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Recent US State and Federal Drinking Water Guidelines for Per- And Polyfluoroalkyl Substances (PFAS)

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INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) in drinking water are of increasing concern in the U.S., as well as worldwide, due to their widespread detection in public water systems and private domestic wells, extreme environmental persistence and evidence for adverse human health effects from environmentally relevant exposures. PFAS are a class of thousands of synthetic aliphatic compounds containing at least one totally fluorinated carbon atom that have been produced for industrial and commercial uses for over 70 years. Perfluoroalkyl carboxylates and perfluoroalkyl sulfonates, known collectively as perfluoroalkyl acids (PFAAs), are a subset of PFAS with totally fluorinated carbon chains of varying length and a negatively charged carboxylate or sulfonate group. PFAAs have been the main focus of attention as drinking water contaminants thus far, primarily because they are included in the standard analytical methods currently approved for routine drinking water monitoring while specialized methods are needed to detect most other types of PFAS.

PFAAs and other PFAS are unique among organic drinking water contaminants because of their persistent, bioaccumulative and toxic (PBT) nature. They have been called “forever chemicals” because they persist indefinitely in the environment due to the great strength of their carbon-fluorine bonds. Long-chain PFAAs (>8 carbons for carboxylates; >6 carbons for sulfonates) and other long-chain PFAS are highly bioaccumulative in humans. While other well-known PBT chemicals (e.g. chlorinated dioxins, polychlorinated biphenyls) are lipophilic with dietary fat as the primary exposure source, PFAS are water soluble and are important as drinking water contaminants.

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Because of their long human half-lives (several years), body burdens of long-chain PFAAs remain elevated for many years after exposure ends (Post et al. 2017). Infants are a sensitive subpopulation for the adverse effects of PFAS, and their exposures from contaminated water, either from prepared formula or via maternal transfer to breastmilk, are much higher than in older individuals (Post et al. 2017; Goeden et al. 2019). Toxic effects of PFAS in laboratory animals include liver damage, immune system suppression, adverse reproductive and developmental effects and, in some cases, cancer. There is substantial evidence for multiple human health effects of long-chain PFAAs commonly found in drinking water, including increased serum cholesterol and decreased antibody response to vaccinations, at exposure levels prevalent in the general population and communities with contaminated drinking water (Post et al., 2017).

There are no national drinking water standards (i.e. Maximum Contaminant Levels; MCLs) for PFAS in the U.S., and no MCLs for new contaminants have been established by the U.S. Environmental Protection Agency (EPA) under the lengthy and complex process for national regulation of new drinking water contaminants established by legislation in 1996. In 2016, EPA (2016a, 2016b) finalized non-regulatory Lifetime Drinking Water Health Advisories of 70 ng/L (parts per trillion) for the individual and total concentrations of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), the 8 carbon PFAAs that are the most well-known and thoroughly studied members of the PFAS class. These Lifetime Health Advisories updated the earlier EPA Provisional Short-term Health Advisories (applicable to exposure durations of weeks to months) of 400 ng/L for PFOA and 200 ng/L for PFOS that were established in 2009. As of May 2020, 9 U.S. states have concluded that the EPA Lifetime Health Advisories are

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not sufficiently protective and have developed more stringent drinking water standards or guidance values (referred to in this paper collectively as "guidelines") for PFOA and PFOS, while no state has developed less stringent guidelines. Additionally, some states have developed guidelines for other PFAS, and the U.S. Agency for Toxic Substances and Disease Registries (ATSDR 2018) and the European Food Safety Authority (EFSA 2020) developed draft toxicity factors for PFOA and PFOS that are about an order of magnitude lower than EPA's.

Detections of PFAS in drinking water in many locations throughout the U.S. have brought attention to the various guidelines developed by EPA, states and other agencies. While this is a topic of current interest, the factors considered in the development of these guidelines and the reasons for their similarities and differences may not be clearly understood by researchers and the general public. This focus article will discuss the scientific basis for state and EPA drinking water guidelines for PFOA and PFOS (defined here as including proposed and final regulatory standards and non-regulatory guidance values). PFOA and PFOS are emphasized because they are the PFAS for which the most guidelines are available, and the same principles apply to the development of guidelines for other PFAS.

CURRENT DRINKING WATER GUIDELINES FOR PFAS

Current guidelines for PFAS in drinking water developed by U.S. states and EPA are shown in Table 1, and the technical basis for these guidelines are provided at the websites listed in Text Box 1. Additional state guidelines for PFOA, PFOS and other PFAS continue to be developed, and current information can be found in the Interstate

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Technology and Regulatory Council Table of PFAS Water and Soil Values, which is updated frequently, at https://pfas-1.itrcweb.org/fact-sheets/.

Of the 12 states included in Table 1, 9 states have their own guidelines for PFOA and PFOS, and 10 states have guidelines for other long-chain PFAAs (perfluorononanoic acid, PFNA; perfluorohexane sulfonate, PFHxS; perfluoroheptanoic acid, PFHpA; perfluorodecanoic acid, PFDA), short-chain PFAAs (perfluorobutanoic acid, PFBA; perfluorohexanoic acid, PFHxA; perfluorobutane sulfonate, PFBS), and/or GenX (hexafluoropropylene oxide-dimer acid; a 6 carbon perfluoroalkylether carboxylate that replaced PFOA when it was phased out due to its bioaccumulative properties and potential health effects). In general, drinking water guideline values for short-chain PFAS are 1 to 2 orders of magnitude higher than for long-chain PFAS, reflecting the much shorter human half-lives of short-chain, as compared to long-chain, PFAS. Because they are much more rapidly excreted, the exposure levels (e.g. drinking water concentration) of short-chain PFAS that are needed to reach internal doses associated with adverse health effects are generally much higher than for long-chain PFAS.

As shown in Figures 1 and 2, with the exception of New Jersey's 2007 PFOA guideline of 40 ng/L which is similar to current values, drinking water guidelines for PFOA and PFOS have decreased by orders of magnitude since the early 2000s. These decreases in guideline values over time are due to both the emergence of new health effects information and newer interpretations of the information that was available when the older guidelines were developed.

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Current state drinking water guidelines range from 8 to 35 ng/L for PFOA and 10 to 40 ng/L for PFOS (Table 1). The differences among states' guidelines have become a focus of public concern and have been described as a "patchwork" in the popular media. In fact, however, the approximately 4-fold range among state guidelines is not large or unexpected in the context of independently derived risk-based values, especially as compared to older values that were generally in the range of 100s to 1000s of ng/L, and up to 150,000 ng/L for the West Virginia PFOA guideline from 2002. While all states generally follow EPA risk assessment guidance when developing drinking water guidelines, risk assessment involves scientific judgement such that different scientists reviewing the same data may come to different conclusions. Additionally, information relevant to health effects and risk assessment of PFAS continues to become available for consideration as newer guidelines are developed.

HOW ARE DRINKING WATER GUIDELINES DEVELOPED?

The 2 primary considerations in the development of drinking water guidelines are the toxicity factor and the exposure assumptions. The generic equations for drinking water guidelines based on non-carcinogenic and cancer effects are shown in Text Box 2. The parameters included in these equations are discussed in detail in the subsections on "Development of toxicity factors for PFAS" and "Exposure assumptions in PFAS drinking water guidelines."

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Development of toxicity factors for PFAS

When suitable data are available, human studies are preferred as the basis for risk assessment. There is substantial evidence for multiple human health effects from PFOA, PFOS and some other long-chain PFAAs, and the draft EFSA (2020) Tolerable Daily Intake for long-chain PFAS is based on human data. However, states and EPA have concluded that the human data have limitations that preclude their use as the primary basis for risk assessment. For example, because human exposures to multiple PFAS are frequently correlated, the dose-response relationship for a health endpoint often cannot be determined for individual PFAS (Post et al. 2017). Therefore, animal toxicology data are the quantitative basis for all current U.S. drinking water guidelines for PFAS. As discussed in the section on "Increases in Serum PFAS Levels from Drinking Water Exposure," human health effects are associated with the PFAA exposure levels that are prevalent in the general population from sources such as food and consumer products, even without additional exposure from drinking water. These human data indicate the need for concern about additional exposures from even low concentrations of PFAAs in drinking water and provide support for public health protective approaches in the development of PFAA drinking water guidelines.

