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Assessing Human Health Risks from Per- and Polyfluoroalkyl Substance (PFAS)-Impacted Vegetable Consumption: A Tiered Modeling Approach

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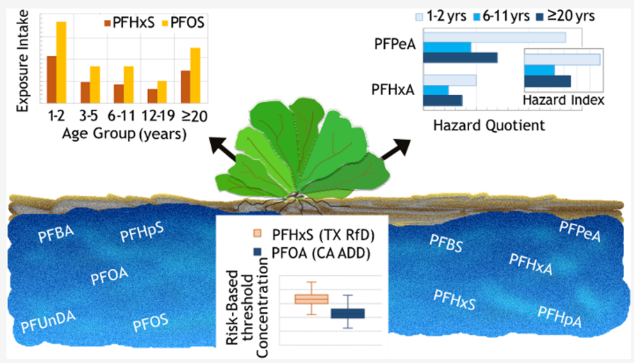
ABSTRACT: Irrigation water or soil contaminated with per- and polyfluoroalkyl substances (PFASs) raises concerns among regulators tasked with protecting human health from potential PFAS-contaminated food crops, with several studies identifying crop uptake as an important exposure pathway. We estimated daily dietary exposure intake of individual PFASs in vegetables for children and adults using Monte Carlo simulation in a tiered stochastic modeling approach: exposures were the highest for young children (1−2 years > adults > 3−5 years > 6−11 years > 12−19 years). Using the lowest available human health toxicity reference values (RfDs) and no additional exposure, estimated fifth percentile risk-based threshold concentrations in irrigation water were 38 ng/L (median 180 ng/L) for perfluorooctanoate (PFOA) and 140 ng/L (median 850 ng/L) for perfluorooctane sulfonate (PFOS). Thus, consumption of vegetables irrigated with PFAS-impacted water that meets the current 70 ng/L of PFOA and PFOS U.S. Environmental Protection Agency's lifetime health advisory for drinking water may or may not be protective of vegetable exposures to these contaminants. Hazard analyses using real-world PFAS-contaminated groundwater data for a hypothetical farm showed estimated exposures to most PFASs exceeding available or derived RfDs, indicating water-to-crop transfer is an important exposure pathway for communities with PFAS-impacted irrigation water.



INTRODUCTION

Extensive contamination of the environment has resulted from the use of per- and polyfluoroalkyl substances (PFASs) in industrial and consumer products (e.g., paper and food packaging, nonstick products, chrome plating, aqueous film-forming foam [AFFF], textiles) and their unique hydrophobic and lipophobic properties.[1] Long-chain perfluoroalkyl carboxylates (PFCAs; i.e., perfluorooctanoate [PFOA] and longer) and long-chain perfluoroalkyl sulfonates (PFSAs; i.e., perfluorohexane sulfonate [PFHxS] and longer) are characterized as extremely persistent, bioaccumulative, and toxic.[2−4] The short-chain PFCAs and PFSAs bioaccumulate less in animals, and yet they bioaccumulate and readily translocate in plants. However, their occurrence, behavior, fate, and toxicity are poorly characterized.[5−7]

Diet is a major exposure pathway for PFASs in humans,[8−10] although the relative contribution ranges widely. Literature-derived fractional dietary contribution estimates for adults range from 16 to 99% for PFOA, 81−100% for perfluorooctane sulfonate (PFOS), and 38−96% for other PFCAs and PFSAs.[11] Studies near PFAS-contaminated sites indicate some foods, including eggs,[12,13] grains,[14,15] vegetables and fruits,[12,16,17] or milk and meats,[18,19] produced in and near these sites may contain elevated concentrations of PFASs. Emmett et al. found a significant association between locally grown vegetable and fruit servings and PFOA concentrations in the serum of nonoccupationally exposed residents near a fluoropolymer plant.[20] While the United States has not set regulatory limits for daily exposure to PFASs in food and drinking water, Food Safety Australia New Zealand recommends tolerable daily intakes (TDIs) for PFOA (160 ng/kg$_{bw}$-day) and PFOS/PFHxS (20 ng/kg$_{bw}$-day) for use in evaluating risk to human health near PFAS-contaminated sites.[21] The European Food Safety Authority (EFSA) recently (2020) released a scientific evaluation of a tolerable weekly intake (TWI) of 4.4 ng/kg$_{bw}$-week (0.63 ng/kg$_{bw}$-day) for the sum of PFOA, PFNA, PFHxS, and PFOS in food; this follows their previously established TWIs of 6 ng/kg$_{bw}$-week for PFOA (0.8 ng/kg$_{bw}$-day) and 13 ng/kg$_{bw}$-week for PFOS (1.8 ng/kg$_{bw}$-day) in 2018.[22,23] However, assessing risk from consuming foods grown with

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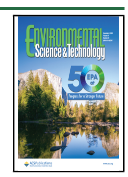

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Table 1. Identified Human Health Toxicity Reference Values for Selected Perfluoroalkyl Acids[a]

	PFCAs (ng/kg_{bw}-day)[b]											PFSAs (ng/kg_{bw}-day)[b]			
agency	PFBA	PFPeA	PFHxA	PFHpA	PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTrDA	PFTeDA	PFBS	PFHxS	PFOS	PFDS
International															
EFSA TDI[c]					**0.80**									**1.8**	
FSANZ TDI[d]					160								20	20	
Canada TDI[e]					21									60	
United States															
EPA RfD[f]					**20**							**20 000**		**20**	
CA ADD[g]					**0.45**									**1.8**	
MA RfD[h]				**5**	5	5	**5**						5	5	
MI RfD[i]					3	3						**230**	**20**	2	
MN RfD[j]	**2900**				18							430	9.7	3.1	
NH RfD[k]					6.1	4.3							4.0	3.0	
NJ RfD[l]					2	**0.74**								**1.8**	
TX RfD[m]	**2900**	**3.8**	**3.8**	**23**	12	12	**15**	**12**	**12**	**12**	**12**	1400	**3.8**	23	**12**
VT RfD[n]				20	**20**	**20**							**20**	**20**	

