Comments on Wisconsin's Department of Natural Resources' (DNRs')
proposed groundwater standards
for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS)

Laura C. Green, Ph.D., D.A.B.T. and Edmund A.C. Crouch, Ph.D.
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Introduction and Overview

The Wisconsin Department of Natural Resources (DNR, 2019) has proposed an allowable upper limit, for groundwater, of a concentration of 20 nanograms per liter (20 ng/L) for the sum of two perfluoroalkyl substances (PFAS). These two PFAS are:

- perfluorooctanoic acid (PFOA), and
- perfluorooctane sulfonic acid (PFOS)

Unfortunately, DNR's proposed PFAS standard for groundwater, like the Wisconsin Department of Health Services (DHS) recommended standard for drinking water on which it is based, is not grounded in current scientific evidence: accordingly, it should be revised.

In what follows, we offer technical suggestions for such revision. We hope that they prove helpful to the Department; and would, of course, be pleased to engage in conversation *re* same.

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Among other issues, DNR's and DHS's suggested standards for PFOA and PFOS:

- Are based almost entirely on a draft and provisional, rather than a final, PFOS guideline-value (termed a "minimal risk level," or MRL; which is not, even were it a final value, an enforceable standard) that was proposed in 2018, for public comment, by the federal Agency for Toxic Substances and Disease Registry (ATSDR);
- Are thus based almost entirely on dose-response data from one, and only one, laboratory-rodent study, which is a study of PFOS in rats (Luebker et al., 2005) that reported "delayed eye opening" and reduced birth weights in neonates;
- Do not reflect well-established, marked differences in sensitivities to PFOA and to PFOS between and among laboratory rats, mice, monkeys, and humans;
- Ignore reliable, relevant evidence from controlled studies of PFOA and PFOS in laboratory monkeys; and
- Fail to account for relevant clinical and epidemiological studies of PFOA.

With regard to the first point, not only is toxicologic value (that is, ATSDR's MRL) merely a draft, presumably temporary, value: ATSDR received numerous, thoughtful, critical comments on this

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and other PFAS draft values — some of which comments provided reliable, scientific bases for different guideline-values.[1] Given this flux, should not DHS and DNR holistically evaluate, for themselves, the current, relevant, toxicologic evidence on PFOA and PFOS?

More broadly, is it DHS and/or DNR policy to rely on draft, as opposed to final, federal non-enforceable guidelines when regulating toxic substances? And if/when such provisional guidelines are revised/finalized, whether to become more stringent or less stringent, is it DHS and/or DNR policy to merely follow suit?

Regarding the second point, it remains the case that epidemiologic and/or clinical evidence has so far failed to establish that any PFAS harms human health at or near environmental exposure-levels (ATSDR, 2018). Notably, cancer patients in a phase 1 trial have been dosed with massive amounts of PFOA (up to 1.2 grams per patient per week), as an experimental chemotherapeutic drug, with no apparent harm to their livers (the organ most clearly and adversely affected by PFOA in laboratory rodents) or other organs (Convertino et al., 2018).[2]

High-level, experimental exposures to some PFAS do harm the health of laboratory animals, and it is entirely appropriate to base health-protective guidelines on exposure-response data derived from laboratory animal studies (in the absence of, or in addition to, usable exposure-response data from studies of humans).

Ideally, health-based guidelines and standards should be based on controlled studies of (i) humans, (ii) monkeys, and/or (iii) other laboratory mammals known to mimic humans with regard to relevant biological responses. Unfortunately, the rodent studies on which DHS and DNR rely are in none of these three categories.

In what follows, we present constructive criticisms of DHS and DNR's approach, and offer alternate bases for regulation.

In particular, we show that the results from studies of PFOS and PFOA in laboratory monkeys can, and should, be used to derive highly protective, evidence-based "reference doses" (essentially, acceptable daily intakes), which in turn should be used to fashion regulations intended to protect public health, with an ample margin of safety.

[1] Docket ATSDR-2015-0004 on https://www.regulations.gov.

[2] As is typical for cancer chemotherapeutic drugs, these large doses of PFOA did cause fatigue, nausea, vomiting, and diarrhea, which were considered tolerable by the patients. PFOS also has anti-tumor activity (Wimsatt et al., 2016), although to our knowledge, clinical trials using PFOS have not been undertaken.

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The evidence-based, highly conservative, reference doses that we derive herein are:

- For PFOA, 89 ng per kg body weight per day, and
- For PFOS, 240 ng/kg-day.

Health-risks from PFOS

The toxicology of PFOS has been studied in laboratory rats, rabbits, and monkeys (Case et al., 2001; Seacat et al., 2002; Chang et al., 2012 and 2017).

