the rules and telling others that they don't need to follow them, MDH makes the Health Standards law meaningless. The result: the Health Standards law for safe drinking water that requires a reasonable margin of safety to adequately protect the health of infants, children, and adults does not protect the health of infants, children, and adults.

MDH argues that it does not have to enforce HRLs because statutes don't tell it how HRLs should be used. "Except for the requirements for water resources protection (See Minn. Stat. § 103H.275, subd. 1(c)(2)), neither Minnesota statute nor current HRL rules specify how HRL values should be used." SONAR p.7 "Because the HRL rules must establish limits for contaminants, rather than specify how to apply the health-protective numbers, MDH does not apply or enforce them." SONAR p. 78

That argument ignores the statute setting out the commissioner of health's responsibilities.

144.05 GENERAL DUTIES OF COMMISSIONER; REPORTS.

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

Subdivision 1.General duties. The state commissioner of health shall have general authority as the state's official health agency and shall be responsible for the development and maintenance of an organized system of programs and services for protecting, maintaining, and improving the health of the citizens. This authority shall include but not be limited to the following:
....
(3) establish and enforce health standards for the protection and the promotion of the public's health such as quality of health services, reporting of disease, regulation of health facilities, environmental health hazards and personnel;

Minn. Stat. 144.05 requires the commissioner to develop and maintain “an organized system of programs and services for protecting, maintaining, and improving the health of the citizens ” and it directs the commissioner to “establish and enforce health standards for the protection and the promotion of the public's health…such as... environmental health hazards….” The statute further says the authority is not limited to the the specific list that the statute provides. The commissioner is obligated to enforce standards, HRL rules that have the force and effect of law; the manner is left up to the commissioner.

Yet, in the SONAR, MDH rejects this responsibility. In its own words:

“The amendments have no direct regulatory impact because the HRA Unit at MDH does not enforce or regulate the use of health-based guidance. MDH provides recommended values for use by risk assessors and risk managers in making decisions and evaluating health risks.” SONAR p. 81.

“HRL values are but one of several sets of criteria that state groundwater, drinking water, and environmental protection programs may use to evaluate water contamination. Each program must determine whether to apply an HRL or whether site-specific characteristics justify deviation from HRL values.” SONAR p. 8.

‘HRL values are only one set of criteria that agency risk managers use to evaluate whether a contaminant’s concentration in groundwater poses a risk to health. HRL values are not intended to be bright lines between ‘acceptable’ and ‘unacceptable’ concentrations.” SONAR p.78.

“MDH cannot anticipate all the situations in which HRL values might provide meaningful guidance. Nor can MDH anticipate all the factors that its partners might weigh to determine whether applying an HRL value is appropriate. Each agency or program must decide whether to apply an HRL value or whether site-specific characteristics justify deviation from HRL values. SONAR p. 82.

“The proposed amendments allow risk managers and stakeholders flexibility in determining how best to protect the public from potentially harmful substances in our groundwater. HRL values provide a scientific and policy context within which the risks posed by a particular situation may be analyzed. Following the risk analysis, risk managers and stakeholders, including other regulatory agencies, may examine the options and make decisions on a course of action.” SONAR p. 82.

“The amendments simply provide health-based levels for certain water contaminants. Other agencies might choose to implement and enforce these amendments.” SONAR p. 76.

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

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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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Tap Water for 500,000 Minnesotans Contaminated With Elevated Levels of Nitrate

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Tap Water for 500,000 Minnesotans Contaminated With Elevated Levels of Nitrate

By Sarah Porter, Senior GIS Analyst, and Anne Weir Schechinger, Senior Analyst of Economics

TUESDAY, JANUARY 14, 2020

Drinking water for an estimated half a million Minnesotans is drawn from groundwater contaminated with elevated levels of nitrate, a toxic pollutant that is linked to cancer and is especially dangerous for infants, according to an EWG analysis of federal and state test data.

About one in eight Minnesotans served by groundwater-based public water systems consume tap water that, in tests performed over the past 10 years, had at least one detection of nitrate at or above the level the state considers a marker of potentially worsening contamination. Tens of thousands more Minnesotans are drinking from private household wells with elevated nitrate.

Nitrate is a chemical component of fertilizer and manure that can run off of farm fields and seep into groundwater. Our analysis shows that nitrate contamination is far worse in parts of Minnesota where the types of soil and geology make it easier for nitrate in fertilizer and manure to get into groundwater.

To its credit, Minnesota is implementing a Groundwater Protection Rule to reduce nitrate in drinking water. The rule – three years in the making and administered by the Minnesota Department of Agriculture – is a welcome first step that must be implemented quickly and robustly. But EWG's analysis shows that even full implementation of the new rule may be too little, too late to protect Minnesotans – especially those drinking water from private household wells – from unsafe levels of nitrate.

Nitrate's Health Effects

Under the federal Clean Water Act, the legal limit for nitrate in drinking water is 10 milligrams per liter, or mg/L.1 This limit was set, in 1962, to guard against so-called blue baby syndrome, a potentially fatal condition that starves infants of oxygen if they ingest too much nitrate.

But newer research indicates that drinking water with 5 mg/L or even lower is associated with higher risks of colorectal cancer and adverse birth outcomes, such as neural tube birth defects. And the Minnesota Department of Health says a level of 3 mg/L indicates that "human-made sources of nitrate have contaminated the water and the level could increase over time."

In June, EWG researchers released a peer-reviewed study that found nitrate pollution of U.S. drinking water at levels far below the legal limit may cause up to 12,594 cases of cancer a year. The article reviewed epidemiological studies of the health effects of nitrate-contaminated drinking water. Recent large-scale studies in

Spain and Italy and in Denmark found statistically significant increases in colorectal cancer risk associated with nitrate in drinking water at levels of 0.7 to 2 mg/L.

In 2017, the Environmental Protection Agency began the work needed to review and revise the current legal limit for nitrate. But in April 2019, the agency announced it would no longer consider that re-evaluation a high priority. Drinking water with nitrate levels at or below 10 mg/L meets federal standards, but it is clear that protecting public health requires keeping the contamination level far below the legal limit.

Nitrate in Public Water Systems

Data from the U.S. Environmental Protection Agency show that 472,983 Minnesotans – more than the population of Minneapolis – are served by a total of 727 public water systems that were contaminated with at least 3 mg/L of nitrate. Almost 300,000 people drink from public systems contaminated at or above 5 mg/L, and more than 150,000 from public systems with at least 10 mg/L.

Table 1. Minnesota Public Water Systems With Elevated Levels of Nitrate, 2009-2018

	With at Least 1 test >= 3 mg/L		With at Least 1 test >= 5 mg/L		With at Least 1 test >= 10 mg/L	
System Type	Systems	People Served	Systems	People Served	Systems	People Served
Community	95	405,386	55	258,985	20	146,202
Non-community	632	67,597	358	38,251	104	8,448
All public ground water systems	727	472,983	413	297,236	124	154,650

Source: U.S. EPA Safe Drinking Water Information System, from tests by public water systems.

Many public systems have nitrate tests that are dangerously high. Twenty-two systems serving 4,178 people had nitrate tests at twice the legal limit or more, with two of those systems testing close to 50 mg/L – five times the legal limit.

Public water systems are either community or non-community systems. Community water systems mostly serve residents in cities and towns year-round. There are far more non-community systems, which serve sites like churches and schools with their own source of drinking water, but they serve much smaller populations and usually for only part of the year. Out of the 727 public systems that supply drinking water contaminated with nitrate at or above 3 mg/L, 95 are community systems and 632 are non-community systems.

Nitrate in Private Wells

Tests by the Minnesota Department of Health and Department of Agriculture in the past 10 years show that 7,657 Minnesota households drink from private wells with at least one test at or above 3 mg/L of nitrate. Even if those wells serve just three people each, it means almost 23,000 more Minnesotans are drinking water contaminated with nitrate at or above that level.

Table 2. Private Drinking Water Wells in Minnesota With Elevated Levels of Nitrate, 2009-2018

	At least 1 test at or above 3 mg/L	At least 1 test at or above 5 mg/L	At least 1 test at or above 10 mg/L

Households with Private wells	7,657	5,825	3,364

Sources: Minnesota Department of Health, Minnesota Department of Agriculture Township Testing Program and Central Sands and Southeast Minnesota Volunteer Nitrate Monitoring Networks.

Of the households that drink from private wells, almost 6,000 wells were contaminated at or above 5 mg/L, and more than 3,000 were contaminated at or above the federal legal limit of 10 mg/L. At least 164 households had private wells that tested at or above twice the legal limit, or 20 mg/L.

Mapping Nitrate Contamination

EWG's interactive maps show the locations and levels for nitrate in Minnesota's public water systems and private household wells.

The Minnesota Fertilizer Nitrogen Management Plan, released in 2015 and updated this year, found that the millions of pounds of fertilizers and manure applied to cropland each year are the leading sources of nitrate that can pollute drinking water. More importantly, the report found that without careful management, much of the nitrate remains after crops are harvested and can seep into drinking water.

EWG's maps confirm that nitrate contamination is far worse in regions of Minnesota where the types of soil and geology make it easier for nitrate in fertilizer and manure to get into groundwater. The area of highest vulnerability makes up almost one-fourth of the state and is home to 2.5 million acres of cropland and 6,287 livestock feedlots.

Almost 90 percent of public water systems with nitrate levels at or above 3 mg/L draw on groundwater in or very near areas considered highly vulnerable to nitrate contamination. About the same percentage of private household wells also draws on groundwater in these highly vulnerable areas. If you live in one of these areas, you are very likely drinking nitrate-contaminated water.

Who Is Affected?

Nitrate contamination of drinking water is a largely rural issue. Eighty-five percent of public water systems with at least one test at or above 5 mg/L served people living in rural Minnesota. Fully 98 percent of townships where at least one test of domestic wells revealed nitrate contamination at or above 5 mg/L were located in rural areas.

About half of the communities and households affected by high nitrate levels are located in areas where household incomes fall below the state median. Of 413 public water systems with at least one test at or above 5 mg/L, 203 are located in U.S. Census block groups where household income is less than the state median. Of 617 townships with at least one private well detection at or above 5 mg/L, 299 are also in areas with household income below the state median.

Groundwater Protection Rule May Be Too Little, Too Late

Minnesota's Groundwater Protection Rule was finalized in June 2019 and will be implemented starting in 2020. The rule is a welcome first step, but it is likely to fall short. Here's why:

- Most troubling is that the new rule is designed to prevent nitrate in community water systems from exceeding the EPA's legal limit of 10 mg/L – despite the growing evidence that the existing legal limit is not safe. The research cited earlier – that nitrate levels as low as less than 1 mg/L may increase the risk of colorectal cancer – means the target level should be set far lower.
- The new rule bans the application of nitrogen fertilizer in the fall or on frozen soil in highly vulnerable areas. That will affect about 2.2 million acres of cropland and also applies to about 310,000 crop acres around public wells with high nitrate that are designated for protection. But a 2014 survey by the state agriculture department and USDA found that statewide, 61 percent of fields received more nitrogen fertilizer, and 71 percent more manure nitrogen, than recommended by the University of Minnesota. Even higher proportions of fields in highly vulnerable southeast Minnesota received more nitrogen than recommended. To ensure groundwater is safe to drink, state-of-the-art fertilizer and manure management practices are needed on far more fields in the highly vulnerable areas than is required by the new rule.
- To improve the way farmers and landowners use and manage fertilizer and manure, the rule relies heavily on their voluntary participation. Mandatory best management practices can be enforced but only in areas to protect community water systems with contamination approaching the legal limit. Provisions in the rule could delay enforcement of mandatory measures for years. EWG has steadfastly supported voluntary programs, but they have proven to be too slow and poorly targeted to succeed at addressing the challenges Minnesota faces to make sure people have safe drinking water.
- Analysis of the nitrate data shows that private wells are also likely contaminated with pesticides and bacteria. People on well water cannot rely on the monitoring and regulatory oversight their neighbors on public water enjoy. The health department directs public education and outreach initiatives to help private well owners but says that in the end, "private well users are responsible for making sure their water is safe for everyone in the household to drink." There must be far more frequent and systematic testing of private wells, for more contaminants, and more technical and financial assistance designed to help households make sure their water is safe.
- Finally, the data show that nitrate contamination of Minnesota groundwater, the focus of this analysis, is a serious problem in highly vulnerable areas. If contamination of surface water were included in this analysis, the state's nitrate problem would appear even worse.

Reliance on treating drinking water so that it has safe levels of nitrate is an expensive and often ineffective way to protect people. It is more effective to prevent nitrate contamination of drinking water in the first place. What is needed is an aggressive policy and programmatic approach that strategically combines voluntary and mandatory approaches to cleaning up Minnesota's sources of drinking water.

To see more results of this study, click here.

Special thanks to Soren Rundquist, Director of Geospatial Analysis, and Craig Cox, Senior VP, Agriculture and Resources, for their help in completing this report. This report was produced with the generous support of the McKnight Foundation, the Walton Family Foundation and the Pisces Foundation.

NOTES

- 1. One milligram per liter is equal to one part per million, or ppm, a measurement often used for reporting water contamination levels. A part per million is about four drops in a 55-gallon barrel of water. The State of Minnesota measures nitrate contamination in milligrams per liter.

Methodology

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Methods and Detailed Results: Tap Water for 500,000 Minnesotans Contaminated With Elevated Levels of Nitrate

By Sarah Porter, Senior Geospatial Analyst, and Anne Weir Schechinger, Senior Analyst of Economics

Nitrate is found in groundwater used as drinking water throughout the state of Minnesota. EWG's report, "Tap Water for 500,000 Minnesotans Contaminated With Elevated Levels of Nitrate,"[1] analyzed nitrate levels in groundwater used by public water systems and private household wells as sources of drinking water. This summary provides descriptions of how that analysis was performed, as well as more-detailed results.

Public Water System Analysis

Public water systems are defined as those supplying drinking water for at least 15 people a year all year, or an average of at least 25 people for 60 days a year.[2] These systems can be publicly or privately owned and are regulated by the U.S. Environmental Protection Agency. However, the EPA commonly delegates regulatory authority to state agencies. In Minnesota, the Minnesota Department of Health, or MDH, directs the state's Drinking Water Protection program.[3]

Public water systems include community water systems such as cities and towns, or what most people consider to be "municipal systems," that serve their customers year-round and can serve up to millions of people. Non-community systems are also public water systems, but these systems include places like schools, gas stations, churches or campgrounds that tend to serve much smaller populations for shorter amounts of time.

Public water systems are required by the EPA to test their finished drinking water for nitrate. Testing frequency depends on how many customers each water system serves, and whether the system is a community or non-community system. In Minnesota, MDH monitors public water systems' nitrate testing schedule and collects the results for the EPA. These tests can be found through the EPA's Safe Drinking Water Information System, or SDWIS.[4]

EWG analyzed finished-water nitrate test results from all public water systems in Minnesota between 2009 and 2018. All data came from public records requests fulfilled by the Minnesota Department of Health. Data for 2009 through 2017 are included in EWG's Tap Water Database.[5]

In analyzing the public water system data, we looked at every nitrate test that each system conducted between 2009 and 2018, specifically for SDWIS contamination code number 1040. The analysis looked only at tests for systems that are currently active according to the SDWIS database and that use groundwater as their main source of drinking water.

There are 6,626 active groundwater systems in the state. Of those, 6,566 tested for nitrate at least once between 2009 and 2018. Eighty-seven percent of the systems are non-community systems, but they serve just 16 percent of people (a little more than 575,000 people). Only 13 percent of the systems were community systems, but they serve 84 percent of people (more than 3 million).

Public Water System Results

The frequency of testing for nitrate varies by system type, but most systems tested every year. Of the 6,566 systems that tested for nitrate, 82 percent tested in all 10 years between 2009 and 2018 (Figure 1). However, community water systems tested more often than non-community systems – 87 percent of community systems tested every year, whereas 81 percent of non-community systems tested every year. Some systems also tested more often than once a year – 29 percent, or 1,911 systems, tested more than 10 times between 2009 and 2018.

Figure 1. Eighty-two Percent of Public Water Systems Tested Every Year Between 2009 and 2018.

EWG also looked at which public water systems had at least one test at or above 3, 5 or 10 milligrams per liter, or mg/L, between 2009 and 2018. We chose the 3 mg/L threshold because MDH considers that level of contamination an indication that groundwater is contaminated by human-generated sources and that contamination may increase.[6] Studies have found increased risk of different cancers with long-term ingestion of water with nitrate around 5 mg/L,[7] as well as birth defects in babies whose mothers consumed water with 5 mg/L of nitrate.[8] We also chose 10 mg/L because it is the legal limit. If public water systems are at or above this level, they are legally required to act to reduce levels.[9]

Of the 6,566 active groundwater systems that tested for nitrate, 11 percent, or 727 systems, had at least one test at or above 3 mg/L. Table 1 shows the number of systems with at least one test at or above 3, 5 or 10 mg/L, along with the population served. There is also an interactive map showing the spatial distribution of these systems here (hyperlink to map).

Table 1. Eleven Percent of Systems Tested Between 2009-2018 Had at Least One Test at or Above 3 mg/L for Nitrate.

	With at Least 1 test >= 3 mg/L		**With at Least 1 test >= 5 mg/L**		**With at Least 1 test >= 10 mg/L**	
System Type	Systems	Population	Systems	Population	Systems	Population
Community	95	405,386	55	258,985	20	146,202
Non-Community	632	67,597	358	38,251	104	8,448
Total	727	472,983	413	297,236	124	154,650

Vulnerability

EWG also analyzed which public water systems were near groundwater that is highly vulnerable to contamination. We used the Minnesota Water Table Aquifer Vulnerability shapefile from the Minnesota Geospatial Commons to determine which areas in the state were vulnerable to contamination, and we looked only at areas that were considered to have "high vulnerability."[10] We then looked at how many public water systems that tested at or above 3, 5 or 10 mg/L for nitrate were also within one mile of one of these highly vulnerable groundwater areas.

Most public water systems that tested at or above 3, 5 or 10 mg/L were within one mile of a highly vulnerable groundwater area. Eighty-nine percent of systems with at least one test at or above 3 mg/L were near a highly vulnerable groundwater area, whereas 92 percent of systems with at least one test at or above 5 mg/L and 91 percent of systems with at least one test at or above 10 mg/L were near a highly vulnerable groundwater area. Table 2 contains the number of systems and their populations with at least one test at or above 3, 5 or 10 mg/L that were within one mile of a highly vulnerable groundwater area.

Table 2. Nitrate Levels in Public Water Systems Within One Mile of a Highly Vulnerable Groundwater Area.

	With at Least 1 Test >= 3 mg/L		With at Least 1 Test >= 5 mg/L		With at Least 1 Test >= 10 mg/L	
System Type	Systems	Population	Systems	Population	Systems	Population
Community	87	383,225	51	257,063	20	146,202
Non-Community	559	60,193	327	34,888	93	7,833
Total	646	443,418	378	291,951	113	154,035

Private Well Analysis

The Minnesota Department of Health calculates the number of Minnesotans who rely on private wells by subtracting the number of people served by a community water system from the total state population.[11] According to community water system population information from the EPA, almost 4.4 million people in Minnesota are served by a community water system, which is 78 percent of the total state population. Just under 1.3 million people, or 22 percent of the state population, get their drinking water from private wells.

Nitrate results were collected from four different state programs in Minnesota focused on nitrate testing of private wells. Each program, described below, has a different geographic focus, testing frequency and scale at which the data were provided. All test results collected between 2009 and 2018 were analyzed and aggregated to the township level using the Minnesota City, Township, and Unorganized Territory layer provided on the Minnesota Geospatial Commons.[12] Within each township, the total number of tests collected from each program and the number of tests at or above 3, 5 and 10 mg/L nitrate was recorded. An interactive map showing the spatial distribution of test results by township can be found here (hyperlink to map).

Township Testing Program

The Minnesota Department of Agriculture, or MDA, Township Testing Program began in 2013 with the goal of assessing nitrate-nitrogen concentrations in private wells at the township scale.[13] The program is intended to support the 2015 revised Nitrogen Fertilizer Management Plan, or NFMP, and focuses on townships across the state that have been identified as vulnerable to groundwater contamination and have significant row crop production. As of February 2019, 306 vulnerable townships from 42 counties have participated in the program.

All available township-level results were assembled from online PDFs. Initial test results were used for all townships, except two in Washington County and three in Morrison County, for which only final test results were provided. Wells with construction issues or nearby potential point sources of nitrogen were removed from final test results, which are intended to include only wells potentially impacted by applied commercial agricultural fertilizer. Townships that had completed final testing reported the number of wells with test results at or above a 3, 5 and 10 mg/L nitrate level. This was about two-thirds of the total number of wells tested through the program. The other one-third of wells were located in townships that had not yet completed final testing and reported only the number of wells at or above the legal limit of 10 mg/L. For those townships, it was assumed that tests at or above 10 mg/L were also above 3 and 5 mg/L. In total, results for 30,656 unique wells were assembled.

As part of the Township Testing Program, a follow-up nitrate sample was offered to all homeowners who had a detectable level of nitrate in their initial test. Location data and test results were provided by MDA for those households that participated in follow-up testing. Follow-up test results were assigned to the township in which the well was located, and the number of tests at or above 3, 5 and 10 mg/L within each township was recorded. In total, 4,665 nitrate test results were provided for 4,282 wells as part of the follow-up testing.

Southeast Voluntary Nitrate Monitoring Network

The MDA Southeast Voluntary Nitrate Monitoring Network initially began in 2006 as a coordination among nine southeast Minnesota counties.[14] The goal of the program was to monitor long-term trends of nitrate concentrations in private drinking water wells in southeast Minnesota, as karst geology makes this region vulnerable to groundwater contamination. The first sampling took place in 2008. In 2014, MDA coordinated with county water planners and the Southeast Minnesota Water Resources Board to ensure nitrate sampling continued on an annual basis and that the original well network was kept intact. The program attempts to sample the same wells – around 650 unique wells – on an annual basis. Wells are tested once annually, in August.

MDA provided EWG with Southeast test results in the form of 2-mile-diameter buffers around the actual location of the one or more sampling wells located within the buffer. In total, 4,392 nitrate test results were provided for 651 wells since 2009. Data was aggregated to the township scale by assigning each buffer to the township in which its centroid was located, and the number of tests at or above 3, 5 and 10 mg/L within each township was recorded.

Central Sands Private Well Network

The MDA Central Sands Private Well Network is a voluntary testing program focused on 14 counties in the Central Sands portion of Minnesota.[15] The program began in 2011 in response to concerns about high nitrate levels in private drinking water wells. The goal of the program is to determine nitrate trends through an effort to sample the same wells, around 550 unique wells, at least once annually. Wells are tested once a year, in March.

MDA provided EWG with Central Sands test results in the form of 1.5-mile diameter buffers, with a single sampling well located somewhere inside each buffer. Well locations represent the long-term sampling network of the Central Sands program. In total, 3,463 nitrate test results were provided for 551 wells since 2011. Data was aggregated to the township scale by assigning each buffer to the township in which its centroid was located, and the number of tests at or above 3, 5 and 10 mg/L within each township was recorded.

New Domestic Well Nitrate Testing

The Minnesota Department of Health maintains a database of nitrate tests collected during construction of private drinking water wells across the state.[16] The agency has been collecting data since the early 1990s, although only samples collected between 2009 and 2018 were used for this analysis. MDH provided EWG with location data and test results for each of the 45,598 wells sampled during the past 10 years. Test results were assigned to the township in which the well was located, and the number of tests at or above 3, 5 and 10 mg/L within each township was recorded.

Private Well Results

The large majority (91 percent) of nitrate tests of private wells in Minnesota were collected as part of the MDH New Domestic Well or the MDA Township Testing Program (Figure 2). Both programs primarily collected only one sample from each well. Exceptions to this are wells that participated in the Township Testing Follow Up Program, for which one or more repeated tests were collected. The frequency of testing for the Central Sands and Southeast Monitoring Programs, which are focused on establishing a long-term monitoring network, is once per year. Private wells in the Central Sands monitoring network have an average test frequency of 6.3 tests per well since 2013, whereas private wells in the Southeast monitoring network have an average test frequency of 6.7 tests per well since 2009.

Figure 2. Number of Private Well Nitrate Tests Collected by Program

The number of tests collected, and the number and percentage of tests at or above 3, 5 or 10 mg/L from each domestic well program, are listed in Table 3. Not surprisingly, the Township Testing Follow Up program, which tests only wells that had already been found to have elevated nitrate, reported the highest percentage of contaminated wells. The Southeast monitoring program reported the second-highest percentage of contaminated wells, followed by initial results from the Township Testing program and the Central Sands program. The MDH New Domestic Well program had the lowest percentage of tests with elevated nitrate, with only four percent of tests at or above 3 mg/L and one percent of tests at or above 10 mg/L. The MDH New Domestic Well program is also the only dataset analyzed in which sampling was not specifically targeted to vulnerable groundwater areas of the state.

Table 3. Distribution of Nitrate Tests at or Above 3, 5 and 10 mg/L

Program	Number of Tests Collected	Number of Tests >= 3 mg/L	Number of Tests >= 5 mg/L	Number of Tests >= 10 mg/L
Township Testing Initial	30,656	5,494 (18%)	4,449 (15%)	2,773 (9%)
Township Testing Follow-Up	4,665	2,799 (60%)	2,197 (47%)	1,175 (25%)
Central Sands	3,463	373 (11%)	232 (7%)	115 (3%)
Southeast	4,392	1,397 (32%)	1,050 (24%)	423 (10%)
MDH New Domestic Well	45,598	1,843 (4%)	1,121 (2.5%)	450 (1%)
Total	88,774	11,906 (13%)	9,049 (10%)	4,936 (6%)

Private Well Household Analysis

Only unique wells with elevated nitrate reported from the Township Testing (initial results), Central Sands, Southeast and MDH new domestic well programs were used to estimate the number of households with elevated nitrate in their drinking water. Follow-up results from the township testing program were excluded, because these households are already captured in the initial test results. There may be some duplication of households between the MDH New Domestic Well program and the other three programs. However, the lack of exact well locations in those three programs made it impossible to identify any duplication. Table 4 lists the number and percentage of households from each program with at least one test at or above 3, 5 or 10 mg/L.