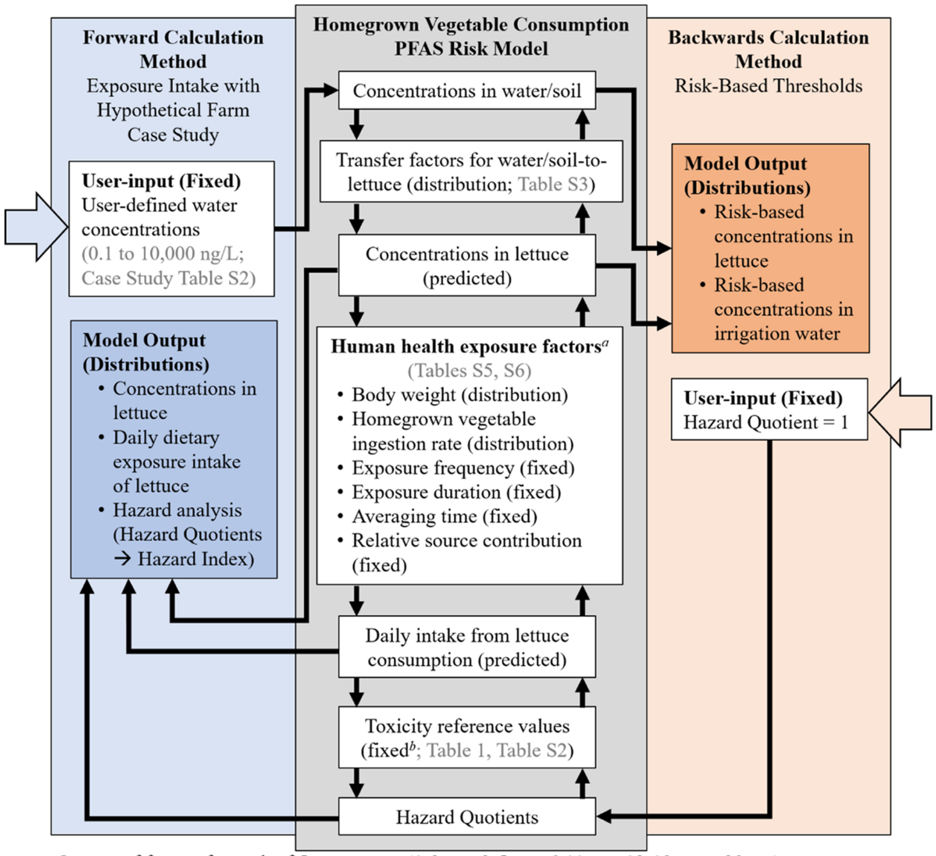
[a]Values in boldface used in one or more risk modeling simulations; other state and international values provided for context (not comprehensive); values based on most recent chronic noncancer health assessments available. See Table S1 in the Supporting Information (SI) for compound information. PFHpS (not shown) has no toxicity reference doses available but are included in the model. [b]ng/kg_{bw}-day, nanograms per kilogram body weight per day; some values are not associated with a promulgated rule for drinking water. [c]Tolerable daily intake (TDI) based on human epidemiological data as determined by the European Food Safety Authority (EFSA).[22] [d]Health-based guidance values determined TDI for PFOA and PFOS/PFHxS by Food Standards Australia New Zealand (FSANZ).[21] [e]Health Canada TDIs: used to establish maximum acceptable concentrations in drinking water.[37,38] [f]Oral noncancer toxicity reference dose (RfD) determined by EPA: used to determine lifetime health advisory for PFOA and PFOS.[34,35] Provisional RfD for PFBS determined by EPA.[39] EPA states the RfDs pertain to exposure from drinking water, but the lack of federal guidance for exposure from food consumption necessitates using available RfDs as initial evaluative criteria to assess risk from the dietary pathway. [g]Acceptable daily dose (ADD) used to establish notification levels in drinking water for the CA State Water Resources Control Board.[40] [h]MA Department of Environmental Protection extended EPA toxicity values for drinking water and employed an additive toxicity approach.[41] [i]Determined by MI Department of Health and Human Services: used to establish screening levels for drinking water.[42] [j]Determined by MN Department of Health:[43−47] used to establish health risk limits in drinking water and groundwater. [k]Determined by NH Department of Environmental Services: used to establish ambient groundwater quality standards.[48] [l]Determined by NJ Department of Environmental Protection:[49−51] used to establish maximum contaminant levels for drinking water. [m]Developed by TX Commission on Environmental Quality: used to establish Tier 1 protective concentration levels for groundwater.[52] [n]VT Department of Health expanded from EPA RfDs[34,35] to include additional PFASs:[53] used to establish drinking water and groundwater health advisories.

contaminated irrigation water and soil remains largely uncharacterized.

Bioaccumulation factors for perfluoroalkyl acids (PFAAs: a subset of PFASs that include the PFCAs and PFSAs) from water and soil into plants, which indicate accumulation of PFASs in above ground plant tissues, support the need to assess potential human health risks from consumption of food crops.[24−26] Uptake studies in agricultural plants found that short-chain PFAAs tend to accumulate more in plants than long-chain PFAAs, and PFCAs tend to accumulate more than PFSAs.[7] Contaminant transfer into food crops is influenced by concentrations and mixtures of PFASs, plant species and compartment(s), soil organic carbon and other soil characteristics, as well as growth conditions. Gaseous or particle-bound aerial transport of neutral precursors (i.e., fluorotelomer alcohols and sulfonamides) has also been identified as a potentially important contaminant-to-produce pathway.[7,27−29] Neutral PFASs could be taken up by plants and transformed into PFAAs, which could be important in areas near fluorochemical production facilities or in areas where no local sources of PFASs are present.[29,30] However, limited bioaccumulation data are available for PFASs other than PFAAs. A focus on PFOA and PFOS (the two most frequently studied PFAAs) may present an incomplete picture of risk associated with uptake into food crops as different compounds may accumulate in different plant compartments when plants are exposed to a mixture of PFASs.[31]