In developmental toxicity studies in both rabbits and rats (Case et al., 2001), the highest dose rates of PFOS caused frank maternal toxicity, which in turn led to some fetal losses and reversible, delayed ossification. However, per the study-authors, "detailed external gross, soft tissue, and skeletal fetal examinations failed to reveal any compound-related malformations in either species," giving a NOEL for developmental toxicity of 1 mg/kg-d. Moreover, "[t]he finding that PFOS was not a selective developmental toxicant to rabbit fetuses concurs with results of previously conducted rat developmental toxicology studies."

Chang et al. (2017) dosed male and female cynomolgus monkeys with one, two, or three doses of PFOS at various times during a 422 day experiment, examining clinical chemistry parameters and measuring serum PFOS concentrations. PFOS serum concentrations at the highest extreme reached values close to those demonstrating overtly toxic effects in an earlier bioassay (Seacat et al., 2002): nonetheless, all clinical chemistry parameters remained within normal biological limits during the experiment. As expected, serum concentrations of two exposure-markers, total thyroxine (TT4) and high density lipoprotein (HDL), did decrease with PFOS treatment, although these varied only within the normal range. Moreover, again as expected, the PFOS-associated decreases in serum TT4 (due presumably to competitive binding) were not accompanied by alterations in serum concentrations of thyroid stimulating hormone (TSH), thus indicating no toxicologically significant effect of PFOS on thyroid function (Chang et al., 2017).

A benchmark concentration (BMC) analysis using individual animal data, based on the conservative assumption that the slight decrements in serum HDL were adverse, yielded a BMCLo (1 SD) of 74,259 and 76,373 ng/ml for males and females respectively. Once again, as in the case of PFOA, evaluation using individual animal data is essential since standard analyses (not shown) based on the published grouped data provide substantially different results (both higher and lower, depending on the assumptions made), presumably because of the large variation in serum concentration to dose ratios.

Extrapolating an average point of departure of 75,300 ng/ml to humans, using an interspecies factor of 3 and an intraspecies factor of 10 (again, larger than the expected major component of such intraspecies factor, the dose-to-serum concentration ratio, which is approximately a factor of 3 between 5th and 95th percentiles, Li et al., 2017, 2018), leads to a human plasma concentration of 2,510 ng/ml. All potential effects of PFOS exposure in animal models are seen

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with short induction times, so no factor is required for extrapolation from subchronic to chronic exposure. Assuming a distribution volume of 0.2 L/kg (ATSDR 2018, Table A-4) and a human half-life of 3.4 years (Li et al., 2017, 2018) gives a reference dose for PFOS of 280 ng/kg-day.

We recommend that DHS and DNR consider using this more reliable and relevant value for PFOS as it continues to refine its approach for the regulation of this chemical. MassDEP should also note that this most sensitive effect — a slight reduction in serum HDL — was, as noted by the study-authors, *of no significance to the health of the test-animals*. Indeed, serum lipid levels decreased overall with PFOS-exposure, and this is not adverse.

Health-risks from PFOA

Based on minor, transient, developmental effects in newborn CD-1 mice exposed to high doses of PFOA (Lau et al., 2006), U.S. EPA, California EPA, and others (Goeden et al., 2019), and now Wisconsin also, assume that PFOA poses a risk of developmental toxicity to humans as well. ATSDR (2018) choses a different set of studies in mice (Onishchenko et al., 2011, and Koskela et al., 2016) which are, nominally, studies of developmental toxicity as well.[3]

As it happens, as explained below, the fundamental uncertainties in this assumption render all of these mouse bioassay results unsuitable for purposes of assessing risks to human health. Fortunately, as for PFOS, controlled, reliable, and relevant studies of the toxicity of PFOA in monkeys have been peer-reviewed, published (Butenhoff et al., 2002, 2004a, and 2004b), and can serve as a predictor of effects in humans.

Importantly, the developmental (and many other) effects of PFOA in mice are mediated via the cell-nuclear hormone receptor, peroxisome proliferator-activated receptor alpha (PPARα; Abbott et al., 2012; Albrecht et al., 2013).[4] However, the activity-levels, structures, and functions of PPARα vary substantially among rodent-species and other animal-species; and, importantly, vary substantially between laboratory, "wild-type" mice (such as CD-1 mice) and humans (Bell et al., 1998; Corton et al., 2018). Abundant evidence indicates that rats and mice are highly susceptible to the effects (both adverse and beneficial) of chemicals (both endogenous and exogenous) that act via PPARα, while humans and other mammals — including guinea pigs, hamsters, rabbits, and monkeys — are relatively resistant to these effects (Klaunig et al., 2003 and 2012; Hoivik et al., 2004; Corton et al., 2018).