Table 4. Distribution of Households With at Least One Test at or Above 3, 5 or 10 mg/L Nitrate

Program	Number of Households Sampled	Number of Households With at Least 1 Test >= 3 mg/L	Number of Households With at Least 1 Test >= 5 mg/L	Number of Households With at Least 1 Test >= 10 mg/L
Township Testing Initial	30,656	5,494 (18%)	4,449 (15%)	2,773 (9%)
Central Sands	551	88 (16%)	62 (11%)	40 (7%)
Southeast	651	232 (36%)	193 (30%)	101 (16%)
MDH New Domestic Well	45,598	1,843 (4%)	1,121 (2.5%)	450 (1%)
Total	77,456	7,657 (10%)	5,825 (7.5%)	3,364 (4%)

Vulnerability

EWG also determined the number of households with elevated nitrate that were near groundwater that is highly vulnerable to contamination. We classified each township by the proportion of land area occupied by a “high vulnerability” classification. Townships with at least 25 percent of their land area occupied by a high vulnerability classification were considered vulnerable to groundwater contamination. 890 of 2,696 townships in Minnesota fell under this vulnerable classification.

Sixty-four percent (56,627 of 88,774) of all nitrate tests of private wells in Minnesota in the past 10 years were collected from a vulnerable township. Eighty-eight percent (10,478) of tests at or above 3 mg/L were located in a vulnerable township, whereas 89 percent (8,060) of tests at or above 5 mg/L, and 90 percent (4,445) of tests at or above 10 mg/L, were located in a vulnerable township. Table 5 lists the number of tests with elevated nitrate that are located within a vulnerable township from each program.

Table 5. Most Private Well Tests With Elevated Nitrate Are in a Vulnerable Township

Program	Number of Tests Collected From a Vulnerable Township	Number of Tests >= 3 mg/L	Number of Tests >= 5 mg/L	Number of Tests >= 10 mg/L
Township Testing Initial	27,347	5,164	4,179	2,609
Township Testing Follow-Up	4,221	2,573	2,017	1,076

Central Sands	1,933	252	149	75
Southeast	3,304	1,280	974	406
MDH New Domestic Well	19,822	1,209	741	279
Total	56,627	10,478	8,060	4,445

The proportion of households with elevated nitrate that were located within a vulnerable township was also analyzed (Table 6). Township Testing Follow Up results were again excluded to prevent duplication of households. Of the 7,657 household wells with at least one test at or above 3 mg/L, 6,638 wells, or 87 percent, were located in a vulnerable township. Eighty-eight percent, or 5,132, of the wells testing at or above 5 mg/L, and 89 percent, or 3,005, of wells at or above 10 mg/L were located in a vulnerable township.

Table 6. Most Private Well Households With Elevated Nitrate Are in a Vulnerable Township

Program	**Number of Households Tested in a Vulnerable Township**	**Number of Households With at Least 1 Test >= 3 mg/L**	**Number of Households With at Least 1 Test >= 5 mg/L**	**Number of Households With at Least 1 Test >= 10 mg/L**
Township Testing Initial	27,347	5,164	4,179	2,609
Central Sands	313	58	38	23
Southeast	475	207	174	94
MDH New Domestic Well	19,822	1,209	741	279
Total	47,957	6,638	5,132	3,005

Demographic Analysis

To find out who is being impacted the most by nitrate contamination of groundwater in Minnesota, we looked at data from the U.S. Census for both public water systems and private wells. We found that most public systems

and private wells that had elevated levels of nitrate are in rural areas, and that many are in areas with median household incomes below the state's income.

Median Household Income

We used data from the 2017 American Community Survey to determine which public water systems and private wells were in areas with median household incomes below Minnesota's median household income.[17]

Specifically, we found the 2013-2017 five-year median household income for every census block group in the state. Census block groups are the smallest census unit and provide the most-detailed information possible.

For the public water systems, we assigned the median household income to each public water system based on which census block group the systems were located in. For the private well township-level data, we assigned the median household income to each township based on which census block group contained the center of the township. In both cases, a public system or township was considered to have a median income below the state's income if their income was less than $65,559, the 2013-2017 median household income for the state of Minnesota.

More than half of public water systems and private well townships are in census block groups with median household incomes below the state's income. Table 7 gives the number of public water systems and private well townships where median household income is below the state average, as well as their percentages compared to all public water systems and all private well townships with at least one nitrate test at or above 3, 5 and 10 mg/L.

Table 7. Over Half of Public Water Systems and Private Well Townships With at Least One Nitrate Test at or Above 3 mg/L Had Median Household Incomes Below the State's Average

	With at Least 1 Test >= 3 mg/L		**With at Least 1 Test >= 5 mg/L**		**With at Least 1 Test >= 10 mg/L**	
	Count Below State Income	Percent Below State Income	Count Below State Income	Percent Below State Income	Count Below State Income	Percent Below State Income
Public Water Systems	392	54%	203	49%	63	51%
Townships With Private Wells	377	51%	299	48%	209	47%

Many of the public water systems and private well townships that are near vulnerable areas are also in census block groups with median income below the state's income. Out of the 646 public water systems that had at least one test at or above 3 mg/L and were within one mile of highly vulnerable groundwater, 347 had a median income below the state's income. And out of the 427 townships that had private wells with at least one test at or above 3 mg/L, and had 25 percent of their land area in the high vulnerability area, 232 had a median income below the state's income.

Rural Versus Urban

To find out whether the public water systems and private well townships with elevated nitrate were in rural or urban areas, we used the 2010 Census Urban and Rural

Classification.[18]

Using specific population density numbers, the census delineates which areas in the country are urban. Places outside of these urban areas are delineated as rural.

If a public water system is located in one of these census-delineated urban areas, it was considered to be an urban system, and if not, it was labeled rural. For the townships that contain private well tests, if 50 percent of their area is within an urban area, they were classified as urban. If not, they were considered rural.

Almost all public water systems and private well townships with at least one nitrate test at or above 3 mg/L are in rural areas. Table 8 provides the number of public water systems and private well townships that are in a rural area, as well as their percentages compared to all public water systems and all private well townships with at least one test at or above 3, 5 and 10 mg/L.

Table 8. Most Public Water Systems and Private Well townships With at Least 1 test at or Above 3 mg/L Are in a Rural Area.

	With at Least 1 Test >= 3 mg/L		**With at Least 1 Test >= 5 mg/L**		**With at Least 1 Test >= 10 mg/L**	
	Rural Count	Rural Percent	Rural Count	Rural Percent	Rural Count	Rural Percent
Public Water Systems	597	82%	352	85%	108	86%
Townships With Private Wells	710	96%	602	98%	438	99%

Most of the public water systems and private well townships that are near vulnerable areas are also rural. Out of the 646 public water systems that had at least one test at or above 3 mg/L and were within one mile of highly vulnerable groundwater, 525 were in a rural area. And out of the 427 townships that had private wells with at least one test at or above 3 mg/L and had 25 percent of their land area in the high vulnerability area, 404 were rural.

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[1] https://www.ewg.org/interactive-maps/2020_nitrate_in_minnesota_drinking_water_from_groundwater_sources/

[2] https://www.epa.gov/dwreginfo/information-about-public-water-systems

[3] https://www.health.state.mn.us/communities/environment/water/dwp.html

[4] https://iaspub.epa.gov/enviro/sdw_form_v3.create_page?state_abbr=MN

[5] https://www.ewg.org/tapwater/

[6] https://www.health.state.mn.us/communities/environment/water/wells/waterquality/nitrate.html

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[8] https://ehp.niehs.nih.gov/doi/10.1289/ehp.1206249

[9] https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations

[10] https://gisdata.mn.gov/dataset/water-aquifer-vulnerability

[11] https://www.health.state.mn.us/communities/environment/water/docs/waternumbers.pdf

[12] https://gisdata.mn.gov/dataset/bdry-mn-city-township-unorg

[13] https://www.mda.state.mn.us/township-testing-program

[14] https://www.mda.state.mn.us/southeast-minnesota-volunteer-nitrate-monitoring-network

[15] https://www.mda.state.mn.us/central-sands-private-well-network

[16] https://www.health.state.mn.us/communities/environment/water/wells/waterquality/nitrate.html

[17] https://www.census.gov/programs-surveys/acs/news/data-releases.2017.html

[18] https://www.census.gov/programs-surveys/geography/guidance/geo-areas/urban-rural/2010-urban-rural.html

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Agriculture pollutes underground drinking water in Minnesota. Well owners pay the price.

By: Madison McVan, Investigate Midwest - January 17, 2023 6:00 am

Hydrologist Paul Wotzka looks out at Beaver Creek in Wabasha County, Minnesota. Photo by Nicole Neri for Investigate Midwest.

WEAVER, Wabasha County — The water that pours out of the taps at Jeff Broberg's house is crystal clear, refreshing and odorless.

But Broberg, 68, doesn't drink it. The issue is only visible on the molecular scale.

Like Broberg, many rural Minnesotans rely on private wells, which tap into groundwater systems spread underneath rolling crop fields and livestock operations. When nitrates from the agriculture operations seep into the water and make it unsafe to drink, well owners pay the price.

When Broberg, a geologist, bought his farm in 1986, he tested the well water. The nitrate levels were elevated, but still below the Environmental Protection Agency's contamination limit. With each periodic test, the nitrate concentration increased until it surpassed the EPA's safety standard of 10 parts per million in 1990 and eventually climbed to 22 ppm.

Nitrogen is a naturally occurring element critical to human and plant life, and it's a core component of the fertilizers and manure spread in mass quantities on farms in the Midwest. When the nitrogen mixes with oxygenated water, it forms nitrate.

Drinking water with high levels of nitrate can cause methemoglobinemia or "blue baby syndrome," a potentially life-threatening condition affecting the blood's ability to carry oxygen throughout the body. Nitrates also have been linked to thyroid disease and certain cancers.

Nitrate pollution is largely caused by agricultural runoff. Rainwater picks up the nitrogen in fertilizer and manure and carries it to bodies of water.

When nitrate reaches the underground drinking water supply, it's the well owners' responsibility to treat their water — with limited, often expensive options — or find another water source.

In Minnesota, nitrate pollution disproportionately impacts low-income communities, according to a 2021 study by the Environmental Working Group.

The American Farm Bureau Federation, the largest lobbying group representing farmers, opposes any mandatory measures that would reduce commercial fertilizer use, often referred to as "low-input" or "reduced-input" practices.

"There isn't a one-sized approach to the implementation of reduced-input farming practices, especially in a state like Minnesota with a diverse climate, soil and crop production range," a Minnesota Farm Bureau representative said in an email.

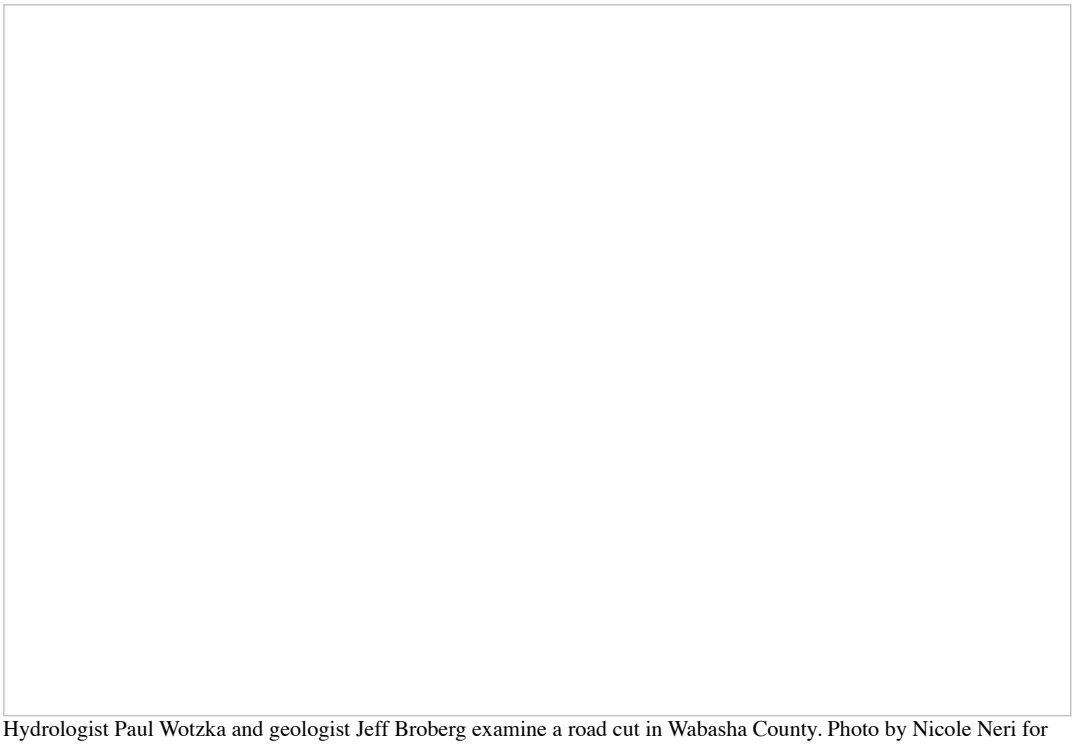
After the nitrate concentration in his water reached unsafe levels, Broberg drove his truck to a friend's property every two weeks, where he filled jugs and hauled them back to his home. A couple years ago, he decided he was "too old" to keep up with the routine and spent more than $250 on a reverse osmosis filtration system.

The standalone dispenser, separate from all other taps in his home, uses filter cartridges that cost upwards of $100 and need to be replaced yearly.

Broberg is trying to help other private well owners dealing with nitrate pollution. He co-founded the Minnesota Well Owners Organization with hydrologist and neighbor Paul Wotzka. Together, they host water testing clinics and advocate for policy changes that would benefit water quality for rural well owners.

In Minnesota, 1.2 million people drink well water. A 2016 Minnesota Department of Health survey found fewer than 20% of well owners regularly test their water.

"It's a public health crisis in the making," Wotzka said.



Hydrologist Paul Wotzka and geologist Jeff Broberg examine a road cut in Wabasha County. Photo by Nicole Neri for Investigate Midwest.

Government programs emphasize testing, lack funds for solutions

Recognizing the issue of nitrate pollution and its impact on private well owners, the Minnesota Department of Agriculture administered a program from 2013 to 2019 that offered free well water testing to residents of vulnerable townships.

The department tested more than 32,000 wells in 344 townships, mostly in the southeast and central parts of the state. In those areas, a combination of intensive agriculture and vulnerable geography — areas where groundwater is easily contaminated — resulted in a high risk of nitrate pollution.

Nine percent of the wells tested had nitrate levels over the safety standard, according to the program's initial results.

"I think our township testing program has really brought to light that there's a lot of vulnerable areas in Minnesota, and they're generally happening in the vulnerable areas where there's a lot of row crop production," said Kim Kaiser, a hydrologist at the Minnesota Department of Agriculture who administered parts of the testing program.

The township testing program was meant to determine the impact of fertilizer runoff, so in its final well water dataset and analysis, officials removed wells that were likely contaminated for other reasons.

Poorly constructed wells and wells located near feedlots or septic systems were excluded from the final data. But these wells still represent a significant portion of households without safe drinking water.

In seven townships located in Rock County, more than a quarter of wells tested were located on properties with livestock, and 34% were located less than 300 feet from an active or inactive feedlot.

In that testing area, half of the 171 wells tested were over the safety standard for nitrate. MDH estimated that more than 900 residents could be consuming water with unsafe levels of nitrate.

For wells that tested high in nitrates, Minnesota Department of Agriculture staff reached out to the well owners to educate them on options available to remedy the issue. While MDA doesn't pay for remedies — like purchasing bottled water, installing a filter or replacing a well — the Minnesota Department of Health has some limited funds for that purpose, said MDH water policy manager Tannie Eshenaur.

"We have some information on financial support, but it's very limited and it's not easy to get," Eshenaur said. "There's not a lot available for folks if they face financial challenges. There just aren't a lot of programs out there."

Because nitrate particles are so small, many common methods of water filtration don't remove nitrate. Reverse osmosis filters are most effective in removing nitrates, but they're more expensive than other kinds of filter systems.

Many well owners also hire a plumber to ensure the system is installed correctly. Because most home reverse osmosis systems are "point of use" filters, they are only connected to one tap, not the entire home. The filters also require replacement cartridges over time.

Eshenaur said MDH is requesting Clean Water funds to pay for solutions for private well owners, particularly those who are low-income and whose water is not safe to drink. Clean Water funds are taxpayer dollars distributed by the Minnesota Clean Water Council with the goal of improving the state's water quality.

Those funds would be used to expand on pilot programs like Tap In, a program in southeast Minnesota that helps low-income well owners remedy nitrate issues.

The pilot program started in 2021 with a $100,000 grant from the Clean Water Fund. The funds paid for well testing, installation of reverse osmosis systems, well repair and construction of new wells for low-income households.

The initial grant covered 186 tests, seven reverse osmosis filtration systems, six new wells and one well repair.

Reaching at risk well owners a challenge

Well owners can be difficult to reach with public health messaging, said Jason Kloss, environmental health manager at Southwest Health and Human Services, the public health agency covering six counties in southwest Minnesota.

The agency offers water testing for multiple contaminants, including nitrates. The tests are free for those receiving assistance via the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC).

In the counties covered by Southwest Health and Human Services, many residents get water from the rural water system, in part because the shallow distance from the surface to groundwater makes wells vulnerable to pollution.

"We've tried advertising, we've tried promoting this, but it's really difficult because the population that it pertains to is scattered," Kloss said.

In order to test their water, well owners have to collect a sample and deliver it to the lab. If the testing determines the water is unsafe, the well owner then has to find a solution if they want to avoid drinking the polluted water — purchasing bottled water, installing a treatment system or even drilling a new well.

"That's a lot of moving parts for an individual to follow through, and that's another challenge," Kloss said.

The lab Kloss oversees tested 81 samples for nitrates in 2021 and 74 through Dec. 2, 2022.

Terri Peters, district water manager for the Wabasha County Soil and Water Conservation District, said lack of education on drinking water risks is another reason well owners may not follow through on testing or treating water.

"One of the bigger challenges is that people sometimes don't know or understand that they should be testing their wells for contaminants, or testing for nitrates in general," Peters said. "So (we're) trying to educate on that piece of it, that they should understand what's in their drinking water."

Wotzka said distrust of government agencies is another reason why well owners are hesitant to test their water, particularly through state programs.

Wotzka and Broberg have organized several water testing clinics since they founded the Minnesota Well Owners Organization in 2018, testing more than 1,300 wells.

"Biases that people have about testing their water are often fear-based," Wotzka said.

Well owners have asked him if the government will force them to replace their wells, Wotzka said. Government agencies don't have the authority to force well owners to make changes to their water source, even if pollution is detected.

A 2021 Environmental Working Group study found that community water systems most affected by nitrate pollution are more likely to be low-income. Data on well users is harder to come by because unlike public water systems, well water is not regulated by the Environmental Protection Agency.

Renters are another vulnerable group Minnesota Department of Public Health is targeting for outreach, Eshenaur said.

"Often in these areas, there isn't a lot of affordable rental housing," Eshenaur said. "Renters may not know whether the owner has tested the water, or whether or not it's safe to drink."

Advocates want public policy to address root causes of pollution

Wooded hills surround Wotzka's small farm, which overlooks row crop fields across the paved road.

When Wotzka bought the farm in 1997, the well — drilled in 1928 — had high nitrate levels. Over the past 24 years, using organic farming practices like opting for organic compost instead of commercial fertilizer, the nitrate level dropped until the compound was nearly nonexistent.

He pours glasses of water from his kitchen sink and serves them with pride.

"Everybody understands the importance of water down here," he said.

Ben Daley, one of the owners of Daley Farm, a family-owned dairy operation in Winona County, said his family's well water has also been impacted by the livestock and fertilizer on their land. Multiple family wells have tested above the safety standard for nitrates, he said, in part because the wells are shallow and near current or active feedlots.

Families with kids purchased reverse osmosis systems to treat the drinking water.

"We all drink that water, and we bathe in it — we've got kids," Daley said. "We're doing the same things everyone else has to, so it's a big deal to us."

Daley Farm has been scrutinized and protested by environmental groups and government officials as the family seeks to expand its operations to hold 6,000 animal units, well beyond Winona County's feedlot cap of 1,500 animal units.

Daley said his farm uses cover crops and adheres to fertilizer application guidelines, but protesters have taken issue with the scale of the operation. The operation relies on the cow manure to fertilize the vast majority of the acreage and applies commercial fertilizer only in areas the manure doesn't reach.

"We're well above some standards that even environmentalists have asked the state to mandate farmers to do," Daley said.

Daley said he advocated for cover crops to be incorporated by other farmers in the area because they've been an effective and profitable way to manage nitrogen.

In southeast Minnesota, where Daley and Wotzka live, the land is especially "locally sensitive," meaning that land use has more of a direct impact on groundwater than in other areas, Wotzka said.

Southeast Minnesota is dominated by Karst geography, where groundwater and surface water are closely connected.

The geography is one reason why the area was selected as a focus of the state's large-scale testing program.

Wotzka co-founded the Minnesota Well Owners Organization because he sees nonprofits as a key player in addressing nitrate contamination. Nonprofits can do "what the government can't and businesses won't" do — advocate for public policy to address the root causes of nitrate pollution, Wotzka said.

The Minnesota Department of Agriculture is charged with protecting groundwater, but most agricultural practices that would reduce nitrogen runoff are voluntary.

The American Farm Bureau Federation opposes any mandatory "low input methods of farming," according to the organization's 2022 Policy Book. Commercial fertilizer is considered an input.

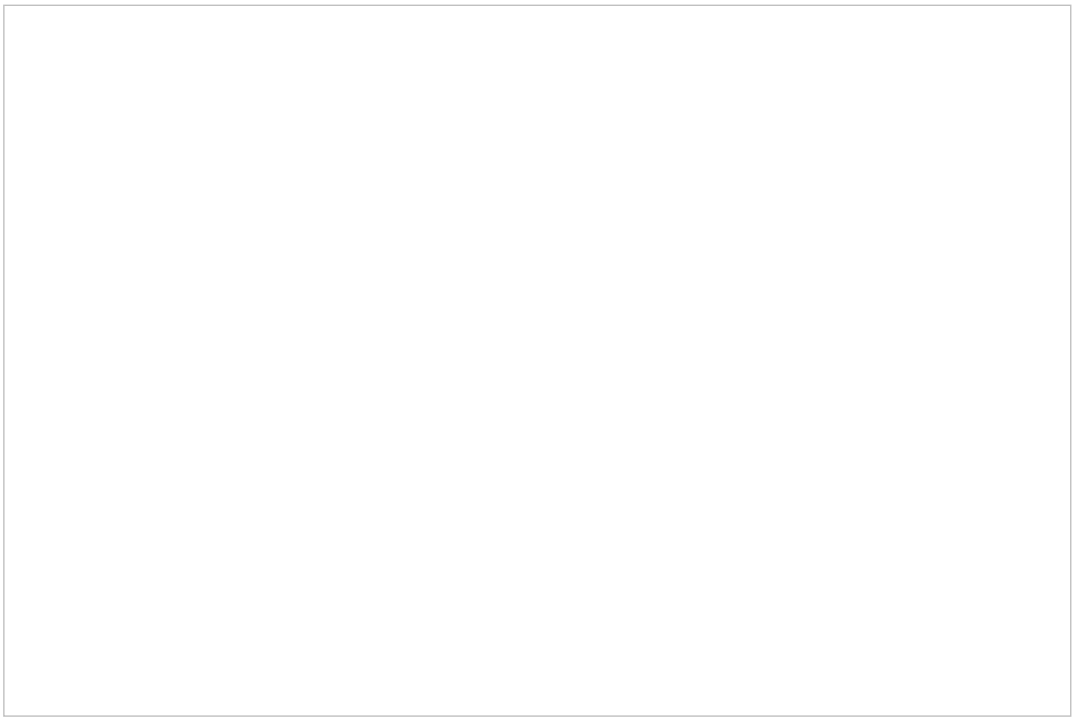
The Minnesota Groundwater Protection Rule, enacted in 2019, was meant to encourage adoption of farming practices that reduce nitrogen runoff. The rule created groups of local farmers, agronomists, government officials and other stakeholders in each Drinking Water Supply Management Area (DWSMA) with nitrate tests showing concentrations of 8 ppm or higher. The groups are charged with encouraging the adoption of nitrogen "best management practices" on 80% of the farmland — excluding soybean acres — within each DWSMA in the next few years.

If, after at least three growing seasons, the 80% target isn't reached for these higher-risk DWSMAs, or if nitrates have continued to increase in the corresponding water supply, MDA can implement mandatory adoption of the best management practices.

A Minnesota Farm Bureau representative said the group is working with the Minnesota Department of Agriculture to develop the best management practices.

"The Minnesota Farm Bureau supports innovative practices such as controlled draining, temporary storage outlet valves, and drainage system designs for lowering nitrates," a Minnesota Farm Bureau representative said.

The spokesperson also stated that the Minnesota Farm Bureau supports "reasonable fees on pesticides and fertilizers, including those used in nonagricultural applications, to partially fund groundwater protection programs."



Beaver Creek runs through Wabasha County, Minnesota Wednesday, Dec. 14, 2022. Photo by Nicole Neri for Investigate Midwest.

But Wotzka wants to see the best management practices implemented beyond the DWSMAs, which are focused on municipal water supplies.

He believes the nonprofit also can circumvent some of the biases around government programs. Wotzka and Broberg both said sharing their personal experiences as well owners helps them build trust with others in similar circumstances.

Wotzka and Broberg view well owners as an underserved class worth advocating for.

"People in Minnesota are very proud of their water," Wotzka said. "They're also very concerned."

This story has been updated to accurately reflect that the Tap In program operates in southeast Minnesota.

Republish

Minnesota Center for Environmental Advocacy

February 14, 2022

Mary H. Lynn
Cathy O'Dell
Minnesota Pollution Control Agency
520 Lafayette Road North
St. Paul, MN 55055-4194

Via OAH Comments Portal

RE: Request For Comments on Possible Amendments to Rules Governing Water Quality Standards – Use Classification 1, Minnesota Rules chapters 7050, 7052, 7053, and 7060, Revisor's ID Number R-04727
OAH Docket No. 5-9003-37887

Dear Ms. Lynn and Ms. O'Dell:

The Minnesota Center for Environmental Advocacy ("MCEA") is a nonprofit environmental advocacy organization with offices in St. Paul and Duluth. Since 1974, MCEA has defended Minnesota's natural resources, water, air and climate, and the health and welfare of Minnesotans. MCEA is driven by the principle that everyone has a right to a clean and healthy environment, and that decisions must be based on fact, science, and the law.

MCEA submits these comments in response to the Minnesota Pollution Control Agency ("MPCA") request for comments on proposed changes to water quality standards ("WQS") as referenced above.

1. MPCA should ensure that all groundwater is protected from degradation, including groundwater that is located on private property.

