**Comments on Massachusetts Department of Environmental Protection's (DEP's)
groundwater and soil standards
for perfluoroalkyl substances (PFAS)
in the Department's proposed 2019 amendments
to the Massachusetts Contingency Plan**

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Introduction and Overview

The Massachusetts Department of Environmental Protection (MassDEP, 2019) proposes new standards for the sum of six perfluoroalkyl substances (PFAS):

- perfluorooactanoic acid (PFOA),
- perfluoroheptanoic acid (PFHpA),
- perfluorononanoic acid (PFNA),
- perfluorodecanoic acid (PFDA),
- perfluorooctane sulfonic acid (PFOS), and
- perfluorohexane sulfonic acid (PFHxS).

Unfortunately, MassDEP's proposed PFAS standards are not based on current evidence, but could and should be revised. Among other issues, MassDEP's currently proposed standards:

- Are not based on any reliable evidence of adverse effects in humans;
- Are instead based almost entirely on only two studies in rodents:
  - One study of PFOA in laboratory mice (Lau et al., 2006), in which minor, transient, developmental effects were reported; and
  - One study of PFOS in laboratory 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 other PFAS 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 recent, relevant, clinical and epidemiological studies of PFOA.

With regard to the first 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). MassDEP should make this clear, but currently it does not.

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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 two studies on which MassDEP rely are in none of these three categories.

In what follows, we present constructive criticisms of MassDEP's approach, and offer alternate bases for regulation. In particular, we show that the results from studies of PFOA and PFOS 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.

The evidence-based, highly conservative, reference doses that we derive herein are 89 ng PFOA per kg body weight per day and 240 ng PFOS/kg-day. We also note that reference doses for other PFAS should be based on chemical-specific evidence.

Health-risks from PFOA

Based on minor, transient, developmental effects in CD-1 mice exposed to high doses of PFOA (Lau et al., 2006), U.S. EPA, California EPA, and others (Goeden et al., 2019) assume that this PFAS poses a risk of developmental toxicity to humans. And MassDEP, by extension, assumes the same for all of the six PFAS that it proposes to regulate, despite zero such evidence for at least four of these PFAS (all but PFOS, about which more below).

As it happens, the fundamental uncertainties in this assumption render these CD-1 mouse bioassay results entirely unsuitable for purposes of assessing risks to human health — even from exposures to PFOA, let alone from exposures to the other five PFAS of interest to MassDEP. Why did MassDEP rely on this single study in CD-1 mice, when, as explained below, controlled, reliable, and relevant studies of PFOA in monkeys have been peer-reviewed, published (Butenhoff et al., 2002, 2004a, and 2004b), and serve as much better predictors of effects in humans?[1]

[1] One answer is that MassDEP decided to simply accept U.S. EPA's (2016) reference dose at face value; despite the facts that EPA's derivation of its PFOA reference dose has not been peer-reviewed and has not been relied upon by EPA for standard-setting. Moreover, environmental guidelines and standards for PFOA, as established by various regulatory expert-groups internationally, *vary by 750-fold* (Dourson et al., 2019): this alone is indication that various analysts' assumptions and subjective judgments — rather than a set of objective, verifiable, unambiguous, health-effects data — are what drive these disparate, bottom-line numbers for "acceptable" exposures to PFOA.

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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).[2] 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).

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.

MassDEP currently takes no notice of this important study. U.S. EPA also did not even mention this rabbit bioassay in its assessment of PFOA (U.S.EPA, 2016), which is surprising, since the study-report is included in EPA's Administrative Record.

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* U.S. FDA (2017):

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[2] 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 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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> 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.*

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,[3] 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

[3] Individual animal data for this study are available in Thomford (2001) and 3M Environmental Laboratory (2001).

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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).

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**).