Risk assessments for carcinogenic effects are based on the "non-threshold assumption" that there is some risk from any dose. As shown in Text Box 2, drinking water guidelines for carcinogenic effects are developed with a cancer potency factor $(ng/kg/day)^{-1}$ that relates dose to cancer risk and a specified cancer risk level which is a policy choice, not a scientific decision. While PFOA and PFOS are classified by EPA as

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having "Suggestive Evidence of Carcinogenic Potential," current state and EPA guidelines for these PFAS are based on non-cancer effects (i.e. a Reference Dose), with the exception of California's recent PFOA and PFOS guidelines which are based on cancer potency factors and a cancer risk level of 1-in-10,000 (10^{-4}) for Response Levels; Notification Levels (not shown in Table 1) use a risk level of 1-in-1 million (10^{-6}). Some states, including New Jersey, and EPA concluded that their guidelines for non-cancer effects are also protective for cancer at the 1-in-1 million risk level. However, these earlier evaluations did not consider the recent chronic rat study of PFOA conducted by the National Toxicology Program (NTP 2020) which is the basis for California's PFOA guideline. The results of this study indicate a higher cancer potency for PFOA than previous chronic studies and support the NTP (2020) conclusions of "clear evidence for carcinogenicity" in male rats and "some evidence for carcinogenicity" in female rats.

Risk assessments for non-carcinogenic effects assume that there is a "threshold" dose below which the effect will not occur. Drinking water guidelines for non-carcinogenic effects are based on a Reference Dose (ng/kg/day; Text Box 2), defined by EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." A Reference Dose is based on a critical effect, which is the most sensitive toxicological endpoint that is well established, adverse and considered relevant to humans (when animal data are used). It is derived by applying appropriate uncertainty factors (discussed in the subsection on "Similarities and differences in state and EPA PFAS Reference Doses") to the point of

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departure (POD) for the critical effect. The POD can be a BMDL (lower confidence limit on the Benchmark Dose, which is the dose predicted from modeling to cause a specified minimal change such as 10% or 1 standard deviation), No Observed Adverse Effect Level (NOAEL), or Lowest Observed Adverse Effect Level (LOAEL).

The general process for development of PFOA and PFOS Reference Doses is shown in Figure 3. Because PFOA and PFOS are excreted much more slowly in humans than laboratory animals, with half-lives of days to weeks in animals and several years in humans, the same administered dose results in a much higher internal dose (serum level) in humans than animals. To account for the much higher internal dose in humans, an important component of PFAS Reference Dose development is that animal-to-human comparisons are made on the basis of blood serum PFAS concentration (e.g. ng/mL, ng/L) rather than administered dose (mg/kg/day; µg/kg/day). As shown in Figure 3, uncertainty factors are applied to the serum level at the POD to obtain a "Target Human Serum Level," which is equivalent to a Reference Dose but in terms of internal rather than administered dose. Chemical-specific clearance factors (L/kg/day) that relate the serum level (ng/L) to the human administered dose (ng/kg/day) are available for PFOA and PFOS, and these clearance factors are used to convert the Target Human Serum Level to the Reference Dose.

Similarities and differences in state and EPA PFAS Reference Doses

Of the 9 states with their own PFOA and PFOS drinking water guidelines, 7 states developed Reference Doses for both PFOA and PFOS, while Vermont uses the EPA Reference Doses without modification and the California guidelines use cancer potency

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factors. The detailed information for each of the state and EPA Reference Doses provided in Tables 2 and 3 illustrates the similarities and differences in the derivation of these values.

PFOA. State Reference Doses for PFOA range from 1.5 to 18 ng/kg/day, and the EPA Reference Dose is 20 ng/kg/day. All of the state Reference Doses consider toxicological effects that are more sensitive and/or are judged to be more appropriate than the developmental effects (delayed ossification, accelerated puberty) used by EPA, either as the critical effect or through the application of an uncertainty factor for database limitations.

The critical endpoint for 3 state Reference Doses is increased relative liver weight, a well-established and sensitive effect of PFOA that follows a monotonic dose-response, with effect increasing with dose. In contrast, the dose-response relationships for the developmental endpoints used by EPA are non-monotonic (Figure 4), with the greatest effect at the lowest dose and smaller effects as the dose increases. Since the dose-response relationship below the LOAEL is undefined for dose-response curves of this type, the validity of EPA's use of an uncertainty factor to extrapolate from the LOAEL to the NOAEL for these data is unclear (DWQI 2017a). While EPA (2016a) did not consider increased liver weight in the absence of other hepatic effects to be an adverse effect of PFOA, state evaluations (e.g. DWQI 2017a) conclude that increased liver weight caused by PFOA co-occurs and/or progresses to more severe hepatic effects and is relevant to humans based on mode of action data. In 2 states, Reference Doses are based on the same developmental endpoints as EPA, but (as discussed later in this subsection)

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use different uncertainty factors. The Reference Doses of 2 other states use more sensitive developmental endpoints (neurobehavioral effects, skeletal effects that persist to adulthood) that are also the basis for the draft ATSDR (2018) Intermediate (15 days to 1 year) Minimal Risk Level for PFOA.

As discussed in "Development of toxicity factors for PFAS," PODs in PFAS risk assessment are based on serum PFAS levels (i.e. internal doses) rather than orally administered doses to account for the much greater bioaccumulation of PFAS in humans than laboratory animals. The human dose predicted to result in the serum PFAS level at the POD is calculated using a chemical-specific clearance factor based on human half-life and volume of distribution (Figure 3). The points of departure for increased liver weight are BMDLs derived from serum PFOA levels measured at the end of the dosing period in the animal studies, while those for developmental effects are LOAELs based on modeled average serum PFOA levels in the animal studies. For PFOA, the same clearance factor was used by all states and EPA (Table 2). It is based on a human half-life of 2.3 years estimated from the decline in serum PFOA levels in a community after exposure to contaminated drinking water ended.

The total uncertainty factor used in the state and EPA PFOA Reference Doses ranges from 100 to 1000. All of these Reference Doses use the default intraspecies uncertainty factor (for sensitive human subpopulations) of 10, an interspecies (animal-to-human) uncertainty factor of 3 rather than the default value of 10, and a less-than-chronic duration uncertainty factor of 1 (i.e. no adjustment is made). The default animal-to-human uncertainty factor of 10 is composed of 2 factors of $10^{0.5}$ (rounded to 3) each, to

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account for interspecies toxicokinetic and toxicodynamic differences. Since toxicokinetic differences are accounted for through use of serum PFOA levels as the dose metric, only the toxicodynamic portion (3) of the uncertainty factor is applied. No adjustment is made for exposure duration (i.e. uncertainty factor of 1) for the developmental endpoints because exposure in the relevant studies occurred throughout the time period of concern for these effects (gestation and early postnatal life), or for increased liver weight because review of the relevant studies indicates that PFOA causes this effect within a short timeframe. A LOAEL-to-NOAEL uncertainty factor of 3 or 10 is used when the POD is a LOAEL, while no adjustment is made when the POD is a BMDL.

All 7 Reference Doses developed by states include an uncertainty factor of 3 or 10 for database limitations. This uncertainty factor accounts for more sensitive toxicological effects that were not used as the critical endpoint and/or gaps in the toxicological database such as lack of an appropriate 2-generation reproductive study. In particular, delayed mammary gland development is a sensitive, well-established and persistent developmental effect of PFOA in mice, and its potential human relevance is supported by several human studies associating PFOA with decreased duration of breast feeding (DWQI 2017a). If delayed mammary gland development were to be used as the critical effect, the resulting Reference Dose would be about 200-fold lower than the Reference Dose based on increased liver weight alone (DWQI 2017a). While this effect is not the primary basis for any state's Reference Dose for reasons including lack of precedent for its use as the critical effect for risk assessment, several states concluded that an uncertainty factor is needed to account for delayed mammary gland development and

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other low-dose developmental effects (persistent liver toxicity, neurobehavioral effects, persistent skeletal changes) of PFOA. In contrast, EPA (2016a) dismissed delayed mammary gland development from consideration in risk assessment for reasons (mode of action is unknown; dose causing the effect differs among mouse strains; functional significance is unclear) that do not appear to have a valid scientific basis and/or apply equally to the endpoints that are the basis for the EPA Reference Dose (DWQI 2017a).