MCEA agrees with MPCA's proposal to "ensure the rule language clearly conveys that the standards apply to all groundwater." Consistent with this goal, MPCA should revise the rules to ensure that standards protecting groundwater from degradation are not applied at property boundaries, but instead apply to all groundwater. The rules should be clarified to specify that it is not acceptable for a regulated party to degrade groundwater or exceed water quality standards applicable to groundwater because it may be possible to deploy a remediation measure prior to reaching the property boundary that will reduce the level of contaminants in the groundwater. The MPCA should ensure that regulated parties employ measures (such as competent liners) that prevent groundwater pollution, not remediate groundwater pollution after it has happened.

2. MPCA should expand the Class 1 designation to connected surface waters.

Scientists studying the fate and transport of perfluorinated alkyl substances (PFAS) have demonstrated that these pollutants can flow freely from groundwater to surface water and back again. *See* Jennifer Geulfo, State Agencies Liaison, Brown SRP, Subsurface Fate and Transport of Poly- and Perfluoroalkyl Substances (PFAS) (May 23, 2016); Andrea K. Tokranov, Denis R.

LeBlanc, Heidi M. Pickard, Bridger J. Ruyle, Larry B. Barber, Robert B. Hull, Elsie M. Sunderland & Chad D. Vecitis, *Surface-water/Groundwater Boundaries Affect Seasonal PFAS Concentrations and PFAA Precursor Transformations*, 23 Env't Sci.: Processes & Impacts 1893 (2021).[1] Similarly, as MPCA has noted, nitrate has the potential to move freely from contaminated surface waters into groundwater and vice versa. As a result, MCEA strongly supports MPCA's adoption of a provision allowing the application of Class 1 standards where it can be shown that surface water has the potential to impact the quality of groundwater protected as Class 1 waters. Similarly, MPCA should have the authority to impose more stringent conditions on sources impacting groundwater if that groundwater has the potential to affect a surface water subject to more stringent standards. Minn. R. 7050.0210, subp. 13 already expresses this authority, insofar as it states that "The quality of any waters of the state receiving sewage, industrial waste, or other waste effluents shall be such that no violation of the standards of any waters of the state in any other class shall occur by reason of the discharge of the sewage, industrial waste, or other waste effluents."

MCEA also supports adoption of a rule that designates "sensitive areas" where surface conditions and surface waters are known to directly impact groundwater (for example, karst) to ensure that Class 1 standards are protected, but that rule must also allow for a process to identify areas that fit the criteria for a "sensitive area" outside the regions where the land surface/groundwater connection is known to be prevalent.

3. MPCA should update the scientific basis for the numeric Class 1 water quality standards.

MCEA supports MPCA's reassessment of the health-basis for the Class 1 water quality standards in coordination with the Minnesota Department of Health ("MDH"), but needs additional information to determine what the best method is for adding new standards to the rule.

MCEA supports combining the standards into a single set of standards without subclasses based on treatment. The availability of treatment should not be considered in setting standards and, as a result, subclasses based on treatment should be eliminated. The fact that water can be treated to achieve safe consumption levels is concern that should not be considered in either a narrative or a numeric standard intended to protect Class 1 waters. Similarly, the standards should not distinguish between health-based standards or standards based on other deleterious characteristics caused by pollutants, as discussed below in part 5.

In setting any new standards, MPCA and MDH should consider populations that are especially vulnerable due to traditional consumption patterns and ensure that any standards adopted recognize these populations, including tribal standards that have been adopted. MCEA also supports MPCA's consideration of climate-change induced changes to toxicological impacts when establishing standards.

[1] References cited in this comment letter are attached.

MPCA should use this rulemaking to update the water quality standards based on more recent research demonstrating that a higher level of protection must be maintained. The narrative standard in Minn. R. 7050.0221, subp. 6 should be more clearly identified as such. The following standards should be updated.

Nitrate

MPCA and MDH should reexamine the 10 mg/L standard for nitrate because scientific consensus is growing that a lower number would be more protective. A number of scientific studies demonstrate that nitrate levels lower than 10 mg/L are implicated in heightened risk for colorectal cancer, thyroid disease, and neural tube defects. *See* Sarah Porter & Anne Weir Schechinger, *Tap Water for 500,000 Minnesotans Contaminated With Elevated Levels of Nitrate*, Env't Working Grp. (Jan. 14, 2020), https://www.ewg.org/interactive-maps/2020_nitrate_in_minnesota_drinking_water_from_groundwater_sources/; Jayne Richards, Tim Chambers, Simon Hales, Mike Joy, Tanja Radu, Alistair Woodward, Alistair Humphrey, Edward Randal & Michael G. Baker, *Nitrate Contamination in Drinking Water and Colorectal Cancer: Exposure Assessment and Estimated Health Burden in New Zealand*, 204 Env't Rsch., Mar. 2022, at 112322, 2; Mary H. Ward, Rena R. Jones, Jean D. Brender, Theo M. de Kok, Peter J. Weyer, Bernard T. Nolan, Cristina M. Villanueva & Simone G. van Breda, *Drinking Water Nitrate and Human Health: An Updated Review*, 15 Int'l J. Env't Rsch. & Pub. Health, Jul. 2018, at 1557. MDH itself has noted that "a growing body of literature indicates potential associations between nitrate/nitrite exposure and other health effects such as increased heart rate, nausea, headaches, and abdominal cramps." Minn. Dept. of Health, *Nitrate and Methemoglobinemia* 3 (2018). MDH also affirms that "[s]ome studies also suggest an increased risk of cancer, especially gastric cancer, associated with dietary nitrate/nitrite exposure, but there is not yet scientific consensus on this question." *Id.*

Sulfate

Although originally classified by U.S. Environmental Protection Agency ("EPA") as a secondary water quality standard needed for "such as taste, color, and odor," more recent research demonstrates that sulfate has health impacts, particularly diarrhea and other gastrointestinal related issues. Muhammad Tariq Bashir, Salmiaton Ali & Adnan Bashir, *Health Effects from Exposure to Sulphates and Chlorides in Drinking Water*, 6 Pak. J. Med. & Health Sci. 648, 651-52 (2012); Muhammad Mohsin, Samira Safdar, Faryal Asghar & Farrukh Jamal, *Assessment of Drinking Water Quality and its Impact on Residents' Health in Bahawalpur City*, 3 Int'l J. Human. & Soc. Sci. 114, 120 (2013); Patricio Moreno, Hal Aral & Angelica Vecchio-Sadus, Environmental Impact and Toxicology of Sulphate at EnviroMine 2009: First International Seminar on Environmental Issues in the Mining Industry 6 (2009). Based on this research, MPCA should establish a WQS that will ensure that vulnerable populations are protected.

Other Pollutants

Other contaminants are still a major concern for public health, both in short- and long-term exposure. Fluoride, for example, has a primary Maximum Contaminant Level ("MCL") at 4.0 mg/L set by the EPA (EPA, National Primary and National Secondary Drinking Water Regulations), but research by the American Cancer Society ("ACS") suggests that long term exposure to this contaminant may cause skeletal fluorosis, causing a secondary MCL standard to be set at 2.0 mg/L to help protect children. Am. Cancer Soc'y, *Water Fluoridation and Cancer Risk* 2-3 (2015). Manganese is another contaminant of concern due to its impacts on the nervous system, with higher risks for the elderly and infants. The World Health Organization ("WHO") recommends that manganese in drinking water be limited to 0.08 mg/L, and MDH has established a Health Risk Limit ("HRL") for manganese at 0.1 mg/L, indicating a need for reassessment of the guidance for this contaminant in drinking water, particularly in regards to sensitive populations such as infants. World Health Org., *Manganese in Drinking-Water* 14-15 (2011). Aluminum is another contaminant that has neurological impacts, with connections to Alzheimer's and dementia. The secondary MCL for aluminum is currently 2.0 mg/L, but recent studies have shown that aluminum can have harmful impacts to human health at 0.1 mg/L. Virginie Rondeau, Hélène Jacqmin-Gadda, Daniel Commenges, Catherine Helmer & Jean-François Dartigues, *Aluminum and Silica in Drinking Water and the Risk of Alzheimer's Disease or Cognitive Decline: Findings From 15-Year Follow-Up of the PAQUID Cohort*, 169 Am. J. Epidemiology 489, 489 (2009).

MCEA supports MPCA's proposal to add WQS for some emerging pollutants of concern, including per-and polyfluoroalkyl substances (PFAS), pesticides, *see* Muhammad Syafrudin, Risky Ayu Kristanti, Adhi Yuniarto, Tony Hadibarata, Jongtae Rhee, Wedad A. Al-onazi, Tahani Saad Algarni, Abdulhadi H. Almarri & Amal M. Al-Mohaimeed, *Pesticides in Drinking Water—A Review*, 18 Int'l J. Env't Rsch. & Pub. Health, Jan. 2021, at 468, pharmaceuticals, *see* World Health Org., *Pharmaceuticals in Drinking-Water* (2011), algal toxins, *see* Env't Protection Agency, *Algal Toxin Risk Assessment and Management Strategic Plan for Drinking Water* (2015), disinfection by-products, *see* Xing-Fang Li & William A. Mitch, *Drinking Water Disinfection Byproducts (DBPs) and Human Health Effects: Multidisciplinary Challenges and Opportunities*, 52 Env't Sci. & Tech. 1681 (2018), and/or additional industrial chemicals.

4. MPCA should not eliminate standards that were based on secondary MCLs.

MPCA claims that "[u]nder the federal Clean Water Act (CWA), WQS for the protection of domestic consumption should be solely based on human health considerations." (Class 1 Concepts, p. 2). The CWA does not limit state water quality standards intended to protect water for domestic consumption solely to a "health" basis. In fact, the CWA directs that such standards "shall be such as to protect the public health *or welfare*" and that "such standards shall be established taking into consideration their use *and value* for public water supplies…" 33 U.S.C. § 1313(c)(2)(A). Nothing in state law is to the contrary. *See* Minn. Stat. § 115.03. Indeed, numerous state laws express the policy that potable waters are deserving of the highest protection. *See, e.g.,* Minn. Stat. § 115.063; Minn. Stat. § 103H.001. Removing protections for

domestic consumption waters based on taste, color or odor will simply increase costs for those who consume those waters, or for public water treatment systems that must prepare waters for public consumption.

Conclusion:

MCEA supports amendments to the Class 1 standards provided those amendments serve to preserve and enhance the protections that currently exist for groundwater and surface waters used for domestic consumption. MPCA should not adopt any amendments that are directed toward reduction of costs for industry, and maintain protections that are consistent with current state policy to protect all sources of water for domestic consumption from degradation, even if that degradation is argued to be without health impacts. To the extent that any might argue that the current standards place an unreasonable cost burden on certain dischargers or users, MPCA should recognize that these costs should be dealt with through means other than removing regulatory standards that protect public health and welfare.

MCEA also notes (as it did in its Triennial Review comment (April 9, 2021)) that it appears that MPCA's ideas about what to address in this Class 1 rulemaking are still developing. As a result, MCEA encourages MPCA to continue to share the options that it is considering with stakeholder groups, so that interested parties can develop a better understanding of the choices as this rulemaking moves forward.

An index to the attached cited references follows.

Sincerely,

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Water Policy Associate

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References

Jennifer Geulfo, State Agencies Liaison, Brown SRP, Subsurface Fate and Transport of Poly- and Perfluoroalkyl Substances (PFAS) (May 23, 2016).

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Sarah Porter & Anne Weir Schechinger, *Tap Water for 500,000 Minnesotans Contaminated With Elevated Levels of Nitrate*, Env't Working Grp. (Jan. 14, 2020), https://www.ewg.org/interactive-maps/2020_nitrate_in_minnesota_drinking_water_from_groundwater_sources/.

Jayne Richards, Tim Chambers, Simon Hales, Mike Joy, Tanja Radu, Alistair Woodward, Alistair Humphrey, Edward Randal & Michael G. Baker, *Nitrate Contamination in Drinking Water and Colorectal Cancer: Exposure Assessment and Estimated Health Burden in New Zealand*, 204 Env't Rsch., Mar. 2022, at 112322.

Mary H. Ward, Rena R. Jones, Jean D. Brender, Theo M. de Kok, Peter J. Weyer, Bernard T. Nolan, Cristina M. Villanueva & Simone G. van Breda, *Drinking Water Nitrate and Human Health: An Updated Review*, 15 Int'l J. Env't Rsch. & Pub. Health, Jul. 2018, at 1557.

Minn. Dept. of Health, *Nitrate and Methemoglobinemia* (2018).

Muhammad Tariq Bashir, Salmiaton Ali & Adnan Bashir, *Health Effects from Exposure to Sulphates and Chlorides in Drinking Water*, 6 Pak. J. Med. & Health Sci. 648 (2012).

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Am. Cancer Soc'y, *Water Fluoridation and Cancer Risk* (2015).

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Muhammad Syafrudin, Risky Ayu Kristanti, Adhi Yuniarto, Tony Hadibarata, Jongtae Rhee, Wedad A. Al-onazi, Tahani Saad Algarni, Abdulhadi H. Almarri & Amal M. Al-Mohaimeed,

Pesticides in Drinking Water—A Review, 18 Int'l J. Env't Rsch. & Pub. Health, Jan. 2021, at 468.

Env't Protection Agency, *Algal Toxin Risk Assessment and Management Strategic Plan for Drinking Water* (2015).

Xing-Fang Li & William A. Mitch, *Drinking Water Disinfection Byproducts (DBPs) and Human Health Effects: Multidisciplinary Challenges and Opportunities*, 52 Env't Sci. & Tech. 1681 (2018).

Virginie Rondeau, Hélène Jacqmin-Gadda, Daniel Commenges, Catherine Helmer & Jean-François Dartigues, *Aluminum and Silica in Drinking Water and the Risk of Alzheimer's Disease or Cognitive Decline: Findings From 15-Year Follow-Up of the PAQUID Cohort*, 169 Am. J. Epidemiology 489 (2009).

March 31, 2023

Ms. Jean Wagenius
4804 11th Ave South
Minneapolis, MN 55417

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 Jean Wagenius:

Thank you for your comments of March 4, 2023, and March 6, 2023, on the proposed Health Risk Limits Rules Amendments via the Office of Administrative Hearing's Rulemaking eComments website.

As you correctly note, Minnesotans are exposed to nitrate in their drinking water, both from public and private sources. Recognizing this, the Health Risk Assessment unit has a long-standing history of surveilling the published scientific literature for new nitrate data and follows the regulatory and risk assessment actions in other states and by the federal government. We are ready to reassess the nitrate Health Risk Limits (HRL) when the scientific literature points to the need and/or the literature reports new data in a way that can be used by MDH for HRL development.

At the time of this rulemaking, we believe that the federal nitrate Maximum Contaminant Level (MCL) used as the basis for the MDH nitrate HRL is sufficiently health protective for the most well-documented effect of nitrate, methemoglobinemia in infants. There are several reasons we continue to use the MCL standard. Unlike the vast majority of HRLs, the nitrate MCL is based on epidemiology data from human infants exposed to nitrate. Most HRLs are based on laboratory animal data, and MDH staff must extrapolate from effects seen in a rodent, dog, or rabbit to effects we think we will see in humans. There is uncertainty in this process that does not occur in epidemiology studies in humans. Additionally, the epidemiology studies are in infants, the most sensitive population for nitrate health effects. While the epidemiology data for nitrate is old (from the 1940s and 1950s), there have not been well-conducted peer reviewed studies since then that showed that nitrate can cause methemoglobinemia at concentrations below the MCL.

In addition, MDH staff conducted an investigation in 2018 to determine how many cases of methemoglobinemia had occurred in Minnesota in the previous two decades. After scouring medical records, staff identified 11 cases of methemoglobinemia in infants. Of these, only five were related to nitrate in drinking water. Methemoglobinemia is not a reportable disease in Minnesota, so it is likely that the five cases identified are an underestimation. Methemoglobinemia is also hard to diagnose because of its subtle symptoms in infants — fussiness, diarrhea, vomiting, lethargy. Most cases resolve when the water source is removed, and no medical intervention is needed. It is not clear from the identified cases whether Minnesota infants are getting sick from water with nitrate concentrations below the MCL in large numbers. Mandated reporting would help fix this issue, but that is outside the scope of this rulemaking.

There is growing concern within MDH and the risk assessment community at large about the health impacts related to long-term nitrate exposures from drinking water and other sources. There have been studies suggesting drinking water with nitrate concentrations below the MCL for a lifetime may cause cancer, including colon cancer. Currently, the epidemiology literature is not robust enough for MDH to calculate a new HRL. Most of the epidemiology studies that report illnesses, including cancer, from these types of low-concentration long-term exposures are considered 'ecological' studies. Ecological studies are designed as a preliminary investigation into a hypothesis and are also called 'hypothesis generating' studies because they inform and focus future, better quality studies. They truly are not designed to describe a dose response relationship between a chemical and a health outcome (e.g., as the concentration of a chemical increases, the number or severity of health effects increases). A quantitative reporting of data in a format that can be used for risk assessment is very rare in epidemiology, and a HRL cannot be based on a study that lacks this type of reporting.

One of the limitations also inherent in this type of study is a lack of evaluation of other exposures that can cause the health outcome being studied. Many of the recent nitrate studies did not complete a suitable exposure review that would have looked for the presence of trihalomethanes or other disinfection byproducts in the drinking water, smoking, eating red meat, lack of vitamin C, sedentary behavior, and/or alcohol consumption. All of these factors are associated with increased risk for cancer and chronic disease. Because the researchers did not look to see if people in the study had any of these confounding factors, we cannot be certain that it is the nitrate, and not the cigarettes, for example, that causes the cancer reported in the study participants.

In addition, these studies often lack any true measurement of exposure to nitrate, rather, using estimated population-level values. This would mean that instead of actually sampling the wells

in the study for nitrate levels, the researchers might apply an average nitrate concentration, or a concentration developed from a computer model, across the entire study population. This approach fails to catch natural variability in the environment. For example, in instances where there is the expected outcome, such as cancer, in a study participant, but little or no nitrate in their well water, this practice will link the cancer to a set value, rather than the actual value the person was exposed to. It will also not detect a situation where the well water is much higher in nitrate than the average concentration or the modeled concentration and the participant develops the health outcome, such as cancer. These types of inconsistencies are not acceptable in studies used for HRL development because again, we cannot accurately quantify the dose of the chemical that is causing the health effect.

Your comment quoted our Health Standards Statutes (MN Statutes 144.0751) and cites reports from the Environmental Working Group and Minnesota Center for Environmental Advocacy as reasons a new HRL is warranted. Neither of these reports qualify as information that can be used to develop a HRL under this statute. These reports are neither "scientifically acceptable, peer-reviewed information" nor "conducted by individuals with substantial knowledge and experience in toxicology, health risk assessment, or other related fields as determined by the commissioner," as required by the Health Standards Statute. Rather, these are policy reports that cite the epidemiology studies discussed above, which again, are not suitable for quantitative risk assessments that form the basis of HRLs.

The state of California published a review of epidemiology studies in 2018 (California Environmental Protection Agency, 2018) as part of their process to develop a new Public Health Goal for nitrate, which are similar to MDH's HRLs. Their review walked through the scientific literature, publication by publication, and cited why each study was or was not appropriate for risk assessment purposes. MDH paid careful attention to this document and reviewed it in 2018-9. California concluded that the epidemiology literature available was not sufficient to update their public health goal to a value different than the current MCL. Additionally, the United States Environmental Protection Agency (EPA) suspended its review of nitrate in 2018, citing other more important priorities.

MDH has a long history of leading the nation with safe, health-based values that protect the public health of our residents, notably including our work on PFAS. One only needs to look at our 20-year track record of providing values for PFAS, despite a lack of such action from US EPA. However, MDH also has a track record of standing on the science and not developing "policy" numbers. Our HRL authority and the methods derived under it for developing or updating values directs us to base them on careful quantitative scientific considerations (2009 SONAR, Appendix C; Minn. R. 4717.7830.) The available recent and historic toxicology information from

animal studies and epidemiology studies on nitrate and its health effects are not sufficient for the development of a new nitrate HRL. This may change as new information becomes available.

It is not reasonable to remove the HRLs for 37 contaminants from rulemaking just because a specific chemical is not included. This reasoning would allow anyone to provide an argument for any chemical as a reason to stop rulemaking. For example, there are three PFAS in this current rulemaking. Using this logic would allow a company that manufactures the three PFAS to simply say iron, for example, which is found in groundwater sometimes at very high levels, is not in this rulemaking and that makes the entire proposed rule null and void, stopping the three PFAS from being adopted into rule.

In your comment you also asserted that MDH must enforce the HRLs, apparently as industry regulations, based on its separate and general authority to enforce standards for "environmental health hazards" in a statute (144.05). This statute makes no mention of HRLs themselves. The legislature, however, specifically requires HRLs to be set in rule and defines them, not as directly enforced limits on any particular party's conduct, but as baselines for operationalizing the point where a concentration of a given substance becomes a potential health risk (103H.005, subd. 3). That MDH has general statutory authority to regulate environmental health hazards does not prohibit MDH from complying with a clear directive from the legislature to set HRLs in rule. In more than 20 years MDH has not interpreted the statute this way, nor has any administrative law judge during previous rulemakings.

Sincerely,

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I.2.b. Written Comment: Pre-Hearing Comment

I.2.b.i. Comment
Date: March 6, 2023
Chemical: HRL Rules Enforcement
Commenter: Jean Wagenius

I.2.b.ii. Minnesota Department of Health's Preliminary Response
Date: March 31, 2023

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.

March 31, 2023

Ms. Jean Wagenius
4804 11th Ave South
Minneapolis, MN 55417

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

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Your comment quoted our Health Standards Statutes (MN Statutes 144.0751) and cites reports from the Environmental Working Group and Minnesota Center for Environmental Advocacy as reasons a new HRL is warranted. Neither of these reports qualify as information that can be used to develop a HRL under this statute. These reports are neither "scientifically acceptable, peer-reviewed information" nor "conducted by individuals with substantial knowledge and experience in toxicology, health risk assessment, or other related fields as determined by the commissioner," as required by the Health Standards Statute. Rather, these are policy reports that cite the epidemiology studies discussed above, which again, are not suitable for quantitative risk assessments that form the basis of HRLs.

The state of California published a review of epidemiology studies in 2018 (California Environmental Protection Agency, 2018) as part of their process to develop a new Public Health Goal for nitrate, which are similar to MDH's HRLs. Their review walked through the scientific literature, publication by publication, and cited why each study was or was not appropriate for risk assessment purposes. MDH paid careful attention to this document and reviewed it in 2018-9. California concluded that the epidemiology literature available was not sufficient to update their public health goal to a value different than the current MCL. Additionally, the United States Environmental Protection Agency (EPA) suspended its review of nitrate in 2018, citing other more important priorities.

MDH has a long history of leading the nation with safe, health-based values that protect the public health of our residents, notably including our work on PFAS. One only needs to look at our 20-year track record of providing values for PFAS, despite a lack of such action from US EPA. However, MDH also has a track record of standing on the science and not developing "policy" numbers. Our HRL authority and the methods derived under it for developing or updating values directs us to base them on careful quantitative scientific considerations (2009 SONAR, Appendix C; Minn. R. 4717.7830.) The available recent and historic toxicology information from

animal studies and epidemiology studies on nitrate and its health effects are not sufficient for the development of a new nitrate HRL. This may change as new information becomes available.

It is not reasonable to remove the HRLs for 37 contaminants from rulemaking just because a specific chemical is not included. This reasoning would allow anyone to provide an argument for any chemical as a reason to stop rulemaking. For example, there are three PFAS in this current rulemaking. Using this logic would allow a company that manufactures the three PFAS to simply say iron, for example, which is found in groundwater sometimes at very high levels, is not in this rulemaking and that makes the entire proposed rule null and void, stopping the three PFAS from being adopted into rule.

In your comment you also asserted that MDH must enforce the HRLs, apparently as industry regulations, based on its separate and general authority to enforce standards for "environmental health hazards" in a statute (144.05). This statute makes no mention of HRLs themselves. The legislature, however, specifically requires HRLs to be set in rule and defines them, not as directly enforced limits on any particular party's conduct, but as baselines for operationalizing the point where a concentration of a given substance becomes a potential health risk (103H.005, subd. 3). That MDH has general statutory authority to regulate environmental health hazards does not prohibit MDH from complying with a clear directive from the legislature to set HRLs in rule. In more than 20 years MDH has not interpreted the statute this way, nor has any administrative law judge during previous rulemakings.

Sincerely,

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References

California Environmental Protection Agency (CalEPA). (2018) Public Health Goals for Nitrate and Nitrite. https://oehha.ca.gov/media/downloads/water/chemicals/phg/nitratephg051118.pdf . Retrieved from web 3-20-2023.

I.2.c. Written Comment: Pre-Hearing Comment

I.2.c.i. Comment
Date: March 8, 2023
Chemical: PFAS
Commenter: American Chemistry Council

I.2.c.ii. Minnesota Department of Health's Preliminary Response
Date: March 31, 2023

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.

March 8, 2023

Brooke Cunningham, MD
Commissioner
Minnesota Department of Health
625 Robert Street North
St. Paul, MN 55155

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 4587, OAH Docket No. 5-9000-38941

Dear Commissioner Cunningham:

The American Chemistry Council (ACC) appreciates the opportunity to submit comments on the proposed amendments to the Health Risk Limits (HRLs) Rules announced on February 6, 2023. As discussed below, ACC opposes the proposed health risk limits (HRLs) for perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS) and salts, and perfluorohexanoate (PFHxA) and salts. For all three substances, the Department inappropriately uses the results of a short-term study as the basis for its proposed subchronic and chronic HRLs, despite the fact that data from longer-term studies are available. For all three substances, MDH also inappropriately applies a database uncertainty factor (UF_D) – 3 in the case of PFBS and 10 in the case of PFHxS and PFHxA.

Perfluorobutane Sulfonate

The database for PFBS includes multiple sub chronic-duration toxicity studies of laboratory animals, multiple developmental toxicity studies with mice and rats, and a two-generation reproductive toxicity study with rats. MDH selected the results of a short-term study, however, despite the fact that the biological significance of the Department's critical effect from that study (*i.e.*, decreased T4 in adult euthyroid animals) is unclear in the absence of additional signs of overt thyroid toxicity (*e.g.*, reflex increase in thyroid stimulating hormone and/or alterations in tissue weight or histology).[1]

[1] USEPA. Human health toxicity values for perfluorobutane sulfonic acid (CASRN 375-73-5) and related compound potassium perfluorobutane sulfonate (CASRN 29420-49-3). EPA/600/R-20/345F. Office of Research and Development. Washington, DC (2021), at 82.

