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Critical Review

Considerations and challenges in support of science and communication of fish consumption advisories for per- and polyfluoroalkyl substances

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Abstract

Federal, state, tribal, or local entities in the United States issue fish consumption advisories (FCAs) as guidance for safer consumption of locally caught fish containing contaminants. Fish consumption advisories have been developed for commonly detected compounds such as mercury and polychlorinated biphenyls. The existing national guidance does not specifically address the unique challenges associated with bioaccumulation and consumption risk related to per- and polyfluoroalkyl substances (PFAS). As a result, several states have derived their own PFAS-related consumption guidelines, many of which focus on one frequently detected PFAS, known as perfluorooctane sulfonic acid (PFOS). However, there can be significant variation between tissue concentrations or trigger concentrations (TCs) of PFOS that support the individual state-issued FCAs. This variation in TCs can create challenges for risk assessors and risk communicators in their efforts to protect public health. The objective of this article is to review existing challenges, knowledge gaps, and needs related to issuing PFAS-related FCAs and to provide key considerations for the development of protective fish consumption guidance. The current state of the science and variability in FCA derivation, considerations for sampling and analytical methodologies, risk management, risk communication, and policy challenges are discussed. How to best address PFAS mixtures in the development of FCAs, in risk assessment, and establishment of effect thresholds remains a major challenge, as well as a source of uncertainty and scrutiny. This includes developments better elucidating toxicity factors, exposures to PFAS mixtures, community fish consumption behaviors, and evolving technology and analytical instrumentation, methods, and the associated detection limits. Given the evolving science and public interests informing PFAS-related FCAs, continued review and revision of FCA approaches and best practices are vital. Nonetheless, consistent, widely applicable, PFAS-specific approaches informing methods, critical concentration thresholds, and priority compounds may assist practitioners in PFAS-related FCA development and possibly reduce variability between states and jurisdictions. *Integr Environ Assess Manag* 2024;00:1–20. © 2024 The Author(s). *Integrated Environmental Assessment and Management* published by Wiley Periodicals LLC on behalf of Society of Environmental Toxicology & Chemistry (SETAC).

KEYWORDS: Fish consumption advisories; Fish sampling; PFAS; Risk assessment; Risk communication

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INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) are a class of synthetic chemicals that are the subject of growing research and regulatory scrutiny due to their widespread usage and occurrence, environmental persistence, and toxicity. While the definitions of PFAS vary, current research and regulatory actions have focused on compounds that have been

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produced since the 1930s and incorporate a fully or partially fluorinated alkyl chain that imparts hydrophobicity, coupled with a hydrophilic functional group (Buck et al., 2011; Gaines et al., 2023; Organisation for Economic Cooperation and Development [OECD], 2018; Wallington et al., 2021). The amphiphilic nature of PFAS combined with remarkable molecular stability make these chemicals useful in many diverse industrial and commercial applications. These characteristics also contribute to their environmental persistence and subsequent detection in nearly all environmental and biological matrices sampled worldwide including air (Saini et al., 2023), surface waters (Podder et al., 2021), groundwater (Xu et al., 2021), soils and sediment (Brusseau et al., 2020), wildlife (Nakayama et al., 2019), and human tissues (Jian et al., 2018).

For humans, the major routes of PFAS exposure include ingestion from food and water, dust, and hand-to-mouth contact (Agency for Toxic Substances and Disease Registry [ATSDR], 2021), although the contributions from air and dust inhalation or dermal absorption are not as well characterized (De Silva et al., 2021). Dietary ingestion is the predicted dominant pathway among the general population, with the consumption of freshwater and marine fish and shellfish (hereinafter collectively referred to as "fish") being a primary source of PFAS for those without exposure from contaminated drinking water or occupational exposures (Augustsson et al., 2021; European Food Safety Authority [EFSA], 2020; Sunderland et al., 2019). Several monitoring efforts in the United States have detected PFAS in the edible tissues of farmed and wild-caught fish from freshwater, estuarine, and marine environments, with edible tissues from freshwater fish containing the highest observed concentrations (Barbo et al., 2023; Christensen et al., 2017; Giffard et al., 2022; Pickard et al., 2022; Pulster et al., 2022; Ruffle et al., 2020; Stahl et al., 2023; Young et al., 2022). Yet, inter- and intraspecies differences within the same body of water and regional differences can lead to significant variations in tissue PFAS burdens (Ankley et al., 2021). For example, a synthesis of multiple USEPA datasets from across the United States found that the median levels of total PFAS concentrations across multiple freshwater fish species collected in urban locations were almost three times higher compared with those collected from nonurban settings (Barbo et al., 2023).

Some fish contain unsafe chemical concentrations that prompt federal, state, tribal, or local entities in the United States to issue fish consumption advisories (FCAs or advisories). At a national level, USEPA and FDA offer recommendations about fish consumption to reduce mercury exposure (USEPA, 2024a). Additionally, all 50 states and territories issue FCAs to encourage safer consumption of locally caught fish containing chemicals of concern. Such advisories are typically framed in response to measured or estimated tissue concentrations of bioaccumulative contaminants (e.g., mercury, dioxins, polychlorinated biphenyls) and recommend safe meal consumption frequencies for fish from a specified waterbody (USEPA, 2023b). In the absence of national FCAs for PFAS, several states, alone or in collaboration, have issued their own consumption guidelines for one or several PFAS (Maryland Department of the Environment, 2021; Michigan Department of Health and Human Services [MIDHHS], 2023; North Carolina Department of Health and Human Services [NCDHHS], 2023; New Hampshire Department of Environmental Services [NHDES], 2021). Many current PFAS advisories focus on one frequently detected PFAS known as perfluorooctane sulfonic acid (PFOS; Figure 1). However, there can be significant variation between tissue PFAS concentrations that determine state-issued FCAs, referred to as trigger concentrations (TCs), with TCs between states or waterbodies differing by two orders of magnitude in some cases; this results in significant variation in the resulting recommended consumption frequencies. This disparity creates challenges for risk communication and efforts to protect public health. Advisories based on only PFOS likely also underestimate exposures to other bioaccumulative PFAS of potential concern.

A recent session at the 43rd North America Society of Environmental Toxicology and Chemistry (SETAC) conference focused on the challenges involved with deriving PFAS-related FCAs (Pulster et al., 2023). The present review summarizes the session discussions on addressing existing challenges, knowledge gaps, and needs related to issuing FCAs for PFAS. The challenges discussed herein include (1) the current state of the science and the variability influencing numerically derived FCAs; (2) sampling and analytical methodologies used for generating FCAs; and (3) key risk management, risk communication, and policy challenges for PFAS-related FCAs.

NUMERICALLY DERIVED FCAs

Federal, state, tribal, and local entities in the United States typically use an equation consisting of four key parameters, with inherent assumptions, for the risk-based derivation of daily, weekly, or monthly trigger tissue concentrations to determine FCAs (Cleary et al., 2021; Scherer et al., 2008; Smith & Sahyoun, 2005; USEPA, 2000) (Figure 2). These can be targeted for the entire population or different FCAs can be issued for high-risk or vulnerable populations (i.e., women of childbearing age, young children, and certain ethnic groups). To date, several states have issued FCAs for PFAS, although the respective TCs and the number of waterbodies subject to advisories are in flux. A map of the US states and territories with existing FCAs and TCs for PFOS are provided in Figure 1. However, there is no central repository actively tracking information about the calculation of PFAS FCAs or associated TCs across the United States, nor are there repositories for FCAs of other chemicals. The Environmental Council of States and the Interstate Technology and Regulatory Council are interstate entities that publicly share PFAS-related information and have recently compiled an informal list of current PFAS FCAs for participating states (Hughes, 2023; Interstate Technology & Regulatory Council [ITRC], 2022).