PFOS. State Reference Doses for PFOS range from 1.8 to 5 ng/kg/day, and the EPA Reference Dose is 20 ng/kg/day (Table 3). Decreased immune response in mice is a more sensitive toxicological effect of PFOS than the developmental endpoint (decreased body weight in offspring) used as the critical effect by EPA (2016b), and its human relevance is supported by epidemiological associations of PFOS with decreased vaccine response and increased incidence of infectious disease, analogous effects in humans (DWQI, 2018; EFSA 2020). All of the Reference Doses developed by states consider decreased antibody response to a foreign antigen in mice either as the critical effect (6 states) or through a database uncertainty factor for more sensitive effects (Massachusetts). Additionally, the draft ATSDR (2018) Intermediate Minimal Risk Level for PFOS (2 ng/kg/day) and the draft EFSA (2020) Tolerable Daily Intake for the total of 4 long-chain PFAAs including PFOS (1.1 ng/kg/day) consider immunotoxicity and are close to or lower than the state Reference Doses. The ATSDR Minimal Risk Level incorporates a modifying factor of 10 for “concern that immunotoxicity may be a more sensitive endpoint …. than developmental toxicity,” and the EFSA (2020) Tolerable

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Daily Intake is based on human epidemiology data linking maternal PFAS exposure with decreased antibody response to vaccinations in breastfed children.

As is the case for PFOA, serum PFOS levels are used as PODs, and Target Human Serum Levels are converted to Reference Doses with a clearance factor (Figure 3). The PODs for all state and EPA PFOS Reference Doses are NOAELs. For the 6 state Reference Doses based on decreased immune response, the NOAELs are serum PFOS levels measured at the end of dosing in the mouse studies, while the NOAELs for developmental effects used by 2 states and EPA are modeled average serum PFOS levels from the rat study. The EPA (2016b) clearance factor based on a human half-life of 5.4 years in retired fluorochemical workers was used by 4 states and EPA, while a clearance factor based on a shorter human half-life (3.4 years) estimated from the decline in serum levels after community exposure to contaminated drinking water ceased was used by 4 other states (Table 3).

The total uncertainty factor used in the state and EPA PFOS Reference Doses ranges from 30 to 100 (Table 3). For the same reasons discussed for PFOA above, all of the state and EPA Reference Doses use the default intraspecies uncertainty factor (for sensitive human subpopulations) of 10, an interspecies (animal-to-human) uncertainty factor of 3 rather than the default value of 10, and a less-than-chronic duration uncertainty factor of 1 because no adjustment is made for developmental effects and decreased immune response occurs within a short timeframe. Since the PODs for all state and EPA Reference Doses were NOAELs, no adjustment for LOAEL-to-NOAEL extrapolation (i.e. uncertainty factor of 1) was needed. An uncertainty factor of 3 for

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more sensitive toxicological effects was used to account for decreased immune response at lower doses in the Massachusetts Reference Dose, for which the developmental effect identified by EPA is the primary basis. Additionally, an uncertainty factor of 3 to account for potential thyroid effects at doses below the NOAEL for decreased immune response was used by 3 states.

Exposure assumptions in PFAS drinking water guidelines

While perhaps not as widely appreciated by non-risk assessors, exposure assumptions are equally important as toxicity considerations in the development of drinking water guidelines for PFAS. As shown in Text Box 2, exposure considerations for drinking water guidelines based on non-cancer effects include the drinking water ingestion rate (L/kg/day) and the Relative Source Contribution (percent), a factor that accounts for exposure from sources other than drinking water (e.g. food, consumer products, air).

EPA and most states generally use the upper percentile drinking water ingestion rate for adults (e.g. 0.029 L/kg/day, based on a body weight of 70 kg and an ingestion volume of 2 L/day[1]) as the default in drinking water guidelines protective for chronic (lifetime) exposure. Infants and young children consume more water on a body weight basis than older individuals, and a few states use the age-weighted average lifetime ingestion rate as their default. A higher ingestion rate for a specific sensitive

[1] EPA recently updated these assumptions to 80 kg and 2.4 L/day; the resulting drinking water intake of 0.030 L/kg/day is virtually identical to the previous value of 0.029 L/kg/day.

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subpopulation may be used when appropriate, resulting in a more stringent (lower) drinking water guideline than if the default rate were used. For example, the EPA drinking water standard for nitrate is based on methemoglobinemia (blue baby syndrome) resulting from short-term exposures in infants and therefore uses the drinking water ingestion rate for infants rather than the adult default.

The Relative Source Contribution is the percent of total exposure assumed to come from exposure to drinking water at the guideline concentration. It is intended to ensure that total exposure from all sources (drinking water and non-drinking water) does not exceed the Reference Dose (the daily dose unlikely to pose a risk of adverse effects). For example, when the Relative Source Contribution is 20%, the drinking water guideline is based on 20 percent of the Reference Dose, with 80 percent of the Reference Dose assumed to come from non-drinking water sources. Therefore, a lower Relative Source Contribution results in a more stringent (lower) drinking water guideline. Since the Relative Source Contribution represents daily exposure from drinking water as a fraction of the Reference Dose, it is independent of the concentration that is present in contaminated drinking water, a concept that is often misunderstood by those who are unfamiliar with development of drinking water guidelines. EPA risk assessment guidance specifies a Relative Source Contribution of 20 to 80 percent, with a default of 20 percent (the most stringent possible value) when data on exposures from non-drinking water sources needed to derive a chemical-specific value are not available. If chemical-specific data show that drinking water contributes less than 20 percent of the Reference Dose, a “floor” Relative Source Contribution of 20 percent is used since further reductions of the

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drinking water guideline through a Relative Source Contribution below 20 percent would not significantly reduce total exposure to the contaminant. If drinking water is known to contribute more than 80 percent of the Reference Dose, a "ceiling" Relative Source Contribution value of 80 percent is used to protect for non-drinking water exposures that may not have been otherwise taken into account.

Exposure assumptions for state and EPA drinking water guidelines for PFOA and PFOS are shown in Tables 4 and 5. Infants consume several times more fluid (breast milk or formula) than older individuals on a body weight basis, and PFOA and PFOS concentrations in breast milk are similar to or higher than in the mother's drinking water source (Goeden et al. 2019). Therefore, exposures to these PFAS are much higher in infants than in older individuals, particularly from breast milk but also from formula prepared with contaminated drinking water. Because infants are a sensitive subpopulation for the developmental effects of these PFAS, Vermont based its guidelines on the drinking water ingestion rate for infants and Massachusetts and EPA used the ingestion rate for lactating women; both of these ingestion rates are substantially higher than the default adult rate. While emphasizing concerns about the greater exposures and susceptibility of infants to PFOA and PFOS, New Jersey used the default adult ingestion rate rather than a higher rate for infants or lactating women due to toxicokinetic considerations. Specifically, New Jersey concluded that the Reference Doses for PFOA and PFOS are based on steady-state serum levels resulting from several years of exposure, and the higher ingestion rates in infants and lactating women apply to time periods that are much shorter than needed to reach steady-state (DWQI 2017b). New

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Jersey further concluded that use of a protective Relative Source Contribution of 20 percent, while not explicitly intended for this purpose, at least partially accounts for the higher PFAS exposures in breastfed and formula-fed infants because young infants do not receive additional exposure through the diet, generally believed to be the greatest non-drinking water exposure source.

A toxicokinetic model was recently developed by the Minnesota Department of Health (Goeden et al. 2019) to predict early life exposures to PFAS from contaminated water. This model takes into account the impact of maternal ingestion of contaminated water on transplacental exposure to the fetus, exposure through breastmilk or formula prepared with contaminated water from birth until age 1 year, and ingestion of contaminated water from early childhood through adulthood (Figure 5). For PFOA, for example, peak serum levels are predicted to be 6 times higher in breastfed infants than in adults. This model was used instead of the standard approach based on a defined drinking water ingestion rate in the recent PFOA and PFOS drinking water guidelines developed by Minnesota and 3 other states (Michigan, New Hampshire, and Washington).

Regarding the choice of Relative Source Contribution for PFOA and PFOS drinking water guideline, 3 states and EPA used the default value of 20 percent, the most protective available option. This decision was based on the conclusion that available information on non-drinking water exposure sources to these PFAS is insufficient to develop chemical-specific Relative Source Contribution values, and, as mentioned, to account for higher exposures during sensitive developmental life stages. For PFOA and PFOS guidelines based on the toxicokinetic model that predicts early life exposures

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(Goeden et al. 2019), a Relative Source Contribution of 50% for infants was selected based on subtraction of upper percentile serum PFAS levels in children and adults not exposed to contaminated drinking water from the Target Human Serum Level. Finally, New York used a Relative Source Contribution of 60% based on mean serum PFAS levels from National Health and Nutrition Examination Survey (NHANES) participants, a study group that is representative of U.S. residents.

