



WHITE PAPER

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June 2019

PFAS Toxicology

What is Driving the Variation in Drinking Water Standards?



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PFAS Toxicology – What is Driving the Variation in Drinking Water Standards

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Abstract

The growing awareness of per- and polyfluoroalkyl substances (PFAS) in drinking water throughout the U.S is driving the demand for technically defensible, risk-based drinking water standards. In May 2016, the U.S. Environmental Protection Agency (EPA) issued lifetime health advisory levels of 70 parts per trillion (ppt) individually or for the sum of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), as guidance. In February 2019, the EPA decided to move forward with the development of a PFOA and PFOS maximum contaminant level (MCL) process as part of their National PFAS Action Plan under the Safe Drinking Water Act. In the absence of federally-developed enforceable standards, individual states are using their authority to develop and enforce drinking water standards and guidelines. This has resulted in a wide variation of PFAS drinking water guidelines and standards across State and Federal agencies. This variation is related to limited and developing knowledge regarding the critical health effects associated with PFAS exposure over time and largely reflects discordant risk assessment principles and practices among the regulatory agencies. Specifically, the differences in these recommended limits reflect selection of different critical health effects, target populations, uncertainty factors, and additional relative source contribution (RSC) used to derive state specific drinking water criteria. In this technical review, we examine the body of toxicological research being used by individual states and other developed nations to establish allowable exposure levels for individual PFAS compounds in humans. The primary focus of the discussion will be the points of departure in the development of these standards. Until the EPA issues enforceable health-based drinking water MCLs or action criteria for individual PFAS, State agencies may be required by statute or even stakeholder pressure to assess and issue their own drinking water guidelines. Based on the factors reviewed in this paper, we recommend that the EPA, as well as other State agencies, consider 1) the clinical relevance of more recently identified critical health endpoints; 2) the recent criticisms of physiologically-based pharmacokinetic (PBPK) modeling and its effect on the derivation of the human equivalent dose (HED); 3) the representativeness of exposure factors and overly conservative uncertainty factors being considered by State agencies; and 4) the potential potency differences among individual PFAS and the effects of different PFAS in a mixture. The development of any MCL or drinking water guideline should be based on robust science and risk-based criteria and should consider all relevant societal costs including a robust cost-benefit analysis.

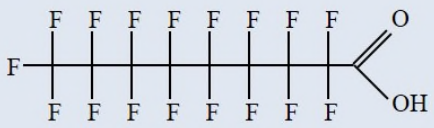
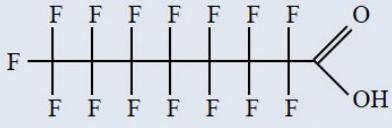
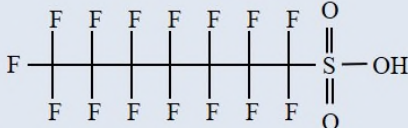
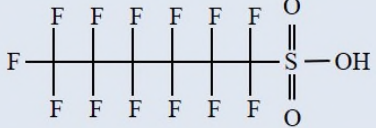
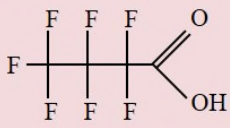
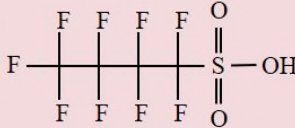
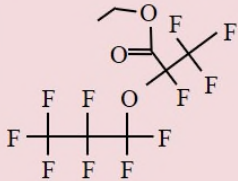
Introduction

Per- and polyfluoroalkyl substances (PFAS), are a broad, diverse group of several thousand man-made chemicals that have been widely used since these compounds were developed in the 1930s. Due to their chemistry, these compounds possess unique physical and chemical characteristics. While the basic structure of PFAS is a chain of carbon atoms bonded to fluorine atoms, they differ in that all carbon atoms (except the last one) in perfluoroalkyl substances are attached to fluorine atoms, whereas at least one, but not all,

carbon atoms are attached to fluorine atoms in polyfluoroalkyl substances, as seen in Figure 1. For the purposes of this discussion, perfluoroalkyl carboxylic acids with seven or more perfluoroalkyl carbons and perfluoroalkyl sulfonic acids with six or more perfluoroalkyl carbons are considered long-chain PFAS; in contrast, those with less perfluoroalkyl carbons are considered short-chain PFAS.^(1,2)

The chemical bond between the carbon and fluorine atoms is incredibly strong. The size of the fluorine atom creates steric hindrance around

Figure 1. Description of the most frequent PFAS compounds currently being assessed for specific State action levels and discussed in this paper.

Long Chain	Perfluorononanoic acid (PFNA)	$C_9HF_{17}O_2$	
	Perfluorooctanoic acid (PFOA)	$C_8HF_{15}O_2$	
	Perfluorooctane sulfonic acid (PFOS)	$C_8F_{17}SO_3H$	
	Perfluorohexane sulfonic acid (PFHxS)	$C_6HF_{13}O_3S$	
Short Chain	Perfluorobutanoic acid (PFBA)	$C_4HF_7O_2$	
	Perfluorobutane sulfonic acid (PFBS)	$C_4HF_9O_3S$	
	2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate (GenX)	$C_6HF_{11}O_3$	

the carbon backbone, blocking other atoms from forming bonds with the carbon backbone. The carbon-fluorine portion of these compounds is both hydrophobic and oleophobic, meaning they repel water and fats. Conversely, the compound also contains a reactive hydrophilic portion at one end of the molecule, with the functional group generally a carboxylic acid, sulfonic acid, phosphonic acid, or phosphinic acid. These