The generic TC equation is presented in Figure 2, where TC is the trigger concentration. Toxicity factors can either be

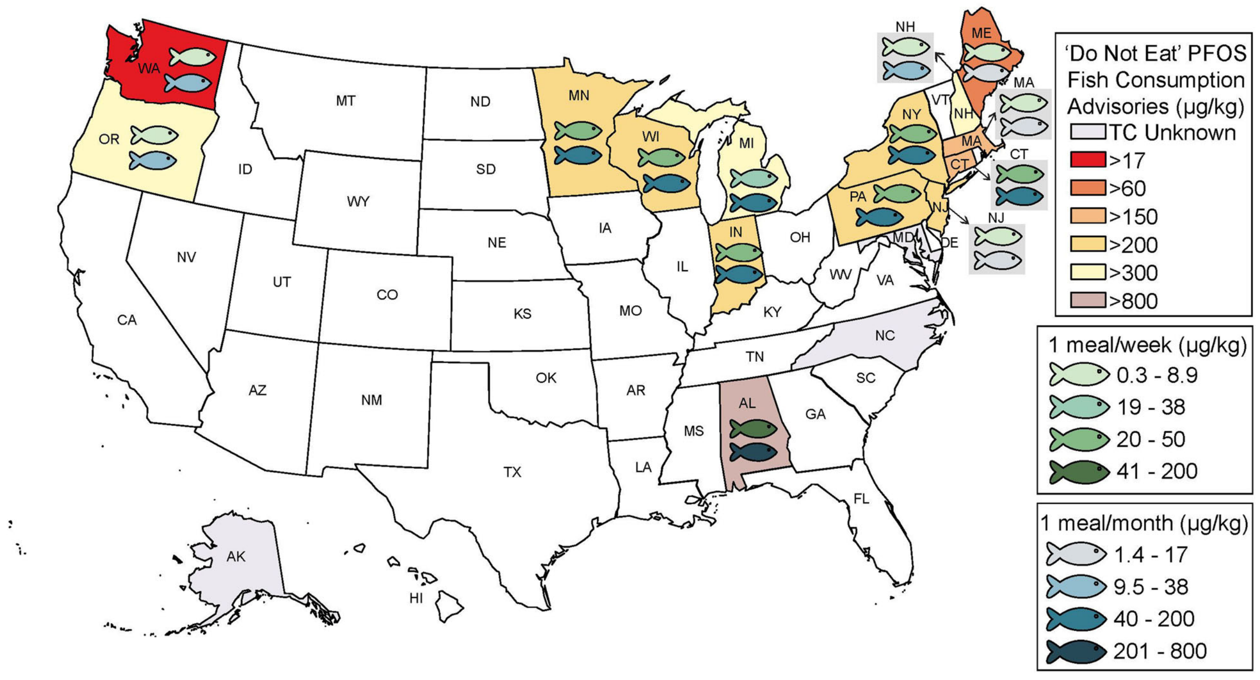
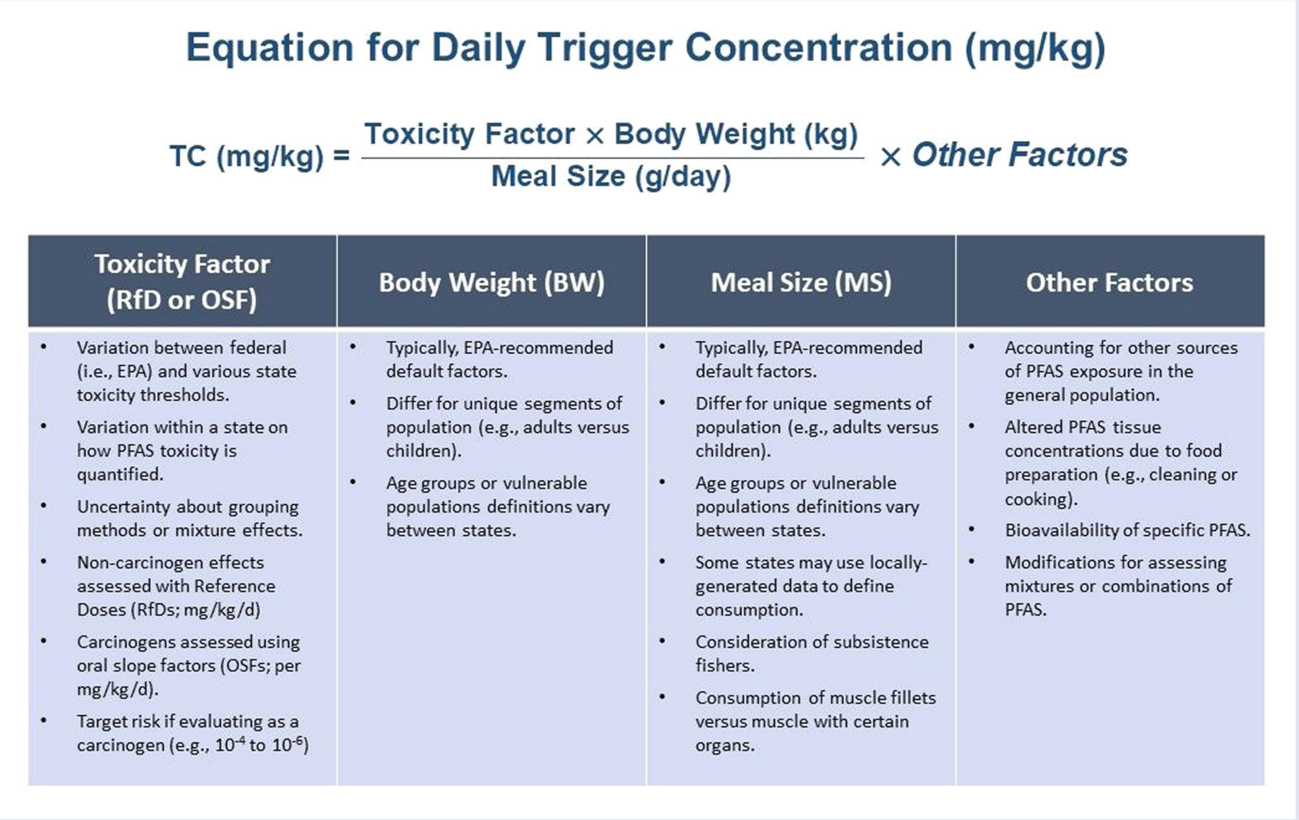


FIGURE 1 Map for edible fish species depicting the variation in available "Do Not Eat" (shaded state) and meal frequency (shaded fish icon) fish consumption advisories (FCAs) for perfluorooctane sulfonic acid (PFOS) in the United States. Unknown trigger concentrations (TCs) are depicted and shaded in gray for those states that have FCAs but do not list the TCs used in their calculations. States without any available FCAs are not shaded


Equation for Daily Trigger Concentration (mg/kg)

$$\text{TC (mg/kg)} = \frac{\text{Toxicity Factor} \times \text{Body Weight (kg)}}{\text{Meal Size (g/day)}} \times \textit{Other Factors}$$

Toxicity Factor (RfD or OSF)	Body Weight (BW)	Meal Size (MS)	Other Factors
• Variation between federal (i.e., EPA) and various state toxicity thresholds. • Variation within a state on how PFAS toxicity is quantified. • Uncertainty about grouping methods or mixture effects. • Non-carcinogen effects assessed with Reference Doses (RfDs; mg/kg/d) • Carcinogens assessed using oral slope factors (OSFs; per mg/kg/d). • Target risk if evaluating as a carcinogen (e.g., 10^{-4} to 10^{-6})	• Typically, EPA-recommended default factors. • Differ for unique segments of population (e.g., adults versus children). • Age groups or vulnerable populations definitions vary between states.	• Typically, EPA-recommended default factors. • Differ for unique segments of population (e.g., adults versus children). • Age groups or vulnerable populations definitions vary between states. • Some states may use locally-generated data to define consumption. • Consideration of subsistence fishers. • Consumption of muscle fillets versus muscle with certain organs.	• Accounting for other sources of PFAS exposure in the general population. • Altered PFAS tissue concentrations due to food preparation (e.g., cleaning or cooking). • Bioavailability of specific PFAS. • Modifications for assessing mixtures or combinations of PFAS.

FIGURE 2 Example of the formula and key parameters or factors typically used by US state and federal public health agencies when deriving fish consumption advisories for contaminants (USEPA, 2000) and the associated challenges or sources of uncertainty for each parameter with examples of per- and polyfluoroalkyl substances (PFAS)-specific considerations for other factors

oral reference doses (RfDs) for noncancer effects or oral slope factors (OSFs) for carcinogens, BW is the body weight (kg), meal size (kg/day) represents an estimate of a typical portion size for the target population, and other factors are used to account for different uncertainties or exposure-related adjustments (USEPA, 2000). This equation is used to determine the fish tissue concentration of a chemical that would exceed an allowable target dose if consumed as part of a typical meal size. In general, this numeric approach is almost always deterministic, using a single value for the exposure assumptions (body weight and meal size) and toxicity factor to establish a single threshold concentration for the chemical(s) being evaluated for a given waterbody or region. For PFAS, this deterministic framework presents challenges for recommending FCAs as (1) the critical health effects and relevant life stages differ for existing toxicity factors, (2) PFAS in fish tissues exist as mixtures of precursor PFAS, terminal PFAS such as perfluoroalkyl acids (PFAA), and other unquantified PFAS analytes, (3) standard exposure assumptions including consumption patterns and relative source contribution (RSC) may be mismatched with the populations that they are intended to protect, and (4) there is uncertainty about the effect of food preparation and other processes on the final concentrations in consumed tissue.