Though critical to human health risk assessments, limited toxicity reference values currently exist for PFAAs (Table 1 for toxicity reference values; Table S1 in the Supporting Information (SI) for compound information). The U.S. Environmental Protection Agency's (EPA) toxicity reference dose (RfD) of 20 ng/kg_{bw}-day for PFOA[32] and PFOS[33] were used to derive the federal lifetime health advisory of 70 ng/L for PFOA and PFOS (separately or combined) in drinking water.[34,35] The limited number of toxicity reference values for PFASs outside of PFOA and PFOS and differences between values for the same PFAA have resulted in considerable uncertainty on the potential for adverse effects from exposure to the many other PFASs present in the environment. Some U.S. states have adopted an additive approach to evaluating toxicity from multiple PFASs (e.g., MA, VT), but addressing mixtures of PFASs continues to challenge the risk assessment and regulatory communities. Other efforts to address mixtures include the relative toxicity potential approach developed in the Netherlands to express the potency of other PFAAs relative to PFOA.[36] Efforts continue on developing regulatory standards for PFASs in drinking water, but no promulgated standard exists in the United States to evaluate risk to consumers from PFASs in food.

The aim of this study was to describe and quantify potential human health risks for children and adults consuming vegetables grown in PFAS-impacted irrigation water or soil. We developed a stochastic vegetable consumption risk model



[a] One set of factors for each of 5 age groups (1-2 yrs; 3-5 yrs; 6-11 yrs; 12-19 yrs; ≥20 yrs).
[b] Toxicity reference values from state or federal sources or derived using relative potency factor approach.

Figure 1. Schematic of the stochastic homegrown vegetable consumption PFAS risk model.

that uses estimated concentrations of PFASs in vegetables based on assumed or measured irrigation water concentrations to: (1) calculate daily dietary exposure intake of individual PFASs via consumption of vegetables to compare relative exposures for various PFASs and relative sensitivities of produce versus drinking water exposure pathways; (2) conduct a PFAS exposure and hazard analysis to examine risks from consuming vegetables impacted by a mixture of PFASs in irrigation water for a hypothetical farm case study; and (3) estimate risk-based threshold concentrations of PFASs in irrigation water and vegetables to provide screening levels for assessment.

■ MATERIALS AND METHODS

Modeling Overview. To address specific risk-driven questions about the consumption of homegrown PFAS-contaminated vegetables, we developed a tiered stochastic modeling approach using Monte Carlo simulation to capture the variability and uncertainty of model variables (Figure 1). Data on uptake of individual PFASs into lettuce (using lettuce as a proxy for vegetables) were compiled to obtain a distribution of transfer factors for each compound. Daily dietary exposure intakes of PFASs were estimated for children and adults consuming vegetables from PFAS-impacted agricultural areas using the transfer factors and a range of user-defined irrigation water concentrations in a forward calculation method. A hazard analysis was conducted using real-world AFFF-contaminated groundwater data to represent a hypothetical farm's irrigation water. The hypothetical farm case study examined potential human health risks from consuming vegetables impacted by a mixture of PFASs in irrigation water using an "additive RfD approach" compared to a "relative potency factor approach." Lastly, risk-based threshold concentrations of PFASs in irrigation water were estimated by incorporating available toxicity reference doses using a backward calculation method.

Monte Carlo Simulation Methodology. The use of Monte Carlo simulation is a way of describing uncertainty around the estimation of a particular value. As there is no one "right" value for model input parameters, they are best described by a distribution. Likewise, a distribution best describes model outputs by providing low, middle, and high model estimates (e.g., mean and percentiles). In this manner, the Monte Carlo simulation captures the "most likely values" and the uncertainty surrounding them.

To assess risk outcomes using the model, 1000 simulations were assigned to each applicable parameter using Oracle Crystal Ball, a Microsoft Excel add-in. While risk assessment approaches often employ fixed values for model inputs (e.g., 95th percentile for ingestion rate), our model predictions produced Monte Carlo simulation-derived distributions that incorporated the variability and/or uncertainty of model parameters providing a realistic range of estimates of risk. For example, uncertainty (imprecision) of water, soil, and lettuce concentration measurements were captured by the sample standard deviation. Inherent variability (heterogeneity) associated with model parameters represented by multiple values were captured by the central tendency and range of

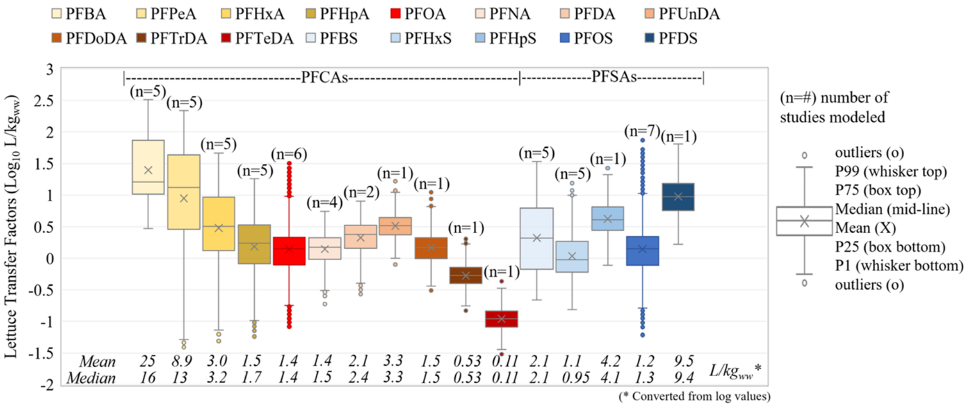


Figure 2. Distribution of modeled transfer factors using Monte Carlo simulation for PFASs from available lettuce uptake studies (1000 simulations/study). See Table S3 for summary statistics of modeled irrigation water-to-lettuce transfer factors.

likely values (mean and 5th, 50th, and 95th percentiles of population and consumption). The predicted daily dietary exposure intakes were modeled using Monte Carlo simulation-derived distributions of population-specific human health exposure factors[54] to capture variability within the five age groups. Applying Monte Carlo simulation to incorporate the full range of uncertainty and variability into the multiple parameters used to evaluate risk from consuming PFAS-contaminated vegetables is a novel application. While the median results can be used to understand the most probable risk profile, using the 95th percentile results for exposure intake and hazard values (or 5th percentile in the case of risk-based threshold concentrations), one can also evaluate the conditions that lead to the most protective risk profile.