INCREASES IN SERUM PFAS LEVELS FROM DRINKING WATER EXPOSURE

The significance of the increased serum PFAS levels that result from drinking water exposure was considered in the development of PFAS drinking water guidelines by several states including New Jersey, New York, Michigan, New Hampshire and Washington. For PFOA and PFOS, the increase in serum levels from a given drinking water concentration (i.e. serum to drinking water ratio) can be predicted (Text Box 3) from the ratio of the ingestion rate (L/kg/day) to the clearance factor (L/kg/day) that relates external dose (ng/kg/day) to serum PFAS level (ng/L) (DWQI, 2017a, 2017b). As shown in Figure 6, continued exposure to drinking water contaminated with even relatively low concentrations of PFOA is predicted to substantially increase serum levels from those prevalent in the general population, and this is also true for PFOS and other long-chain PFAS (Post et al. 2017).

The equations in Text Box 3 predict increases in serum level that are, on average, 114 times the drinking water concentration for PFOA (DWQI 2017a) and almost 200 times the drinking water concentration for PFOS (DWQI 2018). These predictions are

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supported by both empirical data from exposed populations and toxicokinetic modeling (DWQI 2017a; Post et al. 2017). These increases are of concern because multiple human health effects (e.g. increased serum cholesterol, decreased response to vaccinations and others) are associated with the serum PFAS levels prevalent in the general population, even with no additional exposure from contaminated drinking water, with the steepest portion of the dose-response curve for several of these effects falling within the general population serum PFAS range (DWQI 2017a, 2018; Post et al. 2017).

At the EPA Health Advisory of 70 ng/L, an average rate of drinking water ingestion is predicted to increase serum PFOA levels by about 5-fold and serum PFOS levels by about 4-fold from the U.S. general population means (DWQI 2017a; DWQI 2018). Several states including New Jersey (DWQI 2017a, 2018) and Michigan (MI SAP 2018) concluded that these predicted serum levels are well above those associated with several human health effects, and that a Health Advisory that results in increases of this magnitude is therefore unlikely to be sufficiently protective of public health. However, although the equations in Text Box 3 are clearly valid, EPA does not acknowledge their use to predict increases in serum levels from exposure to PFAS in drinking water, as stated in EPA comments to the New Jersey Drinking Water Quality Institute (DWQI 2017b).

APPLICATION OF GUIDELINES TO TOTAL CONCENTRATIONS OF MULTIPLE PFAS

As shown in Table 1, drinking water guidelines in 3 states (Connecticut, Massachusetts, Vermont) are applied to the total concentration of 5 or 6 long-chain

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PFAAs. While there are little or no relevant health effects data for one of the PFAAs included (PFHpA), this approach is based on the public health protective assumption that the toxicity of these PFAAs is additive, with the rationale that they are known or presumed to have long human half-lives and sufficiently similar toxicological effects and potencies. Similarly, the EPA applies its Health Advisory is to the total concentration of PFOA and PFOS because they have similar toxicity and identical Reference Doses. Additionally, Minnesota uses a Health Risk Index (the sum of the ratios of the concentrations of each chemical in water to the chemical's guideline) to address co-occurrence of multiple contaminants, including PFAS and others, that have a similar health endpoint (e.g. liver effects, thyroid effects). Other states address PFAS individually as a matter of process and/or because they have concluded that the most sensitive effects and modes of action among these long-chain PFAAs are not sufficiently similar for an assumption of additive toxicity.

ADDITIONAL CONSIDERATIONS

Drinking water guidelines (single ng/L to 10s of ng/L) for PFOA, PFOS and other long-chain PFAAs are relatively low compared to those for many other contaminants. One important reason is that these PFAAs bioaccumulate in humans to a much greater extent than most other drinking water contaminants, such that body burdens associated with health effects result from exposures to very low concentrations in drinking water. Additionally, while health-based drinking water values for numerous other contaminants (e.g. arsenic, vinyl chloride) are similar to or lower than for PFAS, many of these health-based levels are below the analytical Practical Quantitation Levels (the level at which the

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contaminant can be reliably measured) achievable by drinking water laboratories and/or cannot be reached with available treatment removal methods. In these cases, the final guidelines are often based on analytical or treatment removal limitations and are set higher than the health-based levels. In contrast, even the lowest health-based drinking water guidelines that have been developed for PFAS (i.e. < 10 ng/L) are achievable by drinking water laboratories and available drinking water treatment approaches, and all PFAS guidelines have thus been set at the health-based levels.

CONCLUSION

To date, 9 U.S. states have developed drinking water guidelines for PFOA and PFOS that are more stringent than the Health Advisories of 70 ng/L that were finalized by EPA in 2016, while no state has developed a less stringent guideline. Additionally, 10 states have developed guidelines for other PFAS. The similarities and differences among state guidelines for PFOA and PFOS relate to both toxicity considerations and exposure assumptions. The approximately 4-fold range among these guidelines (8 to 35 ng/L for PFOA; 10 to 40 ng/L for PFOS) is not large or unexpected since they were developed by different scientists at different time points, and especially when compared to older guidelines that were generally several orders of magnitude higher. Additional state guidelines for PFOA, PFOS and other PFAS are expected to continue to become available.

Acknowledgment—This paper is based on the author's presentation "Human Health Risk Characterization: A States Perspective" at the SETAC North America Focused Topic Meeting on Environmental Risk Assessment of PFAS held in Durham, NC in August

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Disclaimer—The views expressed herein do not necessarily reflect those of the New Jersey Department of Environmental Protection (NJDEP).

Data Availability Statement—Data, associated metadata, and calculation tools are available from the corresponding author (Gloria.Post@dep.nj.gov).

Text Box 1

TECHNICAL BACKGROUND FOR STATE PFAS DRINKING WATER GUIDELINES

California https://oehha.ca.gov/media/downloads/water/chemicals/nl/final-pfoa-pfosnl082119.pdf

Connecticut https://portal.ct.gov/-/media/Departments-and-Agencies/DPH/dph/environmental_health/eoha/PFAS/PFAS-Action-Level-Derivation---10-23-19-with-DPH-logo.pdf?la=en

Massachusetts https://www.mass.gov/doc/per-and-polyfluoroalkyl-substances-pfas-an-updated-subgroup-approach-to-groundwater-and/download

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Michigan https://www.michigan.gov/documents/pfasresponse/Health-Based_Drinking_Water_Value_Recommendations_for_PFAS_in_Michigan_Report_659258_7.pdf

Minnesota

https://www.health.state.mn.us/communities/environment/risk/guidance/gw/table.html

New Hampshire https://www4.des.state.nh.us/nh-pfas-investigation/wp-content/uploads/June-PFAS-MCL-Technical-Support-Document-FINAL.pdf

New Jersey https://www.state.nj.us/dep/watersupply/g_boards_dwqi.html

New York https://www.youtube.com/watch?v=2JIXCla6cHM&feature=youtu.be

North Carolina

https://epi.dph.ncdhhs.gov/oee/pfas/NC%20DHHS%20Health%20Goal%20Q&A.pdf

Ohio https://epa.ohio.gov/Portals/28/documents/pfas/PFAS-Technical-Information-Supporting-Documentation.pdf

Vermont https://anrweb.vt.gov/PubDocs/DEC/PFOA/PFOA%20-%20PFOS%20Health%20Advisories/Vermont/PFOA_PFOS_HealthAdvisory_June_22_2016.pdf

Washington

https://www.doh.wa.gov/Portals/1/Documents/4200/PFASToxicologicalAssessment.pdf

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Text Box 2

Generic Equations for Drinking Water Guideline Development[a]

Non-carcinogenic effects:

$$\text{Guideline (ng/L)} = \frac{\text{Reference Dose (ng/kg/day)} \times \text{Relative Source Contribution (\%)}}{\text{Ingestion Rate (L/kg body weight/day)}}$$

Carcinogenic effects:

$$\text{Guideline (ng/L)} = \frac{\text{Target Cancer Risk Level (unitless)}}{\text{Cancer Potency Factor (ng/kg/day)}^{-1} \times \text{Ingestion Rate (L/kg body wt/day)}}$$

[a]As discussed below, all current state and EPA guidelines for PFAS are based on non-cancer effects, except for California's PFOA and PFOS guidelines which are based on cancer risk.