Toxicity values for individual PFAS

A number of government agencies and state health agencies have developed draft or final toxicity values for noncancer (RfD) and cancer (OSF or CSF) health endpoints for PFOS and perfluorooctanoic acid (PFOA) as well as for other PFAS (Ali et al., 2021; ATSDR, 2021; EFSA, 2020; Massachusetts Department of Public Health [MADPH], 2023a; MIDHHS, 2021; Post, 2021; USEPA, 2021a, 2023d). These oral toxicity values are an input value for a number of health-based criteria including FCAs and human health drinking water criteria, which have received considerably more attention than FCAs (Post, 2021). Briefly, RfDs for PFOS and PFOA may be derived using different critical toxicity endpoints or different uncertainty factors. Current health assessments proposing RfDs or comparable values (e.g., minimal risk levels [MRLs] or tolerable daily intakes [TDI]) of either PFOS or PFOA support health effects including liver toxicity, altered lipid metabolism, reduced immune system function, altered thyroid hormone function, developmental toxicity (e.g., birth weight impacts), and cancer (ATSDR, 2021; EFSA, 2020; Post, 2021; USEPA, 2016b, 2016c, 2024f). There are also health or toxicity assessments for other PFAS that have been frequently detected in fish, such as perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUnDA), as well as certain short-chain PFAA that are less frequently detected in fish tissues like perfluorobutane sulfonic acid (PFBS), perfluorobutanoic acid (PFBA), and perfluorohexanoic acid (PFHxA) (Ali et al., 2021; ATSDR, 2021; EFSA, 2020; MADPH, 2023a; MIDHHS, 2021; Post, 2021; USEPA, 2021a, 2023d). For example, New Jersey has developed TCs for four PFAS (PFOS, PFOA, PFNA, and PFUnDA) under a variety of consumption frequencies and for both general and high-risk populations (Goodrow et al., 2020; Toxics in Biota Risk Subcommittee, 2022). The bioaccumulative nature of certain PFAS, such as PFOA, PFOS, and PFUnDA, results in persistent elevation of internal (i.e., serum) doses following ingestion of PFAS-contaminated food or water; therefore, these chemical-specific RfDs are calculated to provide protection from chronic exposure.

As a part of current efforts to establish PFAS National Primary Drinking Water Regulation (NPDWR) under the Safe Drinking Water Act (SDWA), the USEPA's Office of Water released finalized toxicity assessments of both cancer and noncancer health effects for PFOA and PFOS. These toxicity assessments systematically reviewed the noncancer literature according to recently published EPA systematic review methods to derive draft noncancer RfDs, resulting in updated values that are orders of magnitude lower than EPA's 2016 values (USEPA, 2016a, 2016b, 2016c). The current EPA 2024 assessments reflect the additional recent scientific information published since 2016 and consider available epidemiological studies quantitatively (USEPA, 2024c, 2024d). The 2016 noncancer RfDs for PFOA and PFOS were based on critical effects observed in animal studies with different uncertainty factors, whereas the 2024 noncancer RfDs are based on critical effects observed in human epidemiological studies (USEPA, 2024c, 2024d). These assessments found that co-critical effects for PFOA include developmental, cardiovascular, and immune outcomes, whereas co-critical effects associated with PFOS are developmental and cardiovascular health outcomes. The noncancer RfD for PFOS (rounded to 1×10^{-7} mg/kg/day or 0.1 ng/kg/day) (USEPA, 2024c) is significantly lower than the previous EPA RfD of 20 ng/kg/day (USEPA, 2016b, 2016c) or RfDs developed by several states (reviewed by Post, 2021), attributable to reliance on newer studies and epidemiologic studies as compared with the animal studies. Application of this RfD may have a significant impact on establishing FCAs if used when evaluating other ingestion-related exposure to PFOA or PFOS aside from drinking water, potentially resulting in TCs lower than fish tissue concentrations measured across the United States (Dell et al., 2023; USEPA, 2024c, 2024d).

For agencies that recommend FCAs based on cancer risks, the USEPA's reclassification of PFOA and PFOS as *likely carcinogens* along with more protective OSFs may also trigger new or updated FCAs depending on acceptable cancer risk tolerance (USEPA, 2024c, 2024d). Policy decisions such as acceptable risk levels, notably for cancer risk endpoints, also vary between jurisdictions by orders of magnitude from one-in-ten thousand (10^{-4}) to one-in-a million (10^{-6}), which is a significant driver of differences in FCAs between certain jurisdictions (Cleary et al., 2021). As reviewed by Cleary et al., there is typically limited information as to how varying acceptable risk levels are derived and interpreted across jurisdictions (Cleary et al., 2021).

Assessing mixtures of PFAS

Fish consumption advisories are usually based on estimates for individual chemicals rather than addressing classes or mixtures of chemicals; this singular approach contrasts with the environmental occurrence of PFAS, which occur as complex mixtures. In nearly all fish tissues sampled to date, PFOS is detected with the greatest frequency and concentration (Barbo et al., 2023; Knutsen et al., 2018; Munoz et al., 2022); however, other PFAS classes including long-chain PFAAs, ether-based PFAS, and sulfonamido precursors that can transform into PFAAs are also frequently detected in fish tissue (Pickard et al., 2022). The potential for adverse health effects following co-exposure to mixtures of these other PFAS is a concern, given their increased detection in biota and structural similarities to PFAS with established toxicity factors. While some national guidance for FCAs suggests approaches for estimating exposure from contaminant mixtures of other chemicals (USEPA, 2000), this information lacks definitive or current guidance specific for a chemical class as complex as PFAS.

Debate over the use of existing qualitative and quantitative toxicity data has resulted in different applications of grouping methods for PFAS. Some public health agencies have applied a summation approach for drinking water protection that assumes additive toxicity of each PFAS included in the advisory and equivalent toxicological potency (reviewed by Post, 2021). This approach is consistent with fish advisory guidance from USEPA that says, “In the absence of quantitative information on interactive effects, these guidelines suggest the use of an additive approach to evaluation of chemical mixtures for carcinogens and for noncarcinogens that are associated with the same adverse health endpoints” (USEPA, 2000). Outside of the United States, the Ontario Ministry of Environment, Conservation and Parks has developed FCA benchmarks (i.e., TC) for the summation of 13 measurable PFAS at 63 nanograms total PFAS per gram fish tissue (ng/g). In most cases, they determined that PFOS accounted for nearly 90% of the total PFAS, and an advisory concentration of 70 ng total PFAS/g fish tissue (Satyendra Bhavsar, Ontario Ministry of the Environment, written communication, 09/12/2023).

While the relative simplicity of the additive approach is attractive, it has had mixed acceptance by US public health agencies because of differences in toxicokinetics (e.g., physiological half-lives) between PFAS chemistries (Anderson et al., 2022). Application of a hazard index (HI) is a modified additive approach to addressing mixtures of noncarcinogens that requires individual toxicity factors for the chemicals in question (USEPA, 1999). While this approach can reduce uncertainty of the additive approach by accounting for differences in PFAS toxicokinetics, it is limited to PFAS for which there is adequate information to develop noncancer toxicity factors (e.g., RfDs). The USEPA recently applied the HI approach in development of maximum concentration levels in drinking water for drinking water protection that includes four PFAS based on noncancer effects (GenX, PFBS, PFHxS, and PFNA) (USEPA, 2024b). Perfluorooctanoic acid and PFOS were omitted from this proposed HI grouping due to potential reclassification of these two PFAS as carcinogens and because PFOA and PFOS exposure levels at which health effects are expected to occur are well below current analytical feasibility (USEPA, 2024c, 2024d). Adoption of additive risk assessment approaches by regulatory bodies developing FCAs remains uncommon, while such an approach is utilized by some research studies to characterize the combined risks of measured PFAS in fish tissues (He & Ren, 2022) and other biological samples (Bil et al., 2023; Brown et al., 2020).

An established approach to developing FCAs for a complex class of chemicals (e.g., dioxin-like chemicals) is the application of relative potency factors (RPFs) (USEPA, 2023c, 2023e). Relative potency factors are used to create a summation for chemicals with the same toxic mode of action where the relative toxicity of the individual chemicals has been quantified. The RPF approach also assumes additive toxicity and similarity in dose–response relationships. Application of this approach is a barrier for PFAS mixtures as the modes of action and relative toxicity for the majority of PFAS remain uncertain, with no clear agreement within the scientific community. USEPA guidance posits that dose additivity interpretation can be relaxed to the level of receptor toxicological similarity in the absence of mode of action data and applied in component-based mixture assessment methods (USEPA, 2000, 2023c). This approach (i.e., relying on common health domains) was supported by the EPA Science Advisory Board during review of recently drafted USEPA guidance discussing approaches to PFAS mixtures (USEPA, 2023c, 2023e). In the research sphere, RPFs were developed for 22 PFAS relative to PFOA potency for adverse effects on the liver (Bil et al., 2021; Zeilmaker et al., 2018) but have not been developed for more sensitive developmental endpoints used for RfDs. While the RFP approach was developed for the National Institute for Public Health and the Environment in the Netherlands, it has not been used to set US federal- or state-level consumption guidance in the United States (Bil et al., 2021; Zeilmaker et al., 2018).