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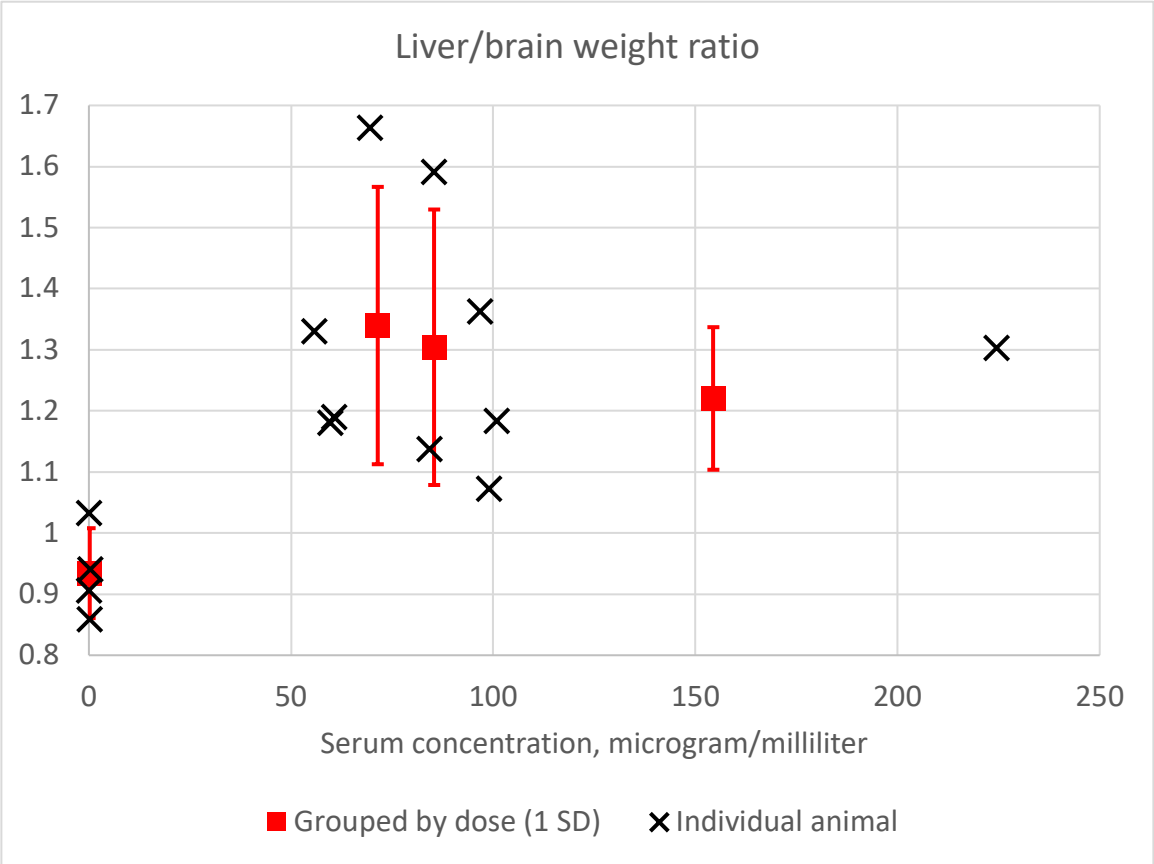

Figure 1 Liver/brain weight ratio in Butenhoff et al. (2002)

	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).

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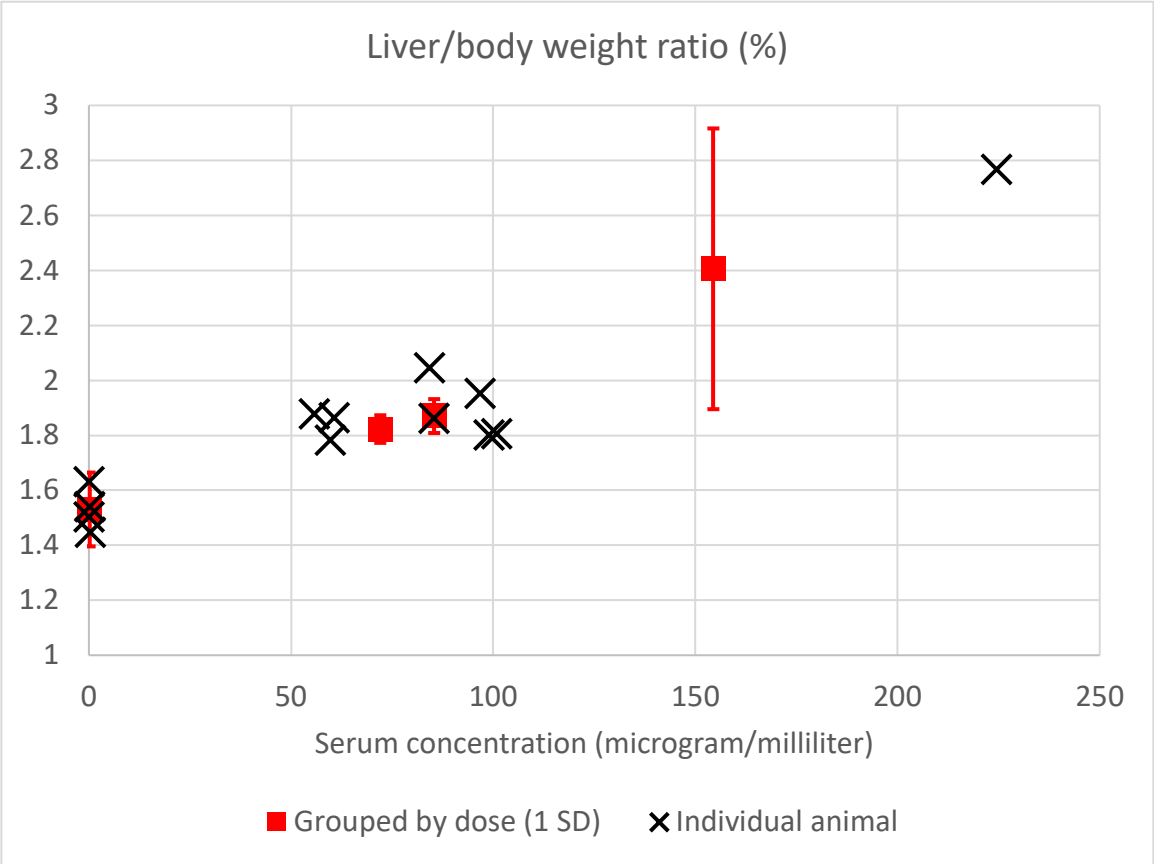