Model Parameters—Concentrations in Water. Soil pore water concentrations from 0.1 to 10 000 ng/L were used to estimate daily dietary intake from vegetable consumption to capture a wide range of possible irrigation water conditions. Assumed fixed values (e.g., 70 ng/L) were used to evaluate differences in dietary intake predictions between individual PFASs, which reflect differences in uptake to lettuce for individual PFASs. The irrigation water concentrations used for the hypothetical farm case study hazard analysis were obtained from real-world AFFF-impacted groundwater (Table S2; distribution and limits for these values described in the SI).[55] For this hypothetical farm case study, we assumed that the long-term use of PFAS-impacted irrigation water would lead to equivalent soil pore water concentrations.

Model Parameters—Lettuce Transfer Factors. Transfer factors for lettuce were compiled from peer-reviewed bioaccumulation studies and one government-sponsored study and used to model the transfer of individual PFASs into vegetables from irrigation water.[24,31,56−59] Lettuce served as a conservative proxy for vegetable consumption due to its high water content (>94%)[54] and the generally higher transfer factors as compared to root or stem vegetables.[7] Although uptake data for other plants were considered, lettuce had the largest number of controlled uptake studies across the widest range of PFAAs, as described in the SI. This model focuses only on the soil and irrigation water pathways for the 16 PFAAs with lettuce bioaccumulation data. Though aerial deposition of gas-phase precursors onto plants and subsequent transformation to PFAAs could be important in some areas, due to the very limited data and the complexity of modeling transformation processes, incorporating this pathway into the model was outside the scope of this effort.

Only water and soil-dosing studies from controlled uptake experiments with sufficient metadata to calculate transfer factors were included, such as fraction of organic carbon for spiked soil experiments and explicit units (e.g., dry weight or wet weight for lettuce concentrations). Individual study details are provided in the SI. For the soil-to-plant studies, the concentrations in soil (C_s) were converted to soil pore water concentrations (C_{pw}). Conversions, assumptions, and the equations used to calculate the transfer factors (see eqs S1 and S2) are described in the SI. While these lettuce studies had commonalities, they varied by dosing concentrations, specific PFASs evaluated, and experimental conditions, including bioavailability in soils, lettuce varieties, growth conditions, and the inherent variability in biological data. Incorporating this variability in uptake into the model ensured a range of potential impacts on exposure were evaluated.

Uptake from soil pore water into lettuce varied by study and compound (Figure 2; Table S3 provides summary statistics of the intra- and interstudy modeled transfer factors for individual compounds). We conducted a sensitivity analysis to assess the impact of interstudy variability of transfer factors for individual compounds, as detailed in the SI. Only one uptake study was available for some compounds. Concentration-independent uptake was assumed for all PFASs due to the small sample sizes and variable findings between studies for the same compounds. Table S4a and Figures S1 and S2 summarize the analysis of the lettuce concentration-uptake relationships.

In an effort to validate the uptake component of our model with a field study, we included a brief uptake model validation analysis using concentrations of five PFASs measured in homegrown leafy greens (herbs, Brussel Sprouts, cabbage, kale, leek, lettuce, spinach, and Swiss chard) from gardens irrigated with PFAS-contaminated groundwater from Scher et al. (Table S4b).[60] In general, the concentrations measured in leafy greens in the Scher et al.[60] study were well predicted by our uptake model.

Model Parameters—Human Health Exposure Factors. Exposure model predictions relied on homegrown vegetable ingestion rates, body weights, and other standard exposure parameters for five population subgroups (1−2; 3−5; 6−11; 12−19; and 20 years or older) as determined from the Exposure Factors Handbook and detailed in the SI.[54] Monte Carlo simulation incorporated the variability in model parameters (e.g., body weight for adults based on mean, 5th (lower limit), 75th, and 95th (upper limit) percentiles, Table S5) and resulted in a distribution of exposures.

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Model Calculations—Daily Dietary Exposure Intake. Using the distribution of transfer factors for lettuce (a proxy for all vegetables), daily dietary exposure to individual PFASs were estimated based on user-defined water concentrations and human health exposure factors (Figure 1; forward calculation method). Tables S5 and S6 define the model parameters and describe the distributions and limits used for the calculations. Estimated daily dietary exposure intake was calculated using the equation 1:

$$EI\left(\frac{\mathrm{mg/kg_{bw}}}{\mathrm{day}}\right) = \left(\frac{(C_{pw} \times TF_{lett}) \times \left(BW \times \frac{IR_{HGV}}{1000}\right) \times EF_{120} \times ED)}{(BW \times AT)}\right) \quad (1)$$

where

EI = distribution of daily dietary exposure intake (mg/kg$_{bw}$-day).

C_{pw} = user-defined water concentration (mg/L).

TF_{lett} = distribution of transfer factors of PFASs into lettuce from pore water from modeled TF_{lettss} values (L/kg$_{ww}$).

BW = distribution of age-specific body weight (kg).

IR_{HGV} = distribution of age-specific homegrown vegetable ingestion rate (g$_{ww}$)/(kg$_{bw}$-day).

EF_{120} = exposure frequency of 120 days (days/year) (see Table S5 for more details).

ED = age-specific exposure duration based on maximum years for each child age group and 20 years for adults (years).

AT = averaging time is 365 × ED (days).

Model Calculations—Hazard Analysis: Hypothetical Farm. A hypothetical farm scenario using representative concentrations for PFAS-contaminated irrigation water from AFFF-impacted groundwater (Table S2)[55] was used to evaluate the potential human health risks associated with exposure to a realistic mixture of nine PFAAs (Figure 1; forward calculation method). We chose this hypothetical scenario to be reflective of potential real-world conditions but recognize that site-specific scenarios may be quite different, and thus may lead to a different total risk profile and associated uncertainty. To illustrate methods for quantifying potential risks from a mixture of PFAAs, predictions using an additive RfD approach were compared to predictions using a "relative potency factor" approach.