How to best address PFAS mixtures in the development of FCAs, in risk assessment, and establishment of effect thresholds remains a major challenge, as well as a source of uncertainty and scrutiny. While Martin et al. (2003b) found broad-based literature support for the default assumption of dose additivity for estimating mixture effects of diverse chemical classes, some whole-organism toxicity studies focused specifically on mixture effects of PFAS suggest potential additivity, others do not, and most existing studies focus on commonly detected PFAS (i.e., PFOS and PFHxS) as binary mixtures (McCarthy et al., 2021). Overall, debate remains around the most appropriate evidence-based approach to address exposure to PFAS mixtures (Anderson et al., 2022; Deepika et al., 2022; Goodrum et al., 2021; Rosato et al., 2022), as relevant through fish consumption.

Exposure factors and vulnerable populations

Many agencies evaluate risk for three target groups, with some degree in variability in how these are exactly defined, which include general population adults, women of childbearing age, and young children. Exposure factors, such as body weight and meal size, vary between these groups and influence the final FCA for any chemical. Default values for exposure factors are often used when deriving FCAs in the United States that are based on the trigger point calculation presented in Figure 2 and reflect recommended values from either the USEPA or Agency for Toxic Substances and Disease Registry (ATSDR, 2023; USEPA, 2000, 2014a, 2014b). The default exposure factor values applied vary between jurisdictions and influence the resulting FCAs.

A recent survey of PFAS FCAs issued in 46 US states (Cleary et al., 2021) identified that assumptions about average body weight range from 60 to 80 kg for the general population, 60 to 70 kg for women of childbearing age, and 11.6 to 35 kg for young children (median 15 kg). Similarly, meal size values for the general population and women of childbearing age range from 113 to 283 g/meal and range from 39 to 116 g/meal for young children. Presently, the most protective advisories target young children and women of childbearing age, with advisories for the general population being potentially less protective (Binnington et al., 2014; Scherer et al., 2008). Default exposure factor values in risk equations may not reflect individuals whom the FCA ultimately seeks to protect as localized fish consumption patterns, body weight, and other sociodemographic factors may not be readily available (von Stackelberg et al., 2017). This challenge is amplified when considering that vulnerable populations, such as individuals who are high-frequency consumers of fish and self-harvested seafood, are inherently difficult to survey but likely differ in relevant exposure factors (von Stackelberg et al., 2017). While tailored FCAs can improve public health protection for vulnerable populations, they can also cause confusion among consumers who may compare FCAs to those in other towns or states.

Implementation of FCAs carries a risk of disproportionate impacts on certain populations based on ethnicity, age, sex, and socioeconomic status. Fish consumption rates vary widely along these axes of identity, and consumption reduction may not be an acceptable economic or cultural option for many ethnic groups. For example, in a study of anglers in New York, primarily African American, referred to as "urban anglers," Karen and other Burmese participants displayed elevated serum levels of PFOS and PFDA compared with the NHANES 2015–2016 cohort as a reference for a background exposure in the US adult population, whereas the urban angler population did not have significantly higher PFAS serum levels compared to the same reference population. Having a better understanding of fish consumption rates and frequencies is particularly important for these communities and Indigenous communities that may have a higher than average consumption of fish (Fraley et al., 2020). Such examples inherently raise questions about environmental justice and equity, especially given the USEPA current interests under its Environmental Justice initiatives (USEPA, 2023a). The USEPA offers general guidance about designing and conducting surveys to best characterize contemporary fish consumption rates, including high-frequency consumers, but there remains a lack of PFAS-specific standardized guidance as to what specifically relates to risk assessment and regulatory processes for environmental justice efforts (USEPA, 1996, 2016d).

Nevertheless, when assessing human exposure from fish consumption, decisions about which factors are important to deriving an FCA should be tied to the specific consumer profile of the population that the FCA aims to protect. Using local or regional fish consumption data can provide valuable insight about actual exposures among the population of interest and provide useful information for sample collection (Terry et al., 2018). Access to this type of data will influence where and when to collect fish samples, which species to collect, target size of those species, and which tissue types should be measured (e.g., fillet, fillet with skin on, certain organs, or whole body). This is especially relevant for PFAS where differences in the occurrence and magnitude of contamination among fish species and harvesting locations necessitate nuance in development and public communication of PFAS-related FCAs.

Additional FCA factors

The TC equation can be further modified beyond the core equation described above by including variables for other chemical-specific considerations such as differential partitioning in tissues or multiple sources of exposure. One such modification to this standard formula is the inclusion of an apportionment factor to account for exposure to PFAS from sources other than fish consumption (i.e., water, dermal contact, inhalation). Dietary intake is estimated to be the predominant source of PFAS exposure among the general population relative to inhalation or dermal contact, but this can vary substantially across individuals (De Silva et al., 2021). In drinking water risk assessment, a factor used to account for other sources of exposure is referred to as the RSC (USEPA, 2000). An RSC of 20%, a USEPA default assumption, is used to estimate water consumption of PFAS, implying that upward of 80% of exposure to PFAS typically comes from other nondrinking water sources (Hu et al., 2019; Post et al., 2017; USEPA, 2016a), or up to 75% of the total exposure for those close to contaminated sites (Hoffman et al., 2011; Vestergren & Cousins, 2009). For fish and other seafood, the European Food Safety Authority estimates that up to 86% of total dietary exposures in adults exposed to PFOS may be due to seafood consumption (Knutsen et al., 2018). Application of an RSC improves the health protection of consumption guidance and has been used to develop FCAs in some states (e.g., 70%–80% applied by Maine and New Hampshire, respectively) (Ali & Larson, 2020; Maine Center for Disease Control and Prevention, 2022). To improve development and application of RSCs, the relative importance of different exposure sources across demographic groups and different populations is needed. Useful approaches include measurements of human serum concentrations of PFAS to identify predominant exposure sources using a chemometric approach or population survey data to assess consumption patterns and product usage across populations (Hu et al., 2018; Sunderland et al., 2019).

An additional and significant concern for PFAS exposure has been through fetal transfer and concentrations in human milk. As seen with drinking water, exposures that are acceptable for the direct health risks to a woman may present unacceptable exposures to fetuses or breastfed infants (Goeden et al., 2019; LaKind et al., 2023). This issue has been acknowledged for drinking water exposures (Goeden et al., 2019) and fish consumption relative to site-specific water quality criteria (Preimesberger, 2020), but has not been incorporated broadly into PFAS FCA derivation due to broader reliance on USEPA guidance. If this is addressed through exposure estimation components of the FCA calculation, existing exposure models (Preimesberger, 2020) might be applied to derive TCs that are protective to breastfed infants in addition to women of childbearing age.

Cooking and preparation of fish tissue is another factor that may influence FCAs. If cooking or preparation of seafood reduces the final concentrations of a contaminant in fish being consumed, a factor (e.g., proportion reduction) may be applied to the equation, resulting in more relaxed FCAs. While limited evidence suggests that different cooking methods such as frying or boiling might alter tissue PFAS concentrations in seafood by transfer of PFAS from tissues into cooking media such as sauces or oils, results are mixed (Chen et al., 2023; Sun et al., 2023; Taylor et al., 2019). Additionally, differences in PFAS composition across fish tissues complicate current conclusions about contaminant reduction by cooking method (Bhavsar et al., 2014). For many chemicals, this consideration is ignored in favor of a more conservative development of FCAs.

SAMPLING AND ANALYSIS CHALLENGES FOR PFAS IN FISH TISSUES

The challenges of fish sampling and PFAS determination that inform PFAS FCAs fall broadly into three main overlapping categories that involve analytical, biological, and environmental limitations. Analytical limitations may include the selection of compounds for FCA development and the associated instrumentational challenges (e.g., precursors, available standards, analytical methodology). Considerations such as the sampling design and statistical representations of analytical results can also complicate data interpretation. For purposes of this discussion, we define the biological limitations as an organism's physiological and ecological mechanisms (e.g., diet and phenology, species-specific metabolism, and human interventions on the population via stocking activities) and the interactions of these factors with chemical characteristics (e.g., solubility, partitioning behaviors) that may impact accumulation into edible tissues. Environmental challenges mainly include regional or temporal sampling considerations that affect interpretation and applicability of FCAs (e.g., seasonality, precipitation events, types of waterbodies, environmental transport).

Analytical challenges for FCA sampling

There are numerous analytical challenges to consider when measuring PFAS in fish tissues for determining FCAs. Table 1 provides a list of the various available analytical methods for the analysis of PFAS, precursors, and organic fluorine and their applicability for deriving FCAs. To date, PFAS FCAs are mostly derived based on PFOS concentrations measured using a targeted approach. However, the need to broaden the list of PFAS analytes has been recognized with increasing evidence of detectable levels of other PFAS such as sulfonamido precursors and PFAS mixtures in fish tissues (Munoz et al., 2022; Pickard et al., 2022; Ren et al., 2022; Young et al., 2022). Which PFAS to include in FCAs will be largely driven by the availability of toxicity data (i.e., defensible RfDs or OSFs) combined with standardized analytical methods that are applied to analyte lists based on availability of analytical standards and ability to achieve required detection limits. The availability of standardized analytical methods will likely have the greatest influence on which PFAS are analyzed and reported in fish tissues.