properties of water-repellency and oil-repellency while simultaneously having a reactive portion make these compounds useful as surfactants and dispersants which are utilized in numerous industries, including, but not limited to, fire-fighting foams, carpet, textile and leather treatment, chromium plating, photolithography, semi-conductor manufacturing, coating

additives, food packaging coatings, cleaning products, and biocides.⁽¹⁾

PFAS and their precursor compounds can be released into the environment by any number of ways, including, but not limited to, during manufacturing; via landfilling of coated products such as food packaging, carpeting, or electronics; via land-spreading of sewage sludge on agricultural fields; and during use of fire-fighting foams. When these chemicals are released into the environment, they are considered recalcitrant compounds, meaning that due to their chemistry they are generally not broken down by photolysis or microbial organisms in the soil or water. PFAS compounds typically are soluble in water. Due to their solubilities in water and resistance to breakdown, they are environmentally mobile and persistent chemicals, and can therefore be found world-wide and in virtually all environmental media. They are taken up by plants and animals throughout the food web, and can therefore concentrate, or bioaccumulate, up through the food web.

There are a variety of ways that people can be exposed to these chemicals. Workers in industries or activities that manufacture, manipulate, or use products containing PFAS may be exposed to higher levels than the general population. However, their exposures are through inhalation whereas the non-occupationally exposed general population is primarily, if not solely, exposed through ingestion of contaminated food and drinking water. For the general population, ingestion of PFAS may also occur, to a lesser degree, through hand-to-mouth transfer from surfaces treated with PFAS-containing stain protectants, nonstick products, polishes, waxes, paints, and cleaning products.⁽²⁾

Recently, U.S. federal agencies as well as international groups have conducted extensive toxicological reviews on PFAS.⁽²⁻⁵⁾ The goal of this paper is not to present an exhaustive review of the published toxicological studies, but to discuss the toxicokinetic differences between long- and short-chain PFAS as well as the exposure variables utilized by various regulating authorities to derive PFAS guidance levels for drinking water. The focus will be on the impact

of the selection of the variables chosen by the various regulatory bodies and the effect of these choices on the proposed drinking water guidelines.

Toxicokinetics of PFAS Compounds

Toxicokinetics is the study of the absorption, distribution, biotransformation, and excretion of a chemical within an organism. By evaluating the toxicokinetics of individual PFAS, toxicologists can determine whether various PFAS chemicals affect the body differently. The chemical composition, chain length, and branching of the various PFAS structures all impact the toxicokinetics. The following is a brief summary of the toxicokinetic studies described in detail in the 2018 Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Perfluoroalkyls* (Figure 2).⁽²⁾ Based on epidemiological and limited human studies, it is assumed that the human's toxicokinetic mechanisms are similar, if not identical, for both the ingestion (oral) and inhalation exposure pathways.

Absorption: Animal studies have measured a very rapid absorption of both long- and short-chain PFAS orally administered to animal models. In toxicokinetics, chemicals are evaluated by the duration (time) required for half of the chemical to achieve an outcome of interest, referred to as half-life ($t_{1/2}$). For example, the absorption rate in the gastrointestinal tract of rats has been estimated to be $t_{1/2} < 2$ hours or that half of the chemical dose administered was absorbed in less than 2 hours. Notably, the absorption rate for PFOA in female rats was an order of magnitude faster than that in male rats (1.1 hours vs. 10 hours). The underlying mechanism contributing to the different toxicokinetic factors in females as compared to males is not completely understood but is believed to involve hormonal differences influencing the uptake of these chemicals.

Distribution: PFAS are distributed throughout the body via plasma, where PFAS bind to serum albumin and other plasma proteins. The highest extravascular