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[3] In addition to being inappropriate, as detailed below, the studies chosen by ATSDR are technically so flawed as to be inadequate a basis for any evaluation (Crouch and Green, 2018)

[4] PPARs are present in all animal-species, although with different forms in different species. As explained by Hall et al. (2012):

> PPARs regulate lipid and cholesterol metabolism through induction of (peroxisome proliferator response element (PPRE)) containing target genes resulting in increased beta-oxidation of fatty acids (Xu, Li, and Kong 2005). Natural ligands for PPARα include

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In addition to mice, laboratory rabbits have been used to assess the developmental effects of PFOA (Gortner et al., 1982). As just noted, rabbits can serve as faithful models for humans with regard to the actions of peroxisome proliferators on PPARα (Staels & Auwerx, 1998). In the relevant study, pregnant New Zealand White/Minikin rabbits were dosed with the ammonium salt of PFOA at 0, 1.5, 5, and 50 mg/kg-day on gestational days 6 through 18 (Gortner et al., 1982). The highest dose-rate, as expected, caused significant, temporary weight loss in the pregnant rabbits; but their fetuses at gestational day 29 showed zero indications of reproductive toxicity, embryotoxicity, or gross, skeletal, or internal malformations, or any other adverse effects, in *any* PFOA dose-group, including the highest.

DHS and DNR take no notice of this important study. U.S. EPA also did not even mention this rabbit bioassay in its draft assessment of PFOA (U.S.EPA, 2016), which is surprising, since the rabbit study-report is in fact included in U.S. EPA's Administrative Record for PFOA.

Standard regulatory guidance (and common sense) dictates that when extrapolating results from developmental studies, health risk-assessors should rely on laboratory animal-species *that best mimic humans with regard to relevant biological mechanisms*. *Per* ICH (2017):

> The rabbit has proven to be useful in identifying human teratogens that have not been detected in rodents; and the rabbit is routinely used as the non-rodent species based on the extensive historical background data, availability of animals, and practicality.

Importantly, the epidemiology on PFOA does not indicate that this chemical harms human development. As noted by ATSDR (2018):

> . . . most [epidemiological] studies found *no association* between maternal serum PFOA levels and the risk of low birth weight infants (typically defined as <2,500 g) . . . or found a *decreased* risk of low birth weight infants . . . [*emphasis* added]

And summarizing the literature on infant birth-weights *in the normal range*, ATSDR (2018) notes that although three sets of studies on women exposed to background concentrations *did* report inverse associations between maternal serum PFOA and birth weight, another *twelve similar studies found no such associations.*

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saturated and unsaturated fatty acids, eicosinoids, and linoleic acid metabolites. However, a diverse range of xenobiotics from many classes and structures are also able to activate PPARα such as the fibrate hypolipidaemic agents (clofibrate, fenofibrate, gemfibrozil amongst others), methaphenilene, thromboxane synthetase inhibitors, dehydroepiandosterone, non-steroidal anti-oestrogens, ibuprofen, Wy-14,643, diphenyl ether herbicides, and phenoxy herbicides (Greaves, 2007).

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Thus, although the CD-1 mouse data on the biological and toxicological effects of PFOA are of little-to-no relevance with regard to effects of PFOA on humans, more reliable and relevant data on the biological and toxicological effects of PFOA have been generated in laboratory monkeys (Butenhoff et al., 2002,[5] 2004a, and 2004b); and these primate data, combined with information from studies in humans, can be used to generate estimates of risks to human health from PFOA. We do so as follows.

Butenhoff and co-workers (2002, 2004a, and 2004b) examined the effects of the ammonium salt of PFOA (APFO) in male cynomolgus monkeys, during and after oral dosing for 6 months. The dose-rates were 3, 10, and 30 mg of APFO/kg body weight/day, although because the monkeys in the high dose-rate reduced their food intake and failed to gain weight, this highest dose-rate was reduced 20 mg/kg-day.

Doses of 30 and/or 20 mg/kg-day were plainly toxic, with evidence of liver injury in the highest dosed monkeys, but doses of 10 mg/kg-day and 3 mg/kg-day were not: no histopathologic evidence of liver injury was observed in monkeys in these middle and low dose-groups, and concentrations of liver enzymes in their blood-sera were normal.

All doses of APFO did increase the relative weights of the monkeys' livers, due to proliferation of liver mitochondria. This effect was expected, since statin drugs and other peroxisome proliferators (which act like PFOA in the liver) also cause increased biosynthesis of mitochondria. Although this is clearly a chemically-induced (and drug-induced) effect, it is not clear that it is an *adverse* effect, as opposed to merely an adaptive effect (Berthiaume and Wallace, 2002; Butenhoff et al., 2002; Hall et al., 2012; Convertino et al, 2018).