Updates to advisory levels, thresholds, or criteria for environmental matrices by regulatory agencies are creating a demand for increased capacity of state-of-the-art instrumentation that can measure a wide array of PFAS analytes and achieve parts per quadrillion (ppq) levels (Barbo et al., 2023; NCDHHS, 2023; USEPA, 2023e). Achieving these levels is challenging considering that the gold standard for targeted PFAS analysis is liquid chromatography tandem mass spectrometry (LC-MS/MS), which typically has detection limits in the parts per trillion (ppt) range. Public dissemination of USEPA Method 1633, which includes 40 PFAS analytes and other standardized and/or accredited methods with clear performance benchmarks, is a key step toward accurate, reproducible analytical measurements with appropriately low detection limits (USEPA, 2024e).

Currently available standardized targeted methods, such as the USEPA methods, still present challenges; the analytical method, instrumentation, sample matrix, and compound- and lab-specific detection challenges may all significantly influence the limits of detection and limits of reporting even within standardized methods. Additionally, the use of low-resolution mass spectrometry, which is the more commonly used and affordable approach for routine PFAS monitoring, is not without analytical problems. For instance, compounds present in fish tissue matrices (e.g., lipids, fatty acids, or other biological macromolecules) can interfere with PFAS signals in the mass spectrometer by mimicking the targeted PFAS ion transitions and fragmentation patterns (Bangma et al., 2021, 2023, 2024). If not recognized, this can lead to an inflated signal and, thus, inflated quantitated value for that analyte. In recent decades, investigations of PFAS in blood, serum, muscle, and other biological matrices have identified

TABLE 1 Various available analytical methods for the analysis of per- and polyfluoroalkyl substances (PFAS), precursors and organic fluorine, and their applicability for deriving fish consumption advisories (FCAs)

Analytical method	Method description	Analytical instrumentation	Method utility in the context of FCA derivation (yes/no)
Target analysis	Quantifies known analytes from a finite list of compounds; however, it does not provide a complete understanding of the full extent of contamination or potential for environmental transformations	Liquid chromatography tandem mass spectrometry (LC-MS/MS)	Yes: quantifies the current individual target analytes used for deriving FCAs (e.g., PFOS, PFOA)
Nontarget analysis (NTA)	Scans for unknown PFAS compounds that can help understand the full extent of the contamination	Liquid chromatography with high-resolution mass spectrometry (HRMS) using quadrupole time-of-flight (Q-TOF) or Orbitrap analyzers	No: Unknown PFAS may not have available standards for quantification and may not have available toxicity data
Total oxidizable precursor assay (TOP or TOPA)	Scans both target analytes and oxidizable precursors to provide insight into transformation potential and total contamination	Liquid chromatography tandem mass spectrometry (LC-MS/MS)	Yes: if the target analytes and precursors are quantifiable and have toxicity data
Total or extractable organic fluorine (TOF or EOF)	Quantifies the total or extractable organic fluorine in a sample but assumes that all fluorinated compounds are PFAS, which may overestimate the extent of contamination	Combustion ion chromatography (CIC); proton-induced gamma-ray emission (PIGE)	No: challenges in translating TOF/EOF data into risk assessment and assumes that all organic fluorine is PFAS

matrix-associated compounds that behave as interferents with quantification of PFAS in certain targeted methods (Benskin et al., 2007). Taurodeoxycholate is a bile acid and example of an interferent that has caused challenges for PFOS mass spectrometry/mass spectrometry (MS/MS) quantification using lower-resolution methods. This bile acid is extremely common in blood, eggs, and many other matrices, and may have resulted in some instances of overreporting of PFOS in prior studies. More recently, interferents have been observed for perfluorohexanesulfonate (PFHxS), perfluoropentanoic acid (PFPeA), and perfluorobutanoic acid (PFBA) in serum, placenta, shellfish, chocolate, and air conditioning condensate (Bangma et al., 2021; Bangma et al., 2023; Benskin et al., 2007; Chan et al., 2009; Genualdi et al., 2022; Kato et al., 2018). In the case where such interferents are anticipated for longer-chain PFAA (e.g., PFOS, PFHxS), increased analyte specificity and confidence in reported results can be achieved by including additional qualifying fragment ions, along with enhanced chemical separation with adjustments in solvents and selection of appropriate internal standards (Benskin et al., 2007; Chandramouli et al., 2010; Chandramouli, 2019). However, challenges may remain with shorter-chain PFAA that have limited fragmentation patterns, such as PFPeA, PFBA, perfluoropropionic acid (PFPrA), and trifluoroacetic acid (TFA), because these short-chain PFAAs yield only one MS/MS transition for quantification and lack any secondary transitions necessary for confirmation of the analyte. These shorter-chain PFAA are rarely detected in fish tissues at concentrations similar to their longer-chain counterparts due to their limited bioaccumulative potential. A more in-depth commentary on the existing analytical interferents, how to identify new interferents, and how to remove observed interferents in analytical methods has recently been published (Bangma et al., 2024).

Standard targeted mass spectrometry methods using low-resolution mass spectrometry also pose a major challenge for comprehensively assessing PFAS exposures because this approach can only assess a small fraction of the PFAS used in commerce and released to the environment. Nontargeted and bulk methodologies including suspect screening analysis, total oxidizable precursor (TOP) assay, and organic fluorine analyses are needed to more comprehensively characterize the extent of PFAS contamination (Table 1). A review of these methodologies is beyond the scope of this article, but these have been previously reviewed extensively (Al Amin et al., 2020; Ateia et al., 2023; De Silva et al., 2021; Gauthier & Mabury, 2022; John et al., 2022; Koch et al., 2020; Liu et al., 2019; Pickard et al., 2022; Ruan & Jiang, 2017; Shojaei et al., 2022; Smeltz et al., 2023; Strynar et al., 2023). Although each analytical method, both targeted and nontargeted, may have specific limitations, using multiple methods and analyses in combination will increase the understanding of the potential health impacts to organisms and the totality of exposure potential for fish consumers and thus will have important implications for calculating FCA TCs. Currently, FCAs focus on the limited analytes routinely monitored in environmental matrices using standardized targeted methods assessing predetermined analyte lists, though additional PFAS are frequently detected in fish tissues by studies using the aforementioned more inclusive methods (Pickard et al., 2022). These studies highlight the importance of staying apace as analytical progress continues to facilitate identification of new PFAS and their occurrence in the environment relevant for the establishment of updated FCAs.

Biological challenges for FCA sampling

Evidence suggests that PFAS bioaccumulation in aquatic organisms is directly related to carbon chain length, molecular weight, and chemical structure (i.e., functional groups). A recent review highlighted trends in bioaccumulation from water based on functional groups and carbon chain lengths for the most frequently studied PFAA and certain other PFAS classes, where sulfonic acid groups and longer carbon chain lengths contributed to increased accumulation in aquatic biota (Burkhard, 2021). A similar trend was observed in a review of PFAS bioaccumulation in shellfish, such as bivalves, crustaceans, and other invertebrates (Giffard et al., 2022). Burkhard & Votava completed a similar review of bioaccumulation from sediment, noting that biota-sediment accumulation factors (BSAFs) were greater for carbonyl and sulfonyl PFAS than other classes but were rarely greater than one (Burkhard & Votava, 2023).

Certain PFAS precursor classes may have potential for greater bioaccumulation than PFAA of similar carbon chain lengths (Han et al., 2021; Nouhi et al., 2018; Pickard et al., 2022; Rericha et al., 2022), and species-specific metabolism of these precursors can enhance exposures to the terminal PFAA and may bias estimated bioaccumulation factors (BAFs). Precursors with available analytical standards for quantitative assessment should be included in monitoring analyses to increase current knowledge on their abundance and bioaccumulative potential in fish tissues. As discussed under Analytical Challenges for FCA sampling, the absence of analytical standards for many of these precursors prevents accurate quantification of their concentrations in fish and remains a challenge for full exposure characterization. However, efforts to develop FCAs for quantifiable analytes can continue while methods and standards are being developed for precursors or newly identified analytes.