The developmental study by Feng *et al.* (2017)[2] also reported thyroid effects and is the more appropriate study to use as a basis for the proposed HRL. Feng *et al.* reported decreased serum total thyroxine (T4) in newborn mice which is considered to be important for normal growth of developing offspring across animal species.

For short-chain PFAS like PFBS, use of the default approach of body-weight scaling to estimate the human equivalent dose is consistent with USEPA guidance[3] and the state of the science.[4] Although the data may not be sufficient to model external dose and clearance in humans, the information available for the substance suggests that it is eliminated relatively rapidly and thus will not accumulate.[5] As a result, body-weight scaling is the most appropriate approach to estimating the human equivalent dose – rather than the serum elimination, half-life adjusted approach used by the Department.

In calculating the toxicity value for PFBS, MDH includes a UF_D of 3 based on concerns about developmental and immunotoxicity effects. For PFBS, however, robust data are available on reproductive and developmental effects, including both a prenatal toxicity study and a two-generation reproduction study. Moreover, the developmental effects appear to be "less sensitive than thyroid hormone perturbations in developing mice."[6] Consequently, a toxicity value that protects against effects on thyroid hormones also will protect against developmental effects. The Department provides no explanation for its concern for the potential immunotoxicity of PFBS, moreover. ACC is not aware of available data that would suggest that immunotoxicity is a concern for PFBS, which -- as clearly demonstrated by MDH's analysis -- exhibits dramatically different properties from the PFAS previously evaluated.

Perfluorohexane Sulfonate and Salts

The data selected by the Health Department to derive the proposed HRL for PFHxS come from the results of a 28-day toxicity study conducted by the federal National Toxicology Program (NTP). The Department's analysis provides no discussion of the available chronic

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2 Feng X *et al.* Exposure of Pregnant Mice to Perfluorobutanesulfonate Causes Hypothyroxinemia and Developmental Abnormalities in Female Offspring. *Toxicol Sci* 155(2): 409-419 (2017).

3 USEPA. Recommended Use of Body Weight ¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Risk Assessment Forum. Washington, DC. EPA/100.R11/001 (2011). https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

4 Sharma V and McNeill JH. To scale or not to scale: the principles of dose extrapolation. *Brit J of Pharma* 157(6):907-921 (2009). https://doi.org/10.1111/j.1476-5381.2009.00267.x

5 Xu Y *et al.* Serum half-lives for short- and long-chain perfluoroalkyl acids after ceasing exposure from drinking water contaminated by firefighting foam. *Environ Health Persp* 128:7 (2020). https://doi.org/10.1289/EHP6785

6 USEPA. PFBS Assessment, at 60.

studies conducted by Butenhoff et al (2009)[7] and Chang et el. (2018).[8] While the effects reported by Chang *et al.* (2018) do not represent a significant health effect,[9] the study by Butenhoff *et al.* (2009) has been used by a number of other states to assess the health effects of PFHxS. The Department's analysis also does not address the suggestion by Butenhoff *et al.* that thyroid effects (such as those reported in the NTP study) may be related to hepatocellular hypertrophy caused by activation of the peroxisome proliferator-activated receptor alpha (PPARα) leading to hyperplasia of the thyroid that is likely not relevant to human health risk.[10]

Before committing to an onerous HRL based on thyroid effects, the Department should carefully review interspecies differences and human study data on the relevance of thyroid effects and the variability of thyroid hormones across life. A recent French study reports that PFAS levels at birth were not associated with thyroid stimulating hormone (TSH) levels later in life,[11] and similar studies are underway to continue to add to evaluate the potential significance of TSH variance. Previous study data show a lack of strong evidence to suggest that per- and polyfluoroalkyl substances (PFAS) are associated with overall TSH and free T4, and even at the highest levels, any statistical variance in TSH-PFAS concentration correlations does not persist in humans beyond gestational week 10.[12] This would suggest that, even if a potential mechanism of action included possible competition with T4 for binding to transthyretin (a main carrier protein of thyroid hormone in mammals), observational (community epidemiology) studies do not suggest this effect occurs at relevant human exposures, either in the mother or infant.

The decision to focus on a short-term study for deriving the proposed MCL reflects the limited amount of toxicity data available for PFHxS. This paucity of data is further amplified by the application of a UF_D of 10 based on unspecified concerns about early life sensitivity and the lack of two-generation and immunotoxicity studies. The lack of a two-generation study would

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7 Butenhoff JL *et al.* 2009. Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. *Reprod Toxicol* 27(3-4):331-341 (2009).

8 Chang S *et al.* Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice. *Reprod Toxicol* 78:150-168 (2018).

9 Michigan Science Advisory Workgroup. Health-Based Drinking Water Value Recommendations for PFAS in Michigan. Report developed for the Michigan PFAS Action Response Team. Lansing, Michigan (2019). https://www.michigan.gov/pfasresponse/about/advisory-groups/science-advisory-workgroup

10 Wu KM Farrelly JG. Preclinical development of new drugs that enhance thyroid hormone metabolism and clearance: inadequacy of using rats as an animal model for predicting human risks in an IND and NDA. *Am J Ther* 13(2):141-44 (2006). https://www.doi.org/10.1097/01.mjt.0000209673.01885.b0

11 Dufour P *et al.* Association between exposure to persistent organic pollutants during pregnancy and thyroid function during childhood: a pilot longitudinal study and literature review. *Rev Med Liege* 75:37-42 (2020). https://www.rmlg.ulg.ac.be/

12 Inoue K *et al.* Perfluoroalkyl substances and maternal thyroid hormones in early pregnancy: Findings in the Danish National Birth Cohort. *Environ Health Persp* 127(11):117002 (2019). https://doi.org/10.1289/EHP5482

justify the use of a 3-fold uncertainty factor, based on USEPA guidance. Concern about early-life sensitivity is addressed by Chang *et al.* who reported no treatment-related effects on postnatal survival of development in offspring exposed in utero through PND 36. Although limited, Butenhoff *et al.* did not find evidence of immunotoxicity in rats exposed to up to 10 mg/kg per day by gavage for up to 56 days.

ACC's concerns about using the NTP study results, notwithstanding, the calculation on which the Department rely inappropriately uses a benchmark response (BMR) of 20 percent rather than a BMR of one standard deviation directly observed from study results as advised by USEPA's benchmark dose (BMD) modeling guidance.[13] Although the Department indicates that use of a BMR of 20% provides a more reliable result, that analysis has not been made available for review by external scientists and other stakeholders.

If MDH does not feel that published reports on PFHxS provide a sufficient basis for developing an MCL, the Department should defer establishing standards until more data on chronic effects are available. An assessment of the health effects of PFHxS is scheduled to be available from USEPA within the next year.[14]

Perfluorohexanoate and Salts

The animal evidence for PFHxA consists of short-term, subchronic, and chronic studies in adult male and female Sprague-Dawley rats with exposure durations spanning 28 days to 2 years. In addition, two developmental, gestational exposure, studies and a one-generation reproductive study are available. Despite the potential for a greater risk of bias and exposure extrapolation error, the Department chose the short-term study instead of one of the available subchronic, chronic, or developmental studies. Of these, the chronic study by Klaunig *et al.* (2015)[15] evaluated the standard full suite of organs, clinical observations, clinical pathology, reproduction and developmental effects and cancer following PFHxA exposure and is the logical choice for deriving the proposed HRL.

While the short-term study reported a decrease in thyroid hormones (*i.e.*, total T4), the inconsistency in findings for thyroid endpoints reported across several study designs reduces

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[13] USEPA. Benchmark Dose Technical Guidance. Risk Assessment Forum. Washington, DC. EPA/100/R-12/001 (2012). https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf

[14] https://www.epa.gov/iris/iris-program-outlook

[15] Klaunig JE *et al.* Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats. *Toxicol Pathol* 43(2), 209-220 (2015).

the strength of the available evidence.[16] Moreover, the developmental effects (*i.e.*, decreased pup body weight) reported by Loveless *et al.* (2009) coincided with evidence of maternal toxicity and generally disappeared after weaning. [17] As a result, the authors noted that "NaPFHx [the sodium salt of PFHxA] is therefore concluded not to present a reproductive or developmental hazard." Similarly, Iwai and Hoberman (2014) also reported pup body weight loss only at does resulting in significant maternal toxicity.[18] The decreases in pup weight were not statistically significant at postpartum day 20, moreover, and the authors reported no differences in terminal body weights among the dosage groups.

As with PFHxS, the Department inappropriately applies a UF_D of 10. In the case of PFHxA, MDH points to concerns about developmental, thyroid, and immunotoxicity. As noted however, the available evidence does not provide support for developmental effects and, while limited, the evidence for thyroid effects is inconsistent. With the exception of changes in thymus weights, the available animal evidence does not show a clear pattern of immune effects across studies.

Based on the information provided above, ACC recommends that the Department reevaluate the available evidence for PFBS, PFHxS, and PFHxA to ensure that the proposed HRLs reflect the best available science.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

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16 USEPA. Toxicological Review of Perfluorohexanoic Acid (CASRN 307-24-4) and Related Salts. External Review Draft. EPA/635/R-21/312a. Office of Research and Development. Washington, DC (2022). https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=352767

17 Loveless SE *et al.*Toxicological evaluation of sodium perfluorohexanoate. *Toxicol* 264(1-2), 32-44 (2009)

18 Iwai H and Hoberman AM (2014). Oral (gavage) combined developmental and perinatal/postnatal reproduction toxicity study of ammonium salt of perfluorinated hexanoic acid in mice. *Int J Toxicol* 33(3):219-237 (2014).

March 31, 2023

Mr. Steve Risotto
Senior Director
700 Second St., NE
Washington, DC 20002

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 Steve Risotto:

We thank the American Chemistry Council (ACC) for their written comments on the proposed Health Risk Limits (HRLs) for perfluorobutane sulfonate (PFBS), perfluorohexanoate (PFHxA), and perfluorohexane sulfonate (PFHxS). The Minnesota Department of Health (MDH) presents its written responses below. Text in *italics* is directly quoted from the comments submitted by ACC followed by the response from MDH. For background information on technical topics, please see Attachment A: Risk Assessment Methodology for Health Risk Limits Derivation.

General Comments

1. *For all three substances, the Department inappropriately uses the results of a short-term study as the basis for its proposed subchronic and chronic HRLs even though data from longer-term studies are available.*
    1. The methodology used by MDH for deriving health-protective HRLs was promulgated in the 2008 SONAR[1] and ensures that the derivation process used incorporates the necessary provisions to adequately protect sensitive or highly exposed populations, as required by the 2001 Health Standards Statute (Minnesota Statutes 144.0751)
    2. A key part of the methodology includes careful evaluation of longer-term as well as short-term studies. As recommended by the US Environmental Protection Agency (US EPA)[2], MDH's evaluations carefully consider the relationship between timing, duration, and magnitude of exposure and the subsequent adverse effect(s) in deriving guidance that are protective of sensitive life stages (e.g., development) and short periods of high exposure (e.g., infancy) as well as long-term exposure.
        - MDH has applied this methodology to over 120 chemical reviews; since infants drink large amounts of water for their body weight, it is not unusual for the short-term duration water value to be lower than calculated longer-term water values[3].
    3. By definition, (sub)chronic durations contain exposure periods of short-term duration. Because adverse health effects can result from short-term exposures to fetuses/infants during critical windows of development, relying solely on (sub)chronic studies to derive (sub)chronic HRLs may

underestimate the risk to fetuses and infants, an especially vulnerable population with high water intake rates. To ensure a HRL is health protective for short-term exposures that occur during (sub)chronic durations, the short-term reference dose and/or drinking water guidance value are used for the longer durations if the short-term numbers are lower than those calculated from sub(chronic) studies.

2. *MDH also inappropriately applies a database uncertainty factor (UFD) – 3 in the case of PFBS and 10 in the case of PFHxS and PFHxA.*
    1. Responses to this comment will be located within the respective section for each chemical.

Perfluorobutane Sulfonate

1. *MDH selected the results of a short-term study, however, despite the fact that the biological significance of the Department's critical effect from that study (i.e., decreased T4 in adult euthyroid animals) is unclear in the absence of additional signs of overt thyroid toxicity (e.g., reflex increase in thyroid stimulating hormone and/or alterations in tissue weight or histology). The developmental study by Feng et al. (2017) also reported thyroid effects and is the more appropriate study to use as a basis for the proposed HRL. Feng et al. reported decreased serum total thyroxine (T4) in newborn mice which is considered to be important for normal growth of developing offspring across animal species.*
    1. We are pleased that the commenter agrees about the importance and relevance of thyroid as a critical health endpoint. Thyroxine (T4) is the main hormone produced by the thyroid gland and blood levels of T4 represent a measure of thyroid function. Hypothyroxinemia (low T4 with normal TSH [thyroid stimulating hormone]) has been shown to have adverse effects on human development. Concerns over disruption of thyroid function led to changes in testing guidelines; including measuring blood levels of T4, T3 (triiodothyronine) as well as TSH in response to evidence that changes in serum T4 can produce effects on neurodevelopment without affecting TSH[4] [pages 50-51]. Study testing guidelines recommend using rats as the species for evaluating thyroid related endpoints (e.g., T4, TSH, thyroid weight) and consider hormone level effects observed in these studies to be relevant to human thyroid function[4] [Table 8-1].
    2. MDH selected the National Toxicology Program (NTP) 2019 study[5] as the basis for the proposed HRL to ensure appropriate levels of health protection. The measured decrease in thyroid hormones was much larger in the NTP study conducted in adult rats (~25-75%) compared to the decreases in mice (~10-20%) observed in Feng et al. 2017[6]. While the NTP 2019 study did not directly evaluate pregnant animals or neonatal rats, the significant decrease reported in multiple thyroid hormones surpassed what was seen in pregnant and neonatal animals in Feng et al. This dramatic decline would result in more severe effects on developing fetuses at lower doses than was observed in Feng et al.
    3. MDH's methodology specifies that, in the absence of information to the contrary, identifying and using dose-response information from the most sensitive species is preferred[1] [page 27]. Since Feng et al. demonstrated that maternal PFBS exposures translate to harmful effects in

offspring, the NTP 2019 study, which identified effects at lower doses, was selected as the basis for the proposed PFBS HRL because it is the most health protective.

2. *For short-chain PFAS like PFBS, use of the default approach of body-weight scaling to estimate the human equivalent dose is consistent with USEPA guidance and the state of the science. Although the data may not be sufficient to model external dose and clearance in humans, the information available for the substance suggests that it is eliminated relatively rapidly and thus will not accumulate. As a result, body-weight scaling is the most appropriate approach to estimating the human equivalent dose – rather than the serum elimination, half-life adjusted approach used by the Department.*
    1. Consistent with the state of risk assessment science, the United States Environmental Protection Agency (US EPA) did not use the default body weight scaling approach and but rather derived a chemical-specific dosimetric adjustment factor (DAF) for PFBS.
    2. MDH's analysis was consistent with US EPA's. Accordingly, MDH calculated a DAF in a similar manner, in accordance with the 2008 SONAR[1] [pages 30-31].
    3. Moreover, in the US EPA report Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose cited by the commenter[7], US EPA explicitly defines the preferred hierarchy of approaches for extrapolating doses from laboratory animals to humans as [pages ix-xi]:
        a. Physiologically-based toxicokinetic modeling
        b. Use of chemical-specific data
        c. In lieu of useful information about the chemical in question, default to body weight scaling to ¾ power
    4. Body weight scaling is not a preferred approach and is meant to be used as a default only when the other options are not feasible. As evidenced by US EPA and MDH calculating a PFBS-specific DAF, there clearly are chemical-specific data fulfilling the requirements for Option #2. Because data exist to fulfill Option #2, body weight scaling is not appropriate and any discussion of PFBS accumulation in the body is irrelevant.

3. In calculating the toxicity value for PFBS, MDH includes a UFD of 3 based on concerns about developmental and immunotoxicity effects. For PFBS, however, robust data are available on reproductive and developmental effects, including both a prenatal toxicity study and a two-generation reproduction study. Moreover, the developmental effects appear to be "less sensitive than thyroid hormone perturbations in developing mice." Consequently, a toxicity value that protects against effects on thyroid hormones also will protect against developmental effects.

1. The commenter cites "developmental affects appear to be 'less sensitive than thyroid hormone effects'" as appearing in US EPA's *Human Health Toxicity Values for PFBS* assessment. However, the quoted text is from a 2018 draft[8], which explicitly states that it should not be construed to represent Agency policy. Notably, the quoted text does not appear in a later 2020 version, or

the final version released in 2021[9], indicating that US EPA's analysis of the relative sensitivities of developmental and thyroid effects had been refined.

2. In fact, the final *Human Health Toxicity Values for PFBS* report[9] released in 2021 acknowledges – in many places – the remaining uncertainty around developmental and other effects and the need for additional data [e.g., pages 3, 4, 56, 57].
3. Indeed, the US EPA assigned a $UF_D = 3$ for the same reasons that MDH did:
    a. "A UF_D of 3 is applied due to database deficiencies. […] However, the observation of decreased thyroid hormone is known to be a crucial element during developmental life stages, particularly for neurodevelopment, and the database is limited by the lack of developmental neurotoxicity studies. In addition, because other health effect domains such as immunotoxicity and mammary gland development are effects of increasing concern across several members of the larger PFAS family (Grandjean, 2018; Liew et al., 2018; White et al., 2007), the lack of studies evaluating these outcomes following PFBS exposure is a limitation in the database." [page 84]

4. The Department provides no explanation for its concern for the potential immunotoxicity of PFBS, moreover. ACC is not aware of available data that would suggest that immunotoxicity is a concern for PFBS, which -- as clearly demonstrated by MDH's analysis -- exhibits dramatically different properties from the PFAS previously evaluated.

1. US EPA (see 3-3 above) and MDH have identified immunotoxicity data as an important data gap for PFBS and have applied a database uncertainty factor of 3. The proposed SONAR and the PFBS Summary Sheet posted on the MDH website provide additional background that immunotoxicity has been consistently observed as a sensitive effect for several other PFAS.
2. The epidemiological data are so strong for more well-studied PFAS that multiple state, federal, and international agencies[10-19] have stated that there is sufficient evidence that immune suppression, especially in infants and children, is associated with PFAS exposure. Immune suppression is among the most sensitive health endpoints observed.
3. The purpose of the UF_D is to account for potential health endpoints that have not been adequately evaluated and which could be sensitive endpoints. For plausible but unstudied/understudied endpoints, it is standard risk assessment practice to assign a UF_D until the data gap is filled. As noted in the 2008 SONAR[1], "[a]pplication of the database uncertainty factor may incorporate an evaluation of how thorough testing is with respect to life stage assessment, endpoint assessment, and duration of exposure." [page 32]

Perfluorohexane Sulfonate and Salts

1. *The data selected by the Health Department to derive the proposed HRL for PFHxS come from the results of a 28-day toxicity study conducted by the federal National Toxicology Program (NTP). The Department's analysis provides no discussion of the available chronic studies conducted by Butenhoff et al (2009) and Chang et el. (2018). While the effects reported by Chang et al. (2018) do not*

represent a significant health effect, the study by Butenhoff et al. (2009) has been used by a number of other states to assess the health effects of PFHxS.

1. The Butenhoff et al. 2009[20] and Chang et al. 2018[21] studies were evaluated by MDH as part of the PFHxS review process. MDH's evaluations carefully consider the relationship between timing, duration, and magnitude of exposure and the subsequent adverse effect(s) in deriving guidance that are protective of sensitive life stages (e.g., development) and short periods of high exposure (e.g., infancy) as well as long-term exposure. The point of departure (POD) – that is, the dose where a toxic effect is first identified – in the NTP 2019 study[5] is based on decreased T4 serum levels and was observed at the lowest dose tested. Thyroid hormone serum levels were not assessed in either Butenhoff et al. 2009 or Chang et al. 2018. Thyroxine (T4) is the main hormone produced by the thyroid gland and is critical for normal human development (see response in PFBS 1-1, above). Additionally, the thyroid hormone decreases observed in NTP 2019 are consistent with several other studies discussed below.
2. Finally, as discussed above in General Comments 1 and in keeping with promulgated MDH methodology[1], if a short-term study results in a lower guidance value than available (sub)chronic studies, the short-term value is used for all durations. Because thyroid hormone decreases were the most sensitive and most consistent across available studies, NTP 2019 was used as the basis for the proposed HRL.

2. The Department's analysis also does not address the suggestion by Butenhoff et al. that thyroid effects (such as those reported in the NTP study) may be related to hepatocellular hypertrophy caused by activation of the peroxisome proliferator-activated receptor alpha (PPARα) leading to hyperplasia of the thyroid that is likely not relevant to human health risk.

1. Notably, Butenhoff et al. 2009 did not directly measure thyroid hormone levels but only examined the thyroid histologically. It is not possible from this study to determine the impact of PFHxS on thyroid hormones or overall thyroid function. Additionally, thyroid weights were not reported from this study, making the proposed significant thyroid hyperplasia ambiguous.
    a. Additionally, PPARα activation alone is not sufficient to determine that a health effect is not relevant to human health risk. Fibrates, a class of cholesterol-reducing pharmaceuticals, have been in use since the 1960s and primarily act through activation of PPARα, demonstrating that PPARα is active and biologically relevant in humans[22; 23].
2. There are studies that do not support Butenhoff et al.'s suggestion of hepatocellular hypertrophy as source of the thyroid effects. Ramhøj et al 2018 observed a significant decrease in T4 levels but no change in liver weight in rats, indicating that hepatocellular hypertrophy is unlikely to occur at PFHxS doses affecting thyroid hormones[24].
3. A subsequent study by Ramhøj also demonstrated that thyroid weights and histology were unchanged after PFHxS exposure, further supporting that thyroid hyperplasia secondary to hepatocellular hypertrophy is unlikely to be a significant factor[25].

4. Recent mechanistic studies have suggested that many PFAS, including PFHxS, can disrupt thyroid hormones through non-hepatic interactions, including binding to thyroid hormone transport proteins[26-29].
5. The Agency for Toxic Substances and Disease Registry (part of the Centers for Disease Control) *Toxicological Profile for Perfluoroalkyls*[30], noted that approximately 25% of the gene expression changes caused by PFHxS exposure are independent of any PPARα activity [Table 2-29]; therefore, PFHxS affects cells through mechanisms other than PPARα activation.
6. In total, the evidence for thyroid hyperplasia secondary PPARα-induced liver hypertrophy is woefully insufficient to establish it as the likely mechanism of action, and newer studies suggest that TTR-T4 inhibition may be a major contributor to PFAS-induced thyroid signaling dysfunction.
7. Insufficient thyroid hormone levels during critical periods of development can cause irreversible damage. As noted above, study testing guidelines recommend using rats as the species for evaluating thyroid related endpoints (e.g., T4, TSH, thyroid weight) and consider hormone level effects observed in these studies to be relevant to human thyroid function[4] [Table 8-1]. In the absence of a plausible mechanism of action irrelevant to humans, the severe decrease in thyroid hormones must be assumed to be relevant.

3. Before committing to an onerous HRL based on thyroid effects, the Department should carefully review interspecies differences and human study data on the relevance of thyroid effects and the variability of thyroid hormones across life. A recent French study reports that PFAS levels at birth were not associated with thyroid stimulating hormone (TSH) levels later in life, and similar studies are underway to continue to add to evaluate the potential significance of TSH variance. Previous study data show a lack of strong evidence to suggest that per- and polyfluoroalkyl substances (PFAS) are associated with overall TSH and free T4, and even at the highest levels, any statistical variance in TSH-PFAS concentration correlations does not persist in humans beyond gestational week 10. This would suggest that, even if a potential mechanism of action included possible competition with T4 for binding to transthyretin (a main carrier protein of thyroid hormone in mammals), observational (community epidemiology) studies do not suggest this effect occurs at relevant human exposures, either in the mother or infant.

1. As part of its review process, MDH carefully evaluates all available and relevant human and animal study data. Study design guidelines[4] recommend using rats for evaluating thyroid effects and specifically note "circulating levels of TH [thyroid hormones] can be related to human thyroid function." The cited French study measured only TSH.
2. Epidemiology studies have reported mixed results; some studies have reported associations while others have not. The thyroid is particularly challenging to assess in epidemiology studies, as thyroid hormone levels naturally vary by time of day, fasting state, trimester of pregnancy, and between individuals. Hypothyroxinemia (low T4 <u>but normal TSH levels</u>) have been associated with a higher risk of cognitive delay in early childhood. The cited French study only

measured TSH and did not measure T4 or other thyroid hormones; therefore, hypothyroxinemia or other thyroid hormonal effects were not evaluated.

3. The consistency of observed animal thyroid toxicity without plausible evidence of a mechanism of action irrelevant to humans suggests that the thyroid should be considered a target of PFAS in humans while the epidemiology database continues to grow.
4. In *Human Health Toxicity Values for PFBS*[9], EPA states the following about the human relevance of thyroid as an endpoint [page 57]:
    a. "Overall, based on findings in animal models considered to be informative for evaluating the potential for thyroid effects in humans, the available evidence supports a hazard, and the thyroid is considered a potential target organ for PFBS toxicity in humans."
5. An independent, external peer review report[31] commissioned by EPA for their ongoing PFHxA toxicological review recommended that "EPA conclude that the available evidence indicates that PFHxA exposure is likely to cause thyroid toxicity in humans given relevant exposure circumstances, primarily based on short-term studies in rats reporting a consistent and coherent pattern of effects on thyroid hormones following PFHxA exposure, but also drawing from the consistency of effects when considering evidence from structurally related PFAS." [page 8] and further noted that it is a well-known phenomenon that "some chemicals can reduce serum thyroid hormones without increasing TSH." [page 52]

4. The decision to focus on a short-term study for deriving the proposed MCL reflects the limited amount of toxicity data available for PFHxS. This paucity of data is further amplified by the application of a UF_D of 10 based on unspecified concerns about early life sensitivity and the lack of two-generation and immunotoxicity studies.

1. As explained in MDH's response under General Comments, all available relevant data were considered during MDH's analysis. The use of a short-term study as the basis for the proposed HRL does not directly reflect upon the strengths or weaknesses of the database.
2. As discussed above, the NTP 2019 study[5] was determined to be the most appropriate as the basis of the proposed HRL because it describes the most sensitive effect and ensures that the guidance value is adequately protective of susceptible populations (e.g., developing fetuses and infants).
3. The proposed SONAR and the PFHxS Toxicological Summary Sheet posted on MDH's website provide additional background about the early life concerns regarding decreased T4.
4. MDH does not establish MCLs, which are regulatory values that balance health impacts with cost and feasibility of remediation. HRLs are non-regulatory and are based solely on health effects (Minnesota Statues Chapter 103H).