Nonetheless, the authors (Butenhoff et al., 2004b) erred on the side of safety by using the relative increase in liver weight (expressed as the ratio of animals' liver weight to brain weight) to derive a benchmark concentration (BMC) for PFOA that could be used for purposes of human health risk assessment.

Their BMC analysis used mean values by dose group of concentration and liver-to-brain weight ratio, and omitted the high-dose group. However, there is substantial intraspecies variation in concentrations at fixed dose rates; for example, the two animals in the high dose group differed by almost a factor of 3 in their plasma concentrations of PFOA (averaged over weeks 20 to 26, as used by Butenhoff et al., 2004b; see Butenhoff et al., 2004a or 3M Environmental Laboratory, 2001 for individual animal concentrations in this experiment). The same sort of variation in the ratio of plasma concentration to dose can be expected in humans, since the weight-specific volume of distribution is unlikely to vary substantially between individuals while the half-life varies substantially, as seen in a cohort in Sweden and in the C8 study (Li et al., 2017, 2018).

[5] Individual animal data for this study are available in Thomford (2001) and 3M Medical Department (2001).

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A BMC analysis using individual animal data is sensitive to inclusion/exclusion of the monkey with highest concentration or inclusion/exclusion of the high dose animals (**Figure 1**, **Table 1**).

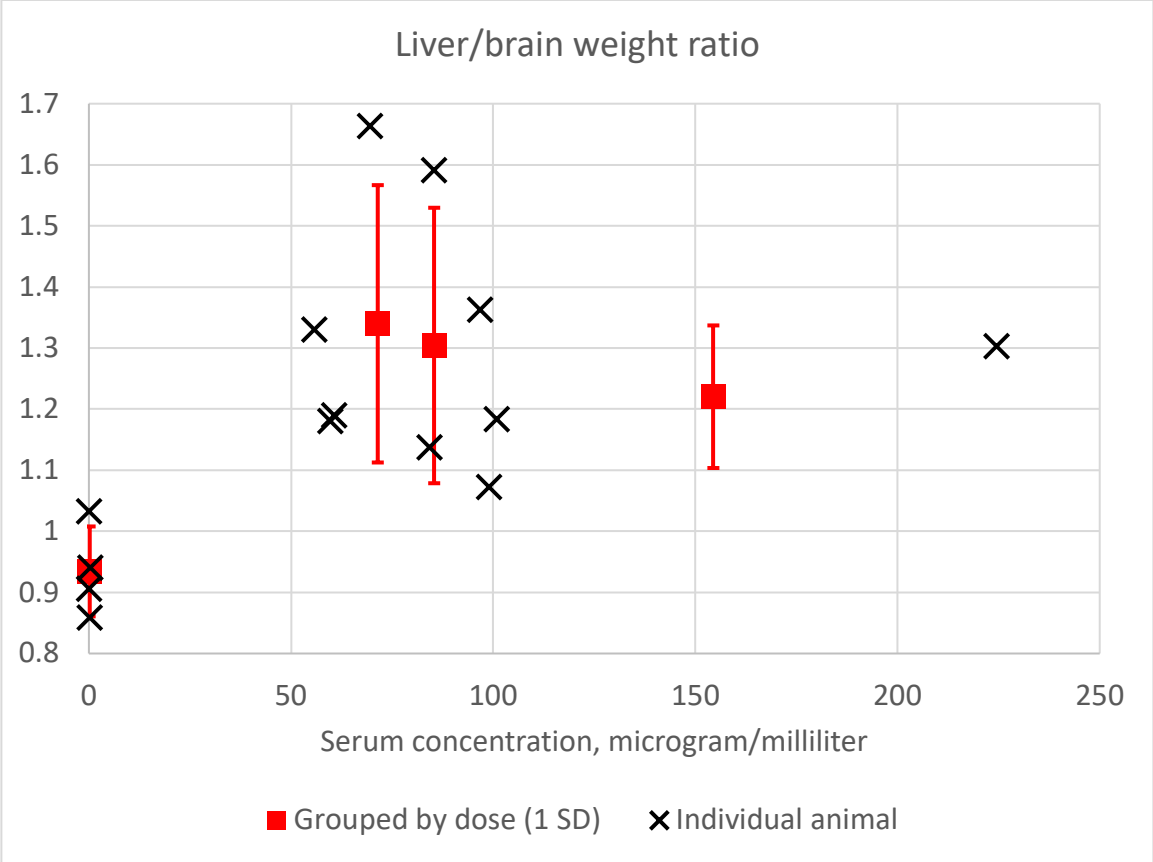

Figure 1 Liver/brain weight ratio in Butenhoff et al. (2002)