Text Box 3

Prediction of Increases in Serum PFAS Levels from Drinking Water Exposure

$$\text{Dose (ng/kg/day)} = \text{Serum Concentration (ng/L)} \times \text{Clearance Factor (L/kg/day)}$$

$$\text{Dose (ng/kg/day)} = \text{Drinking Water Concentration (ng/L)} \times \text{Ingestion Rate (L/kg/day)}$$

$$\text{Serum to Drinking Water Ratio} = \frac{\text{Serum Concentration (ng/L)}}{\text{Ingestion Rate (L/kg/day)}}$$

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Drinking Water Conc. (ng/L) Clearance Factor (L/kg/day)

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DWQI. 2017b. New Jersey Drinking Water Quality Institute. Responses to Comments on DWQI Health Effects Subcommittee Report: “Public Review Draft - Health-Based Maximum

Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA).” New Jersey Drinking Water Quality Institute Health Effects Subcommittee.

DWQI. 2018. Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS). New Jersey Drinking Water Quality Institute Health Effects Subcommittee.

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EPA. 2016a. Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA). Office of Water, United States Environmental Protection Agency. EPA 822-R-16-005.

EPA. 2016b. Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS). Office of Water, United States Environmental Protection Agency. EPA 822-R-16-004.

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

MI SAP. 2018. Scientific Evidence and Recommendations for Managing PFAS Contamination in Michigan. Michigan PFAS Scientific Advisory Panel.

Post GB, Gleason, JA, Cooper, KR. 2017. Key scientific issues in developing drinking water guidelines for perfluoroalkyl acids: Contaminants of emerging concern. PLoS Biol 15(12):e2002855.

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Figure 1. State and EPA drinking water guidelines for PFOA, 2000 to present.

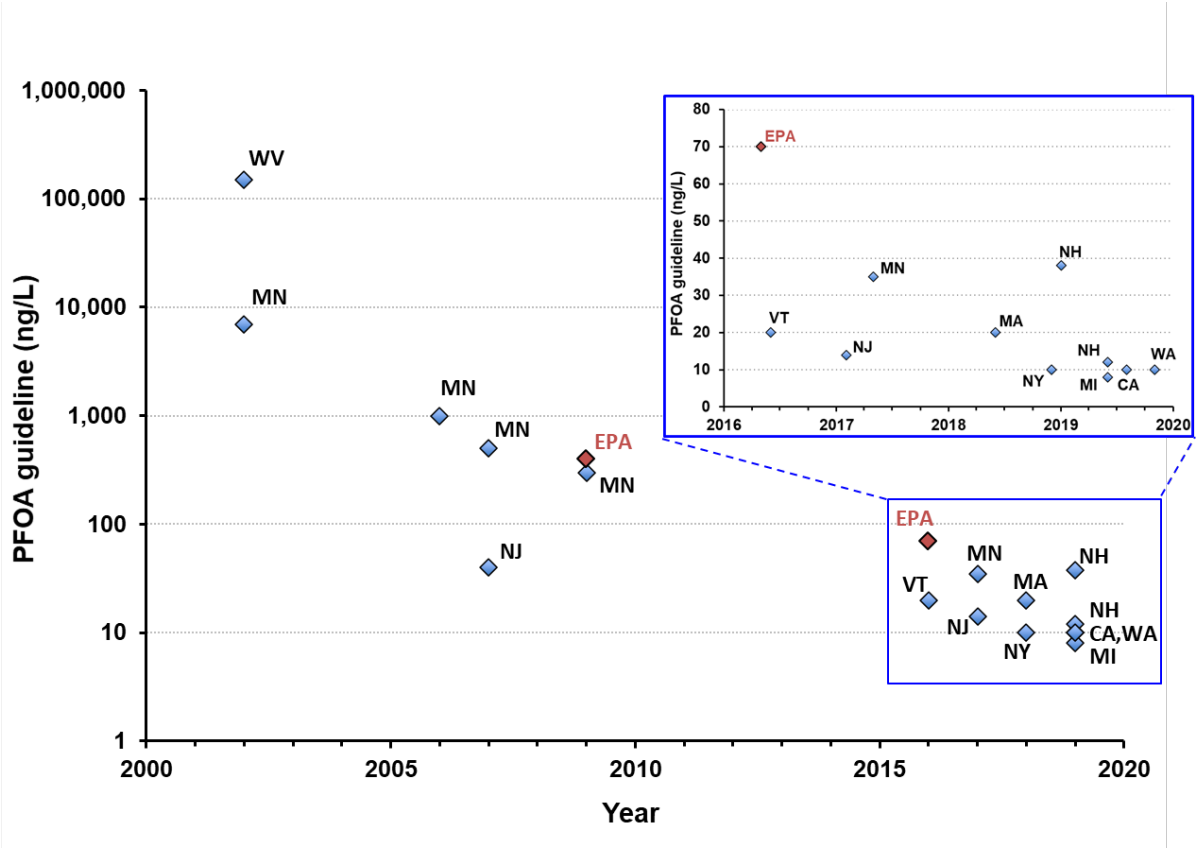

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Figure 2. State and EPA drinking water guidelines for PFOS, 2000 to present.

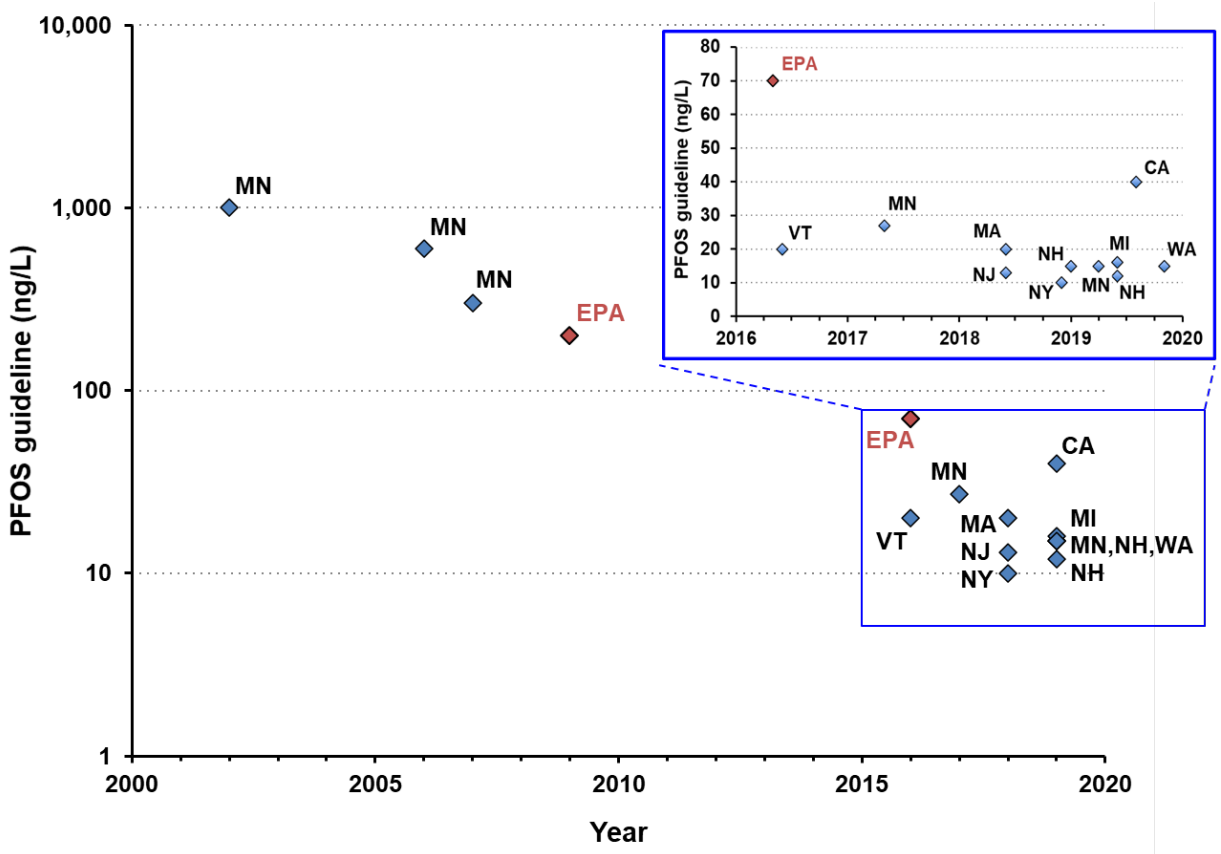

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Figure 3. Process for development of PFAS Reference Doses.