5. The lack of a two-generation study would justify the use of a 3-fold uncertainty factor, based on USEPA guidance. Concern about early life sensitivity is addressed by Chang et al. who reported no treatment-related effects on postnatal survival of development in offspring exposed in utero through PND 36.

Although limited, Butenhoff et al. did not find evidence of immunotoxicity in rats exposed to up to 10 mg/kg per day by gavage for up to 56 days.

1. The rationale for the database uncertainty factor of 10 included thyroid hormone effects in early life and immunotoxicity as well as the lack of a 2-generation study. Two-generation studies traditionally do not adequately assess immune development or neurodevelopment. These are critical data gaps because pre- and neonatal immunological and neurological developmental windows are much more susceptible to disruption than in adults.
2. Decrease in circulating antibodies have been identified as a very sensitive measure of immunotoxicity for other PFAS in both animal studies and epidemiology studies. Decreased antibodies in young children is being used as the basis for regulatory guidance of PFAS by the US EPA[11-14] and European Food Safety Authority[18].
3. The studies by Chang et al and Butenhoff et al assessed survival and physical developmental milestones. Neither included evaluation of sensitive immunological (e.g., circulating antibodies) or neurological endpoints in offspring.
4. The 2002 US EPA report *A Review of the Reference Dose and Reference Concentration Processes*[2] lays out recommendations for the application of database uncertainty factors [Section 4, page 44]:
    a. "If the RfD/RfC is based on animal data, a factor of 3 is often applied if either a prenatal toxicity study or a two-generation reproduction study is missing, or a factor of 10 may be applied if both are missing. […] If data from the available toxicology studies raise suspicions of developmental toxicity and signal the need for developmental data on specific organ systems (e.g., detailed nervous system, immune system, carcinogenesis, or endocrine system), then the database factor should take into account whether or not these data are available"
    b. The EPA guidelines are not to be interpreted as rigid rules that constrain a risk assessor from applying uncertainty factors as appropriate. As noted in the last sentence of the excerpt, when significant questions remain about potential sensitive endpoints, they should be fully accounted for in the UF_D.
5. The outstanding questions about the potential for immunotoxicity from PFHxS indicates the need for a $UF_D = 10$ to address multiple critical data gaps. As noted in the 2008 SONAR[1], "[a]pplication of the database uncertainty factor may incorporate an evaluation of how thorough testing is with respect to life stage assessment, endpoint assessment, and duration of exposure." [page 32]

6. ACC's concerns about using the NTP study results, notwithstanding, the calculation on which the Department rely inappropriately uses a benchmark response (BMR) of 20 percent rather than a BMR of one standard deviation directly observed from study results as advised by USEPA's benchmark dose (BMD) modeling guidance. Although the Department indicates that use of a BMR of 20% provides a more reliable result, that analysis has not been made available for review by external scientists and other stakeholders.

1. MDH has never withheld information from the public; MDH followed standard practices during the review and provided standard detail on the PFHxS Summary Sheet. MDH publishes the initiation and completion of every chemical review, as well as other important unit announcements, via a GovDelivery email list that anyone can join. Initiation of the PFHxS review was announced via GovDelivery email and posted to MDH's website on June 22, 2018. Completion of the PFHxS review was announced via GovDelivery email and review documents were posted to MDH's website on April 3, 2019. MDH is always available for inquiries or to provide additional information during and after a chemical review.
2. Similar to the discussion of body weight scaling (PFBS, Question 2), the US EPA's recommendation of one standard deviation (SD) as the benchmark response (BMR) is meant as a default in the absence of additional information. As stated in the 2012 US EPA *Benchmark Dose Technical Guidance*[32], there is a preference hierarchy for the basis of the BMR. The hierarchy range from a minimal level of change that is generally considered to be biologically significant (most preferred) to a default of one standard deviation (SD) (or lower for more severe effects) from control (least preferred). The default is used in the absence of an idea of what level of response to consider adverse.
3. Clinical literature indicates a perceived toxicological significance in decreased T4 concentration. Haddow et al. 1999[33] reported that a 25% decrease in maternal fT4 during the second trimester was associated with neurodevelopmental and cognitive deficits in children. Additionally, Henrichs et al. 2010[34] associated maternal hypothyroxinemia (low T4 but normal TSH levels) with a higher risk of cognitive delay in early childhood.
4. EPA selected a BMR of 20% relative deviation for decreased thyroid hormone in their 2018 public draft *Human Health Toxicity Values for PFBS*[8], noting "[m]ultiple lines of evidence regarding the degree of thyroid hormone disruption and developmental outcomes in pregnant dams or offspring were considered in the identification of this BMR." [page 55]. This was the best available science regarding a level of change of concern at the time of MDH's review.
5. As a matter of practice during our analyses, MDH performs comparisons with a variety of default BMRs (e.g., 10%, 20%, 1 SD). For this study, the POD calculated using a BMR = 1 SD was ~7% lower than the POD calculated using a BMR = 20%, indicating a negligible difference in potential guidance values.

7. If MDH does not feel that published reports on PFHxS provide a sufficient basis for developing an MCL, the Department should defer establishing standards until more data on chronic effects are available.

1. MDH is confident in the basis of the proposed HRL for PFHxS. The available toxicity and toxicokinetic data support the use of NTP 2019 data indicating potent thyroid toxicity from PFHxS exposure.
2. As noted above in PFHxS Question 4-4, MDH does not establish MCLs.

Perfluorohexanoate and Salts

1. *Despite the potential for a greater risk of bias and exposure extrapolation error, the Department chose the short-term study instead of one of the available subchronic, chronic, or developmental studies. Of these, the chronic study by Klaunig et al. (2015) evaluated the standard full suite of organs, clinical observations, clinical pathology, reproduction and developmental effects and cancer following PFHxA exposure and is the logical choice for deriving the proposed HRL.*
    1. All available relevant data for PFHxA was included in MDH's analysis, including Klaunig et al. 2015.
    2. There is no greater risk of bias or exposure extrapolation error. As addressed above, short-term durations exist within (sub)chronic durations.
    3. The NTP 2019 28-day study resulted in a lower guidance value than the available (sub)chronic studies. As addressed above and as laid out in our methodology[1], a lower guidance value from a shorter duration will always supersede a higher value from a longer duration – this is necessary to ensure health protection for all populations across all durations.

2. *While the short-term study reported a decrease in thyroid hormones (i.e., total T4), the inconsistency in findings for thyroid endpoints reported across several study designs reduces the strength of the available evidence.*
    1. The major concerns of thyroid toxicity and PFAS exposure have been addressed above.
    2. Specifically, for PFHxA, from US EPA's draft *Toxicological Review of Perfluorohexanoic Acid and Related Salts*[35]:
        a. "A single study evaluated potential PFHxA effects on endocrine function specific to thyroid hormones in rats exposed for 28 days (NTP, 2018). Specifically, males showed statistically significant, dose-dependent decreases in thyroid hormones. These outcomes showed a clear dose dependent pattern of effect with treated animals showing reductions of 25–73% or 20–58% for free or total T4, respectively. Smaller decreases in T3 in males also were observed (18–29%), although the dose-dependence of this effect was less clear." [Section 3, page 77-78]
        b. The NTP study was rated high confidence by US EPA due to measure of thyroid hormones, organ weight, and histopathology.

3. Moreover, the developmental effects (i.e., decreased pup body weight) reported by Loveless et al. (2009) coincided with evidence of maternal toxicity and generally disappeared after weaning. As a result, the authors noted that "NaPFHx [the sodium salt of PFHxA] is therefore concluded not to present a reproductive or developmental hazard." Similarly, Iwai and Hoberman (2014) also reported pup body weight loss only at does resulting in significant maternal toxicity. The decreases in pup weight were not statistically significant at postpartum day 20, moreover, and the authors reported no differences in terminal body weights among the dosage groups.

1. The more complete statement regarding reproductive or developmental hazard from Loveless et al (2009)[36] is: "The maternal and developmental toxicity NOAEL was 100 mg/(kg day), based on maternal and fetal bodyweight effects at 500 mg/(kg day). NaPFHx is therefore concluded not to present a reproductive or developmental hazard."
2. MDH agreed with these designations at these dose levels. However, the POD used as the basis for the RfD was higher than the Loveless NOAEL (5% decrease in pup body weight was observed), but lower than the Loveless LOAEL (statistically significant 17% decrease in pup body weight was observed).
    a. Statistical significance and biological significance are not equivalent. Decreases of more than 5% in body weight in developing animals are considered an adverse effect. Since it is likely that the decrease in pup body weight would be higher than 5% at doses similar to the POD, decreased pup body weight was included as a sensitive endpoint.
3. The US EPA draft *Toxicological Review of Perfluorohexanoic Acid and Related Salts*[35] determined that the evidence for decreased postnatal body weight represented an adverse health effect and was suitably sufficient to use it as the basis of their RfD [Section 5, page 26 and 32].
4. MDH's analysis agrees with US EPA's assessment and developmental is included as an additivity endpoint in our proposed HRL.

4. As with PFHxS, the Department inappropriately applies a UF_D of 10. In the case of PFHxA, MDH points to concerns about developmental, thyroid, and immunotoxicity. As noted however, the available evidence does not provide support for developmental effects and, while limited, the evidence for thyroid effects is inconsistent. With the exception of changes in thymus weights, the available animal evidence does not show a clear pattern of immune effects across studies.

1. As noted above, the purpose of the UF_D is to account for potential health endpoints that have not experimentally been determined to be irrelevant. For plausible but unstudied/understudied endpoints, it is appropriate to assign a UF_D until the data gap is filled.
2. In both MDH's and US EPA's analyses, developmental was identified as one of the most sensitive health endpoints. Because of PFHxA's effects on developing animals at low doses, there are several outstanding data gaps in the PFHxA developmental database that need to be addressed, including: a 2-generation study, developmental neurotoxicity study and developmental immunotoxicity study. As noted above in the PFHxS response [Question 5], these represent critical data gaps because neonatal immunological and neurological developmental windows are much more susceptible to disruption than in adults.
3. These multiple data gaps warrant the application of a $UF_D = 10$ to ensure an adequate margin of safety for vulnerable populations.

Conclusions

We again thank ACC for their comments on the proposed HRLs for PFBS, PFHxA, and PFHxS. After careful consideration of each comment, and in keeping with our methodology and in accordance with our obligation and authority under Minnesota Statutes 114.0751 and 103H.201, MDH maintains its proposed HRLs for PFBS, PFHxA, and PFHxS in order to "adequately protect the health of infants, children, and adults."

Sincerely,

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Enclosure: Attachment A, Risk Assessment Methodology for Health Risk Limits Derivation, Summarized from 2023 SONAR

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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

I.2.d. Written Comment: Pre-Hearing Comment

I.2.d.i. Comment
Date: March 8, 2023
Chemical: Nonylphenol
Commenter: Barbara Losey, Alkylphenols & Ethoxylates Research Council

I.2.d.ii. Minnesota Department of Health's Preliminary Response
Date: March 31, 2023

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)

Nonylphenol – Critical Effect

Meeting with Minnesota Department of Health

December 15, 2022

Thomas G. Osimitz, PhD, DABT

Alkylphenols and Ethoxylates Research Council (APERC)

Agenda

- Introductions
- Purpose of Meeting
  - Selection of Critical Effects
- Scientific overview
  - Review of histopathology
  - Adverse? Renal toxicity - weight of evidence
- Regulatory overview
  - Comparative assessments
- Recommendations
- Discussion

Preview – Conclusions

- Renal mineralization seen at some dose(s) in all three pivotal studies
  - It was low incidence and low severity
  - No other renal effects accompany the mineralization
- Mineralization is a frequent finding in rat studies
  - Possible mineral imbalance, gut flora, etc.
- Mineralization alone at the low dose in a single study should not be considered a critical effect

Present MDH Assessment

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 20 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0049 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 21.7 rounded to **20 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.485/100 = 0.0049 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	1.94 mg/kg-d (administered dose $BMDL_{10}$, NTP 1997/Chapin 1999, subchronic exposure)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.94 mg/kg-d x 0.25 = 0.485 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability and 3 for subchronic to chronic extrapolation
Critical effect(s):	Renal mineralization in male rats

Present MDH Assessment

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 40 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

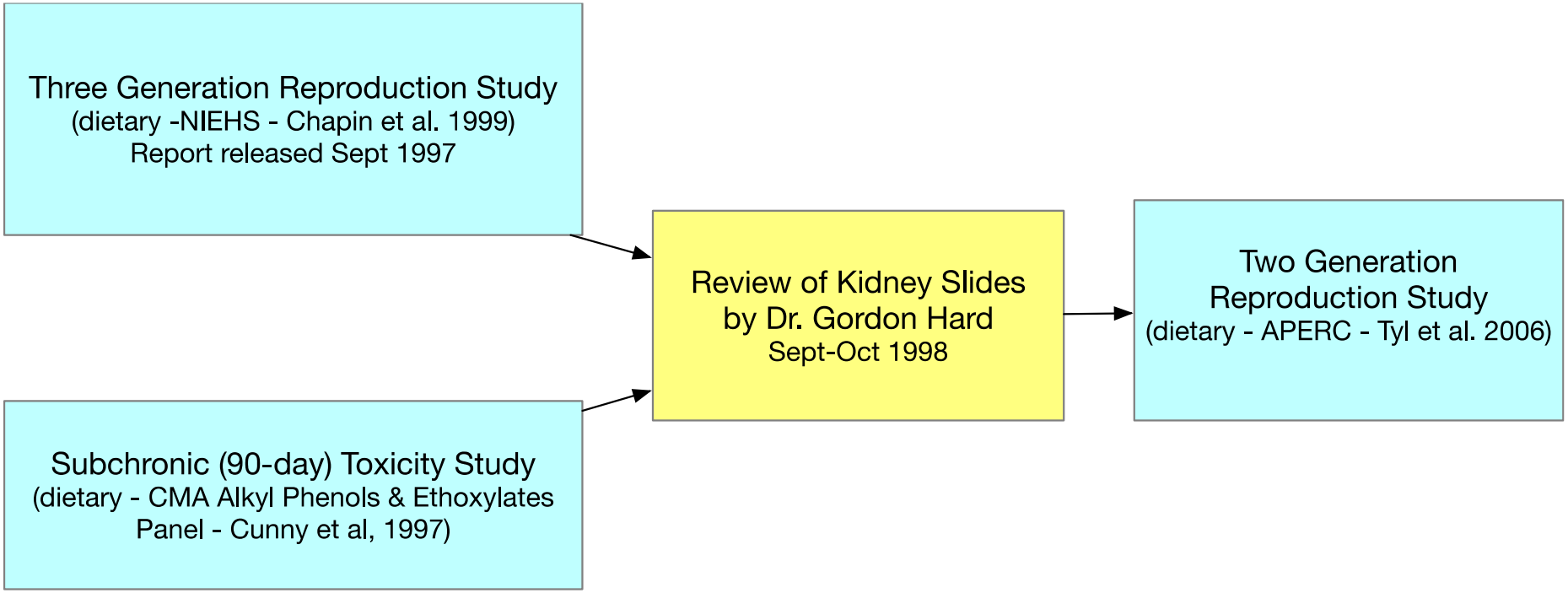
$$= \frac{\text{(0.016 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 43.2 rounded to **40 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.485/30 = 0.016 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	1.94 mg/kg-d (administered dose $BMDL_{10}$, NTP 1997/Chapin 1999)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.94 mg/kg-d x 0.25 = 0.485 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Renal mineralization in male rats
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Focus - Pivotal Studies



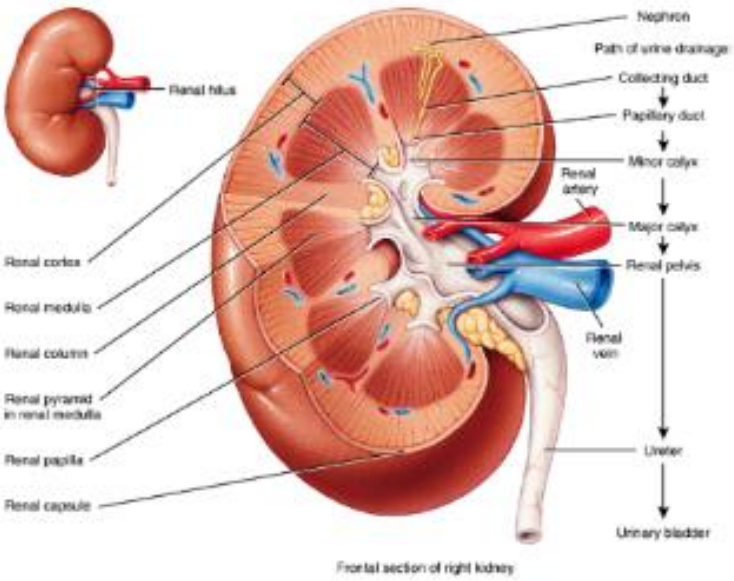
Review of Cunny et al. and Chapin et al.

- Conducted by Gordon Hard, BVSc, PhD, DSc, FRC Pat, FRCVS, FATS (noted renal pathologist)
- Goal: review kidney tissue using same pathologist, criteria, and nomenclature

Renal Mineralization

- Nature of the effect
  - Renal anatomy and pathology
- NP association – study data
- Causes
  - Chemical and non-chemical
- Gauging Adversity
  - LOAEL or LOEL

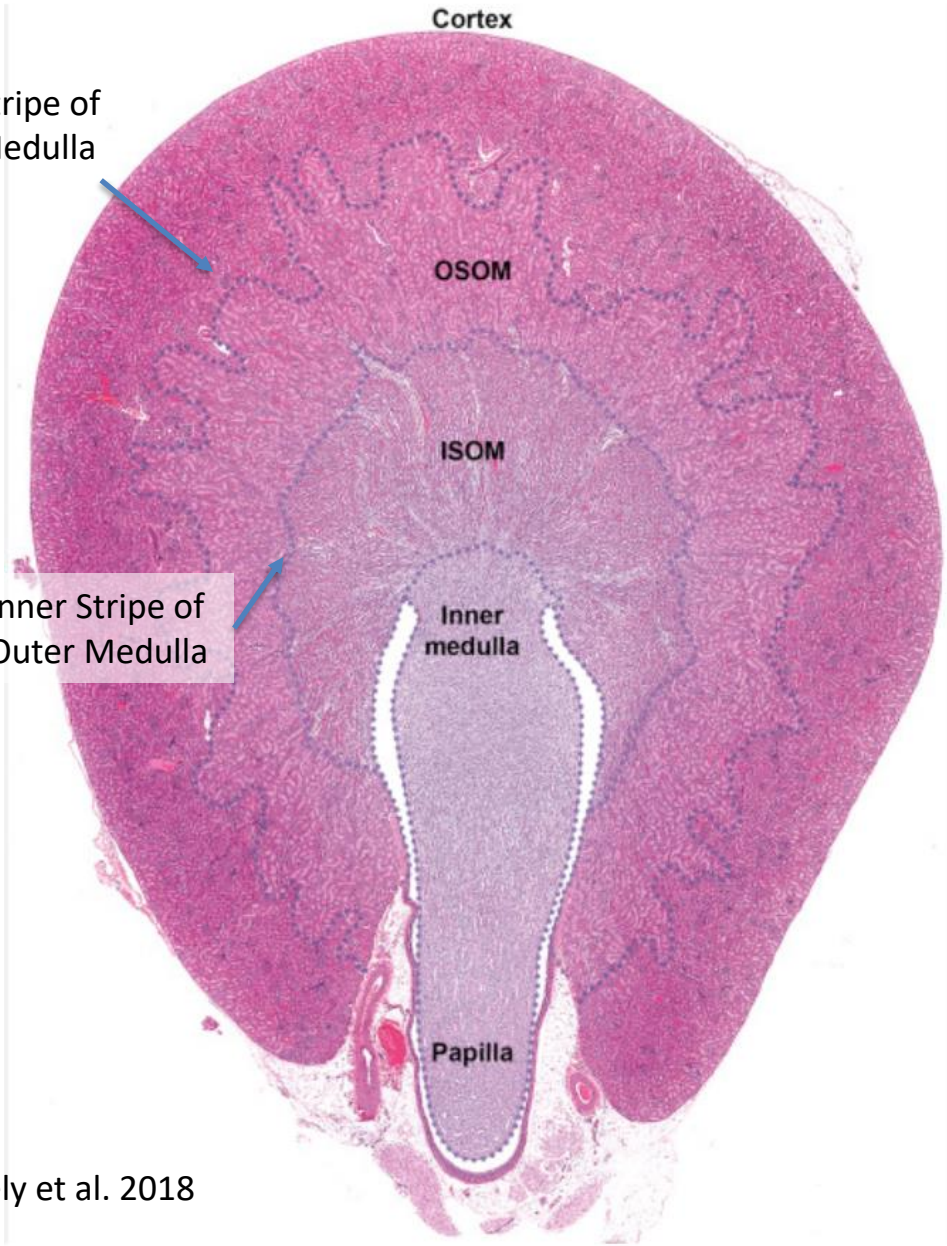
Renal Orientation



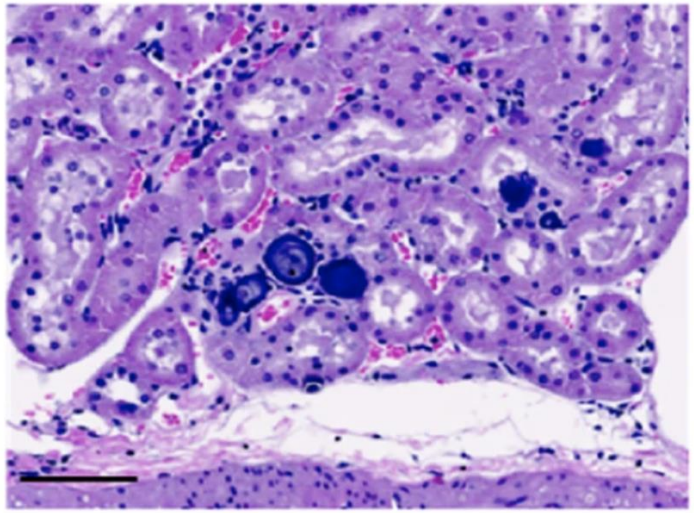
Maurya et al. 2018

Outer Stripe of Outer Medulla

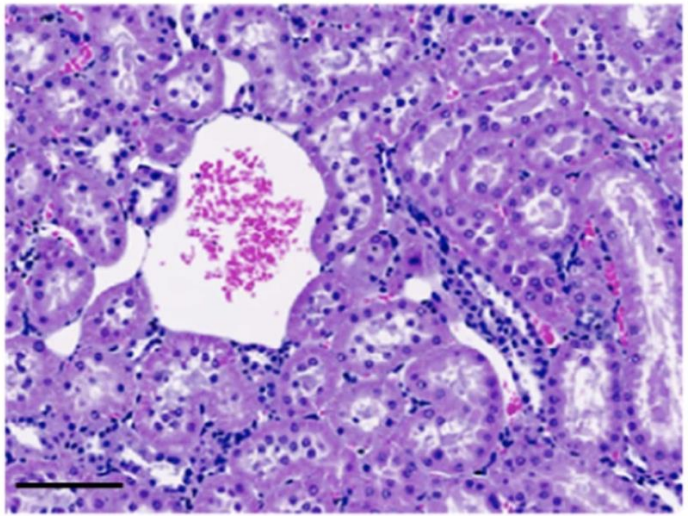
Inner Stripe of Outer Medulla



Seely et al. 2018



Mineralization (tubular)

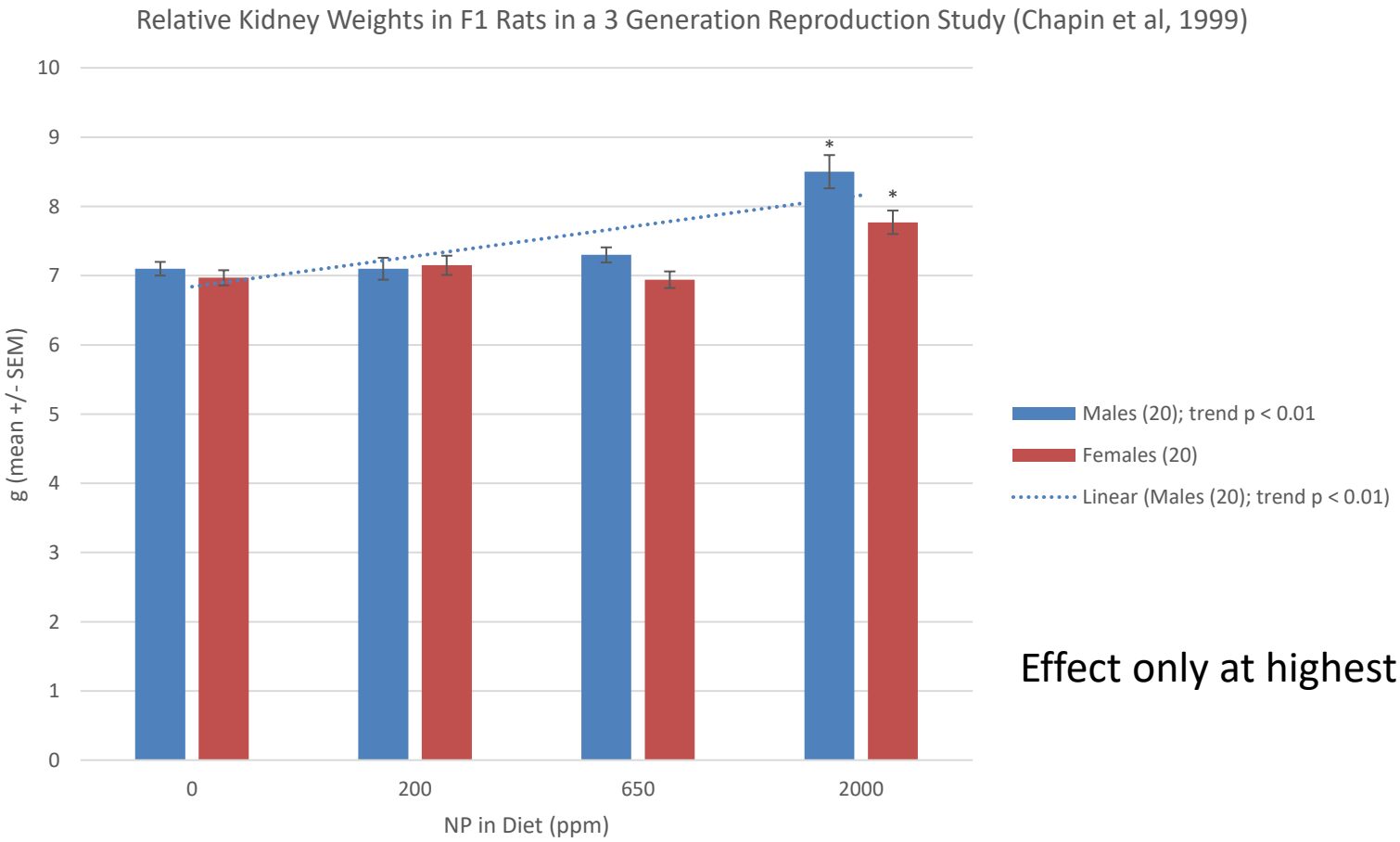


Normal tubular histology

Byun et al. (2022)