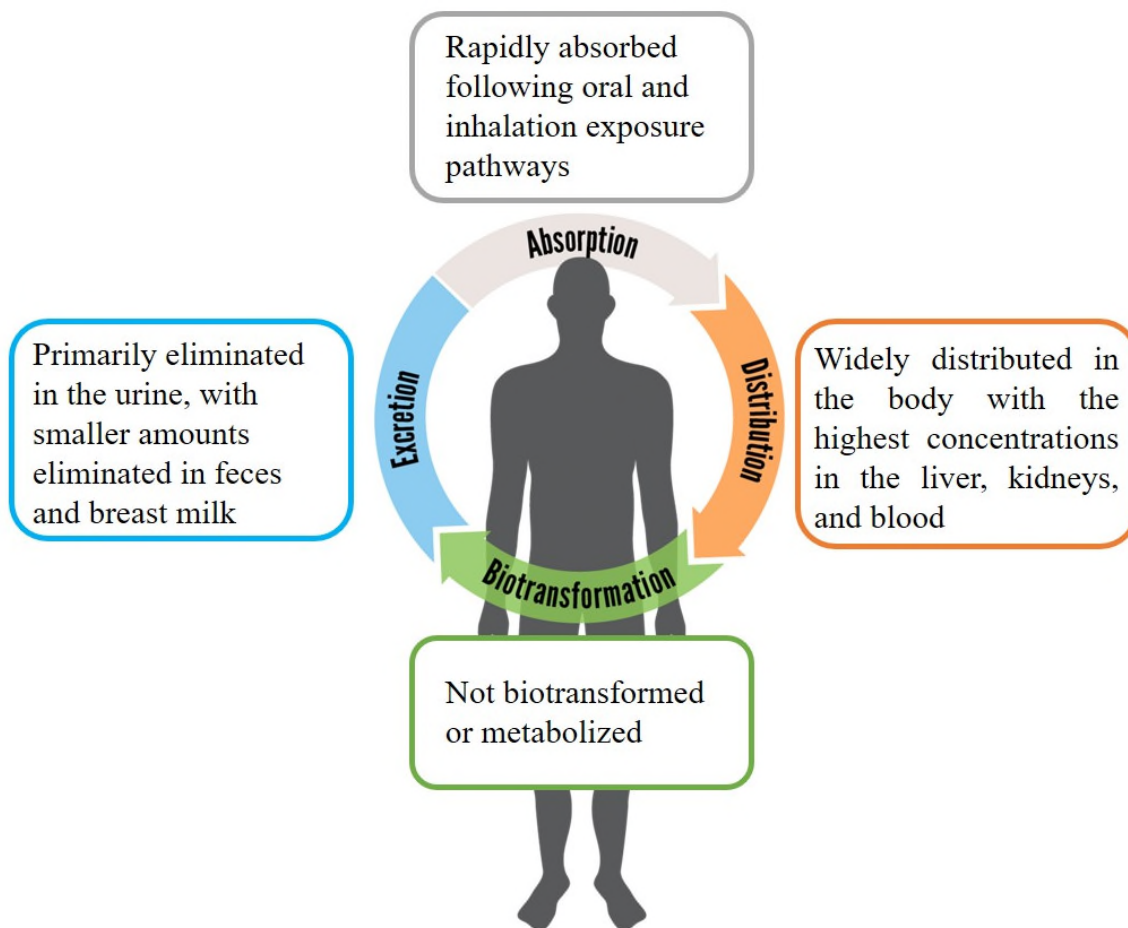
concentrations are found in the liver and kidneys, but the mechanism of transfer from the blood to soft tissues, in particular the liver, has not been identified.⁽²⁾ Of note, it has been shown that PFAS can pass the placental barrier during pregnancy; however, long-chain lengths that contain a sulfonate group notably do not pass as readily.

Biotransformation: Experimental studies suggest that the 14 PFAS discussed in the recent ATSDR toxicological profile are not chemically modified or metabolized within the body.

Excretion: PFAS are primarily eliminated via urine with smaller amounts eliminated in feces

and breast milk. The elimination half-life of PFAS compounds (the time it takes for the amount of PFAS in the body to be reduced by 50 percent) have been documented to be shorter in females than in males.⁽⁷⁾ PFAS have also been detected in excreted menstrual fluids, which may contribute to the sex differences observed in female and male PFAS serum concentrations. The chemical composition, chain length, and branching of the various PFAS chemical structures impacts the excretion rates of the individual PFAS. PFAS containing sulfonates, with greater chain length and branching, have the slowest elimination rates comparatively.

Figure 2: Overview of Toxicokinetics of PFAS. Image adapted from the U.S. National Library of Medicine⁽⁶⁾



While many of the underlying mechanisms involved in the toxicokinetics of the different PFAS are not completely known, differences have been observed among different PFAS. This variability stems from differential pharmacokinetic disposition and varying potency among PFAS. For example, chain length greatly affects serum elimination half-lives. Long-chain PFAS have long half-lives (years) within the body which allows for the possibility of bioaccumulation. Bioaccumulation of PFAS is of concern since it is not currently known whether a threshold dose at which these chemicals may be associated with critical health effects and/or disease development exists. It is more likely that a threshold concentration can be achieved when chemicals bioaccumulate over several years, thereby increasing potential increased risk of adverse health effects.

Toxicological Endpoints

Two general types of data may be used to derive drinking water guidelines: human data and animal data. Studies in humans and animals are inconsistent and inconclusive but suggest that certain PFAS may affect a variety of possible endpoints. Weighing and combining toxicity evidence from human studies, animal studies, and mechanistic studies is complicated. Ideally, these studies would use similar biologically effective doses and directly comparable health outcomes, with clear supporting information regarding the mode of action for toxicity in each species. Unfortunately, this is not a realistic expectation. Rather than expecting concordance of specific study outcomes across animals and humans, related outcomes are grouped broadly by organ or system and then human and animal evidence is compared to determine whether similar organs or systems are affected. For example, liver toxicity is a hallmark of PFAS exposure in rodents, and this is reinforced by increasing evidence that the liver enzyme changes observed in human studies may be attributed to PFAS exposures. It is unclear if the differences in toxicologic effects are species specific or related to dose differences; however, by evaluating similarities in observed endpoint effects in both animal and human studies, researchers can focus on specific target organs to

more precisely identify associations with PFAS exposure.

Human Epidemiology Studies

A wide range of health effects and their potential association with PFAS have been evaluated in numerous epidemiology studies, most of which focus specifically on exposures to long-chain PFAS, specifically, PFOA and PFOS. The three primary populations evaluated in the PFAS epidemiology studies include: 1) occupationally exposed workers at facilities involved in the production or use of PFAS, 2) communities living near a manufacturing facility with high levels of PFAS measured in the drinking water, and 3) populations exposed to background levels of PFAS compounds. Comprehensive reviews conducted by ATSDR and the EPA for PFAS compounds determined that the available epidemiological data suggest associations between PFAS exposures and the following health effects ⁽²⁻⁴⁾:

- Hepatic and metabolic toxicity:
 - Liver damage, as indicated by increased serum enzymes and decreased serum bilirubin (PFOA, PFOS, PFHxS)
 - Increased serum lipids, particularly total cholesterol and LDL cholesterol (PFOA, PFOS, PFNA)
- Reproductive and developmental toxicity:
 - Increased risk of decreased fertility (PFOA, PFOS);
 - Pregnancy-induced hypertension or pre-eclampsia (PFOA, PFOS)
 - Small decrease in birth weight (i.e., <20 g decrease per 1 ng/mL increase in serum PFAS concentration level) (PFOA, PFOS)
- Immunotoxicity:
 - Decreased antibody response to vaccines (PFOA, PFOS, PFHxS)
- Endocrine disruption:
 - Increased risk of thyroid disease (PFOA, PFOS)
- Tumor induction:
 - Increased risk of testicular and kidney cancer in highly exposed individuals

Most of the studies examining these populations are cross-sectional in nature and, therefore, lack the ability to establish causality. Moreover, although the epidemiologic data may provide evidence for an association, it does not imply that the observed effect is clinically meaningful because the magnitude of the change may be within the normal limits or not indicative of an adverse health outcome.

Inconsistencies in the epidemiological evidence are primarily due to the limited information regarding PFAS exposure, which is modeled in some studies to address a lack of exposure history. Since actual estimates of PFAS exposure (i.e., doses/duration) are not currently available, mean or median serum PFAS values are often used as a biomarker for exposure. Serum levels can be used as indicators for long-term PFAS exposure due to the lack of biotransformation and slow excretion rate. Because PFAS exposure is often measured as a biomarker in blood, and the health condition may also be based on a blood biomarker (e.g., serum uric acid, liver enzymes), there is the potential for reverse causality, when physiological change affects serum PFAS levels, rather than the PFAS levels causing the physiological effect. For example, it has been suggested that reverse causality may partially or totally explain the associations observed in the literature between PFAS exposure and decreased birth weight and kidney function.^(8,9) Of note, caution is necessary when examining human PFAS serum levels, since fluorotelomers can biotransform to long-chain PFAS after absorption (e.g., PFOA can be formed from the biotransformation of 8:2 fluorotelomer alcohol).⁽¹⁰⁾ Serum levels represent both direct and indirect exposures and make it more difficult to attribute a specific response to a specific exposure.

There is less epidemiological data available for short-chain PFAS because they are detected in blood serum less frequently than long-chain PFAS due to their more rapid excretion from the body. These short-chain PFAS were introduced in 2000 and the latency period, or duration of time required for an observed effect to manifest, may require decades for specific observed responses or disease development.

Animal Toxicology

The ATSDR reviewed 187 animal studies that examined PFAS toxicity using an animal model in the 2018 *Toxicological Profile for Perfluoroalkyls*. Currently, laboratory animal studies are available for 11 perfluoroalkyl compounds (PFOA, PFOS, PFHxS, PFNA, PFUA, PFBuS, PFBA, PFDeA, PFDoA, PFOSA, and PFHxA); however, the majority of the studies examined PFOA and/or PFOS. Seven types of toxicological effects associated with PFAS exposure have been identified using laboratory animal models: hepatic and metabolic toxicity, reproductive and developmental toxicity, immunotoxicity, endocrine disruption, neurotoxicity, obesogenicity, and tumor induction. These findings are based on well-controlled laboratory experiments, with wide dose ranges (but typically orders of magnitude higher than those observed in human exposure studies) and sometimes multiple species.

The various targets of toxicity identified in laboratory animals are similar to those observed in epidemiology studies. While the PFAS animal toxicology outcomes overlap considerably with the disease outcomes observed in the human epidemiology studies, the evidence from animal toxicology studies does not provide a definitive connection between the adverse health effects observed in animal studies and specific diseases in humans. This is due both to the relative scarcity of human health studies and also an inherent limitation in the ability to extrapolate from small studies of animals with high levels of controlled exposure to large studies of human populations with very low levels of uncontrolled, and often unknown, exposure. The hepatotoxic and metabolic effects, immunotoxicity, and developmental toxicity of PFAS are supported by the strongest weight of evidence in the human health studies, but their effects are subtle at low doses that are most relevant to environmental exposure. Carcinogenic effects of PFAS and their relevance to human health risks are less certain.

Table 1: Pertinent International and U.S. Drinking Water Standards (in ppt) (as of June 2019)

Agency	Standard/Guidance	PFOA	PFOS	PFNA	PFHxS	PFHpA	PFDA	PFBA	PFBS	GenX
WHO	Health-Based Guideline	4000	400							
EPA	Health Advisory	70	70							
CT	Action Level	70	70	70	70	70				
MA	Proposed Health Advisory	20	20	20	20	20	20		2000	
MI	Screening Criteria	8	16	6	51				420	370
MN	Health-Based Guidance	35	15		47			7000	3000	
NH	Proposed MCL	12	15	11	18					
NJ	Proposed MCL	14	13	13						
NY	Proposed MCL	10	10							
NC*	Health Goal									140
VT	Health Advisory	20	20	20	20	20				

*NC adopted EPA health advisory levels for PFOA and PFOS.

Shaded cells indicate the value for which the sum of the shaded PFAS are not to exceed.