	BMCLo	BMC	BMCHi
Grouped, all doses	45.0	79.7	343.9
Grouped, omit high dose	22.6	35.5	79.8
Individual, all animals	57.5	113.2	3099.8
Individual, omit high concentration	29.9	52.4	205.1
Individual, omit high dose	28.3	49.1	178.4

Table 1 BMC estimates (serum concentrations, μg/ml) using liver/brain weight (95% confidence limits, 1 SD, linear model, constant variance)

In fact, in this experiment, the liver/bodyweight ratio provides a more sensitive endpoint (**Figure 2**, **Table 2**). The BMCLo obtained using the individual animal data is the most appropriate for cross-species extrapolation using serum concentration as the relevant metric, so we use that as the point of departure (POD).

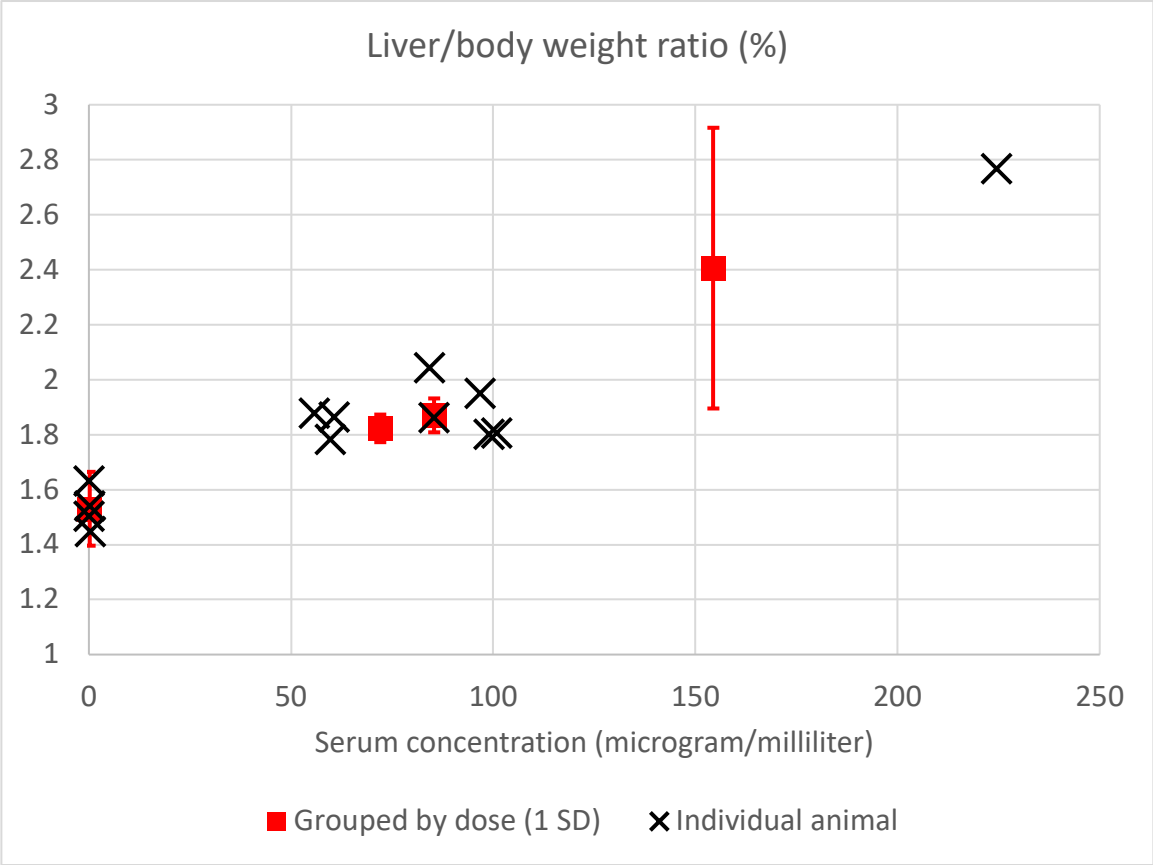

Figure 2 Liver/bodyweight ratio in Butenhoff et al. (2002).