[a]Uncertainty factors were applied after application of clearance factor in some cases; this approach is mathematically equivalent to the approach shown and does not affect the resulting Reference Dose. [b]All uncertainty factors used for state and EPA Reference Doses are shown in Tables 2 and 3.

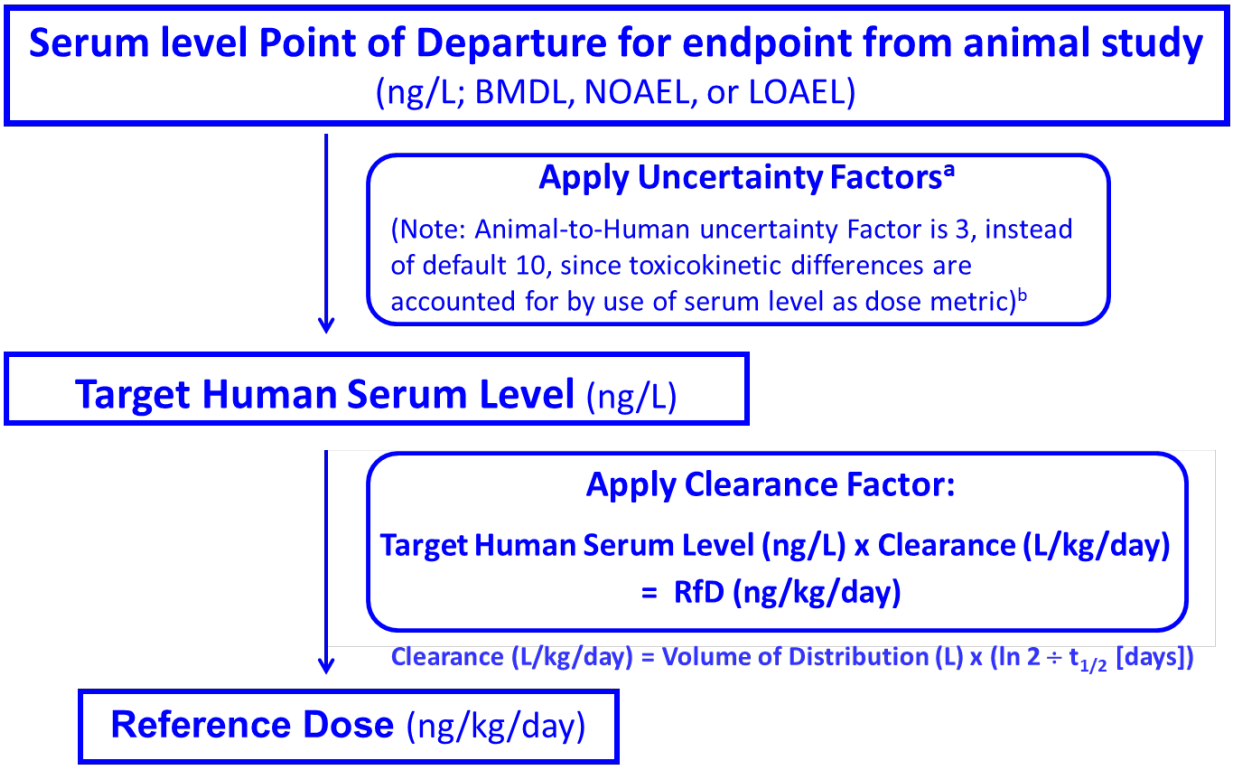

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Figure 4. Data (mean + standard error) for mouse developmental endpoints used as basis for EPA (2016a) PFOA Reference Dose, from Table 5 of Lau et al. (2006). * $p < 0.05$ compared to control. A. Change in day of preputial separation in male offspring compared to controls. Control value is 30.5 days; positive values = acceleration; negative values = delay. B. Number of ossification sites in offspring.

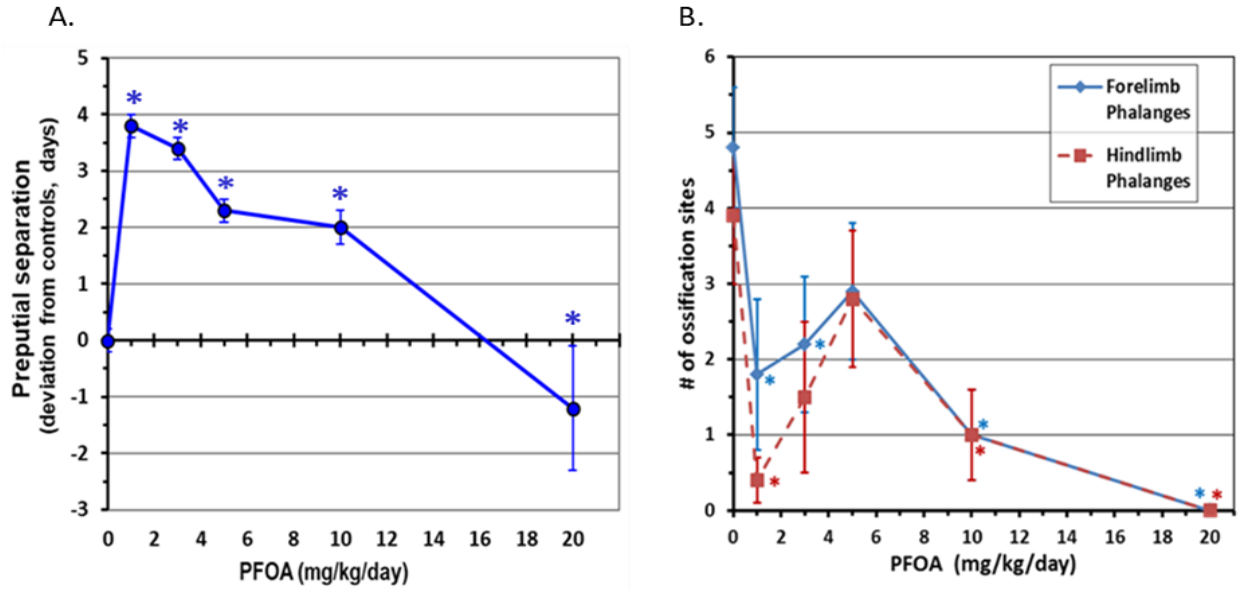

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Figure 5. Toxicokinetic model for early life exposure to PFOA from drinking water (Goeden et al. 2019). A. Conceptual representation of the model for formula-fed and breastfed infant exposure scenarios. B. Predicted serum levels from drinking water at the Minnesota guideline level of 35 ng/L. MDH – Minnesota Department of Health; RME – reasonable maximum exposed.