MCL = Maximum contaminant level

Current Regulatory Advisories/Standards

Currently, there are no federally-developed enforceable drinking water standards for PFAS in the U.S. In 2009, EPA adopted a *provisional* health advisory level of 400 ppt and 200 ppt for PFOA and PFOS, respectively, in drinking water. In May 2016, the *provisional* health advisories were revised and EPA adopted a lifetime drinking water health advisory of 70 ppt for PFOA or PFOS individually or combined (the sum of both measured concentrations). In lieu of a federally-developed enforceable standard, individual states have developed their own drinking water standards. The EPA, ATSDR, and a variety of states have determined advisory levels ranging from around 8 to 70 ppt for PFOA, PFOS, or the sum of PFOA and PFOS in drinking water. Some states are also developing guideline levels for other PFAS. Internationally, the World Health Organization (WHO) published a health-based

guideline for PFOA of 4,000 ppt and 400 ppt for PFOS in 2017. Individual countries have also established regulatory or guidance concentrations for PFAS which are not discussed herein. The WHO and national regulations, advisories, and guidelines regarding PFAS in drinking water are summarized in Table 1.

Key risk assessment issues in development of guidelines

As depicted in Table 1, there is up to a 10-fold difference between the published advisory levels for PFOS and PFOA. This variation is related to limited and developing knowledge regarding the adverse health effects associated with PFAS exposure over time and largely reflects discordant risk assessment principles and practices among the various regulatory agencies. Specifically, the differences in these recommended limits reflect

selection of different critical health effects, target populations, uncertainty factors, and relative source of contribution. In short, the ambiguous association between PFAS and the conflicting data regarding associated adverse health effects has led regulators to select overly cautious and inconsistent attributes when calculating the maximum contaminant level (MCLs) for individual PFAS. Below is a discussion of common factors and decisions that influenced guideline development, with a focus on agencies that differed from those set by EPA. For all guidelines, we reviewed the publicly available risk assessment documents and toxicological summaries prepared by regulatory agencies through June 2019. (3,4,11-28)

Choice of Critical Health Effect

The typical risk assessment practice is to select the most sensitive outcome from a dose-response study, based on the lowest benchmark dose (BMD), no or lowest observable adverse effect level (NOAEL/ LOAEL), in conjunction with expert opinions on the biological plausibility or relevance of that particular outcome. The BMD approach has distinct advantages, and has become the preferred method by the EPA, because the modeled BMD reflects the shape of the dose-response curve and is less affected by the choice of experimental concentrations. However, the BMD approach requires a robust data set, which is not currently available for many of the emerging PFAS.

The determination of the critical health effect is seldom made based on the preponderance of evidence or convergence of findings from animal studies and epidemiological examinations, but rather is an artifact of the dosages chosen for study. The health effects which have been observed can be subtle, and in many cases, transient. Human epidemiology studies are generally preferred as the basis for toxicological guidelines when suitable data are available. Due to the limitations in the human toxicological database, however, animal studies have typically served as the basis for the derived reference dose (RfD) for the PFAS drinking water standards. The RfD is an estimate of the amount of a chemical a person can ingest daily that is unlikely

to lead to adverse health effects. Many of the studies of PFAS and adverse health effects in these animal studies focus on subclinical indicators of potential adverse health effects (e.g., liver enzymes, immunologic markers) and few address clinically significant disease (e.g., chronic liver disease, infection). The critical health effects selected for each PFAS evaluated were non-cancer endpoints in animals, including hepatotoxic and metabolic effects (PFOA, PFNA, PFBA, GenX), delayed development (PFOA, PFOS, PFNA), impaired reproduction (PFHxS), and immunotoxicity (PFOS, PFBS, PFHxS) (Table 2). The non-cancer endpoints of PFAS in the animal studies may be more sensitive (lower dose concentration) than cancer endpoints measured in human populations and thus may be more important for setting conservative regulatory limits. The hepatotoxic and metabolic effects, immunotoxicity and developmental toxicity of PFAS have the strongest associations in the human health studies, but their effects are subtle at low doses that are most relevant to environmental exposure. Interestingly, many of these regulators relied upon a single study indicating an outcome of interest, while choosing different critical effects from the same studies.

Of note, states identified in Table 1 that adopted a sum of multiple PFAS designation (i.e., CT, MA, and VT) relied on the RfD reported by the EPA Health Advisories for PFOA and PFOS. The States indicated that the additional PFAS were included in their guidelines because they share very similar chemical structures and the available data indicates they are likely to exhibit similar toxicities.

Determination of Critical Health Effects for Long-Chain PFAS

There appears to be little agreement among the state and federal agencies on the critical health effect endpoint for PFOA. The difference between the lowest health-based advisories for PFOA and the highest was primarily driven by different health effect outcomes chosen to derive the RfD. All but New Hampshire and New Jersey chose a developmental effect to derive their RfD; however, even among those agencies there was disagreement on which developmental effect was

Table 2: Summary of Critical Health Endpoints

Toxicological Endpoint	Agency
PFOA	
Hepatotoxicity ⁽²⁹⁾	NH, NJ
Developmental effects ⁽³⁰⁻³³⁾	ATSDR, EPA, MI, MN, NY
PFOS	
Developmental effects ⁽³⁴⁾	ATSDR, EPA, MI
Immunotoxicity ⁽³⁵⁾	NH, NJ, NY
PFNA	
Developmental effects ⁽³⁶⁾	ATSDR, MI
Hepatotoxicity ⁽³⁶⁾	NH, NJ
PFHxS	
Thyroid effects ^(37,38)	ATSDR, MI, MN
Reproductive effects ⁽³⁹⁾	NH
PFBA	
Hepatotoxicity ⁽⁴⁰⁾	MN
PFBS	
Thyroid effects ⁽⁴¹⁾	EPA, MI
Kidney hyperplasia ⁽⁴²⁾	EPA, MA, MN
GenX	
Hepatotoxicity ⁽⁴³⁾	EPA, MI, NC