	BMCLo	BMC	BMCHi
Grouped, all doses	26.0	50.9	88.5
Individual, all animals	19.0	32.5	57.4

Table 2 BMC estimates (serum concentrations, μg/ml) using liver/body weight ratio (95% confidence limits, 1 SD, restricted power model, constant variance)

Extrapolating this POD to humans using an interspecies factor of 3 and an intraspecies factor of 10 (compared with the 3-fold difference from 5th to 95th percentile expected solely from the variation in half-lives, Li et al., 2017, 2018), leads to a human plasma concentration of 633 ng/ml. The potential effects of PFOA exposure are seen with short induction times, so no factor is required for extrapolation from subchronic to chronic exposure. Assuming a distribution

volume of 0.2 L/kg (ATSDR 2018, Table A-4) and a median half-life of 2.7 years for humans (Li et al., 2017, 2018) gives a reference dose of 89 ng/kg-day.

This primate results-based, reference dose is highly conservative, since, as noted, it assumes that liver weight gain in PFOA-exposed monkeys, in the absence of any indication of liver damage, is an adverse, as opposed to simply adaptive, effect.

Of course, risk assessment is intended to err on the side of safety, so this conservatism is, we believe, appropriate. We recommend that DHS and DNR consider using this more reliable and relevant value for PFOA as it continues to refine its approach for the regulation of this chemical.

We would add that we think it quite important for risk assessors to communicate that chemicals, such as PFOA, with very small reference doses based on laboratory animal study-results (with multiple safety factors applied) are *not necessarily* highly toxic to humans. Indeed, analysts should make plain that PFAS are *categorically* different from chemicals such as arsenic, lead, mercury, benzene, 2,3,7,8-TCDD, and a multitude of other environmental contaminants for which adverse effects in humans have long been well-established.

As noted above, PFOA has been found to combat certain tumor-types, and has actually, perhaps surprisingly, been administered at extremely large dose-rates — up to 1.2 grams per patient per week, which is about 2,300,000 ng PFOA/kg-day! — to cancer patients in a phase I trial (Convertino et al., 2018). The resulting blood-serum concentrations of PFOA in these phase I study patients were, as noted by Convertino et al. (2018) "the highest ever reported in humans." Yet their serum liver enzyme levels remained normal, and there was otherwise no indication of organ toxicity.

Finally, we note that Wisconsin DHS is, from a scientific point of view, mis-using the results of Kieskamp et al. (2018). Those authors explicitly evaluated the dose-rate to human mothers that would give a defined plasma concentration *in their fetuses*, and not a dose-rate producing that plasma concentration in a 10 kg child drinking 1 L/day, as is used in the Wisconsin derivation.

Moreover, Wisconsin Statutes c 160.13(2)(c) does not strictly call for the approach used in the proposed enforcement standard, which is in fact scientifically meritless. The groundwater enforcement standard could clearly (and scientifically correctly) be derived using the Kieskamp et al. (2018) model such that the dose-rate to the mother (and child) produces the appropriate, protective, serum concentrations in the fetus and also in the child when that child reaches an age corresponding to 10 kg weight.

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Concluding remarks

Assessing risks to public health from PFAS is not straightforward, and there is no one best approach. Nonetheless, we believe that DHS and DNR can and hopefully will improve upon their assessments.

The currently proposed PFAS regulations are both inordinately stringent and unusually poorly justified. We believe that when DHS and DNR take the time needed to evaluate the relevant scientific evidence, from studies in humans and non-human primates alike, the Department will conclude that these two PFAS do not pose the extreme health-threat implied by the currently proposed standards.

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References

Note: Copies of the EPA Administrative Record AR-226 may be requested on CD-ROM from the EPA Docket Office by calling 202-566-0280 or sending an email request to: oppt.ncic@epa.gov .

3M Medical Department. 26-Week Capsule Toxicity Study with Ammonium Perfluorooctanoate (APFO/POAA) in Cynomolgus Monkeys — Determination of the Presence and Concentration of Perfluorooctanoate Fluorochemical in Liver, Serum, Urine and Feces Samples. 3M Environmental Laboratory, Building 2-3E-09, 935 Bush Avenue, St. Paul, MN 55106; and Centre Analytical Laboratories, Inc., 3048 Research Drive, Stage College, PA 16801. Study T-6889.3, FACT TOX-026, LAN-U2782. June 11, 2001. EPA Administrative Record AR226-1052a.

Abbott BD, Wood CR, Watkins AM, Tatum-Gibbs K, Das KP, Lau C. Effects of perfluorooctanoic acid (PFOA) on expression of peroxisome proliferator-activated receptors (PPAR) and nuclear receptor-regulated genes in fetal and postnatal CD-1 mouse tissues. Reproductive Toxicology. 2012 Jul 1;33(4):491–505.

Agency for Toxic Substances and Disease Registry (ATSDR). June 2018. Toxicological Profile for Perfluoroalkyls. Draft for Public Comment. U.S. Department of Health and Human Services.