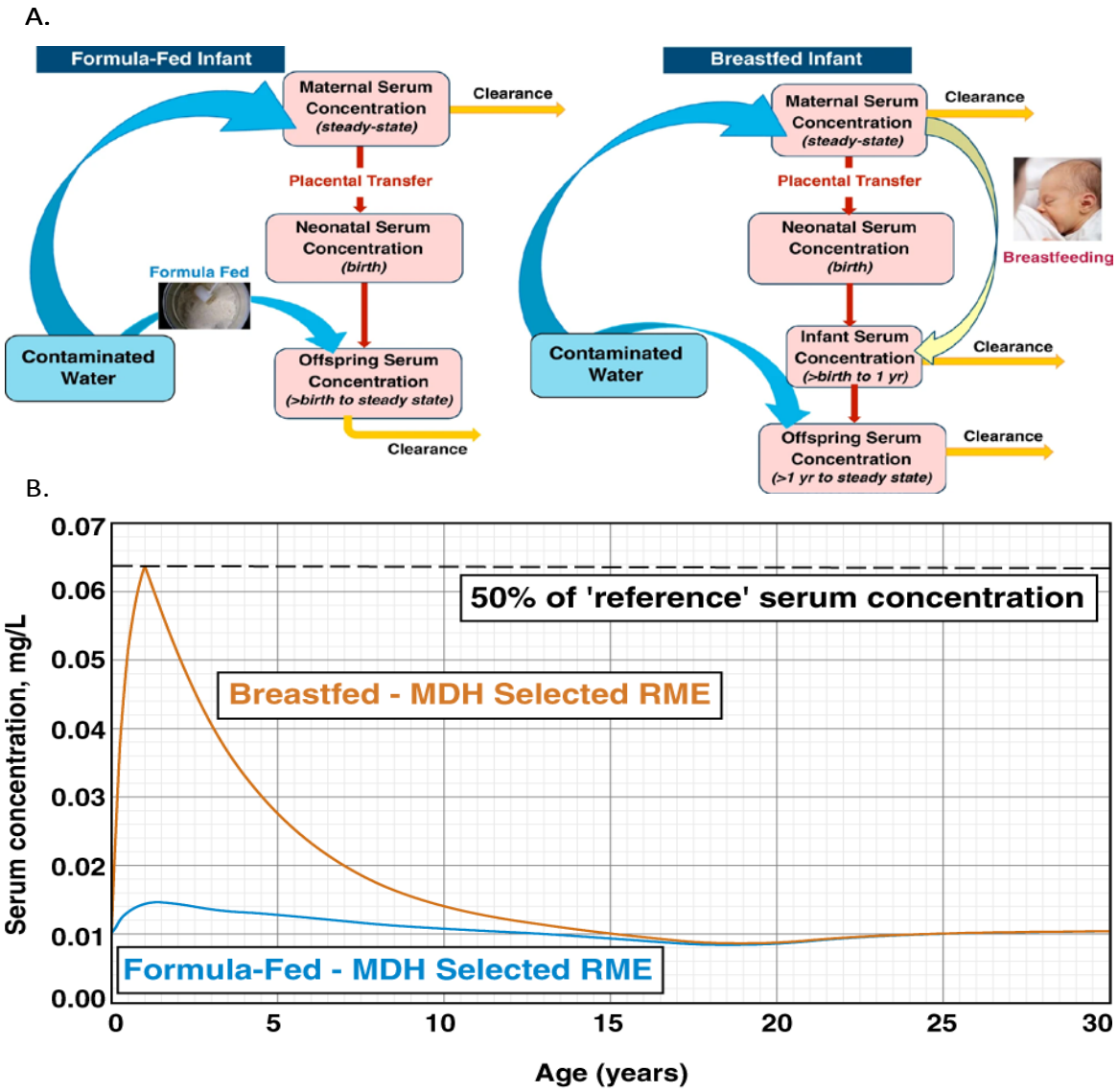

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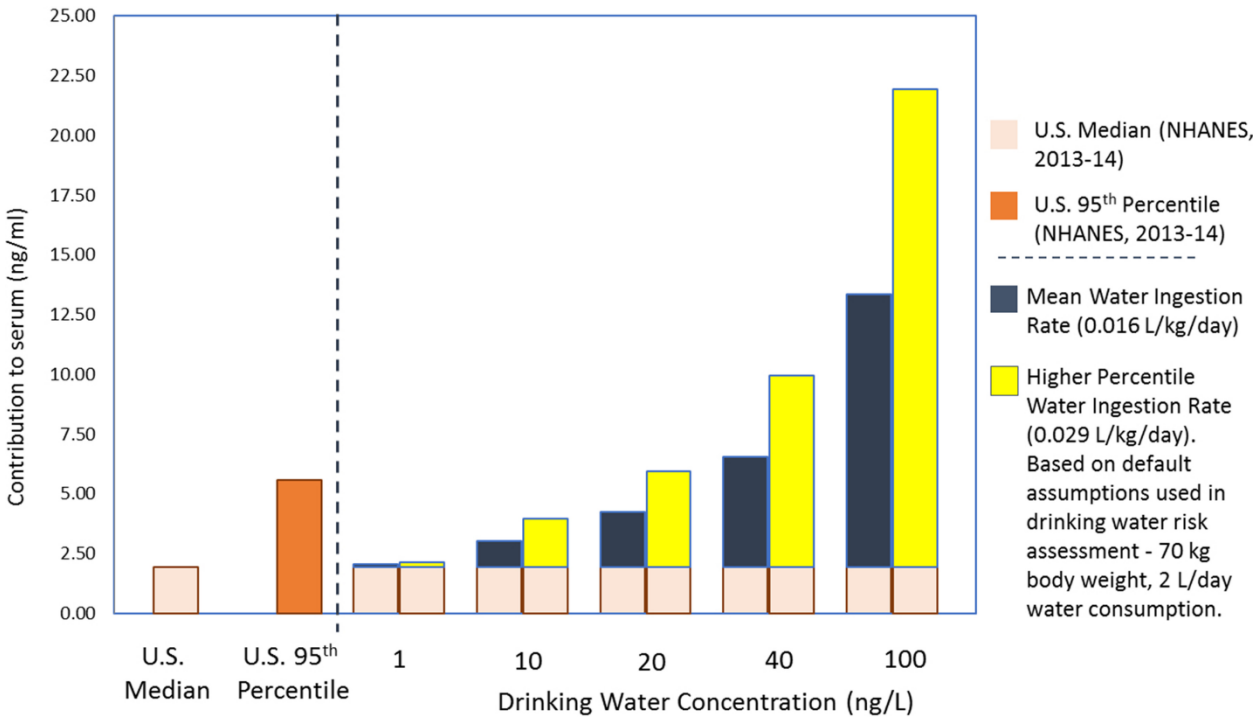
Figure 6. Predicted increases in serum PFOA concentrations from consumption of drinking water with various concentrations of PFOA (Post et al. 2017). Predictions are based on the clearance factor (0.00014 L/kg/day) that relates PFOA dose (ng/kg/day) to serum PFOA concentration (ng/mL) as shown in Text Box 3.



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Graphical abstract caption:

As of May 2020, 12 U.S. states have developed their own guidelines for PFAS in drinking water. Of these states, 9 have developed drinking water guidelines for PFOA and PFOS that are more stringent than the federal EPA's Health Advisories of 70 ng/L, and 10 have developed guidelines for other PFAS.

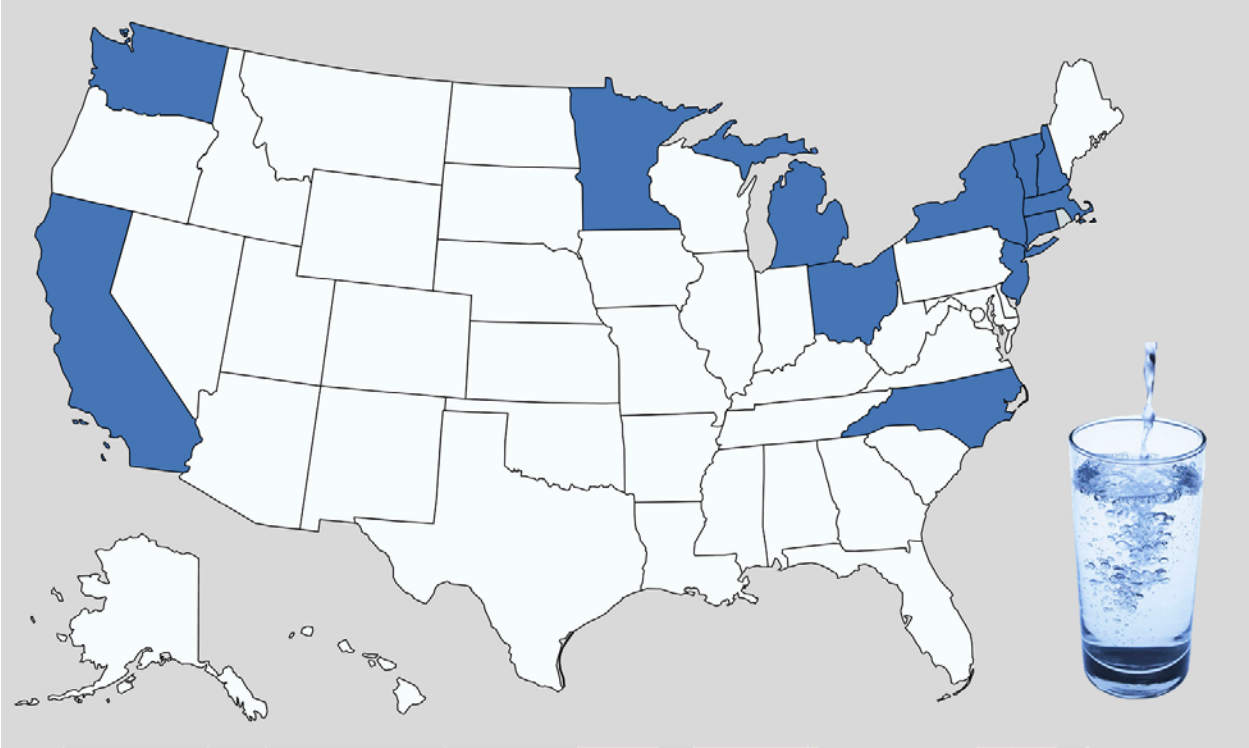

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Table 1. State and EPA guidelines for PFAS in drinking water[a]