Certain physiological mechanisms and ecological interactions can influence PFAS concentrations to some extent (Ankley et al., 2021). Species-specific differences in uptake, elimination, metabolism, reproductive status, feeding strategy, and molt timing can influence accumulation in fish tissues (Bangma et al., 2022; Martin et al., 2003a). Several studies have focused on rainbow trout (*Oncorhynchus mykiss*) as a model species to understand these processes relative to PFAS. For example, absorption of PFAS from spiked diet experiments appears to be >50% (Lee et al., 2012; Martin et al., 2003b). Excretion studies in trout indicate longer half-lives for long-chain PFAS, especially the sulfonic acids (Consoer et al., 2016; Falk et al., 2015; Martin et al., 2003b), which is consistent with trends seen in BAFs. Additionally, maternal transfer of PFAS in fish has been well documented, where maternal tissue concentrations of select PFAS are reduced following egg production in trout and other species (Lee et al., 2017; Peng et al., 2010; Raine et al., 2021; Sharpe et al., 2010; Su et al., 2022). Of relevance to FCA guidance for whole fish or muscle fillets, there is significant distribution and assimilation into the liver, blood, kidneys, and skin tissues (Falk et al., 2015; Goeritz et al., 2013; Martin et al., 2003b; Sharpe et al., 2010), with lower relative accumulation of certain PFAS into muscle tissue (Falk et al., 2015). Review of data assembled by Burkhard (2021) from independent studies suggests significant differences between species. However, more work is needed to understand if these are true physiological differences or the result of the characteristic interaction between different species and their own habitat.

Given current evidence, the primary determinant of tissue contamination or PFAS body burden will be dictated by the degree of contamination in the organism's habitat, particularly the presence and concentration of bioaccumulative PFAS homologs (Sun et al., 2022). Flounder caught near a major aqueous film-forming foam (AFFF) source in Charleston Harbor SC had higher average total PFAS concentrations (24.1 ng/g) (Fair et al., 2019) than flounder caught in Narragansett Bay RI (2 ng/g), where there are fewer identified PFAS sources and potentially greater flushing (Hedgespeth et al., 2023). Similarly, fish sampled from industrialized areas or sites impacted by AFFF tend to have higher PFAS burdens than fish from more rural or remote locations, although PFAS such as PFOS are still detected at some level in these remote locations (Barbo et al., 2023; Goodrow et al., 2020). Factors such as diet and trophic level can influence total PFAS burdens observed in fish collected from impacted urban areas (Macorps et al., 2022). Variations in levels and patterns may be highly dependent on an organism's diet and phenology (e.g., migratory patterns, habitat preferences, seasonality) as these factors mediate an organism's interaction with PFAS sources within its environment (Fair et al., 2019; Hedgespeth et al., 2023).

Collecting recreational sport fish and commercially important species during relevant catch seasons, and of permitted lengths, will assist risk assessors and health departments in identifying plausible exposures. Understanding species-specific migration patterns may provide insight into any observed variability in PFAS levels and compositional profiles and help elucidate potential direct or indirect sources. Considerations such as types of species, number of samples per species, age and size of the fish, trophic level, tissue type, and frequency of sampling or number of sampling events all have an influence on the data that are generated and subsequently used for establishing FCAs. Additionally, PFAS do not follow bioaccumulation trends established for legacy pollutants like PCBs, and associations between PFAS concentration and organism age, size, and trophic level may or may not be applicable depending on PFAS chain length (Conder et al. 2008, Hedgespeth et al., 2023); these unique bioaccumulation trends require careful consideration during study design and data use. Such study design considerations are common components of sampling plans and are often determined when following a process to ensure rigorous data quality (e.g., Quality Assurance Project Plans). These considerations will also depend on the characteristics of the fish-consuming population to be protected and will likely be driven by the policies and funding of the specific agency issuing the FCA.

Environmental challenges for FCA sampling

There are many environmental factors that could be considered when determining the sampling logistics appropriate for deriving FCAs. Concentrations and composition characteristics of PFAS can vary considerably among seasons, location, and across species (Salice & Suski, 2022; Wang et al., 2022). Precipitation, drought, and the hydrodynamics of a system can drastically alter contaminant constituents and levels in surface water and biota (USEPA, 2000). Local or regional PFAS sources and hotspots also play a key role in defining environmental levels and subsequent fish exposure, while ambient environmental levels contribute to PFAS more broadly across the globe.

Deciding on *where* to collect fish for PFAS measurements will depend on the specific needs of the local management agency but should focus on waterbodies where individuals are commonly fishing for consumption and where sources of PFAS contamination are known or suspected. If a local source of PFAS contamination has not yet been identified, it can be expected that sampling waterbodies near potential sources (e.g., wastewater treatment plants, military installations, airports, fire training areas, PFAS associated manufacturing plants, field-applied biosolids, etc.) will likely result in detectable levels of PFAS in the fish (Andrews et al., 2021; Hu et al., 2016; Salvatore et al., 2022). For example, for areas near wastewater treatment plants, discharge variations may cause significant variations in surface water concentrations, and thus the surrounding biota (Bowman, 2019). However, it may also be important to collect and measure PFAS in fish from waterbodies with no known sources of contamination to assess uptake of PFAS at background levels as well as recreational fishing sites in vulnerable or underserved communities. Per- and polyfluoroalkyl substances are known to undergo long-range atmospheric transport and be deposited via wet and dry deposition, which can lead to low-level contamination of waterbodies with no known point sources (Björnsdotter et al., 2022; Cousins et al., 2022; Gewurtz et al., 2019). Site-specific fish sampling from a number of waterbodies led New Jersey to issue advisories mostly for PFOS but also for PFNA at one site (NJDEP, 2019). Since many PFAS have bioaccumulative potential, even low levels of PFAS in the surrounding media could lead to higher levels of PFAS in the fish over time.

For some sampling areas, deciding *when* to collect fish is also an important environmental factor with important considerations, such as (1) seasonal variability in terms of hydrology and water column physicochemical characteristics, food source availability, and during peak fishing seasons, (2) fish stocking periods, and (3) migratory patterns of the species of interest. For example, if these environments include migratory species that are only present a portion of the year, then sampling during just one season could overlook important species that are captured only a portion of the year. Energy demands of the individual fish or of different fish species could vary proportionally with seasonal variations or during spawning, thus impacting PFAS concentrations (Bangma et al., 2022).

The effect of physiochemical and environmental factors on PFAS concentrations in fish samples and the variability between sampling sites, fish species, sampling approaches, and availability of funding for monitoring will influence how management programs can generate meaningful data for FCAs. Seasonal sampling may be required for certain waterbodies such as rivers or coastal environments to characterize human exposures more accurately. While these factors may not always be considered in fish sampling plans for PFAS, recording as much information as possible would improve existing FCAs and future determinations. The purposes of establishing FCAs are to provide advice and recommendations to the greater community to reduce their risk of experiencing adverse health effects.

RISK COMMUNICATION AND RISK MANAGEMENT

Fish consumption advisories are only protective if anglers and the general public in any given region or locality adopt and comply with the recommended guidance. Such adoption is dependent on successful communication between public health agencies and relevant populations, as well as the willingness to adapt to changes in cultural, lifestyle, or economic habits to comply with the guidance (Burger & Gochfeld, 2008; Engelberth et al., 2013). These factors are mediated by individuals' own risk perceptions about PFAS, their understanding of the issued guidance, and their degree of trust in community or regional authorities issuing FCAs. Therefore, while scientific rigor within FCA development is key to ensure evidence-based and defensible FCAs, clear and culturally appropriate risk communication about FCAs is of utmost importance to promote compliance and mitigate risk from fish consumption.

Understanding driving forces behind risk perceptions is critical to tailoring outreach and risk communication efforts related to FCAs. Individuals' risk perceptions about PFAS are partially formed by burgeoning scientific information about adverse health effects but also influenced by the source of the information and an individual's beliefs and experiences. Liu and Yang (2023) found that personal experiences significantly influenced perceived risks from PFAS and associated information-seeking behaviors. However, they also found that personal political beliefs reduced the perceived reliability of information sources such as scientists or public health authorities (Liu & Yang, 2023). Similarly, those with certain political beliefs were less likely to support regulations or government actions on PFAS, despite being motivated to seek out more information about PFAS risks (Dong & Yang, 2023). Mistrust of scientific or public health agencies based on personal or political beliefs is not novel, as seen throughout the COVID-19 epidemic, where changes in risk messaging in response to new information eroded risk perceptions and trust disparately based on intrinsically held beliefs (Ahn et al., 2021; Wang et al., 2023). The constantly evolving nature of PFAS toxicity-related information and the potential for conflicting public health messaging (i.e., risk and benefits of fish consumption) merit caution to avoid the potential for politicization of PFAS as seen with other public health issues, which could ultimately misinform individual risk perceptions around PFAS.