Albrecht PP, Torsell NE, Krishnan P, Ehresman DJ, Frame SR, Chang SC, Butenhoff JL, Kennedy GL, Gonzalez FJ, Peters JM. A species difference in the peroxisome proliferator-activated receptor α-dependent response to the developmental effects of perfluorooctanoic acid. Toxicological Sciences. 2013;131(2):568–582.

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Bell AR, Savory R, Horley NJ, Choudhury AI, Dickins M, Tim JB, Salter AM, Bell DR. Molecular basis of non-responsiveness to peroxisome proliferators: the guinea- pig PPARα is functional and mediates peroxisome proliferator-induced hypolipidaemia. Biochemical Journal. 1998 Jun 15;332(3):689–693.

Berthiaume J, Wallace KB. Perfluorooctanoate, perflourooctanesulfonate, and N-ethyl perfluorooctanesulfonamido ethanol; peroxisome proliferation and mitochondrial biogenesis. Toxicol Lett. 2002 Mar 24;129(1-2):23-32.

Butenhoff J, Costa G, Elcombe C, Farrar D, Hansen K, Iwai H, Jung R, Kennedy Jr G, Lieder P, Olsen G, Thomford P. Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. Toxicological Sciences. 2002 Sep 1;69(1):244–257.

Butenhoff JL, Gaylor DW, Moore JA, Olsen GW, Rodricks J, Mandel JH, Zobel LR. Characterization of risk for general population exposure to perfluorooctanoate. Regulatory Toxicology and Pharmacology. 2004b Jun 30;39(3):363–380.

Butenhoff JL, Kennedy Jr GL, Hinderliter PM, Lieder PH, Jung R, Hansen KJ, Gorman GS, Noker PE, Thomford PJ. Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys. Toxicological Sciences. 2004a Oct 6;82(2):394–406.

California EPA. 2016. Notice of Intent to List: perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Available at https://oehha.ca.gov/media/downloads/crnr/noilpfoapfos.pdf

Case MT, York RG, Christian MS. 2001. Rat and rabbit oral developmental toxicology studies with two perfluorinated compounds. Int J Toxicol 20(2):101–109. (Full reports of the rabbit study are in the EPA Administrative Record AR226-0949 and AR226-1030A003).

Chang ET, Adami HO, Boffetta P, Wedner HJ, Mandel JS. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans. Crit Rev Toxicol. 2016;46(4):279-331.

Chang S, Allen BC, Andres KL, Ehresman DJ, Falvo R, Provencher A, Olsen GW, Butenhoff JL. Evaluation of serum lipid, thyroid, and hepatic clinical chemistries in association with serum perfluorooctanesulfonate (PFOS) in cynomolgus monkeys after oral dosing with potassium PFOS. Toxicological Sciences. 2017 Jan 23;156(2):387–401.

Chang SC, Noker PE, Gorman GS, Gibson SJ, Hart JA, Ehresman DJ, Butenhoff JL. Comparative pharmacokinetics of perfluorooctanesulfonate (PFOS) in rats, mice, and monkeys. Reproductive Toxicology. 2012 Jul 1;33(4):428–440.

Convertino M, Church TR, Olsen GW, Liu Y, Doyle E, Elcombe CR, Barnett AL, Samuel LM, MacPherson IR, Evans TR. Stochastic Pharmacokinetic-Pharmacodynamic Modeling for Assessing the Systemic Health Risk of Perfluorooctanoate (PFOA). Toxicological Sciences. 2018 Feb 16;163(1):293–306.

Corton JC, Anderson SP, Stauber A. Central role of peroxisome proliferator–activated receptors in the actions of peroxisome proliferators. Annual Review of Pharmacology and Toxicology. 2000 Apr;40(1):491–451.

Corton JC, Peters JM, Klaunig JE. The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. Archives of Toxicology. 2018 Jan 1;92(1):83–119.

Crouch, E.A.C., and Green, L.C. (2018). Comments on ATSDR's *Toxicological Profile for Perfluoroalkyls*. Available at: https://www.regulations.gov/document?D=ATSDR-2015-0004-0053.

Dourson, ML, Gadagbui, B, Onyema, C., McGinnis, PM, York, RG. Data Derived Extrapolation Factors for Developmental Toxicity: Preliminary Research Case Study with Perfluorooctanoate. In press. Available at https://www.tera.org/about/DDEFforPFOADevelopmentalToxicity7-3-19.pdf.

DNR, 2019. Recommended Public Health Groundwater Quality Standards Scientific Support Documents for Cycle 10 Substances. June 2019. P-02434V. https://www.dhs.wisconsin.gov/publications/p02434v.pdf.

Goeden HM, Greene CW, Jacobus JA. A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. J Expo Sci Environ Epidemiol. 2019 Mar;29(2):183–195.