Figure 2 Liver/bodyweight ratio in Butenhoff et al. (2002).

	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 MassDEP 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 it happens, 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.[4]

Health-risks from PFOS

Next, PFOS has been studied in laboratory rats, rabbits and monkeys (Case et al., 2001; Seacat et al., 2002; Chang et al., 2012 and 2017); and here again the monkey data can be used to estimate risks to human health.

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

[4] Interestingly, at these high doses, the apparent half-life of PFOA in these patients was on the order of only weeks (Dourson et al., 2019) — substantially lower than the median half-life of 2.7 years that has been derived from people exposed only environmentally (via contaminated drinking water), who have vastly lower plasma concentrations of PFOA.

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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 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 MassDEP 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.

Risks from other PFAS

In deriving its proposed PFAS standards, MassDEP applies an extra safety factor of 4 (further reducing U.S. EPA's reference doses for PFOA and PFOS from 20 ng/kg-day to 5 ng/kg-day), to account for what DEP claims is the possibility that all six PFAS could harm people's immune

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systems at or near these miniscule dose-rates. This factor of 4 is entirely arbitrary, and is not justified by MassDEP by any holistic analysis of the weight of scientific evidence. We would note that such an holistic analysis has been peer-reviewed and published (Chang et al., 2016), and it concludes:

> With few, often methodologically limited studies of any particular health condition, generally inconsistent results, and an inability to exclude confounding, bias, or chance as an explanation for observed associations, the available epidemiologic evidence is insufficient to reach a conclusion about a causal relationship between exposure to PFOA and PFOS and any immune related health condition in humans. When interpreting such studies, an immunodeficiency should not be presumed to exist when there is no evidence of a clinical abnormality.

We would also note that the two rodent bioassays on which U.S. EPA's reference doses for PFOA and PFOS are based reported no effects on the exposed animals' immune systems.

More generally, ATSDR (2018) has extensively reviewed studies of immune system effects for several of the PFAS of interest: the Agency finds no compelling evidence that PFAS-exposure compromises people's immune systems.

With regard to PFOA, ATSDR (2018) notes that "no consistent associations" have been "found between serum PFOA and disease resistance, as measured by episodes of the common cold, cough, fever, or hospitalization for infectious disease."

With regard to PFOS, ATSDR (2018) notes, "Mixed results have been observed in studies evaluating infectious disease resistance. Similarly, inconsistent results have been examined in studies evaluating associations between serum PFOS and hypersensitivity outcomes, such as asthma; no associations were found for eczema, dermatitis, food allergies/sensitizations."

With regard to PFHxS, ATSDR (2018) notes, "In general, the available studies do not suggest an association between serum PFHxS and decreased infectious disease resistance."

And with regard to PFNA, ATSDR (2018) notes, "Most studies examining a possible association between serum PFNA levels and immunosuppression have not found associations."

We would add that MassDEP should regulate each individual PFAS based on the chemical, biological, and toxicological evidence for that specific PFAS — rather than simply, and counterfactually, assuming that all six PFAS (i) act identically and (ii) pose identical risks to public health. Clearly, they do not.

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Concluding remarks

Assessing risks to public health from PFAS is not straight-forward, and there is no one best approach. Nonetheless, we believe that MassDEP can and will improve upon its draft assessment.

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

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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.

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