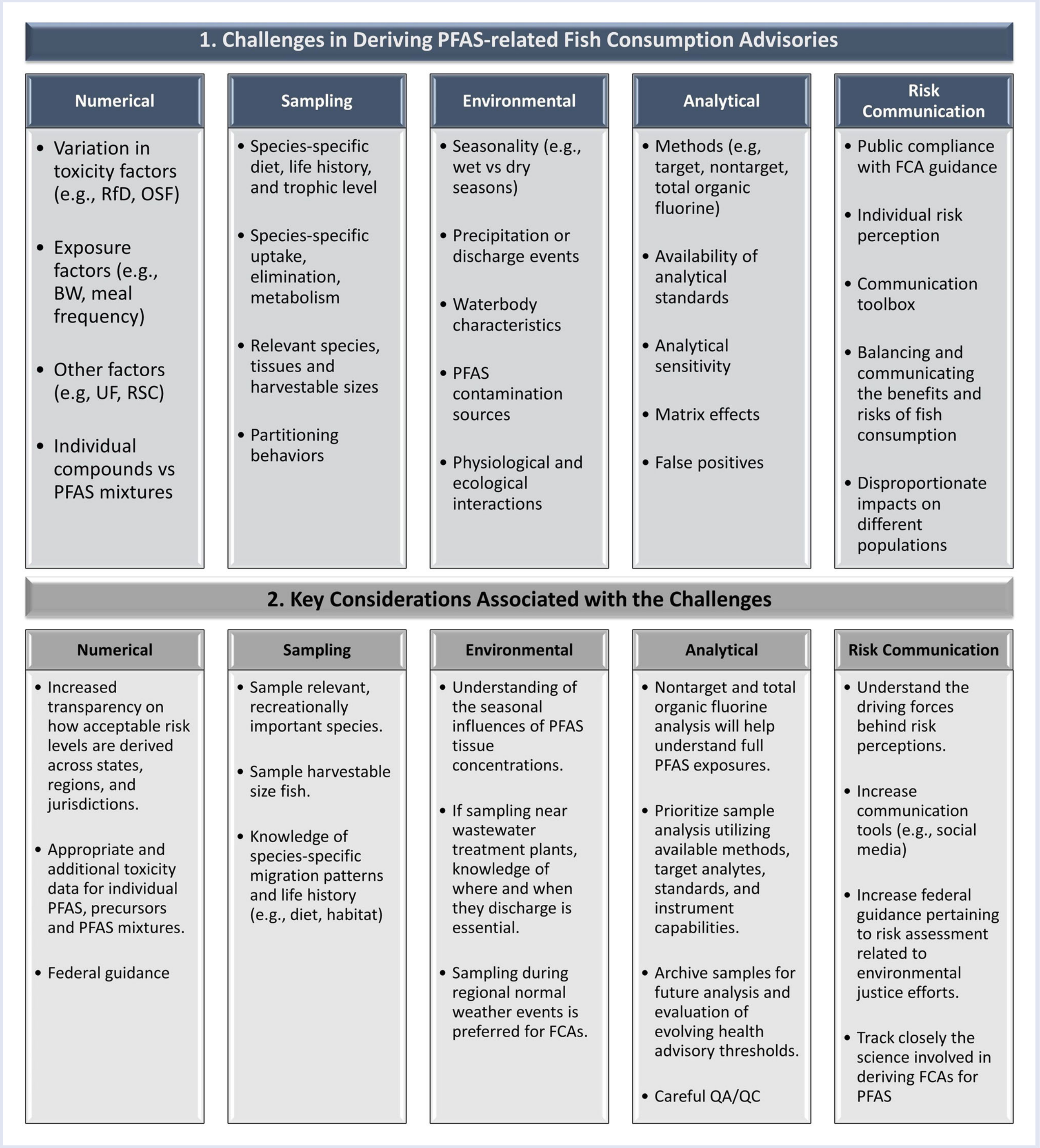
Given the prevalence of PFAS in fish tissues, especially PFOS, public health agencies could consider evaluating their risk communication toolbox for issuing FCAs (USEPA, 2023b). Generally, most programs that develop FCAs rely on state-run websites to post and update advisories to specific waterbodies (MADPH, 2023a, 2023b; MIDHHS, 2023; NCDHHS, 2023; NHDES, 2021), with several instances of posting physical signage at some waterbodies based on contaminants, a waterbody's popularity with the public, and availability of resources to produce signage. However, such signage requires an understanding of frequently spoken languages and literacy within a community, and data on site use and site demographics may either be missing or outdated and require direct engagement with a community to gather and update. Social media platforms have rapidly become a viable avenue of public outreach for regulatory agencies; social media has been suggested as a useful tool for disseminating PFAS information to interested audiences (Tian et al., 2022). Effective use of social media can prove challenging for government agencies due to limited staff fluency with social media (US General Services Administration, 2023), limitations on agency usage of certain platforms, for example, TikTok bans (AP, 2023; Office of Management and Budget, 2023), and limited longevity of some social media platforms or trends. A significant challenge to any agency's toolbox is ultimately staffing and funding, as agencies without staff cannot carry out this work, or programs that are explicitly funded for other contaminants may struggle to add PFAS to existing workloads. Hiring staff with all the skills necessary to meet risk communication needs for FCAs (e.g., multilingual, familiar with the science, tech savvy, public engagement skills, etc.) is challenging, given the ever-competitive job market between public and private sector employers. Thus, without appropriate resources or partnerships with local organizations, it is possible that advisories will prove inefficient because of the aforementioned communication challenges.

Another risk communication challenge for public health agencies involves balancing caution about the risks of contaminants in fish, such as PFAS, while simultaneously promoting certain fish and seafoods as beneficial to a balanced and nutritious diet. Fish can represent an important source of protein that is easily self-harvested to provide low-cost, subsistence nutrition and is also a nutritionally important source of omega-3 polyunsaturated fatty acids (Meyer et al., 2003), all of which reduce risk for a variety of adverse health outcomes (US Food & Drug Administration, 2022). Conflicting messaging between FCAs and the nutritional value of fish complicates risk communication strategies around fish consumption, and these nuanced messages can be perceived as conflicts in public health guidance (Oken et al., 2012). Little effort has gone into quantitatively characterizing the balance of benefits versus risks of fish consumption relative to PFAS, although prior and ongoing efforts related to mercury and overall benefits of seafood consumption might provide helpful insight for future efforts evaluating this problem for the general population and in particular for frequent fish consumers (Dellinger et al., 2018; Ginsberg & Toal, 2009; Ginsberg et al., 2015). These and other issues related to balancing risk and benefits of seafood for sensitive groups, such as children, are the subject of ongoing review by the National Academies of Science, Engineering and Medicine (NASEM, 2022).

Environmental justice concerns (discussed previously) underscore the delicate balance of leveraging FCAs as interim risk mitigation tools while addressing source identification, reduction, and remediation to avoid potentially long-term natural resource loss that disproportionately affects vulnerable groups. As FCAs typically lack regulatory enforcement action in most jurisdictions, they are useful for raising awareness about localized contamination and subsequently public interest in remediation. When faced with similar widespread challenges related to mercury FCAs, several states have simply issued statewide advisories instead of a patchwork of waterbody-specific FCAs (Cleary et al., 2021). However, scientific understanding of mercury speciation and partitioning is well-understood compared to the paucity of data describing environmental behaviors of newly discovered or understudied PFAS (Wang et al., 2004; Wang et al., 2017). Given emerging information about low toxicity thresholds for several PFAS, growing understanding of widespread occurrence and transport of numerous PFAS, and limited information on natural attenuation or efficacy of remedial efforts in aquatic environments, the use of FCAs as interim risk mitigation tools may demand data inputs and risk communication strategies that expand upon those approaches incorporated into development of more broadly applicable mercury FCAs. As such, PFAS-specific FCAs and necessary monitoring may prove difficult for many regions of the United States without appropriate resources. International-, national-, and state-level pollution prevention and upstream management of PFAS in the environment and waste systems (Environment and Climate Change Canada [ECCC], 2023; OECD, 2015; USEPA, 2021b) will be key to reducing PFAS occurrence in aquatic systems and the need for PFAS-specific FCAs.

CONCLUSIONS AND FUTURE DIRECTIONS

The objective of this article was to summarize the existing challenges and needs relative to issuing FCAs for PFAS to protect public health. We addressed this by reviewing the numerical basis for FCAs and sampling and analysis challenges that might occur and discussed problems facing those who need to communicate risks to the public (Figure 3). This review highlights some of the challenges that public health agencies and affected communities encounter when evaluating FCAs derived for their region. While the terminology and application of FCAs described in this review are primarily used by public health agencies in the



1. Challenges in Deriving PFAS-related Fish Consumption Advisories

Numerical
- Variation in toxicity factors (e.g., RfD, OSF)
- Exposure factors (e.g., BW, meal frequency)
- Other factors (e.g, UF, RSC)
- Individual compounds vs PFAS mixtures

Sampling
- Species-specific diet, life history, and trophic level
- Species-specific uptake, elimination, metabolism
- Relevant species, tissues and harvestable sizes
- Partitioning behaviors

Environmental
- Seasonality (e.g., wet vs dry seasons)
- Precipitation or discharge events
- Waterbody characteristics
- PFAS contamination sources
- Physiological and ecological interactions

Analytical
- Methods (e.g, target, nontarget, total organic fluorine)
- Availability of analytical standards
- Analytical sensitivity
- Matrix effects
- False positives

Risk Communication
- Public compliance with FCA guidance
- Individual risk perception
- Communication toolbox
- Balancing and communicating the benefits and risks of fish consumption
- Disproportionate impacts on different populations

2. Key Considerations Associated with the Challenges

Numerical
- Increased transparency on how acceptable risk levels are derived across states, regions, and jurisdictions.
- Appropriate and additional toxicity data for individual PFAS, precursors and PFAS mixtures.
- Federal guidance

Sampling
- Sample relevant, recreationally important species.
- Sample harvestable size fish.
- Knowledge of species-specific migration patterns and life history (e.g., diet, habitat)

Environmental
- Understanding of the seasonal influences of PFAS tissue concentrations.
- If sampling near wastewater treatment plants, knowledge of where and when they discharge is essential.
- Sampling during regional normal weather events is preferred for FCAs.