	Long-chain (ng/L)							Short-chain (ng/L)			
	PFOA	PFOS	PFNA	PFHxS	PFHpA	PFDA	Total	PFBA	PFHxA	PFBS	GenX
# of Carbons	8	8	9	6	7	10		4	6	4	6
EPA	70	70	---	---	---	---	Yes (2)[b]	---	---	---	---
CA	10	40	---	---	---	---	No[c]	---	---	---	---
CT	70	70	70	70	70	---	Yes (5)[b]	---	---	---	---
MA	20	20	20	20	20	20	Yes (6)[b]	---	---	2,000	---
MI	8	16	6	51	---	---	No	---	400,000	420	370
MN	35	15	---	47	---	---	No	7,000	---	2,000	---
NH	12	15	11	18	---	---	No	---	---	---	---
NJ	14	13	13	---	---	---	No	---	---	---	---
NY	10	10		---	---	---	No	---	---	---	---
NC	---	---	---	---	---	---	---	---	---	---	140
OH	70	70	21	140	---	---	Yes (2)[d]	---	---	140,000	700
VT	20	20	20	20	20	---	Yes (5)[b]	---	---	---	---
WA	10	15	14	70	---	---	---	---	---	1,300	---

[a] Proposed and final standards and guidelines as of May 2020. States not listed generally use EPA Health Advisories for PFOA and PFOS.

[b] Guideline applies to total concentration of long-chain PFAS shown (number of PFAS included in total).

[c] Guidelines apply to each long-chain PFAS individually.

[d] Guideline of 70 ng/L applies to total concentration of PFOA and PFOS. Other guidelines apply to individual PFAS.

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Table 2. Toxicological basis of state and EPA Reference Doses for PFOA

	NJ	NH	NY	MI	WA	MN	VT/EPA	MA
Critical Effect	Increased liver weight			Developmental				
				Neurobehavioral; skeletal		Accelerated puberty (males); delayed ossification		
Species	Mouse							
Study	Loveless et al. 2006. Toxicology 220: 203-17		Macon et al. 2011. Toxicol. Sci. 122: 134-45	Onishchenko et al. 2011. Neurotox. Res. 19: 452-61 Koskela et al. 2006. Toxicol. Appl. Pharm. 301:14-21		Lau et al. 2006. Toxicol. Sci. 90: 510–18		
Serum PFOA Metric	Measured			Modeled Average				
Point of Departure[a] (ng/mL)	4350 (BMDL)		1060 (BMDL)	8290 (LOAEL)		38,000 (LOAEL)		
Uncertainty Factor:								
Intraspecies[b]	10							
Interspecies[c]	3							
Shorter-than-chronic	1[d]							
LOAEL-to-NOAEL	1			3	10	3	10	
Database[e]	10	3	3	3	1	3	1	3
Total[f]	300	100	100	300	300	300	300	1000
Clearance Factor[g]	0.00014 L/kg/day (Lorber and Egeghy. 2011. Environ. Sci. Technol. 45: 8006-14)							
Reference Dose (ng/kg/day)	2	6.1	1.5	3.9	3	18	20	5

[a] Serum PFOA level at Point of Departure for critical effect in animal study.

[b] For sensitive human subpopulations.

[c] For extrapolation from animals to humans.

[d] Uncertainty factor of 1 means that no adjustment was made.

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[e] For potentially more sensitive toxicological effects.

[f] Multiplication of two uncertainty factors of 3 (rounded from $10^{0.5}$) results in a value of 10.

[g] Clearance factor converts serum PFOA concentration (ng/L) to human administered dose (ng/kg/day)

Table 3. Toxicological basis of state and EPA Reference Doses for PFOS

	MN/NH/WA	MI	NJ/NY	MA	VT/EPA
Critical Effect	Decreased antibody response to foreign antigen			Developmental– decreased offspring body wt.	
Species	Mouse			Rat	
Study	Dong et al. 2011. Arch Toxicol. 85:1235-44.	Dong et al. 2009. Arch. Toxicol. 83: 805-15		Luebker et al. 2005. Toxicology 215:126-48	
Serum PFOS Metric	Measured			Modeled Average	
Point of Departure[a] (ng/mL)	2620 (NOAEL)	674 (NOAEL)		6260 (NOAEL)	
Uncertainty Factor:					
Intraspecies[b]	10				
Interspecies[c]	3				
Shorter-than-chronic	1[d]				
LOAEL-to-NOAEL	1				
Database[e]	3	1		3	1
Total[f]	100	30		100	30
Clearance Factor[g]	0.00013 L/kg/day (Human $t_{1/2}$ -3.4 yr; Li et al. 2018. Occup. Envir. Med. 75:46-51)		0.000081 L/kg/day (Human $t_{1/2}$ - 5.4 yr; EPA. 2016b)		
Reference Dose (ng/kg/day)	3	2.9	1.8 or 2[h]	5	20

[a] Serum PFOS level at Point of Departure for critical effect in animal study.

[b] For sensitive human subpopulations.

[c] For extrapolation from animals to humans.

[d] Uncertainty factor of 1 means that no adjustment was made.

[e] For potentially more sensitive toxicological effects.

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[f] Multiplication of two uncertainty factors of 3 (rounded from $10^{0.5}$) results in a value of 10.

[g] Clearance factor converts serum PFOS level (ng/L) to human administered dose (ng/kg/day)

[h] Difference due to rounding.

Table 4. Toxicity factors and exposure assumptions used in state and EPA drinking water guidelines for PFOA

	EPA	MA	VT	NJ	MN	MI	WA	NH	NY	CA
Reference Dose[a] (ng/kg/day)	20	5	20	2	18	3.9	3	6.1	1.5	0.7[b]
Drinking Water Ingestion	0.054 L/kg/day Lactating woman (80^{th} percentile)		0.175 L/kg/day Infant, 0-1 yr. (95^{th} percentile)	0.029 L/kg/day Default adult (upper percentile)	Modeled: - Prenatal exposure - Breast Milk (1 yr.) - Lifetime drinking water exposure				Not specified (0.034-0.151 L/kg/day considered)	0.053 L/kg/day Lifetime Daily Average
Relative Source Contribution	20%				50% for infant				60%	NA[c]
Guideline (ng/L)	70	20	20	14	35	8	10	12	10	10

[a] All values shown are Reference Doses except for California. See footnote b.

[b] California guideline is based on a cancer potency factor at the 1-in-10,000 risk level rather than a Reference Dose. Value shown is daily dose (ng/kg/day) estimate to result in 1-in-10,000 lifetime cancer risk.

[c] Not applicable. Relative Source Contribution is not considered in guidelines based on cancer risk.

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Table 5. Toxicity factors and exposure assumptions used in state and EPA drinking water guidelines for PFOS

	EPA	MA	VT	NJ	MI	MN/NH/WA	NY	CA
Reference Dose[a] (ng/kg/day)	20	5	20	1.8	2.9	3	2	2[b]
Drinking Water Ingestion	0.054 L/kg/day Lactating woman (80^{th} percentile)		0.175 L/kg/day Infant, 0-1 yr. (95^{th} percentile)	0.029 L/kg/day Default adult (upper percentile)	Modeled: - Prenatal exposure - Breast Milk (1 yr.) - Lifetime drinking water exposure		Not specified (0.034-0.151 L/kg/day considered)	0.053 L/kg/day Lifetime Daily Average
Relative Source Contribution	20%				50% for infant		60%	NA[c]
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[a] All values shown are Reference Doses except for California. See footnote b.

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[c] Not applicable. Relative Source Contribution is not considered in guidelines based on cancer risk.

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