the most appropriate. For example, the EPA and Minnesota selected reduced ossification of fetal mouse phalanges and accelerated onset of puberty in male offspring after gestational and lactational exposure as one of their drivers during derivation of the RfD for PFOA. This choice was challenged because reduced bone ossification reflects a developmental delay, rather than an induction of an anatomical defect. Alternatively, the ATSDR and Michigan chose neuro-developmental and skeletal effects while New York selected delayed mammary gland development as their critical health endpoints. It should be noted that although delayed mammary gland development appears to be the most sensitive endpoint in mice, both the EPA and ATSDR rejected it because the mode of action is not known and the effect may not represent an adverse functional consequence. New Hampshire and New Jersey, on the other hand, chose to use increased relative liver weight in male mice after subchronic exposure as their critical endpoint. Liver hypertrophy is a hallmark response of PFAS in rodent models; compounded with elevated incidence of fatty liver and necrosis noted at high doses of exposure, hepatotoxic

effects of PFOA are reasonably supported. It should be noted that compared to human levels, rodents have much higher levels of normally occurring liver enzymes known as peroxisome proliferator-activated receptor alpha (PPAR α), with the human liver expressing PPAR α levels approximately an order of magnitude lower than those in rodents. PPAR α is a transcription factor that regulates select liver functions and its overexpression in rodents may lead to toxicity values that may not be meaningful in humans.

Similar to PFOA, the difference between the lowest PFOS health-based advisories and the highest was primarily driven by the selection of different health effect outcomes. The EPA chose reduced rat pup weight at birth after gestational and lactational exposure as an outcome for PFOS. The choice of this developmental toxicity outcome is reasonable, as a systematic review of a similar chemical with the same chain length (PFOA) supported growth retardation as a consistent adverse effect. New Jersey, on the other hand, chose a different toxicological outcome of decreased plaque-forming cell response (an assessment of immune function).

The choice of immunotoxicity is supported by a National Toxicology Program systematic review of PFOA and PFOS, which indicated consistent findings in laboratory animals, as well as several epidemiological studies that reported associations between compromised immune responses and PFAS exposure in humans.⁽⁴⁴⁾ However, it should be noted that most of the available epidemiological data show no significant association between PFOA and PFOS exposure and infectious disease. Therefore, it is unclear if a change in immune response without a corresponding increase in infectious disease would represent truly critical health effects or rather transient, short-term effects. Further, it should be noted that other compounds, including PCBs, phthalates, and brominated flame retardants can have similar effects at similar concentrations.

Health-based advisories of several PFAS other than PFOS and PFOA, which include the long-chain PFNA and PFHxS, are available from different sources. New Hampshire and New Jersey chose increased maternal liver weight of mouse mothers at term after gestational exposure to PFNA as an endpoint. ATSDR and Michigan also evaluated the health risk of PFNA based on the same animal study used by New Hampshire and New Jersey, but they utilized a different endpoint of decreased body weight and developmental delays of the offspring after gestational and lactational exposure. To date, only ATSDR, Michigan, Minnesota, and New Hampshire have issued a health-based value for PFHxS. Increased incidences of thyroid cell hypertrophy, hyperplasia and damage observed in male rat offspring after gestational and lactational exposure to PFHxS was selected as the critical health effect by ATSDR, Michigan, and Minnesota. New Hampshire, on the other hand, has proposed an MCL for PFHxS based on reduced litter size (impaired reproduction) in female mice.

Determination of Critical Health Effects for Short-Chain PFAS

Health-based values for the short-chain PFAS, PFBA, PFBS, and GenX are available from

Massachusetts, Michigan, Minnesota, North Carolina, and the EPA. The driver for health risk evaluation of PFBA is obtained from a 28-day exposure study using rats, where reductions of serum cholesterol and thyroid hormones were observed. By comparison, the outcomes chosen for PFBS are obtained from a rat study where kidney epithelial and tubular/ductal hyperplasia were noted in a two-generation reproduction study. In its *Draft Toxicity Assessment for PFBS*, the EPA noted that the thyroid and kidney are particularly sensitive targets of PFBS-induced toxicity. In addition to requesting comment on an RfD derived using the same study and health effects associated with the kidney as used by Massachusetts and Minnesota, the EPA proposed to base the overall subchronic and chronic RfDs on both the thyroid and kidney health effects associated with oral exposure to PFBS. In addition to developing RfDs for PFBS, the EPA has drafted an oral RfD for GenX using an oral reproductive/developmental toxicity study in mice. While other effects were observed, effects on the liver were observed consistently across the animal studies. Therefore, the EPA chose the liver toxicity as the target outcome when choosing the critical health effect. Michigan and North Carolina chose the same health effect as EPA.

Dose Response Assessment

Although findings in animal toxicity studies are generally applicable to humans, the responses of laboratory animals and humans may differ quantitatively. As such, the animal dose must be converted to a human equivalent dose (HED), which is defined as the dose that would induce the same magnitude of toxic effects in humans as in the experimental animal species. The HED, rather than the administered dose, then serves as the basis for the point of departure used in developing health-based guidance levels. There are a number of quantitative methods for extrapolation of animal toxicity data to humans:

- 1) linear extrapolations based on body weight equivalence (allometric scaling);
- 2) chemical-specific information; and
- 3) physiologically-based pharmacokinetic (PBPK) modeling.