These two approaches were used to estimate a hazard quotient (HQ) for individual compounds and a hazard index (HI) for the mixture of PFAAs, where $HQ = EI/(RSC \times RfD)$ and $HI = \sum HQs$. Daily dietary exposure intake (EI) estimates were calculated using lettuce transfer factor data and the AFFF-impacted groundwater concentrations (eq 1; Table S2). Relative source contribution (RSC) was set as one (unless otherwise specified; see discussion in SI). The relative source contribution specifies the proportion of the total daily exposure attributed to dietary uptake of PFAS-contaminated vegetables; a value of 1 indicates that 100% of the exposure was from a single source. For human health risk assessment, a HQ (or HI) > 1 indicates that potential may exist for adverse effects to occur.

The additive RfD approach was employed as a simple method to sum up HQs for individual PFAAs to calculate a HI for the mixture of nine PFAAs measured in the groundwater. The HQs for each PFAA were calculated using the lowest (more protective) and highest (less protective) identified state or federal toxicity reference values applicable to each compound (see Table S2 for values used) to provide a range of predictions for assessing risk to human health.

As an alternative, a relative potency factor approach was also evaluated that expressed the potency of the PFAAs relative to the well-studied toxicity of PFOA; these potency factors were previously determined relative to PFOA based on comparable liver hypertrophy toxicity data.[36] Hazard quotients for individual PFAAs and HIs (from the sum of the HQs) were calculated using toxicity reference values derived from relative potency factors for individual PFAAs applied to both the EPA RfD for PFOA and the EFSA TDI for PFOA (Table S2) for comparative purposes. These RFD/TDI values represent the least and most protective human health toxicity reference values currently established by federal or international agencies for PFOA, respectively.

Model Calculations—Risk-Based Threshold Concentrations. Risk-based threshold concentrations represent the range of concentrations for individual PFASs in irrigation water (or lettuce) predicted to be below a level of concern and serve as a useful screening tool to evaluate potential risks when only concentrations of PFAS in irrigation water are available (Figure 1; backward calculation method). Equation 2 was used to predict risk-based concentrations in the irrigation water, based on the established toxicity reference values (see Table 1)

$$C_{pwrb}\left(\frac{\mathrm{mg}}{\mathrm{L}}\right) = \frac{\left(\frac{(RfD \times RSC \times HQ) \times BW \times AT}{\left(BW \times \frac{IR_{HGV}}{1000}\right) \times EF_{120} \times ED}\right)}{\left(\frac{C_{lett}}{C_{pw}}\right) = TF_{lett}} \quad (2)$$

where

C_{pwrb} = distribution of risk-based pore water concentrations (mg/L).

RfD = oral toxicity reference dose; acceptable daily dose or tolerable daily intake used in place of RfDs where applicable (mg/kg$_{bw}$-day; values used are identified in Table 1).

RSC = relative source contribution (0 < RSC < 1); set to 1 in model, except where identified (unitless).

HQ = hazard quotient; set to 1 in model (unitless).

Other parameters as previously defined (see eq 1).

These modeled concentrations rely on available toxicity reference values set equal to the exposure intake (i.e., hazard quotient equal to 1; eq 2).

RESULTS AND DISCUSSION

Daily Dietary Exposure Intake. We compared exposure among PFASs and among the different age groups by assuming an irrigation water concentration of 70 ng/L for each compound, as shown in Figure 3a−d, using the forward calculation method of the PFAS risk model (Figure 1). The estimated median daily dietary exposure intake primarily fell between 0.01 and 1.0 ng/kg$_{bw}$-day for each PFAS, except for PFBA and PFDS that exceeded 1 ng/kg$_{bw}$-day. Exposure intake was the highest for the youngest age group (1−2 years > adults > 3−5 years > 6−11 years > 12−19 years), but differences between age groups were relatively small. Assumed concentrations in irrigation water of 70 ng/L (i.e., meeting the current EPA lifetime health advisory for PFOA and PFOS) resulted in estimated exposure intakes below identified state or federal toxicity reference values for all age groups—indicating

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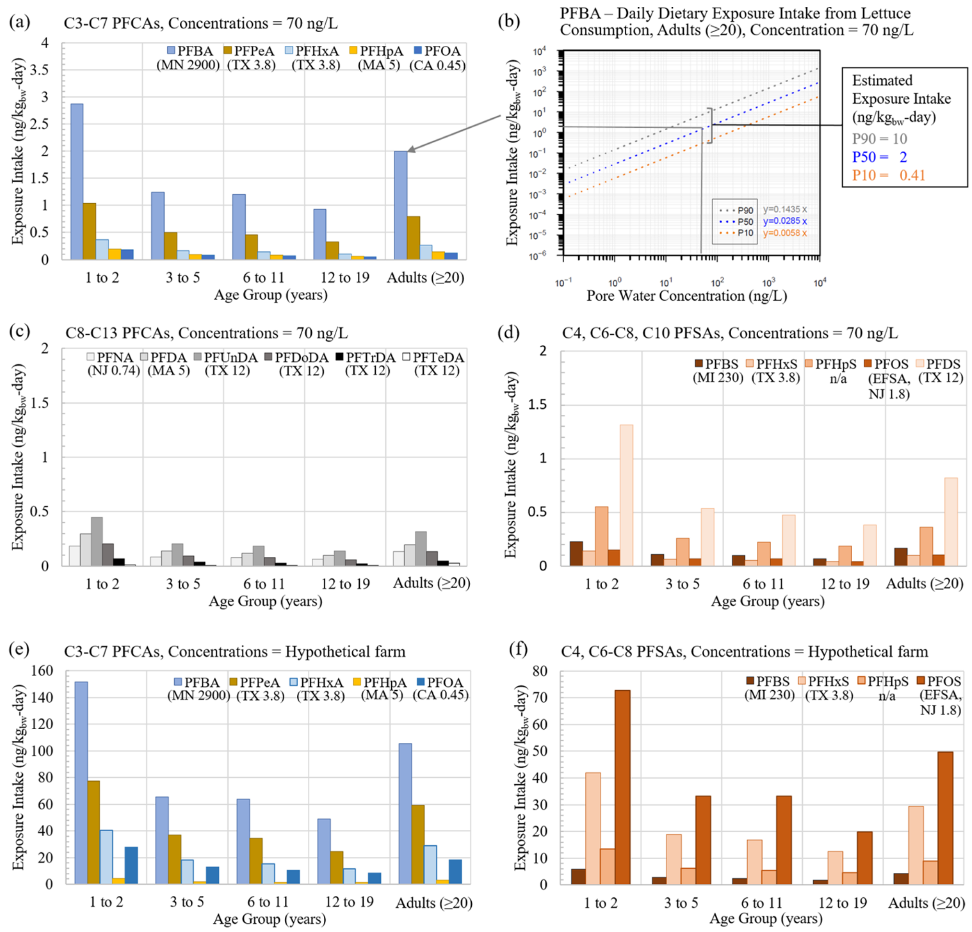