Chapin et al. – Closer Look

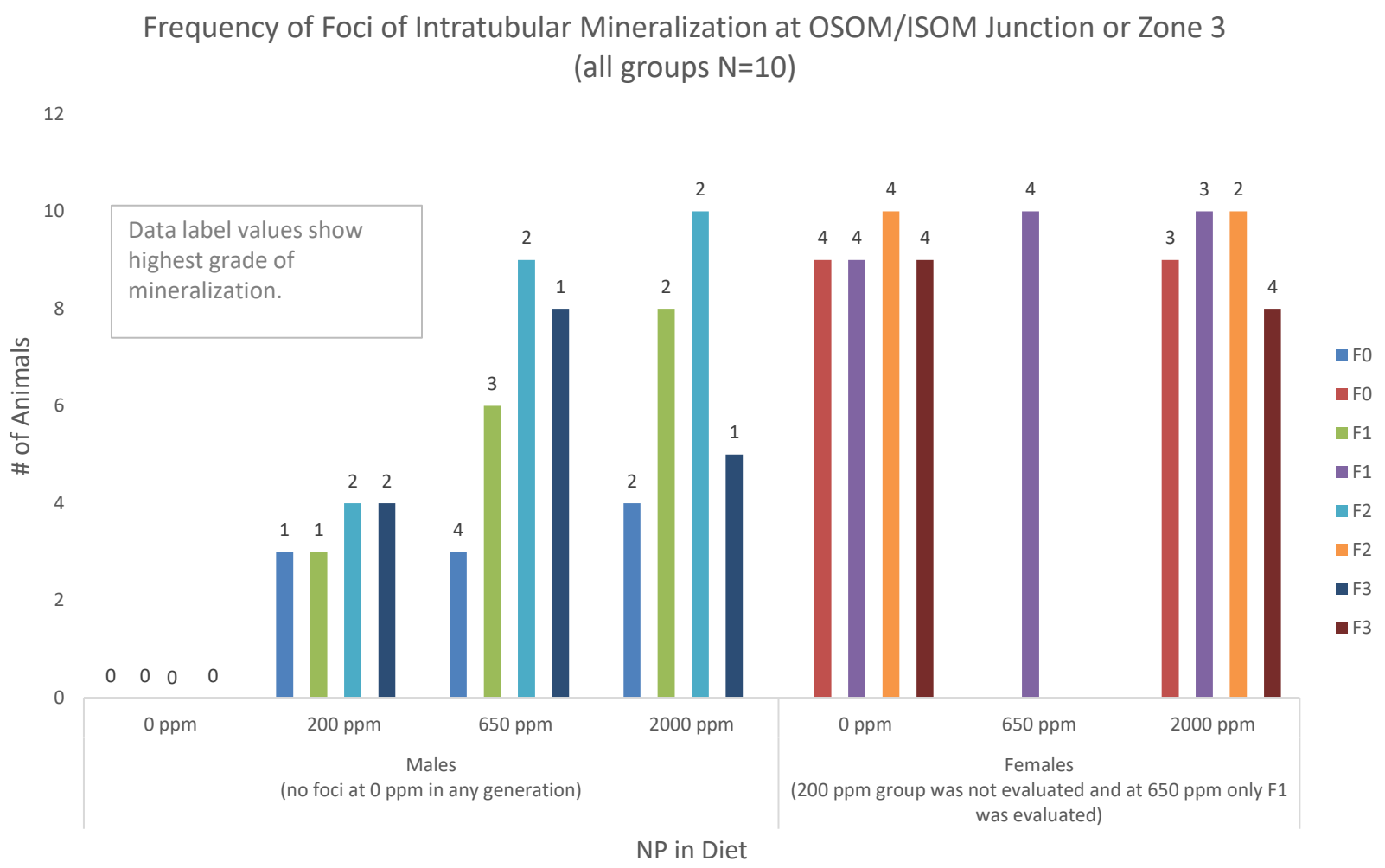
(From Hard, 1998)



Effect only at highest dose

Chapin et al. – Closer Look

(From Hard, 1998)



Mineralization at low grade and low incidence in males at 200 ppm

Chapin et al. – Closer Look

(From Hard, 1998)

Other changes which showed an association with treatment in high-dose (and sometimes mid-dose) rats of the F1, F2 and F3 generations (but not in the 90-day study or F0 generation) were cystic tubules and/or fibrotic areas, scattered or sporadic dilated tubules, granular or cellular casts, and foci of mononuclear cell inflammation, all at the OSOM/ISOM junction or in zone 3. In addition, some treated animals in the F2 and F3 generations had tubular involvement suggestive of pyelonephritis. The PWG identified hydronephrosis above control levels in the males of the F1, F2 and F3 generations, which was generally confirmed during this review. However, the PWG did not consider the observed hydronephrosis to have a definitive treatment relationship. Nevertheless, this condition can reflect chronic inflammation or obstruction in the lower urinary tract (Hard et al., 1998), and possibly may be a further indication of some intercurrent process superimposed on the treatment.

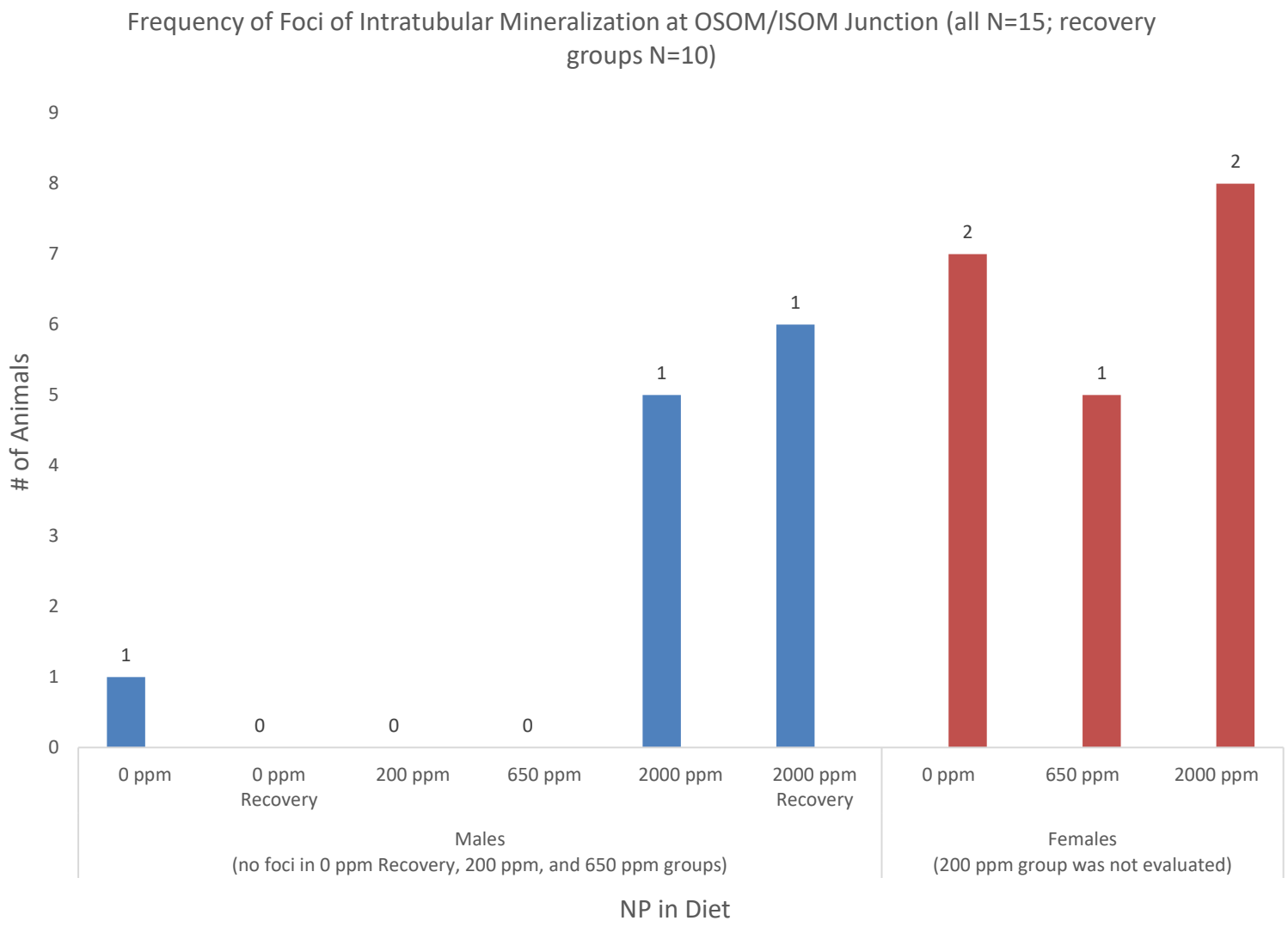
Cunny et al. – Closer Look

(from Hard, 1998)

- "The only treatment-related pathological effect observed was an increase in the frequency of deposits of intratubular mineralization in the P3 (straight) of the proximal tubule at the OSOM/ISOM junction in the high does males. In this group, 11 of 25 rats had such mineral deposits compared to none in the lower dose groups and 1 of 25 control rats. A similar treatment related effect not observed in female rats because foci of intratubular mineralization in all groups, controls were comparable."

Cunny et al. – Closer Look

(from Hard, 1998)



Mineralization in all female dose groups, but only high dose in males

Cunny et al. – Closer Look

(from Hard, 1998)

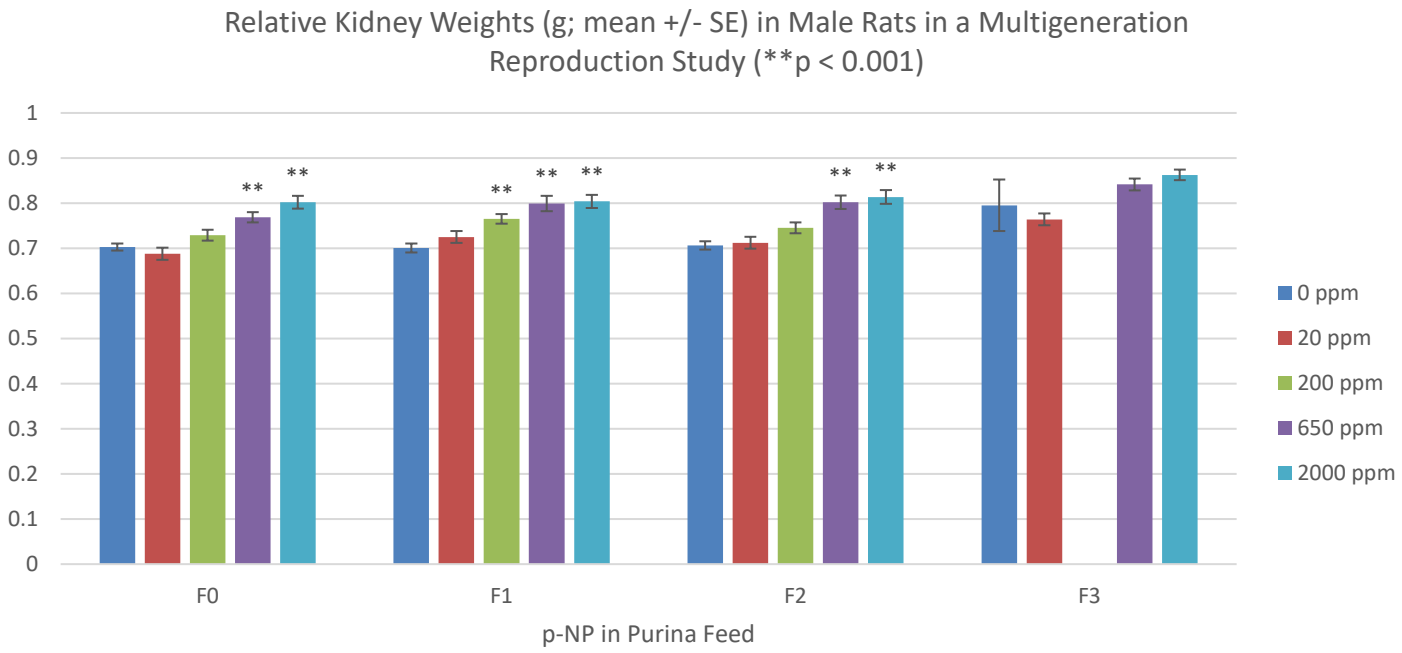
- Mineralization may represent calcium phosphate formation - frequently associated with a decrease in the dietary calcium/phosphorus ratio below 1.0. The rat is considered less able than other species to cope with disturbance in calcium homeostasis, with female rats more prone to renal tubular mineralization than male rats, “as estrogen levels may play a role in the process” (Hard, 1998; p. 8).

Tyl et al. – Another Look

- This study evaluated the potential for dietary para-nonylphenol (NP; CAS No. 84852-15-3) to affect parental fertility and growth and development of three offspring generations in CD (SpragueDawley [SD]) rats, including sperm counts across generations to determine the validity of equivocal reductions observed in the F2 generation by R. E. Chapin et al. (1999, Toxicol. Sci. 52, 80–91). Male rat kidney toxicity was also examined based on inconsistent observations in NP-exposed rats at 2000 ppm but not at 200 or 650 ppm in Purina 5002 (H. C. Cunny et al., 1997, Regul. Toxicol. Pharmacol. 26, 172–178) and at all of these NP concentrations in NIH-07 diet

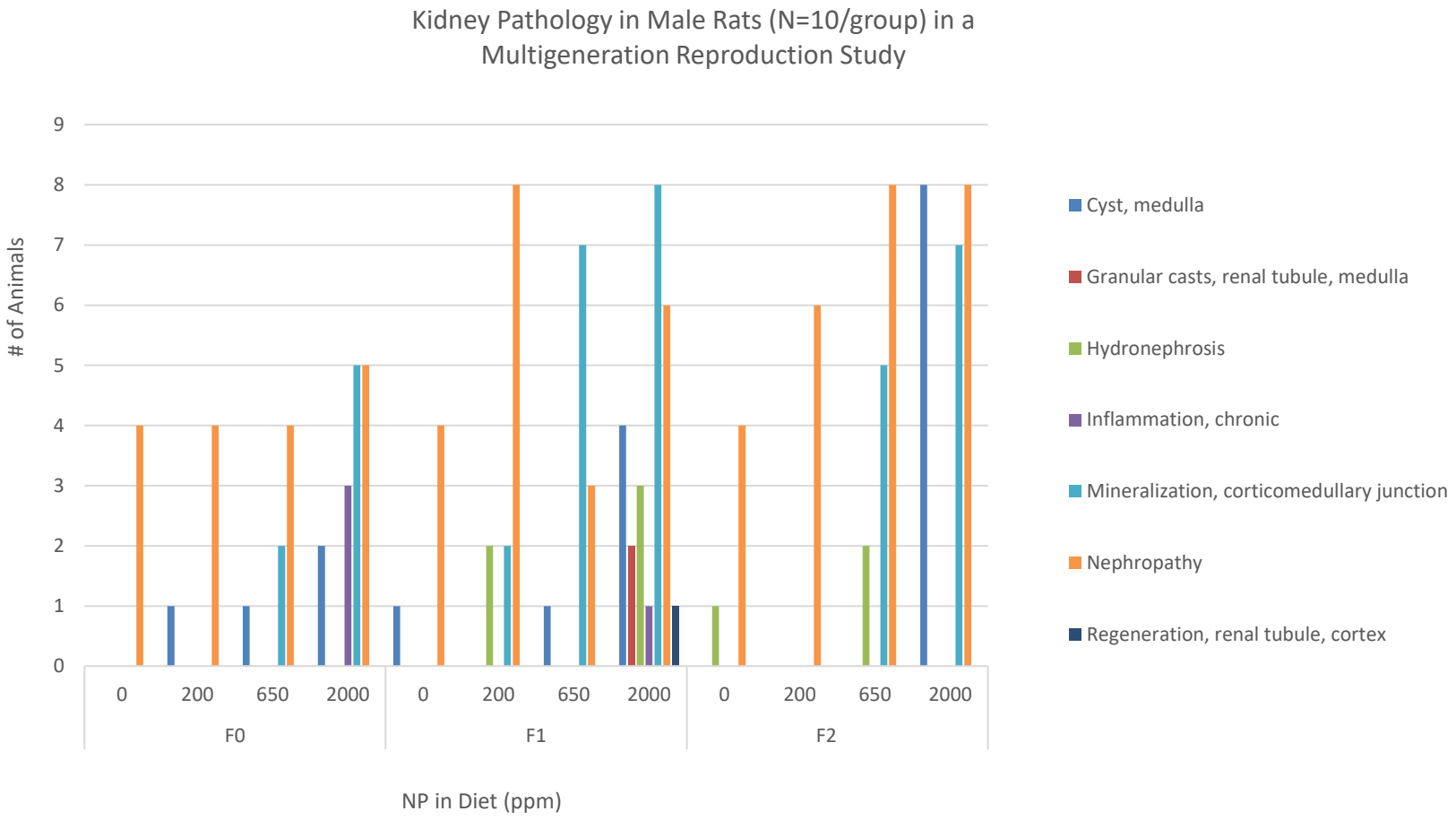
- Kidney toxicity (histopathology) occurred at 650 and 2000 ppm with no clear difference for the two diets.

Tyl et al. – Another Look



Effects if any only at highest 2 or 3 doses

Tyl et al. – Another Look



No mineralization at low dose (200 ppm) in F0, F2, and only 2/10 males in F1

Perspectives on Mineralization

Perspectives on Mineralization

“Renal mineralization is usually seen in female rats fed a semisynthetic diet but is also seen with regular laboratory feed (Figure 11.38). 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 mineralization quickly. Mineralization may be observed with other forms of renal disease including hyaline droplet nephropathy, dystrophic calcification, and end-stage CPN disease.”

Seely et al. 2018

Perspectives on Mineralization

"Mineralization is commonly observed in the area of the outer stripe and inner stripe of the outer medulla."

"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*. Mineralization may be induced by chemicals, hormones, or diet."

"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."

*No evidence for this in NP studies

NTP Non-neoplastic lesion atlas

Perspectives on Renal Effects (including mineralization) in Rats

"Comparing previous studies with this one (where the dose and route of exposure of NP are the same, but the diet is not),the striking difference in the severity of Polycystic Kidney Disease (PKD) observed leads to the conclusion that the renal toxicity of NP is highly dependent on the diet on which the animals are maintained. Furthermore, there appear to be some protective effects associated with soy-meal supplementation, although the dietary factors responsible are unknown.

Because of the reported weak estrogenic activity of NP, it is possible that the minimal mineralization observed in the 3 male groups exposed to the highest doses was an "estrogenic" effect of NP on kidney tubules. This seems more plausible than the possibility that it was a sequela of tubular epithelial necrosis associated with the toxicity of the NP-dietary interaction (e.g., PKD), because severe PKD occurred in 100% of the 2000-ppm group, but mineralization was observed in only 40% of the same group. Furthermore, mineralization was present the 500-ppm group that, like the control and the 3 other lower-dose groups, did not have PKD."

Laterdresse et al. 2001

Regulatory Perspectives

- Danish Environmental Protection Agency (Nielsen, et al. 2000)
- Environment Canada (2001,2002)
- US Forest Service (2003)
- USEPA (2009)

Denmark (Nielsen)

- Nielsen, et al. (2000) conclude with regards to Chapin et al. (1999):

  "Consequently, the conclusion has been drawn from this study that there is a **LOEL** (emphasis added) for repeated exposure of 15 mg/kg/day, based on histopathological changes in the kidneys. Since renal tubular degeneration and/or dilatation 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."

USEPA

- Hazard Characterization Document – September 2009

  "Toxicity was manifested as reductions in terminal body weights at 650 ppm in F2 males (8%) and F1 females (7%) and on post-natal days 55-58 in F3 females (10%) and at 2000 ppm in F1 female (9%), F2 (7%), and post-natal day 55-58 F3 (7%) males and F0 (9%), F1 (12%), F2 (10%), and post-natal day 55-58 F3 (11%) females. Increased relative kidney weights were observed at 650 ppm and/or 2000 ppm in adult males from the F0, F1, and F2 generations and in the F1 2000 ppm adult females. A treatment-related increase in the incidence of renal tubular degeneration/dilatation was seen in the 200, 650, and 2000 ppm males from all generations and in the 2000 ppm females from the F1, F2, and F3 generations and in the 200 and 650 ppm females in the F3 generation."

- Mineralization not included in critical effect determination

Environment Canada (2001)

- “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…”

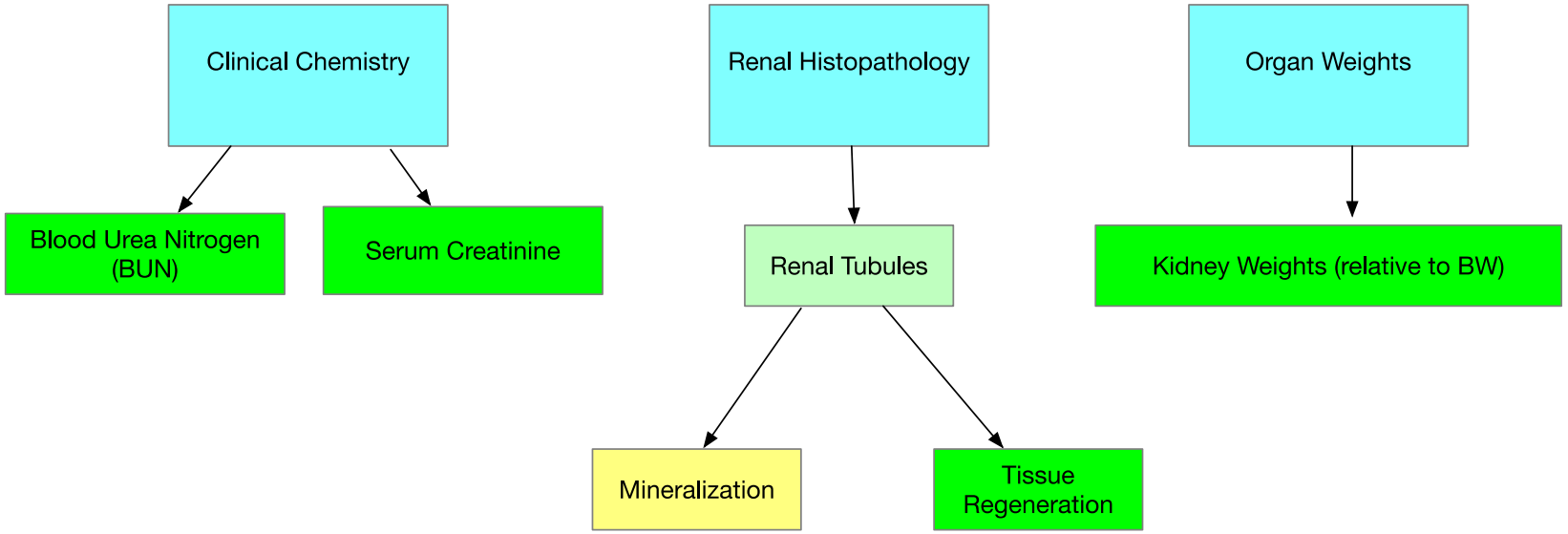
Environment Canada (2002) Canadian Environmental Quality Guidelines for PA & Ethoxylates

- In a multigenerational study, Chapin et al. (1999) examined the effects of nonylphenol administered through dosed food on Sprague Dawley rats (Rattus norvegicus). At a diet concentration of 650 mg·kg -1 (i.e., a dose of 30-108 mg·kg -1 body weight) vaginal opening at an earlier age was observed in the F1 generation. Significant effects observed at a diet concentration of 2000 mg·kg -1 (i.e., a dose of 100-360 mg·kg -1 body weight) included increased relative kidney weights and decreased adult ovary weights in the F1 generation, and increased estrous cycle length in both the F1 and F2 generations.
- Mineralization not included in critical effect determination

US Forest Service

- “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- free diet exacerbated the kidney effects, and the authors surmise that soy in the diet could act to ameliorate these effects.”

Elements of Weight of Evidence Assessment



Overall Weight of Evidence Mineralization

- Renal mineralization seen at some dose(s) in all three pivotal studies
  - It was low incidence and low severity
  - No other renal effects accompany the mineralization
- Mineralization is a frequent finding in rat studies – (mineral imbalance, gut flora, etc.)
- Finding alone (without other indications of renal toxicity should not be considered a critical effect)

Recommendations

- The critical effects in the multi-generation reproduction studies
  - Acceleration of vaginal opening in females (Chapin et al. 1999)
  - Toxicologically significant changes in the kidney from males (Chapin et al. 1999; Nagao et al. 2001; NCTR 2009; Tyl et al. 2006), both of which occurred at doses of >200 ppm.
- Note: no vaginal effects were observed in a five-generation study at doses up to and including 750 ppm (the highest dose tested), whereas kidney effects were seen only at 750 ppm (NCTR 2009).
- Point of Departure = 200 ppm in the diet, equating to approximately 13 mg/kg bodyweight/day

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May 13, 2022

Nancy Rice
Health Risk Assessment Unit
Minnesota Department of Health
P.O. Box 64975
St. Paul, MN 55164-0975

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
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)

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

I.2.e. Written Comment: Pre-Hearing Comment

I.2.e.i. Comment
Date: March 8, 2023
Chemical: Imidacloprid
Commenter: William Reeves, Bayer Crop Science

I.2.e.ii. Minnesota Department of Health's Preliminary Response
Date: March 31, 2023

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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William Reeves · Citizen · (Postal Code: unknown) · Mar 08, 2023 2:37 pm

0 Votes

Please find attached Bayer Crop Science's comments on the health risk level proposal.

Bill Gulledge · Citizen · (Postal Code: unknown) · Mar 08, 2023 4:34 pm

0 Votes

Please see attached comments from the ACC Ethylene Glycols Panel.