Gortner, E.G., Lamprecht, E.G., Case, M.T. 1982. Oral Teratology Study of T-3141CoC in Rabbits. Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota. EPA Administrative Record AR226-0465.

Hall AP, Elcombe CR, Foster JR, Harada T, Kaufmann W, Knippel A, Küttler K, Malarkey DE, Maronpot RR, Nishikawa A, Nolte T. Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes—conclusions from the 3rd International ESTP Expert Workshop. Toxicologic Pathology. 2012 Oct;40(7):971–994.

Hoivik DJ, Qualls Jr CW, Mirabile RC, Cariello NF, Kimbrough CL, Colton HM, Anderson SP, Santostefano MJ, Morgan RJ, Dahl RR, Brown AR. Fibrates induce hepatic peroxisome and mitochondrial proliferation without overt evidence of cellular proliferation and oxidative stress in cynomolgus monkeys. Carcinogenesis. 2004 Sep 1;25(9):1757–1769.

Kieskamp KK, Worley RR, McLanahan ED, Verner MA. Incorporation of fetal and child PFOA dosimetry in the derivation of health-based toxicity values. Environment International. 2018 Feb 1;111:260–267.

Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, DeLuca JG, Lai DY, McKee RH, Peters JM, Roberts RA. PPARα agonist-induced rodent tumors: modes of action and human relevance. Critical Reviews in Toxicology. 2003 Jan 1;33(6):655–780.

Klaunig JE, Hocevar BA, Kamendulis LM. Mode of action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and human relevance. Reproductive Toxicology. 2012 Jul 31;33(4):410–418.

Koskela A, Finnilä MA, Korkalainen M, Spulber S, Koponen J, Håkansson H, Tuukkanen J, Viluksela M. Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. Toxicology and Applied Pharmacology. 2016 Jun 15;301:14–21.

Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB, Strynar MJ. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicological Sciences. 2006 Apr;90(2):510–518.

Li Y, Mucs D, Scott K, Lindh C, Tallving P, Fletcher T, Jakobsson K. 2017. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Report No 2:2017, Occupational & Environmental Medicine in Gothenburg, The Sahlgrenska Academy Institute of Medicine, Goteborgs Universitet. http://hdl.handle.net/2077/52661.

Li Y, Fletcher T, Mucs D, Scott K, Lindh CH, Tallving P, Jakobsson K. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med. 2018;75(1):46–51.

Luebker DJ, Case MT, York RG, Moore JA, Hansen KJ, Butenhoff JL. Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. Toxicology. 2005 Nov 5;215(1–2):126–148.

MassDEP, 2019. 2019 Proposed MCP revisions. https://www.mass.gov/lists/2019-proposed-mcp-revisions.

Onishchenko N, Fischer C, Ibrahim WN, Negri S, Spulber S, Cottica D, Ceccatelli S. Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. Neurotoxicity Research. 2011 Apr 1;19(3):452–461.

Seacat AM, Thomford PJ, Hansen KJ, Olsen GW, Case MT, Butenhoff JL. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in Cynomolgus monkeys. Toxicological Sciences. 2002 Jul 1;68(1):249–264. (Full report in the EPA Administrative Record AR226-1051a.)

Staels, B., Auwerx, J. 1998. Regulation of apo A-1 gene expression by fibrates. Atherosclerosis 137(Suppl.):S19-S23.

Thomford PJ. 26-Week Capsule Toxicity Study with Ammonium Perfluorooctanoate (APFO) in Cynomolgus Monkeys. Covance Laboratories Inc., 3301 Kinsman Boulevard, Madison, Wisconsin 5304-2594. Covance 6329-321. Sponsored by APME Ad-Hoc APFO Toxicology Working Group. Sponsor Study 3M T-6889.3. December 18, 2001. EPA Administrative Record AR226-1052a. (Note: on the material supplied by EPA, the 26-week study file is incorrectly labeled as the 4-week study, and vice versa.)

U.S. EPA, 2016. Health effects support document for perfluorooctanoic acid (PFOA). EPA 822-R-16-003, May 2016.

ICH, 2017. Detection of Toxicity to Reproduction for Human Pharmaceuticals. Draft ICH Harmonised Guideline. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. https://database.ich.org/sites/default/files/S5-R3_EWG_Draft_Guideline.pdf.

Wimsatt J, Villers M, Thomas L, Kamarec S, Montgomery C, Yeung LW, Hu Y, Innes K. Oral perfluorooctane sulfonate (PFOS) lessens tumor development in the APC min mouse model of spontaneous familial adenomatous polyposis. BMC Cancer. 2016 Dec;16(1):942.