Figure 3. Median estimated daily dietary exposure intake of individual PFASs for consumers of vegetables by age groups for irrigation water concentrations set to 70 ng/L (for each compound): (a) C3−C7 PFCAs; (b) estimated exposure intake of PFBA for adults, showing the 10th, 50th, and 90th percentiles for concentration set to 70 ng/L; (c) C8−C13 PFCAs; and (d) C4, C6−C8, and C10 PFSAs. Median estimated daily dietary intake of individual PFASs for consumers of vegetables by age groups for irrigation water concentrations from hypothetical farm case study: (e) C3−C7 PFCAs and (f) C4, C6−C8 PFSAs. Farm irrigation water concentrations for nine PFASs are provided in Table S2. The lowest available state, federal, or international toxicity reference value are shown for each compound (from Table 1). Exposure intake regression plots showing the 10th, 50th, and 90th percentiles and equations for each compound and age group are provided in Figures S3−S7 and summarized in Table S7. [C#, number of fluorinated carbons.].

vegetable consumption is a less sensitive pathway than drinking water ingestion for these compounds. PFBA and PFPeA, followed by PFDS and PFHpS, had the highest exposure intakes across all age groups, but these values fell below all toxicity reference values listed in Table 1. The median exposure intakes increased with decreasing chain length (and increasing transfer factors) for most PFCAs, but the pattern did not hold for some PFCAs (PFNA, PFDA) nor for PFSAs.

For irrigation water at the threshold of what is currently considered safe levels of PFOA and PFOS in drinking water at the U.S. federal level (EPA lifetime health advisory level 70 ng/L), we wanted to consider our model estimated median vegetable exposure intake for adults for PFOA (0.12 ng/kg_{bw}-day) and PFOS (0.11 ng/kg_{bw}-day) as compared to other dietary intake studies. Fromme et al.'s exposure assessment estimated median total daily dietary intakes for adults of 2.9 and 1.4 ng/kg_{bw}-day for PFOA and PFOS, respectively.[61] Based on Fromme et al.'s total dietary exposure intake estimates, our PFOA and PFOS vegetable-only exposure intake estimates were 4 and 8% of an adult's diet, respectively. By comparison, with 1.3 ng/L of PFOA in drinking water (much lower than our scenario), Vestergren et al.[62] estimated a total daily dietary PFOA intake of 3.4 ng/kg_{bw}-day with 85% of an adult male's PFOA exposure from the diet. Vestergren et al.[63] reported estimates for mean dietary PFOS exposure intake between 0.86 and 1.44 ng/kg_{bw}-day based on a set of Swedish market basket samples, which included dairy, vegetables, fruit, fish, and meat. These compare well with Fromme et al.'s PFOS intake estimates but are an order of magnitude higher than the daily vegetable-only exposure intakes calculated here. Papadopoulou et al.[10] estimated total dietary intake for PFOA (0.086 ng/kg_{bw}-day) and PFOS (0.16 ng/kg_{bw}-day), which are comparable to our model estimates. These studies concluded that dietary exposure can be a dominant intake pathway when drinking water concentrations are low and there are no other major exposure routes, but these studies included fish, seafood, or other animal-based products (eggs, meat). Herzke et al.'s survey of 20 vegetable species from retail stores in Europe (grown with likely variable but unknown PFAS concentrations in water or soil) reported a mean of 0.040 ng/kg_{bw}-day for dietary exposure intake of PFOA,[16] which falls within the range of our model estimates. The variability in these exposure intake estimates demonstrate the need to consider a comprehensive evaluation of dietary sources of PFASs—particularly when the

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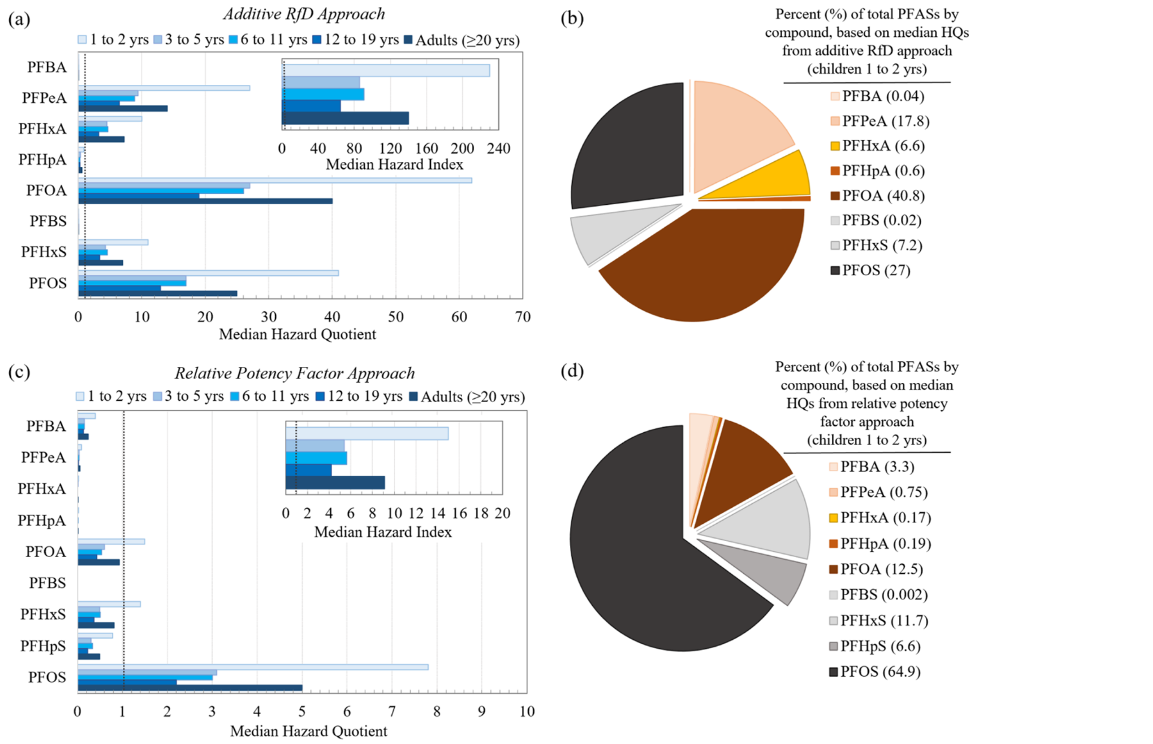