Analytical
- Nontarget and total organic fluorine analysis will help understand full PFAS exposures.
- Prioritize sample analysis utilizing available methods, target analytes, standards, and instrument capabilities.
- Archive samples for future analysis and evaluation of evolving health advisory thresholds.
- Careful QA/QC

Risk Communication
- Understand the driving forces behind risk perceptions.
- Increase communication tools (e.g., social media)
- Increase federal guidance pertaining to risk assessment related to environmental justice efforts.
- Track closely the science involved in deriving FCAs for PFAS

FIGURE 3 Examples of the (1) challenges in deriving per- and polyfluoroalkyl substances (PFAS)-related fish consumption advisories and the associated (2) key considerations identified herein. These challenges and considerations are informative for developing community-appropriate fish consumption advisories and guidance

United States, these concepts and PFAS-specific challenges identified above are applicable to risk assessment approaches and challenges in other jurisdictions with regard to seafood safety and PFAS.

In light of the risk assessment, analytical, and environmental challenges discussed in this review, it is unlikely that, in the near future, there will be a universal approach removing the utility of disparate FCAs across North America. Therefore, it is crucial that risk assessors and policy-makers track the emergent science that influences the derivation of site-specific or regionally specific FCAs, including changing toxicity factors (i.e., RfDs and OSFs), development of tools for assessing exposure to mixtures, and improvements in the understanding of communities and

TABLE 2 The key considerations for the biological, analytical, and environmental challenges involved in deriving per- and polyfluoroalkyl substances (PFAS)-related fish consumption advisories (FCAs)

Sampling challenges	Challenges	Descriptions of challenges	Potential options to overcome challenges
Biological	Species-specific diet and feeding strategies	Diets of pelagic versus benthic species can influence direct exposure of target species and their forage and/or prey.	Select fish samples that adequately reflect PFAS exposure for recreationally important species and are typically consumed.
	Species-specific differences in uptake, elimination, metabolism, and reproductive status	While exposure concentration may be the greatest factor influencing tissue concentration, there may be species-specific differences in toxicokinetics and metabolic processes that also influence overall tissue concentration.	Sample relevant species that are of harvestable size.
	Species-specific home range or migration patterns	Differences in species home range and migration will influence exposure from known point sources.	When collecting samples to reassess the need for advisories, target specific species that consider the biological factors that can pose challenges while achieving the desired level of protection.
Analytical	Precursors	The presence of precursors in tissue may indicate ongoing exposure of biota to PFAS sources and lead to underestimating the exposure to target consumers. FCAs based on data that do not consider precursors may be higher than needed to protect consumers.	Monitoring precursor levels may aid evaluation of source controls and the need or re-evaluation for advisories.
	Matrix interference	In some matrices, signals for other compounds resemble or mask those of PFAS.	Perform data review and validation to minimize false positives and assure accuracy of reporting.
	Analytical level limitations	In sampling for regulatory compliance, analysis aims to achieve various laboratory levels (e.g., method detection limits) below regulatory thresholds.	Prioritize sample analysis around current available analytes, standards, methods, and instrument capabilities. Archive samples for future analysis for detecting the evolving health advisory thresholds.
	Availability of standards	Certified standards are only available for a limited number of PFAS, which limits measurements of additional PFAS (e.g., precursors) that may be needed or required.	Use of total oxidizable precursor (TOP) assay, total organofluorine analysis (TOF), and other nontarget analysis.
	Methods	Most FCAs are based on data from the targeted approach.	Nontarget analysis would expand the understanding of additional PFAS being consumed through efforts toward standardization of incorporating nontarget methods and data would be needed to support this approach.
Environmental	Seasonality	Target species may not be present year-round (e.g., anadromous species). Spring freshet may result in diluted exposure to target species for a portion of the year.	Understanding the seasonal influences on PFAS tissue concentrations will assist in scheduling sampling events and data interpretation. Sampling during wet and dry seasons will provide a more complete understanding of the seasonal variations in concentrations. Yet, sampling during the regional normal periods is advised for deriving FCAs.

(*Continued*)

TABLE 2 (*Continued*)

Sampling challenges	Challenges	Descriptions of challenges	Potential options to overcome challenges
	Precipitation events	Storm surge from qualifying significant storm events can influence the exposure concentrations to biota near point sources.	If data are being collected to support FCAs, adjust sampling events in around storm events or note in sample logs.
	Waterbody and habitat characteristics	Specific features of a waterbody may lend it to preferential fishing for target species. Local seafood "hot spots" may be present due to waterbody characteristics.	Target sampling areas that are accessible to the general public and are popular fishing spots.
	Human influences	Fish stocking practices, dams, and levees for water-level controls.	Local natural resource management practices should be researched and their influence considered before designing a sampling program to establish the need for or to reevaluate an existing FCA.

their utilization of fish and aquatic resources (Table 2). Given the ever-evolving science describing PFAS, convening expert panels to publicly and routinely evaluate the emerging science on PFAS exposure and fish consumption may be the most useful way to inform the development of FCAs for the near/foreseeable future. We also provided several crucial considerations for public health agencies or research teams seeking to implement monitoring programs, including a review of analytical chemistry challenges and study design considerations required to account for factors that may confound measurement utility and interpretability. Given the inherent variability of PFAS occurrence in natural aquatic systems, co-occurrence with other contaminants, and population-specific behaviors around fish consumption, waterbody- or jurisdiction-specific FCAs remain key risk management approaches where resources allow.

As there are currently no national recommendations or guidelines for PFAS-specific FCAs in the USA, there is considerable attention on the USEPA's PFAS Action Plan (USEPA, 2019). The USEPA is currently moving forward with its proposal for national drinking water standards (USEPA, 2023e). A list of PFAS that EPA is recommending be monitored in fish advisory programs will also be provided to states and tribes to inform fish tissue monitoring and advisory programs, which in turn could reduce the variability in PFAS FCAs between regulatory bodies (USEPA, 2019). Other pending or future regulations and initiatives may also influence which PFAS are targeted in fish tissue sampling and the subsequent establishment of FCAs including hazard classification under Comprehensive Environmental Response; Compensation, and Liability Act (CERCLA) (USEPA, 2023f), establishment of Effluent Limitation Guidelines; National Pollutant Discharge Elimination System (NPDES) and other water quality monitoring programs; chemical-specific toxicity assessments through their Integrated Risk Information System (IRIS) (USEPA, 2021c); and Toxic Substances Control Act (TSCA) inventories (USEPA, 2024f). Moving forward, data inputs and approaches specifically considering the multifaceted complexity associated with PFAS may best inform PFAS-specific FCAs or their components (e.g., RfDs). This in turn may harmonize what critical fish tissue body burdens are used for risk assessments to underscore cohesive decisions related to public health protection concerning fish consumption.

AUTHOR CONTRIBUTION

Jonathan Michael Petali: Conceptualization; investigation; project administration; supervision; visualization; writing—original draft; writing—review and editing. **Erin L. Pulster**: Conceptualization; visualization; writing—original draft; writing—review and editing. **Christopher McCarthy**: Conceptualization; visualization; writing—original draft; writing—review and editing. **Heidi M. Pickard**: Visualization; writing—original draft. **Elsie M. Sunderland**: Writing—review and editing. **Jacqueline Bangma**: Visualization; writing—original draft; writing—review and editing. **Courtney C. Carignan**: Conceptualization; writing—review and editing. **Anna Robuck**: Writing—review and editing. **Kathryn A. Crawford**: Writing—original draft; writing—review and editing. **Megan E. Romano**: Investigation; writing—review and editing. **Rainer Lohmann**: Writing—review and editing. **Katherine von Stackelburg**: Writing—review and editing.

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DISCLAIMER

This article has been subjected to review by the New Hampshire Department of Environmental Services (NHDES) and approved for publication. The views expressed in this article are those of the author(s) and do not necessarily represent the views or the policies of the US Environmental Protection Agency or the NHDES. Any use of trade, firm, or product names is for descriptive purposes only and does not imply endorsement by the US Government.

DATA AVAILABILITY STATEMENT

Data, associated metadata, and calculation tools are available from corresponding author Jonathan M. Petali (jonathan.m.petali@des.nh.gov).

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SUPPORTING INFORMATION

The four key challenge areas for developing fish consumption advisories related to per- and polyfluoroalkyl substances (PFAS).

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