The largest discrepancy between international (e.g., WHO) and current U.S. federal and state health-based guidelines for PFAS is the methodology to determine the HED. Allometric scaling is a default adjustment that is utilized in the absence of chemical-specific information. It is based on the assumption that different species are equally sensitive to the effects of a substance per unit of body weight or body surface area. This method is widely accepted and has been utilized by international agencies as well as the EPA in their development of the 2009 Provisional Health Advisories for PFOA and PFOS. In general, this method has resulted in health-based guidance values for PFOA and PFOS one to two orders of magnitude higher than the current guidelines in the U.S. However, it does not take into account differences in chemical sensitivities, such as the liver enzyme response in rodents versus humans.

PBPK modeling was utilized in the derivation of the HED for the most recent 2016 EPA Health Advisories for PFOA and PFOS. PBPK modeling is a method that estimates human dosing based on equivalency in the blood levels in the experimental animal used to characterize the PFAS toxicity. When there is sufficient chemical-specific toxicokinetic information, it is recommended that this approach be used. PBPK modeling and chemical-specific approaches are information intensive and their application is usually limited to a few chemicals with a sufficient database. PBPK modeling is not without limitation or criticism. For example, it has been suggested that the EPA modeling approach ignored saturable uptake by the liver and intestine as well as efflux by the placenta and the brain for which the impact is unknown.⁽⁴⁵⁾

Choice of Target Population

When developing health-based advisories, exposure estimates are directed at protecting the most sensitive populations. To date, Michigan, Minnesota, North Carolina, and Vermont have used drinking water exposure factors to protect a child less than one year of age. It has been postulated that young children are the most at risk of the long-term effects from PFAS exposures because 1) the fetal and early childhood life

stages are still being established and developed, which often makes them less able to metabolize, detoxify, and excrete toxins, and 2) infants, children and pregnant women are often more heavily exposed because they consume more drinking water per unit body weight.⁽⁴⁶⁾ However, the duration of exposures during these critical developmental time periods are also the shortest. In contrast, EPA used drinking water exposure estimates to account for pregnant and lactating women when setting the PFOA and PFOS health advisory limits. Lactating women have the highest assumed rate of water intake of approximately 4.4 liters of water consumed per day for a 175 pound (approximately 79 kilogram) women, which is nearly four times the amount for the average adult of the same weight.⁽⁴⁷⁾ It should be noted though that although lactating women have higher drinking water exposures, they excrete PFAS at higher rates due to excretion during urination, fecal excretion, and lactation. Regardless, the use of the highest rate of water intake to calculate drinking water advisories and guidelines is expected to be safe for pregnant mothers and their fetuses, lactating mothers and their infants, and all children, adolescents, and adults. Instead of choosing a fixed ingestion rate from a single target population, Minnesota and New Hampshire utilized a transgenerational toxicokinetic model that estimates the serum concentration of PFAS due to drinking water exposure and consumption of breastmilk or formula across a lifespan starting at birth.⁽⁴⁸⁾ In contrast to traditional methodology of choosing the most sensitive target population to derive regulatory levels, this model accounts for bioaccumulation and transgenerational exposure incorporates body burden at birth (placental transfer), ingestion of breastmilk, and age-specific water intake rates.

Choice of Uncertainty Factors

The choice of uncertainty factors which are applied to convert the BMD, NOAEL or LOAEL to a RfD have generally followed defaults for interspecies (animal-to-human) and intraspecies (among the same species). In some cases, an additional adjustment was included to account for use of a LOAEL, subchronic to chronic extrapolations, and uncertainties in the database

and selection of a sensitive population. The relationship between the RfD and uncertainty factors is such that the larger the uncertainty, the smaller the RfD.

Knowledge about a chemical's mechanism of action is crucial for evaluating toxicity and relevance toward human health. Some mechanisms of action are unique to certain species or groups of animals and may have limited relevance to human health. To date, there is no known unifying mechanism of action for the wide-array of effects associated with PFAS. Based on current literature, the only demonstrated common target for PFAS appears to be the activation of the liver enzyme PPAR α . As noted above, PPAR α is overexpressed and more sensitive in rodents as compared to humans; therefore, the use of rodent-derived toxicity values based on PPAR α endpoints are three to 10 times more protective. As such, the interspecies uncertainty factor that is used to derive the human doses from these rodent studies may overestimate human sensitivity.

A major challenge in setting standards regulating human exposure to PFAS arises in extrapolating the exposure doses from laboratory animals to humans not only because of differing enzyme systems between the species, as described above, but also due to the profound differences in the rate of elimination of these chemicals between species. For example, there are significant differences in the excretion rates observed using the serum half-life estimates between rodents and humans for some of the PFAS, with half-lives in rodents estimated in days or hours and those in humans estimated in years. These large differences in elimination rates imply that similar PFAS dosages in rodents or humans would be expected to result in substantially different steady-state internal doses of these compounds in each species and in the various target organs within each species. In addition, exposure durations required to achieve steady-state would be expected to be much longer in humans than in rodents. Using an internal dose metric such as serum perfluoroalkyl concentration and PBPK models that can account for these differences in elimination rates can decrease the uncertainty in extrapolating from animals to humans. For

example, in 2016 EPA derived a human equivalent dose (HED) from the serum concentrations in animal studies that corresponded to the critical toxicological effect, thereby, allowing for the use of internal dosimetry at steady-state (rather than administered doses) and bypassing the species-specific toxicokinetic issue related to PFAS. This approach can account for these differences in elimination rates, thereby decreasing the uncertainty in extrapolating from animals to humans.