Figure 4. Hazard analyses for adults and children consuming produce from a hypothetical farm using AFFF-contaminated irrigation water. (a) Estimated median hazard quotients (*HQs*) by age group and compound using the additive RfD approach, based on the lowest (most protective) available toxicity reference values, regardless of toxicity end point. (b) Proportion of individual compound's contribution to the overall hazard, in percent, from the total mixture of PFASs. (c) Estimated median *HQs* by age group and compound using the relative potency factor approach. Hazard quotients derived using the EPA RfD for PFOA with relative potency factors to derive toxicity reference values. (d) Proportion of individual compound's contribution to overall hazard, in percent, of the total mixture of PFASs. Note scale differences for (a) and (c). Vertical lines for (a) and (c) show where *HQs* and *HIs* = 1. Proportions for other age groups are comparable (not shown). Relative source contribution = 1. See Table S9a for estimated median values and hazard estimates using the EFSA TDI for PFOA with relative potency factors used to derive toxicity reference values; see Table S9b,c for the 5th and 95th percentile estimates using the additive RfD approach and the relative potency factor approach; and see Table S1 for compound information.

levels in irrigation water or soil are high, but levels in drinking water are low.

In contrast, using the AFFF-impacted irrigation water concentrations from a hypothetical farm provides a perspective on exposure intake from a site with multiple PFASs measured at elevated levels (Figure 3e,f). With vegetable consumption as the only exposure pathway, and PFOA concentrations measured at 10 700 ng/L, the modeled median exposure intake of PFOA from vegetable consumption for the most vulnerable age group (children 1−2 years; 28 ng/kg_{bw}-day) exceeded the EPA RfD of 20 ng/kg_{bw}-day; exposure intake estimates for adults (18 ng/kg_{bw}-day) approached this RfD. For PFOS concentrations measured at 33 100 ng/L, the modeled median exposure intake of PFOS from vegetable consumption for all age groups (20−73 ng/kg_{bw}-day) equaled or exceeded the EPA RfD of 20 ng/kg_{bw}-day. These estimates are more than 150 times the PFOA and 400 times the PFOS estimated exposure intakes from the 70 ng/L irrigation water. Modeled median exposure intakes for PFPeA, PFHxA, PFHpA, and PFHxS also exceeded their lowest identified toxicity reference values. Even when only considering an individual compound, these results show there may be cases where PFAS-impacted irrigation water could lead to unacceptable risks from vegetable consumption.

The 10th (less protective), 50th, and 90th (more protective) percentile exposure intake estimates for all modeled PFASs and age groups, for pore water concentrations ranging from 0.1 to 10 000 ng/L, can be obtained from Figures S3 to S7 or calculated from the regression equations summarized in Table S7. Table S8 summarizes the transfer factor sensitivity analysis for the exposure intake estimates; conservative (95th percentile) transfer factors increase median exposure intake estimates for some compounds by as much as a factor of 13 (PFPeA), but most change by less than a factor of 6.

Hazard Analysis: Hypothetical Farm. A hazard analysis can identify potentially elevated risk from individual compounds or a mixture of PFASs in contaminated irrigation water near impacted agricultural communities. We estimated potential risks from children and adults consuming PFAS-contaminated vegetables harvested from a hypothetical farm irrigated with AFFF-contaminated water using the forward calculation method of the PFAS risk model (e.g., PFOS = 33 100 ng/L; PFOA = 10 700 ng/L; Table S2 shows measured groundwater concentrations). This farm case study demonstrated a process for evaluating potential risks from consuming vegetables impacted by a mixture of PFASs; it also compared the additive RfD approach and the relative potency factor approach.

Figure 4 and Table S9a summarize the modeled median hazard quotients for individual PFASs and the hazard indices for the mixture of PFASs for adults and children consuming vegetables harvested from the impacted farm; these estimates used the additive RfD approach (with the lowest identified toxicity reference values) or the relative potency factor

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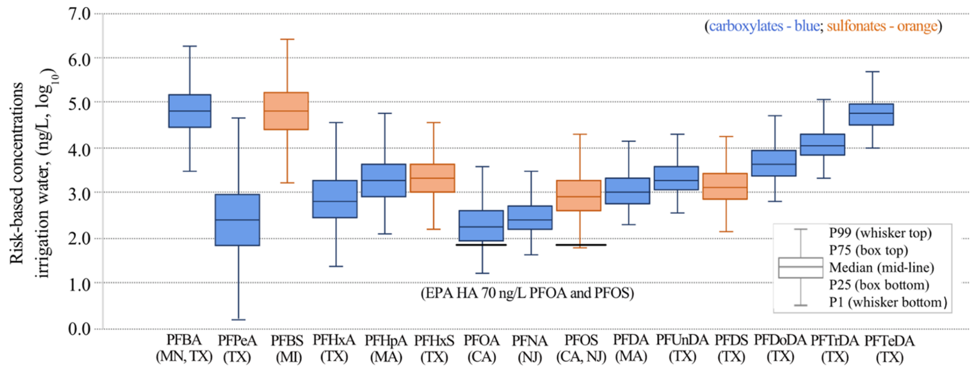

Figure 5. Estimated risk-based threshold concentrations for PFASs for children 1−2 years old. The agency-specific toxicity reference value applied is listed under the compound (Table 1 for toxicity reference values; Table S1 for compound information). There is no toxicity reference value for PFHpS. Relative source contribution is set to 1. [EPA HA, lifetime health advisory for PFOA and PFOS.].

approach. The 5th and 95th percentile modeled *HQ*s and *HI*s are shown in Table S9b (additive RfD approach using the lowest and highest identified toxicity reference values) and Table S9c (relative potency factor approach using RfDs derived from EPA and EFSA). Regardless of approach, the most vulnerable age groups were the youngest children followed by the adults; these groups had the highest median HQs and HIs as well as the largest number of PFASs with hazard quotients exceeding 1 (see Figure 4a,c and Table S9a).