March 8, 2023

Nancy Rice
Minnesota Department of Health
Robert Street North
P.O. Box 64975
St. Paul, MN 55164-0975

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

Thank you for the opportunity to provide public input on the Minnesota Department of Health's proposed groundwater health risk limit for imidacloprid. Bayer Crop Science produces several products that rely on imidacloprid as an active ingredient to control insect pests. Bayer met with the Department of Health on May 23, 2019 to discuss the proposed Health Based Guidance for Water published in March 2019 (651-201-4899). In this document, Minnesota proposed a health-based value of 3 µg/L for groundwater based on a reduced immunologic response in a 28-day mouse study.

Minnesota's regulations for establishing health standards (Minnesota statues 144.0751[1]) require that when establishing drinking water quality standards, the Commissioner of Health must base those standards on scientifically acceptable, peer-reviewed information. Furthermore, Minnesota's regulations for establishing health risk limits (Minnesota statutes 103H.201[2]) require that "the adopted health risk limits shall be derived using United States Environmental Protection Agency (EPA) risk assessment methods using a reference dose, a drinking water equivalent, and a relative source contribution factor."

Minnesota's proposed standard for imidacloprid does not meet any of these requirements because the underlying study Minnesota relied on (Badgujar et al., 2013[3]) is missing key information that would allow it to inform a quantitative risk assessment. Badgujar et al. (2013) does not provide sufficient information for reviewers to understand the details of the experiments they conducted, nor does it provide sufficient detail to determine whether the

[1] Minnesota Statutes 2022. Health Standards. 144.0751. https://www.revisor.mn.gov/statutes/cite/144.0751
[2] Minnesota Statutes 2022. Health Risk Limits. 103H.201. https://www.revisor.mn.gov/statutes/cite/103H.201
[3] Badgujar, P.C., et al. 2013. Immunotoxic effects of imidacloprid following 28 days of oral exposure in BALB/c mice. Environmental Toxicology and Pharmacology. 35:408-418. doi: 10.1016/j.etap.2013.01.012

authors' observations were the result of confounding factors that were unrelated to imidacloprid.

In two separate evaluations, the EPA has specifically considered Badgujar et al. (2013) and rejected it for use in quantitative risk assessments. EPA considered Badgujar et al. (2013) in its 2015 weight of evidence analysis of imidacloprid's ability to interact with the endocrine system[4] and in its 2017 imidacloprid risk assessment for terrestrial organisms[5]. In both cases, EPA concluded that Badgujar et al. (2013) was not of sufficient quality to inform a quantitative risk assessment. EPA's stated reasons included a lack of information about the imidacloprid sample used in the study, the absence of raw data to confirm the findings and statistical analysis, and limited information about test conditions.

Badgujar et al. (2013) purports to demonstrate that imidacloprid caused toxicity to the immune system of female mice that were administered imidacloprid for 28 days. EPA requires specific tests to understand the potential of pesticides to harm immune function. These tests follow internationally- accepted guidelines and must be conducted according to Good Laboratory Practice (GLP) Regulations[6]. These two requirements ensure that the studies are of sufficient quality to inform a quantitative risk assessment and that reviewers can understand whether the conclusions accurately reflect the data.

An immunotoxicity study that followed EPA's required methods and GLP regulations is available for imidacloprid (Kennel, 2010)[7]. The maximum dose in this study was 186 mg imidacloprid/kg body weight/day, 18.6 times higher than the maximum dose that Badgujar et al. (2013) tested. Additionally, Kennel (2010) conducted the study using male rats, in accordance with EPA's guidelines for an immunotoxicity study[8] based on evidence that males are more sensitive than females and rats are more sensitive than mice. Badgujar et al. (2013) tested female mice only. EPA relies on Kennel (2010) in its human health and ecological risk assessments and has concluded that imidacloprid did not cause immunotoxicity at any of the tested doses.

We support Minnesota's efforts to protect public health by adoption of health risk limits for chemicals that could be present in groundwater. We also believe those limits should rely on high quality studies that are of sufficient quality to inform quantitative risk assessments.

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[4] EPA. 2015. EDSP: Weight of Evidence Analysis of Interaction Potential with the Estrogen, Androgen or Thyroid Pathways. Chemical: Imidacloprid. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0844-0137

[5] EPA. 2017. Imidacloprid -Transmittal of the Preliminary Terrestrial Risk Assessment to Support the Registration Review. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0844-1256

[6] 40 CFR Part 160. Good Laboratory Practice Standards. https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-160

[7] Kennel. 2010. Imidacloprid 28-day immunotoxicity study in the male Wistar rat by dietary administration. Bayer Crop Science, Study No. SA 09406; MRID 48298701

[8] EPA. 1996. Health Effects Test Guidelines. OPPTS 870.7800 Immunotoxicity. https://www.regulations.gov/document/EPA-HQ-OPPT-2009-0156-0049

Badgujar et al. (2013) does not meet that standard and this position is consistent with the views of expert risk assessors at EPA. EPA identified an appropriate, health protective value (Reference Dose, RfD) in its human health risk assessment of 0.08 mg/kg body weight/day that should be used to establish groundwater health risk limits for Minnesota.

Best regards,

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DEPARTMENT OF HEALTH

Protecting, Maintaining and Improving the Health of All Minnesotans

March 31, 2023

William R. Reeves, Ph.D.
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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 William Reeves:

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

1. Minnesota's regulations for establishing health standards (Minnesota statues (sic) 144.0751[1]) require that when establishing drinking water quality standards, the Commissioner of Health must base those standards on scientifically acceptable, peer-reviewed information. Furthermore, Minnesota's regulations for establishing health risk limits (Minnesota statutes 103H.201[2]) require that "the adopted health risk limits shall be derived using United States Environmental Protection Agency (EPA) risk assessment methods using a reference dose, a drinking water equivalent, and a relative source contribution factor."

MDH used EPA methods to develop imidacloprid guidance as spelled out in statute[1,2]: we applied a reference dose, a drinking water equivalent, and a relative source contribution factor to develop guidance based on immunotoxicity data from a scientifically acceptable, peer-reviewed study in mice (Badgujar 2013)[3]. In addition, our Statement of Need and Reasonableness (SONAR)[4] states, "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…" MDH selected an adverse effect (reduced delayed-type hypersensitivity) that occurs at a lower dose than the adverse effect chosen by EPA (tremors in dogs from a different study). Consequently, MDH's reference dose is lower than that derived by EPA. MDH is not obligated to use EPA's critical study, adverse critical effect, or reference dose. MDH has its own risk assessors that assess data and come to their own conclusions. The purpose of risk assessment is different between EPA and MDH. EPA's role is to

register pesticides, MDH's role is to derive water guidance that is protective, including a margin of safety, for sensitive and highly exposed individuals in the general population.[1,4]

2. Minnesota's proposed standard for imidacloprid does not meet any of these requirements because the underlying study Minnesota relied on (Badgujar et al., 2013[3]) is missing key information that would allow it to inform a quantitative risk assessment. Badgujar et al. (2013) does not provide sufficient information for reviewers to understand the details of the experiments they conducted, nor does it provide sufficient detail to determine whether the authors' observations were the result of confounding factors that were unrelated to imidacloprid.

MDH disagrees with Bayer Crop Sciences that Badgujar 2013, the 28-day immunotoxicity study in mice, does not meet the requirements to be a critical study used for risk assessment. Badgujar 2013 was published in an acceptable peer-reviewed journal, Environmental Toxicology and Pharmacology, published by Elsevier – an academic publishing company. MDH determined that the data in Badgujar 2013 clearly showed an immunotoxic effect that had a suitable dose-response alongside the correct controls. MDH was able to conduct a proper quantitative risk assessment with the data and information provided in the study. This satisfies Minnesota Statute 144.0751.

3. In two separate evaluations, the EPA has specifically considered Badgujar et al. (2013) and rejected it for use in quantitative risk assessments. EPA considered Badgujar et al. (2013) in its 2015 weight of evidence analysis of imidacloprid's ability to interact with the endocrine system[5] and its 2017 imidacloprid risk assessment for terrestrial organisms[6]. In both cases, EPA concluded that Badgujar et al. (2013) was not sufficient quality to inform a quantitative risk assessment. EPA's stated reasons included a lack of information about the imidacloprid sample used in the study, the absence of raw data to confirm the findings and statistical analysis, and limited information about test conditions.

It is unusual in the open literature for academic peer-reviewed studies to include raw data, and minute study details, due to journal article space and word number constraints. Studies are peer-reviewed to help ensure that study findings and conclusions are scientifically acceptable. As stated above, MDH was able to conduct a proper quantitative risk assessment in accordance with our statutes and within the framework described in our SONAR[1,2,4].

4. Badgujar et al. (2013) purports to demonstrate that imidacloprid caused toxicity to the immune system of female mice that were administered imidacloprid for 28 days. EPA requires specific tests to understand the potential of pesticides to harm immune function[7]. These tests follow internationally- accepted guidelines and must be conducted according to Good Laboratory Practice (GLP) Regulations[8]. These two requirements ensure that the studies are of sufficient quality to inform a quantitative risk assessment and that reviewers can understand whether the conclusions accurately reflect the data.

While it is true that industry uses GLP[8] and follows EPA's Immunotoxicity Guidelines (EPA 1998)[7], academia in the open literature uses peer-review and journal editors to assess the quality of their work. Badgujar 2013 went through a peer-review process and was deemed acceptable to publish in Environmental Toxicology and Pharmacology. This satisfies Minnesota Statute 144.0751.

5. An immunotoxicity study that followed EPA's required methods and GLP regulations is available for imidacloprid (Kennel, 2010)[9]. The maximum dose in this study was 186 mg imidacloprid/kg body weight/day, 18.6 times higher than the maximum dose that Badgujar et al. (2013) tested. Additionally, Kennel (2010) conducted the study using male rats, in accordance with EPA's guidelines for an immunotoxicity study[7] based on evidence that males are more sensitive than females and rats are more sensitive than mice. Badgujar et al. (2013) tested female mice only. EPA relies on Kennel (2010) in its human health and ecological risk assessments and has concluded that imidacloprid did not cause immunotoxicity at any of the tested doses.

EPA's guidelines on immunotoxicity testing do not consider every facet of the immune system, and EPA states "the tests in this guideline do not represent a comprehensive assessment of immune function"[7]. This document also stipulates that both rats and mice are acceptable test subjects for immunotoxicity and that either sex may be used in these studies. Therefore, it is acceptable that the Badgujar study tested immune function in female mice. It is possible that female mice are the most sensitive species, and that delayed-type hypersensitivity is particularly sensitive to imidacloprid's effects. More recently, (Shi 2020)[10] published a peer-reviewed immunotoxicity study where female mice had a less effective response in activating the innate immune response after imidacloprid exposure, providing more weight-of-evidence that imidacloprid does affect different facets of the immune system.

Although Bayer suggests that Kennel is the only acceptable immunotoxicity study for determining the immune effects of imidacloprid exposure, Kennel also has its limitations. Kennel only tested one functional attribute of the immune system – immunoglobin M (IgM) titers in the serum after antigen challenge. In addition, the control group of rats had extremely high standard deviations for their IgM titers, making it difficult to detect any immune differences between the control and treated groups. There was no mention in Kennel as to why the control group animals demonstrated such extreme variability in their immune response. This type of control animal response raises questions about experimental precision and methodology. Lastly, MDH observed that there was evidence of a reduction in IgM after imidacloprid treatment in treated animals, but because of the study limitations, statistical significance was not achieved.

Badgujar tested delayed-type hypersensitivity – a T cell mediated response. Kennel tested IgM concentrations in the serum – an antibody response. Badgujar and Kennel tested different mechanisms of the immune system. It is therefore plausible that imidacloprid acts upon multiple arms of the immune system and that Kennel did not test for the most sensitive immune effect.

6. We support Minnesota's efforts to protect public health by adoption of health risk limits for chemicals that could be present in groundwater. We also believe those limits should rely on high quality studies that are of sufficient quality to inform quantitative risk assessments. Badgujar et al. (2013) does not meet that standard and this position is consistent with the views of expert risk assessors at EPA. EPA identified an appropriate, health protective value (Reference Dose, RfD) in its human health risk assessment of 0.08 mg/kg body weight/day that should be used to establish groundwater health risk limits for Minnesota.

MDH thanks Bayer for their interest in our risk assessment and resulting guidance values for imidacloprid. MDH's expert risk assessors disagree with Bayer Crop Sciences that Badgujar 2013 is not an appropriate critical study for determining health-based guidance and disagree that EPA's RfD is protective of human health. As stated previously in our comments, Badgujar 2013 is a peer-reviewed immunotoxicity study that has been published in an acceptable journal and fulfills Minnesota statute 144.0751. Badgujar used a sensitive species (female mice) to detect changes in a sensitive immunotoxicity endpoint (delayed-type hypersensitivity) that was not tested by Bayer Crop Sciences. The RfD that EPA chose for imidacloprid (tremors in dogs) is not adequately protective of human health. It is 22 times higher than MDH's RfD of 0.0036 mg/kg-d and does not protect for immune effects, sperm effects, and metabolic effects occurring in animals at the lower imidacloprid doses that Badgujar 2013 and others reported in the academic open literature. Furthermore, both the State of Wisconsin and The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) have stated that EPA's RfD for imidacloprid is not health protective.[11,12]

Therefore, in accordance with our obligation and authority under Minnesota Statutes 114.0751 and 103H.201, MDH maintains its proposed HRL for imidacloprid to "adequately protect the health of infants, children, and adults[1]."

Sincerely,

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References

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

[2]Minnesota Statutes. (2022). Health Risk Limits. 103H.201. https://www.revisor.mn.gov/statutes/cite/103H.201

[3]Badgujar, PC et al. (2013). Immunotoxic Effects of Imidacloprid Following 28 Days of Oral Exposure in BALB/c mice. Environmental Toxicology and Pharmacology. 35(3):408-418.

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

[5]EPA. (2015). EDSP: Weight of Evidence Analysis of Interaction Potential with the Estrogen, Androgen or Thyroid Pathways. Chemical: Imidacloprid. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0844-0137

[6]EPA. (2017). Imidacloprid – Transmittal of the Preliminary Terrestrial Risk Assessment to Support the Registration Review. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0844-1256

[7]EPA. (1998). Health Effects Test Guidelines OPPTS 870.7800 Immunotoxicity. https://www.regulations.gov/document/EPA-HQ-OPPT-2009-0156-0049

[8]40 CFR Part 160. Good Laboratory Practice Standards. https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-160

[9]Kennel. (2010). Unpublished. Imidacloprid 28-day Immunotoxicity Study in the Male Wistar Rat by Dietary Administration. Bayer Crop Science, Study No. Sa 09406; MRID 48298701.

[10]Shi, L et al. (2020). Imidacloprid exposure suppresses cytokine production and neutrophil infiltration in TLR2-dependent activation of RBL-2H3 cells and skin inflammation of BALB/c mice. New J. Chem. 44, 19489.

[11]Wisconsin Department of Health Services. (2022). Recommended Public Health Groundwater Quality Standards. Scientific Support Documents for Cycle 10 Substances. https://dhs.wisconsin.gov/publications/p02434v-2.pdf

[12]Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. (2022). Memorandum: OEHHA's Findings on the Health Effects of Imidacloprid Relevant to its Identification as a Potential Groundwater Contaminant. https://www.cdpr.ca.gov/docs/emon/grndwtr/imidacloprid/oehha_findings_health_effects.pdf

I.2.f. Written Comment: Pre-Hearing Comment

I.2.f.i. Comment
Date: March 8, 2023
Chemical: Ethylene Glycol
Commenter: Bill Gulledge, American Chemistry Council Ethylene Glycol Panel

I.2.f.ii. Minnesota Department of Health's Preliminary Response
Date: March 31, 2023

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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William Reeves · Citizen · (Postal Code: unknown) · Mar 08, 2023 2:37 pm

0 Votes

Please find attached Bayer Crop Science's comments on the health risk level proposal.

Bill Gulledge · Citizen · (Postal Code: unknown) · Mar 08, 2023 4:34 pm

0 Votes

Please see attached comments from the ACC Ethylene Glycols Panel.

Via Email: nancy.rice@state.mn.us

March 8, 2023

Ms. Nancy Rice, MPH
Minnesota Department of Health
625 Robert Street North
P.O. Box 64975
Saint Paul, MN 55164-0975

Re: Ethylene Glycol (EG)- Proposed Health Risk Limit Rules

Dear Ms. Rice:

The Ethylene Glycols Panel (EGs Panel) of the American Chemistry Council (ACC) appreciates the opportunity to discuss our progress on developing research to address ethylene glycol (EG) risk assessments. We understand that MDH used what CERHR, 2004 stated was apparently the most sensitive species for developmental effects. However, we also understand that the exposure for a toxicity assessment must be by a route that, as you stated in your January 20, 2023 response to me, should "**represent a similar exposure as a person consuming ethylene glycol in their drinking water daily over a period of time.**"

The EGs Panel published the following studies addressing dose rate to determine the toxic response for EG.

> Pottenger, L. H., Carney, E. W. and Bartels, M. J. Dose-dependent nonlinear pharmacokinetics of ethylene glycol metabolites in pregnant (GD 10) and nonpregnant Sprague-Dawley rats following oral administration of ethylene glycol. Toxicol Sci 2001; 62: 10-9.
>
> E.W. Carney, B. Tornesi, A.B. Liberacki, D.A. Markham, K.K. Weitz, T.M. Luders, K.G. Studniski, J.C. Blessing, R.A. Gies, R.A. Corley, The impact of dose rate on ethylene glycol developmental toxicity and pharmacokinetics in pregnant CD rats, Toxicol. Sci., 119 (2011), pp. 178-188.

The Panel maintains that using the Neeper-Bradley gavage study (fast dose rate) is not the appropriate study to determine point of departure (POD) in risk determination for a drinking-water daily exposure over a period of time, particularly for EG.

Please note that before the death of the major ethylene glycol researcher (Dr. Ed Carney) in the field of developmental toxicity, he published his final set of experiments. In this publication, Dr. Carney provides in detail, the importance of dose rate on EG developmental toxicity and pharmacokinetics. He concludes that for an EG risk determination, gavage administration (fast dose rate) would not be appropriate for determining risk for drinking water contaminated with EG.

Following is a key part of the Carney et al., 2011, paper including references to the Pottenger et al., 2001 that he coauthored (highlights have been added):

> "**In both nonpregnant and pregnant rats (GD 10) given EG via gavage, the dose-dependent shift to nonlinear GA kinetics was evident at dose levels ≥ 500 mg/kg** (Pottenger et al., 2001). The point at which GA kinetics become nonlinear just slightly precedes the apparent threshold for developmental toxicity in rats based on a no-observed effect level (NOEL) of 500 mg/kg/day and a lowest-observed effect level (LOEL) of 1000 mg/kg/day, suggesting that this dose-dependent transition is required for developmental toxicity… **A toxicokinetic study in pregnant rats revealed peak maternal blood GA values at the NOEL (500 mg/kg/day) and LOEL (1000 mg/kg/day) for developmental toxicity of 1.7 and 4.8mM, respectively** (Pottenger et al., 2001). These in vivo data correspond closely with in vitro rat whole-embryo culture data, which indicate a no-effect concentration of 3mM (Klug et al., 2001). Collectively, the available data led to the hypothesis that developmental toxicity in rats requires peak GA levels > 2mM in maternal blood and > 3mM in embryo (Corley et al., 2005b). Such high levels of GA are **plausible only after high-dose bolus exposure and**, **conversely, would seem unlikely to occur for low dose rate and/or low-dose exposures to EG.** Understanding the effect of dose rate is important to human risk assessment because human exposures to EG typically occur via the dermal or inhalation routes where the slow rate of exposure and/or absorption make saturation of GA kinetics highly unlikely (Frantz et al., 1996b; Sun et al., 1995)."

> "Research linking the developmental toxicity, mode of action, and pharmacokinetics of EG has been underway for a number of years with an aim toward refining human health risk assessments of this high production volume chemical. This integrated research program had already established that EG developmental toxicity required administration of very high doses and that saturation of GA oxidation was an essential step in the mode of action (Corley et al., 2005b; National Toxicology Program-Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR), 2004; Slikker et al., 2004). **Based on the linkage between developmental NOELs/ LOELs in vivo and pharmacokinetic data in pregnant rats, it was hypothesized that developmental toxicity in rats required GA levels > 2mM in maternal blood and > 3mM in the embryo (Corley et al., 2005b). These putative threshold values have been widely accepted (e.g., NTP-CERHR, 2004), and it is readily appreciated that very high doses, particularly by the gavage route, are necessary to exceed these threshold values, whereas this is highly unlikely for nongavage exposures.** Nonetheless, the gavage route of

exposure has become entrenched in regulatory assessments for developmental toxicity, and there often is reluctance to base risk assessments and classification/labeling decisions on nongavage studies, even when these studies are available and human exposures occur by nongavage routes. To further our understanding of the impact of gavage versus other modes of human exposure, **the present study examined the variable of dose rate and its impact on pharmacokinetics and developmental toxicity.** To model a high dose, but low dose-rate scenario, a novel implantable and refillable spring-loaded infusion pump system was utilized which allowed for the maintenance of maternal blood GA levels at ~1mM, i.e., below the putative threshold, continuously from GD 6–15. Developmental outcomes following this slow dose-rate regimen were compared with those of rats given equivalent doses of EG in the form of daily sc bolus injections for the same period of time. Based on prior knowledge of EG kinetics, it was expected that the blood levels of the sc bolus group dams would each day temporarily exceed 2mM of the GA metabolite, which would then rapidly clear to undetectable levels by 18–24 h postdose (Carney et al., 1999).

Pharmacokinetic analyses in the present study verified that the sc bolus injections achieved GA concentrations greater than 2mM, whereas the infusion groups maintained GA concentrations below 2mM (Fig. 2B). In support of the hypothesis, developmental toxicity was observed in fetuses from dams given EG as a bolus, whereas no developmental effects were observed when the same doses of EG were given by infusion. The effects in the sc bolus groups were consistent with those seen in previous studies in which similar doses were given by gavage (Carney, 1994). These results also provided further support that a high Cmax, rather than AUC, is the key driver for developmental toxicity. As seen in Table 3, AUC values for embryonic GA were nearly identical in the gavage 1000 mg/kg group (52.1mMh) and 2000 mg/kg infusion groups (50.5mMh), yet only gavage exposure resulted in developmental toxicity. In contrast, Cmax values for embryonic GA were quite different in the 1000 mg/kg gavage group (6.3mM) versus the 2000 mg/kg infusion group (2.4mM), and these differences were correlated with developmental toxicity. Finally, a remarkable degree of correspondence was evident between the Cmax value (6.3mM) for the 1000 mg/kg gavage group (the in vivo LOEL for developmental toxicity) and the LOEC (6.0mM) identified in rat whole-embryo culture (Carney et al., 1996; Klug et al., 2001**). This consistency across in vivo developmental toxicity, in vivo toxicokinetics, and in vitro whole-embryo culture data provides a significant degree of confidence in these conclusions.**

The second part of this study examined the impact of dose rate on pharmacokinetics. Although numerous kinetic studies have been

conducted on EG given to male, female, and pregnant rats, this was the first comprehensive study to include specific analysis of EG, GA, and oxalic acid in maternal target organs (kidney), as well as the developing embryo, and the exocoelomic fluid contained within the visceral yolk sac placenta. A time-course assessment was conducted during GD 11–12, a time period known to show high susceptibility to EG induced teratogenic effects (Khera, 1991). Dose rate only had a moderate effect on the kinetics of unmetabolized EG and essentially no impact on oxalate. The fact that oxalate remained relatively constant across a large dose range further supports its lack of a causative role in EG developmental toxicity. The lack of change in oxalate despite large differences in levels of the upstream metabolite, GA (Fig. 4), is explained by differences in conversion and respiratory elimination of CO2 as shown by others (Frantz et al., 1996a). Based on previous rat developmental toxicity and pharmacokinetic data (Corley et al., 2005a,b; Neeper-Bradley et al., 1995), oxalate-induced kidney toxicity and secondary effects on pharmacokinetics were unlikely to have been present given the doses and relatively short durations of exposure evaluated in this study.

In contrast, the effect of dose rate on the kinetics of its metabolite and proximate teratogen, GA, was dramatic. Peak GA levels in maternal and conceptus tissues/fluids were 49– 100 times higher when 1000 mg/kg of EG was given by oral gavage relative to an equivalent daily dose given by infusion. AUCs also were higher in the gavage group relative to infusion, but the differences were not as great (16- to 38-fold). The profound impact on GA kinetics, especially Cmax values, is consistent with the saturation of GA's metabolism to glyoxylic acid (Fig. 1), which is the key rate-limiting step in EG's metabolic pathway. Another noteworthy finding was that the concentrations of GA in exocoelomic fluid and embryos were consistently higher (1.4- to 3-fold) than maternal blood levels (Figs. 3C and 3D), particularly for the first 6–12 h postdose. These ratios are very similar to those reported in an initial developmental kinetics study (Carney, unpublished data) where exocoelomic fluid levels of GA ranged from 1.3- to 1.8-fold higher than corresponding maternal blood levels in the first 3 h after dosing with either 500 or 2500 mg/kg EG by oral gavage. Most likely the higher levels of GA in rat exocoelomic fluid and embryo were due to pH-dependent ion trapping, driven by the more alkaline pH of rat exocoelomic fluid relative to maternal blood (Carney et al., 2004; Nau and Scott, 1986; Scott and Nau, 1987; Srivastava et al., 1991). **The results of this study strongly support the hypothesis that dose rate is a critical determinant of EG developmental toxicity, a phenomenon which is related to the saturation of the metabolism of GA, the proximate teratogen.**

Quantifying the effect of dose rate is important to human risk assessment because the most common routes of human exposure to EG are dermal,

characterized by very slow rates of absorption (Saghir et al., 2010; Sun et al., 1995), or secondarily, inhalation, for which exposures tend to be spread out over time (NTP-CERHR, 2004). Although the data support a value of 2mM peak maternal blood GA as the critical internal dose metric differentiating safe from potentially teratogenic EG exposures, the preferential disposition of GA in the rat embryo indicates that the critical dose metric at the level of the embryo is even higher. As mentioned previously, rat whole-embryo culture studies identified no-observable and LOEL concentrations of 3 and 6mM, respectively, following 48 h of continuous exposure to these test concentrations (Klug et al., 2001).