Choice of Relative Source Contribution

The relative source contribution, or RSC, is an estimation of the portion of a person's total exposure attributed to water consumption compared to their total exposure from other sources. An RSC of 100 percent means that exposure through drinking water is considered to be the only exposure of concern and that no other exposures exist, which is unlikely. Although older children may be exposed to PFAS through food and water similar to adults, young children have a higher risk of exposure to PFAS from carpet and upholstery treatments and cleaners, largely due to time spent lying and crawling on floors and furniture in their early years as infants/toddlers and greater frequency of hand-to-mouth contact. The health based values derived to date have assumed RSC values ranging from 20 to 50 percent. EPA guidance states that the highest (ceiling) RSC should be 80 percent while the lowest (floor) RSC should be 20 percent. If there are sufficient data to calculate an RSC, one should be calculated. However, it should be noted that if data exist to calculate an RSC, EPA guidance recommends using average exposure values, not high-end values (e.g., 95th percentile). If data are insufficient, EPA recommends using 20 percent as a default value.

Data Gaps and The Potential Impact of Emerging Science

While PFOS and PFOA have been extensively investigated, other PFAS compounds, including the short-chain substitutes, have not been thoroughly evaluated. There are several

Table 3: The relationship between various exposure factors and the MCL.

Selection Variable	Chosen Value	MCL	Example
Uncertainty Factor	↑	↓	Increasing the uncertainty from 30 to 300 results in a 10-fold decrease in the MCL, all other factors the same
Water Intake Rate	↑	↓	Using a rate for an adult vs. a lactating women results in nearly a 2-fold decrease in the MCL, all other factors the same
Relative Source Contribution	↑	↑	Increasing the RSC from 20% to 80% results in a 4-fold increase in the MCL, all other factors the same

consistent reports of several biological effects *associated* with PFAS exposure; however, a direct *causal* relationship between PFAS exposure and critical health outcomes has not been defined. Ongoing epidemiological studies, like those being conducted by the CDC/ATSDR, may reveal causally-related adverse health effects in humans, but it will be difficult, if not impossible, to identify a reference population with zero PFAS exposure. As such, the vast majority of the reliance materials for evaluating PFAS toxicity was, and will likely continue to be, generated using animal models.

Many areas of toxicity and exposure research on PFAS have not achieved scientific consensus; therefore, risk assessors make diverse choices reflecting regional variations in drinking water sources and industrial chemical usage. In large part, the differences between drinking water guidelines reflect responses to scientific uncertainty. As detailed above, health risk assessment requires multiple assumptions and estimates to predict a safe level of exposure for humans. These include identifying critical health effects, quantifying uncertainties, and selecting exposure parameters for the susceptible population. Table 3 highlights the effect of differences in certain exposure factors on the calculated MCL.

The environmental co-occurrence of multiple PFAS is a challenge for using epidemiological data to develop guideline levels for individual

PFAS. However, as described above, considering information from human biomonitoring and epidemiology adds important context to the risk assessment process. Particularly absent in the scientific literature are studies examining the toxicological and toxicokinetic interactions of multiple PFAS compounds.⁽²⁾ There is emerging evidence that suggests that various PFAS may affect similar organs and systems, but these effects occur at differing doses depending on experimental design and the relative potency of the individual PFAS. To our knowledge, a potential synergistic relationship between multiple PFAS has not been evaluated. To address this concern for mixture effects, several regulatory agencies have exercised a risk management strategy, instead of risk assessment, by assuming an additive effect and applying a combined standard for the sum total of multiple PFAS. While perceived as protective, this risk management strategy lacks a scientific basis as the combined toxicity of multiple PFAS is poorly understood. As of now, regulators have established drinking water standards for long-chain compounds at a lower concentration than drinking water standards for the short-chain compounds, and if regulations are adjusted to include “sum of” both long and short chain compounds, they may introduce an unrealistic and overly conservative standard for short chain compounds that is not supported by the scientific studies. It is likely that individual assessments of short-chain PFAS will result in higher drinking water levels as a result of shorter half-lives.

Conclusions

The EPA's toxicological assessments are influential in the state process. The lack of guidance has led to a large range of drinking water guidelines for multiple PFAS. For PFOA and PFOS, the tightening of the guidelines is not attributed to new toxicology findings, but rather to improved exposure research, advances in analytical measurement technologies, improved biomonitoring and toxicokinetic data, and epidemiological findings. Given the number of compounds belonging to the PFAS family, it is easy to assume that they would have similar potencies and effects in humans. However, since the underlying mechanism between the PFAS compounds and resultant potential toxicity has varied in some cases, different PFAS compounds may act differently. Although the toxicity research is incomplete, what is known currently suggests that these compounds as a whole should not be regulated as a group, but individually.

In the February 2019 *EPA Action Plan*, the EPA stated their intention to consider the development of an MCL for PFOA and PFOS, in addition to compiling information to determine if regulation for a broader class of PFAS is appropriate.⁽⁴⁹⁾ If the EPA goes through the process of developing MCLs for PFAS, GZA would recommend that they consider the following:

- Clinical relevance of more recently identified critical health endpoints, such as immunotoxicity;
- Recent criticisms on PBPK modeling assumptions used in the development of the 2016 EPA PFOA and PFOS health advisory levels;
- Consideration of exposure factors, such as water intake rate, which are representative throughout an individual's lifetime as opposed to choosing the most sensitive (and often the shortest) stage of life;
- The use of default uncertainty factors, given evidence suggesting that rodents are more sensitive to PFAS than humans (the default interspecies uncertainty factors used assumes the opposite); and
- The effects of different PFAS compounds in a mixture and the protectiveness or

overprotectiveness of "sum of" regulatory levels.

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