Comparative data suggest that it may be even more difficult to achieve these GA concentrations in the human embryo based on the fact that the celomic fluid of the first trimester human conceptus is ~0.2 pH units more acidic than the maternal blood (Jauniaux et al., 1994). Based on GA's pKa (3.83), the size and direction of the maternal blood-conceptus fluid pH gradient in humans and application of the Henderson-Hasselbach acid-base distribution equation, **one would predict GA concentrations in the human conceptus to be approximately half those of maternal blood GA. Interestingly, the yolk sac cavity fluids surrounding the rabbit embryo also are acidic with respect to maternal blood (Tornesi and Carney, 2003). Embryonic GA levels in the rabbit are correspondingly less than those of the maternal blood (Carney et al., 2008), and EG is not developmentally toxic in the rabbit, even following gavage exposure to doses as high as 2000 mg/kg/day (Tyl et al., 1993).**

Finally, the findings from this study have broader implications for the practice of developmental toxicity testing, as regulatory guidelines for prenatal developmental toxicity studies in animals require testing at maximally tolerated doses, with gavage as the default route of exposure. **This study exemplifies the tremendous disparities in pharmacokinetics that can occur following high-dose and high dose rate exposures relative to expected kinetic profiles at lower doses and dose rates. Increasingly, the wisdom of high-dose and high dose rate exposures, which run the risk of inducing shifts to nonlinear kinetics, is being questioned for the evaluation of chemicals present at low levels in the environment.** For these types of chemicals, an alternative approach to the maximum-tolerated dose garnering support calls for setting the high-dose level based on the point of transition to nonlinear kinetics [*e.g., kinetically-derived maximum dose or KMD*], supported by information on internal dose, so as to increase relevance of the data to humans (Saghir et al., 2009**).**

In the case of EG, we can see clearly that high-dose gavage studies cause a shift from linear to nonlinear GA kinetics, which appears to be a prerequisite for EG-induced developmental toxicity. [*This*

observation is consistent with that made for many chemicals in which bolus gavage exposures achieve nonlinear toxicokinetics at oral doses that are approximately an order of magnitude lower than corresponding continuous oral exposures (Kirman et al., 2003).] However, most human exposures involve much lower doses occurring via the dermal or inhalation routes, which are nonbolus. Given our understanding of GA kinetics, it is clear that gavage studies greatly overestimate the risk of typical environmental and workplace exposures, which occur by the dermal and inhalation routes and are characterized by low doses and/or low dose rates."

To summarize, when large doses of EG are given by a fast dose rate as in gavage, the saturation of the oxidative enzyme systems for EG occurs, and developmental toxicity can occur. This fast rate or gavage would represent a suicide attempt and does not "represent a similar exposure as a person consuming ethylene glycol in their drinking water daily over a period of time." (quote from MDH January 20, 2023 response) **Please also note that this key dose-rate phenomenon has been shown in rats where EG was given at 1000 mg/kg in the diet (slow dose-rate), and no developmental toxicity was observed (Maronpot et al., 1983, Teratogenicity study of ethylene glycol in rats), but when rats were given 1000 mg/kg by gavage (fast dose-rate), developmental toxicity was observed (Neeper-Bradley et al. 1985).**

We now have discovered there are 21 peer-reviewed pertinent additional studies conducted AFTER the CERHR 2004 publication (Appendix I). We incorrectly stated in our March 8th, 2021 submission to MDH that there were only 14 studies. In your January 20, 2023, response it was stated "and while some of these publications were not individually cited, they are **reviewed or summarized** as part of larger reports like the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction's (CERHR) 2004 review." Please note that we have reviewed the CERHR 2004 report in detail and **none of these studies was mentioned.**

We feel that this large, significant, pertinent database is extremely useful in risk assessment determination and must be considered to develop a meaningful risk assessment. We feel that at some point in time, this new research must be recognized.

ACC's reply to statements made by MDH in the January 20, 2023 correspondence to Bill Gulledge

To address some of the MDH statements in the January 20, 2023 response to ACC, we have included your "statements" in quotes and followed with our reply in brackets [ ].

- MDH stated: "MDH identified an administered no observed adverse effect level (NOAEL) of 150 mg/kg-d and an administered lowest observed adverse effect level (LOAEL) of 500 mg/kg-d based on increased **skeletal malformations**."

[We believe this statement is incorrect**. Neeper Bradley, et al., 1985 did not classify the extra 14th rib as a malformation, but as a variation**. And moreover, in the CERHR 2004 report it is stated "The incidences of one individual **skeletal variation (extra lumbar rib)** in litters from the 500 mg/kg bw/day group and 23 individual skeletal variations (i.e., poorly ossified thoracic and lumbar centra, extra lumbar ribs) in litters of the 1,500 mg/kg bw/day group were

significantly increased." Since the OECD Test Guideline definition of a variation is "Variation/Minor Abnormality: Structural change **considered to have little or no detrimental effect on the animal; may be transient and may occur relatively frequently in the control population.**" Please also note in the Neeper-Bradley et al., 1985 publication, this variation was noted in the controls. In addition, in Carney, 1994 (An integrated perspective of the developmental toxicity of ethylene glycol. Reprod. Toxicol. 8 (2), 99–113.), it is discussed that **the mouse and rat are more similar than a quick look at only the NOELs would indicate**. Carney states, "In evaluating species differences in sensitivity, one must consider that the **mouse LOEL of 500 mg/kg/day is based solely on an increase incidence of one skeletal variation** (14^{th} rib). In contrast, **decreased fetal body weights** and **increased incidence of two malformations** and **12 skeletal variations were noted at the rat LOEL of 1000 mg/kg/day.** Thus, rat and mouse embryos/fetuses are probably more similar than a cursory glance at the NOELS would indicate."]

- MDH stated: "Such sophisticated data and models are usually available for only a small subset of chemicals that have extensive databases (SONAR, 2009). While the PBPK database for ethylene glycol may be rich for animal models, it is not complete enough to construct a realistic model for humans. Responses to chemicals are often incongruent between laboratory animals and humans. In the absence of strong evidence showing that the rodent PBPK is similar to humans, MDH defaults to developing an HED using a dosimetric adjustment factor (DAF) using body weight scaling (SONAR 2009)."

[ACC disagrees and believes there is "extensive," "complete enough," and "strong evidence" for the PBPK database for rodents and **humans**. Following are our key publications to support this statement:

E.W. Carney, B. Tornesi, A.B. Liberacki, D.A. Markham, K.K. Weitz, T.M. Luders, K.G. Studniski, J.C. Blessing, R.A. Gies, R.A. Corley, The impact of dose rate on ethylene glycol developmental toxicity and pharmacokinetics in pregnant CD rats. Toxicol. Sci., 119 (2011), pp. 178-188

R.A. Corley, K.E. McMartin, Incorporation of therapeutic interventions in physiologically based pharmacokinetic modeling of **human clinical case reports** of accidental or intentional overdosing with ethylene glycol. Toxicol. Sci., 85 (2005), pp. 491-501

R.A. Corley, M.J. Bartels, E.W. Carney, K.K. Weitz, J.J. Soelberg, R.A. Gies, K.D. Thrall, Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic Acid, in rats and **humans.** Toxicol. Sci., 85 (2005), pp. 476-490.

Corley, R. A., Meek, M. E., and Carney, E. W. Mode of action: oxalate crystal-induced renal tubule degeneration and glycolic acid-induced dysmorphogenesis—renal and developmental effects of ethylene glycol. Crit. Rev. Toxicol. 35, (2005b). 691–702.

R.A. Corley, D.M. Wilson, G.C. Hard, K.E. Stebbins, M.J. Bartels, J.J. Soelberg, M.D. Dryzga, R. Gingell, K.E. McMartin, W.M. Snellings, Dosimetry considerations in the enhanced sensitivity of male Wistar rats to chronic ethylene glycol-induced nephrotoxicity. Toxicol. Appl. Pharmacol., 228 (2008), pp. 165-178

R.A. Corley, S.A. Saghir, M.J. Bartels, S.C. Hansen, J. Creim, K.E. McMartin, W.M. Snellings, Extension of a PBPK model for ethylene glycol and glycolic acid to include the competitive formation and clearance of metabolites associated with kidney toxicity in rats and **humans.** Toxicol. Appl. Pharmacol., 250 (2011), pp. 229-244]

- MDH stated: Our methods state "It is assumed that humans are at least as sensitive as the most sensitive mammalian species for which there are toxicological data. Substantial evidence that the response seen in laboratory animals is due to a mechanism that does not exist in humans can overcome this assumption."

[ACC does not agree with MDH's statement regarding the sensitivity of human vs. rodents' developmental effects of EG proximate toxicant, glycolic acid (GA). Again, there is a clear species difference in the active disposition facilitated by opposite polarity of rodent MCT transporters vs. that of rabbits and humans. Recent investigations conducted after the 2004 CERHR evaluation demonstrated that GA uptake into the rat embryo occurs predominantly by a specific, pH-dependent, active uptake transporters MCT1 and MCT4.]

- MDH stated: "MDH also recognizes that there is evidence of species, strain, and sex differences in the metabolism and clearance of ethylene glycol. As the EGs Panel has pointed out, rabbits exposed in utero to ethylene glycol do not exhibit the same developmental effects as rodents do. The EGs Panel asserts that the mechanistic and toxicokinetic findings from Carney et al. (2008), Ellis-Hutchings et al. (2014), and Moore et al. (2016) conclude that rodents are inappropriate animal models for testing potential developmental effects following exposure to ethylene glycol and rabbits are more appropriate, however, MDH risk assessors do not agree and consider the findings preliminary."
  Research by Ellis-Hutchings et al. 2014 used whole embryo cultures to explore the rat and rabbit's ability to concentrate ethylene glycol. Their findings suggest that the ability of the rat embryo to concentrate glycolic acid is pH dependent and may involve a protein transporter.
  The expression of these transporters has been investigated in the rabbit and rat placenta by Moore et al., 2016, who concluded that the arrangement of transporters in the placenta of rats had an opposite polarity compared to the rabbit placenta, which they report is similar to the humans. There is no functional consequence reported."

[ACC disagrees that there is no functional consequence reported. A clear argument has been made that the major, active pathway of glycolic acid (GA) disposition into the rat and mouse developing embryo is via the MCT transporters located in the placenta. The orientation of the rabbit and human MCT transporters is opposite to rodents; this polarity would not allow for a significant accumulation of GA into rabbit and human embryo during the critical window of development compared with that of rodents where developmental toxicity is observed. While there is a passive disposition of the proximate toxicant into the developing embryos, this accounts for a minor percentage of GA disposition into accumulation within developing embryos.]

- MDH stated: "While the studies cited above do provide some insight as to why there may be species differences in susceptibility to developmental effects due to differences in placental biology, they do not fully elucidate how these differences functionally change the processing of ethylene glycol. They also do not sufficiently demonstrate that the findings from the critical study in mice are irrelevant to human health risk assessment. As directed by our methods (SONAR 2009, p.27, also cited above) MDH selected a POD based on developmental effects from the most sensitive species, the mouse in this case, to derive the short-term guidance value."

[ACC argues that the active disposition of GA via MCT transporters, accounting for major proportion of GA disposition from maternal blood to the developing embryo, underlies the species differences seen in developmental toxicity. TK effects of rodents vs. that not seen in rabbits at 2000 mg/kg/d are not expected for humans. These species differences functionally result in rabbit and human placenta with similar polarity of MCT1 and MCT 4 which is opposite to that of the rat and mouse MCTs. Hence, GA is preferentially sequestered in the mouse and rat embryo and not the rabbit embryo. By extension, rat and mouse developmental effects are not appropriate model for human hazard characterization and risk assessment for EG and GA.]

- MDH stated: "In your letter you mentioned 14 peer-reviewed publications…while some of these publications were not individually cited, they are reviewed or summarized **as part of larger reports like the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction's (CERHR) 2004 review**."

[We appreciate that MDH appears to have spent significant time on reviewing our submission. MDH is not the first regulatory group that has used the CERHR 2004 report as their main supportive evidence for using the Neeper-Bradley et al., 1985 gavage study for the basis of a risk assessment. ACC is hoping that time would allow for one regulatory group to feel as we do, that the database for EG is now extensive with strong evidence that renal toxicity is the best POD for a risk assessment and that gavage or fast dose rate is not appropriate for human health risk assessment. (W.M. Snellings, R.A. Corley, K.E. McMartin, C.R. Kirman, S.M. Bobst, Oral Reference Dose for ethylene glycol based on oxalate crystal-induced renal tubule degeneration as the critical effect. Regul. Toxicol. Pharmacol., 65 (2) (2013), pp. 229-241.)

Unfortunately, none of the following new studies could have been reviewed or summarized, as you stated in the CERHR 2004 report, since they were not completed until after the 2004 CERHR review. We now note that there are a total of 21 new important and pertinent peer-reviewed studies (Appendix I), including many studies on metabolism, pharmacokinetics, and pharmacodynamics, that should be considered when performing a risk assessment on EG. We realize that it would be easier to just stick with the Neeper-Bradley 1985 study but would hope we can help in determining why the EG case should be re-opened for risk determination.]

ACC Conclusion

Finally, we feel strongly that MDH should consider what the **National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction's (CERHR) 2004** review states in **support of our position on the kidney being the appropriate endpoint for risk assessment**. They state in their conclusion:

> "5.3 Overall Conclusions **Available data from rat studies suggest that oral doses associated with developmental toxicity (1,000 mg/kg bw) are greater than doses associated with renal toxicity (500 mg/kg bw).** Developmental toxicity, and evidence of some renal toxicity, are observed in rodents at doses that exceed saturation of glycolic acid metabolism, which clearly occurs at 500 mg/kg bw in rats. Limited human in vitro data suggest that saturation of glycolic acid metabolism occurs at ~125 mg/kg bw, but saturation is expected to require much higher doses for slower dose-rate (non-bolus) exposure or for routes characterized by poor absorption (e.g., dermal). **The Panel believes that ethylene glycol exposures resulting in blood levels below the level of saturation should not result in hazard associated with developmental toxicity in humans.** There are no data that are viewed as reliable estimates of human exposure in the general human population. It was noted that Health Canada had estimated a worst-case-scenario for persons living in the immediate vicinity of an ethylene glycol point source in the range of 0.022–0.088 mg/kg bw/day. The Panel also constructed two occupational exposure scenarios based on data presented in Section 1.2.4.2:
>
> • Occupational inhalation exposure to 188 mg/m3 (irritation limit) for 15 minutes resulting in a burden of 0.8 mg/kg bw for 15 minutes (21 L/minute, 70 kg bw).
>
> • Occupational inhalation exposure of 10 mg/m3 (the Expert Panel-estimated median of deicing data) for 480 minutes resulting in a total exposure burden of 1.4 mg/kg bw/8 hours (21 L/minute, 70 kg bw).
>
> A comparison of the exposures associated with these scenarios to the dose where saturation of human metabolism is estimated to occur (125 mg/kg bw) **shows that all of these expected exposures in the human are at least 100- to 1,000-fold lower than those expected to result in**

> **metabolic saturation. Scenarios involving continuous rather than acute exposures would have even a larger margin of safety due to dose rate phenomena**. This comparison does not take into account the potential impact of human interindividual variability. **The Expert Panel judges the likelihood of adverse developmental toxicity in the humans from such levels of exposure to be of negligible concern. The Panel concludes that the lack of reproductive toxicity in experimental animal studies indicates there is negligible concern for reproductive effects in humans."**

In addition, as stated by another regulatory agency, Environment Canada and Health Canada, in their Final Report (Environment Canada and Health Canada Final Report April, 2010, Priority Substance List Assessment Report, Follow-Up to the State of Science Report, 2000 on Ethylene Glycol. http://www.ec.gc.ca/lcpe cepa/default.asp?lang=En&n=4B7409ED-1.)

> "These PBPK models have predicted that it is unlikely to achieve levels of human blood glycolic acid concentrations that could lead to developmental toxicity. Humans would only achieve the threshold for developmental effects determined in rats of 2 mM if they **consumed bolus oral doses greater than 350 mg/kg** (> 20 g ethylene glycol for a 58 kg female) during the critical window of susceptibility based on simulations of peak maximum blood concentrations of glycolic acid."

We conclude that this along with the point that saturation is expected to require much higher doses for slower dose-rate (non-bolus) exposures **supports that renal toxicity is the critical effect of concern from oral exposures to EG.**

We can shortly supply these 21 publications in **Appendix I** and would offer you any time you may need to discuss these findings or to summarize the importance of each so that you can see that this significant new research should be considered for determining risk and that for the reasons given here that kidney should be used to determine the POD in a health risk assessment.

Should you have any questions regarding these comments, please contact me at (202) 249-6714 or bill_gulledge@americanchemistry.com .

Sincerely,

Bill Gulledge

Bill Gulledge

Senior Director, Chemical Products & Technology Division

Appendix I

Booth et al., 2004. Booth, E.D., Dofferhoff, O., Boogaard, P.J., Watson, W.P. "Comparison of the metabolism of ethylene glycol and glycolic acid in vitro by precision-cut tissue slices from female rat, rabbit and human liver" (Article) Xenobiotica, Volume 34, Issue 1, January 2004, Pages 31-48.

Carney et al., 2004. Carney, E. W., Scialli, A. R., Watson, R. E., and DeSesso, J. M. "Mechanisms regulating toxicant disposition to the embryo during early pregnancy: an interspecies comparison." Birth Defects Res. C Embryo Today 72, 2004, 345–360.

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Cruzan et al., 2004. . G. Cruzan, R.A. Corley, G.C. Hard, J.J. Mertens, K.E. McMartin, W.M. Snellings, R. Gingell, J.A. Deyo. "Subchronic toxicity of ethylene glycol in Wistar and F-344 rats related to metabolism and clearance of metabolites" Toxicol. Sci., 81 (2004), pp. 502-511.

Ellis-Hutchings et al., 2014. R.G. Ellis-Hutchings, N.P. Moore, V.A. Marshall, R.J. Rasoulpour, E.W. Carney. "Disposition of glycolic acid into rat and rabbit embryos in vitro" Reprod. Toxicol., 46 (2014), pp. 46-55.

Guo and McMartin, 2005. C. Guo, K.E. McMartin. “The Cytotoxicity of oxalate, metabolite of ethylene glycol, is due to calcium oxalate monohydrate formation” Toxicology, 208 (2005), pp. 347-355.

Guo et al., 2007. C. Guo, T.A. Cenac, Y. Li, K.E. McMartin. “Calcium oxalate, and not other metabolites, is responsible for the renal toxicity of ethylene glycol” Toxicol. Lett., 173 (2007), pp. 8-16.

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March 31, 2023

Mr. William Gulledge
Senior Director
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Via Electronic Mail: Bill_Gulledge@americanchemistry.com

Re: Ethylene Glycol (EG)- Proposed Health Risk Limit Rules

Dear Mr. Gulledge:

Thank you for submitting comments dated March 8th, 2023, from the Ethylene Glycols Panel (EGs Panel) of the American Chemistry Council (ACC) on the proposed amendment to the Health Risk Limits (HRL) Rule for ethylene glycol. Below is a summary of *your comments (italics)* and MDH's responses.

1. The ACC EGs Panel commented that the Neeper-Bradley (1995) study was not appropriate for use in MDH's calculated drinking water guidance because ethylene glycol was administered to animals via gavage (a procedure where a chemical is administered all at once through a tube, directly to the stomach), creating internal doses that ACC states would not be likely to occur in humans. Additional information outlining processes in rats affecting the internal dose associated with developmental effects, experiments using rats and rabbit embryos, and information on species differential placenta formation were summarized to support the conclusion that humans are not the most sensitive species to the developmental effects of ethylene glycol.

MDH does not agree with the ACC EGs Panel that the gavage route of exposure used in the Neeper-Bradley (1995)[1] developmental mouse study is inappropriate to use in deriving drinking water guidance. As previously stated in MDH's response dated January 20th, 2023, to ACC's prior comments, MDH takes into consideration all available data from toxicology studies using oral routes of administration, including gavage studies, when deriving drinking water guidance. As required by our methodology laid out in the 2008 Statement of Need and Reasonableness (SONAR) [2], MDH takes a health-protective approach that "humans are at least as sensitive as

the most sensitive mammalian species for which there are toxicological data. Substantial evidence that the response seen in laboratory animals is due to a mechanism that does not exist in humans can overcome this assumption." After reviewing the information submitted by the ACC EGs Panel, MDH determined that the limited data on the human kinetics of ethylene glycol's toxic metabolite glycolic acid and placental transfer of glycolic acid in comparison to rodents were insufficient to rule out the possibility that pregnant women exposed to ethylene glycol would not incur developmental effects to their unborn children.

Additionally, the data provided by the EGs Panel only addressed differences between species that could affect the amount of glycolic acid that reached a developing organism. Notably, no evidence was provided that a developing child would be less sensitive to its adverse developmental effects than other species. Therefore, in accordance with MDH's methodology laid out above and MDH's mission to protect the health of all Minnesotans, including sensitive populations and the most vulnerable, MDH selected the developmental endpoint from the Neeper-Bradley (1995)[1] study to derive a guidance value as mice were identified as the most sensitive species for this effect.

2. ACC's EGs Panel commented that 21 publications have come out since the National Toxicology Program (NTP) published their report on ethylene glycol related developmental toxicity in 2004 and they are relevant and must be considered in the human health risk assessment.

MDH appreciates the detailed list of publications provided by the EGs Panel. MDH notes that six of the articles included in the list provided by EGs Panel were, in fact, included in our review and cited on our summary sheet. Additionally, studies that were summarized or cited in other publications were not necessarily cited on our summary sheet for ethylene glycol. NTP's 2004 report[3] is one example of a publication that was cited on our summary sheet and summarized other studies that were not cited individually by MDH.

MDH reviewed the remaining 15 publications the EGs Panel recommended for incorporation into the risk assessment and determined that these publications would not have altered our guidance values and were therefore not cited.

3. ACC's EG Panel commented that the term 'skeletal malformations' is an incorrect characterization of the adverse effect seen in Neeper-Bradley (1995) and 'skeletal variation' is more appropriate to characterize the extra 14th rib observed in some fetuses.

This is an issue of terminology that does not ultimately influence MDH's selection of this endpoint for use in guidance derivation. MDH notes that both an increase in the incidence of an extra 14th rib and an increase in total malformations (including skeletal malformations) were reported in Neeper-Bradley (1995)[1]. Experts in developmental toxicology state that an extra 14th rib may be classified as either a malformation or variation[4,5]. MDH considers this effect adverse, which is a more health-protective approach and is in line with our methodology[2] and developmental toxicity risk assessment guidance from the US Environmental Protection Agency[6].

4. ACC's EGs Panel disagreed with our statement that there is not enough evidence in humans to support the use of the PBPK model published and refined in their provided citations.

MDH acknowledges that the EGs Panel feels there is sufficient evidence supporting the use of the published physiologically based pharmacokinetic (PBPK) model given the thorough documentation of its development cited in their comments, but respectfully disagrees. Basing guidance development decisions on the output from a PBPK model with unresolved uncertainty around human glycolic acid metabolism, especially for glycolic acid kinetics throughout pregnancy, may result in a guidance value that does not protect the most sensitive lifestage against developmental effects. Therefore, in accordance with our methodology[2], MDH will continue to propose basing the short-term guidance value on the Neeper-Bradley (1995)[1] study and use the default body weight scaling methodology to calculate the human equivalent dose.

5. ACC's EGs Panel disagreed with MDH's statement that there is not enough evidence to deviate from MDH's health-protective position that "humans are at least as sensitive as the most sensitive mammalian species for which there are toxicological data. Substantial evidence that the response seen in laboratory animals is due to a mechanism that does not exist in humans can overcome this assumption" (SONAR, 2008/9)" and state that studies they've cited show clear evidence of species differences in placental transporters that demonstrate humans are not more sensitive than rodents.

MDH acknowledges that ACC's EGs Panel considers the presented information on differences in placental transporters between rodents versus humans and rabbits sufficient to demonstrate that humans are not more sensitive than rodents. However, MDH respectfully disagrees and notes there is still uncertainty as to whether the differences observed during those specific gestational days are representative of the kinetics for the comparative species during other potentially sensitive windows in gestation. As MDH stated in its prior response to comments dated January 20, 2023, the function of the placenta is complex and dynamic during the course of pregnancy. Transporters that allow for the passage of nutrients and some chemicals across the placenta may be more or less active and/or present at different times in pregnancy.

Without more information, MDH will retain the health-protective position that humans may be just as susceptible to developmental effects as mice following exposure to ethylene glycol and its toxic metabolite, glycolic acid.

6. ACC's EGs Panel disagreed with MDH's statement that the authors of Moore et al. 2016 did not report functional consequences of their findings. Additionally, ACC argues that the findings from Ellis-Hutchings et al. 2014 and Moore et al. 2016, along with kinetic data, and findings from rodent and rabbit developmental studies provide clear evidence that the rodent animal model is not appropriate for use in human health risk assessment of developmental toxicity.

MDH acknowledges that ACC disagrees with our interpretation of the conclusions stated by Moore et al.[7] MDH is confident in our response because Moore et al. clearly state the need for additional studies to fully compare rodents and humans: "Given the complexity of monocarboxylic acid transport across the trophoblast, further data from specifically designed, integrated studies are required to elucidate the functional significance…" MDH agrees with this statement.

Accordingly, as stated in previous responses above and in the previous response to comments dated January 20th, 2023, MDH does not agree that the presented information sufficiently demonstrates that the findings from the critical study in mice are irrelevant to human health risk assessment. As directed by our methods[2], MDH selected a POD based on developmental effects from the most sensitive species, the mouse in this case, to derive the short-term guidance value.

7. ACC's EGs Panel commented that the 21 studies they noted were not part of the NTP 2004 report and the risk assessment should be re-done to include the additional studies.

Please see response to item #2 for more information on how MDH has reviewed the 21 studies ACC has recommended for incorporation.

8. ACC's EGs Panel concludes that renal toxicity should be the critical effect used in the ethylene glycol oral risk assessment, citing the NTP's 2004 report's conclusions as support. ACC also notes that Environment Canada and Health Canada did not use developmental effects in their review.

MDH follows the risk assessment methodology laid out in our 2008 SONAR[2]. Our analysis, conducted within that methodological framework, resulted in a final guidance value based on a developmental health endpoint. Our analysis also acknowledges experimental and clinical observations of renal toxicity and lists the kidney system as a co-critical effect.

While MDH cannot speak to the methodologies and analytical practices of other agencies or organizations, we do note that both California Environmental Protection Agency[8] and the Agency for Toxic Substances Disease Registry[9] (an arm of Centers for Disease Control) also selected Neeper-Bradley (1995)[1] as the basis of their health-based values.

The proposed MDH HRL resulting from our analysis is necessary to fulfill MDH's mission statement "to protect, maintain, and improve the health of all Minnesotans." Therefore, in accordance with our obligation and authority under Minnesota Statutes 114.0751[10] and 103H.201[11], MDH maintains its proposed HRL for ethylene glycol in order to "adequately protect the health of infants, children, and adults."

Sincerely,

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