When the additive RfD approach was used, the range of median hazard quotients, from highest to lowest by compound (Table S9a), for adults were: PFOA (40) > PFOS (25) > PFPeA (14) > PFHxA (7.2) ∼ PFHxS (7) > PFHpA (0.57) > PFBA (0.03) ∼ PFBS (0.02). This approach resulted in PFOA, PFOS, PFPeA, PFHxA, and PFHxS with median hazard quotients greater than 1; these five compounds dominated the hazard profile (Figure 4b). In contrast, when the relative potency factor approach was used, based on the EPA RfD for PFOA, the range and compound order of median hazard quotients for adults differed (Table S9a): PFOS (5) > PFOA (0.93) ∼ PFHxS (0.82) > PFHpS (0.5) > PFBA (0.24) > PFPeA (0.06) > PFHpA (0.01) ∼ PFHxA (0.01) ≫ PFBS (0.0002). This approach resulted in PFOS, PFOA, and PFHxS with median hazard quotients greater than or near 1, with additional noteworthy contributions to the hazard profile from PFHpS and PFBA (Figure 4d).

The additive RfD approach resulted in estimated individual compound *HQ*s and *HI*s about one order of magnitude higher than the relative potency factor approach—indicating hazard quotients are highly sensitive to the choice of RfD/TDI. This approach was more protective when using the lowest available toxicity reference values (see Table S9b). Despite relatively high concentrations of PFHpA (1500 ng/L) and PFBS (1800 ng/L) in the irrigation water, these compounds had low hazard quotients (both <1; Table S9a) using either approach—showing concentrations of individual compounds should be considered relative to their toxicity reference values and transfer factors to evaluate their potential risk in a mixture for the vegetable consumption pathway. Applying either approach resulted in median hazard indices greater than 1 ($HI > 1$) for all age groups—indicating cumulative risk assessment of PFAS mixtures may be an important consideration when evaluating risks from multiple PFASs.

The choice to evaluate risk in terms of individual compounds or as mixtures has major implications. Research by Gandhi et al.[64] compared fish consumption advisories in the Great Lakes determined by "one chemical most-restrictive contaminant" or "multicontaminant additive effect" approaches for a range of contaminants (including PFOS). They found that half of the currently issued advisories are underprotective using the most-restrictive contaminant approach when compared to a multicontaminant additive approach. Reffstrup et al. provide a comprehensive summary of the most common approaches for evaluating toxicity from chemical mixtures of pesticides.[65] A critical consideration is whether there will be an interaction between the compounds in the mixture; however, it can be difficult to predict chemical−chemical interactions that may lead to a stronger or weaker toxicological response, particularly at low exposure levels. Although not without controversy, these approaches are frequently applied to conduct a cumulative risk assessment for various chemical classes (e.g., dioxins, pesticides);[66] however, cumulative risk assessment for PFASs has remained largely unresolved. For most PFASs, toxicological or applicable epidemiological studies are lacking. Even for the limited number of PFAAs evaluated in this study, toxicity data are limited. Presently, the U.S. EPA considers the co-occurrence of PFOA and PFOS additively, while others apply an additive effect assuming equipotency (e.g., Vermont includes PFNA, PFHpA, PFOA, PFHxS, and PFOS).

There are challenges with using the additive RfD and relative potency factor approaches for PFASs. Both approaches are data intensive as they require comparable toxicity data for individual PFASs in the mixture. Specific to the relative potency factor approach, hepatic hypertrophy is not necessarily indicative of an adverse health effect, although progression to liver toxicity is often observed.[36,67] This end point may be appropriate for PFASs as hepatic hypertrophy is considered a sensitive end point for PFASs, provides the most complete data set for the most PFASs, and it was used to derive the EPA RfDs for PFOA and PFOS.[3,36] While the relative potency factor approach resulted in PFOS assigned a relative potency factor of 2, this differs from the equipotency assumption used for the EPA, Massachusetts, and Vermont RfDs. Gomis et al.[67] evaluated the relative potency of PFBA, PFHxA, PFOA, PFBS, and PFOS in liver and serum concentrations with dose−response curves of liver enlargement converted to internal doses. They found PFOA ≈ PFHxA ≈ PFBA had similar potencies, which differ from the relative potency factors of 1, 0.01, and 0.05 derived using the relative potency factor approach applied by RIVM. The differences between toxicity reference values derived by states, federal, or international

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agencies for the same compound point to the challenge of current human health risk assessment approaches for PFASs. Likewise, there are important differences between agencies as to which PFASs they evaluate for toxicity. Researchers should continue to explore and consider cumulative risk assessment approaches for mixtures of frequently detected PFASs; this will require additional toxicological and epidemiological data.[11,68]

Under a scenario where previously contaminated drinking water is now treated and no longer an exposure pathway, this model could be used to evaluate the efficacy of potential additional risk-reduction scenarios for PFAS-impacted agricultural communities. We evaluated dilution scenarios for irrigation water to examine risk-reduction approaches as detailed in the SI; Table S10a,b summarizes results. The results indicate that dilution of contaminated irrigation water, when possible, may be a practical solution to reduce risk from consumption of PFAS-impacted vegetables.

Risk-Based Threshold Concentrations. We modeled risk-based threshold concentrations to provide ranges of environmental concentrations of individual PFASs in irrigation water and lettuce not expected to result in potential adverse effects via vegetable consumption; estimates for the 5th (more protective), 50th, and 95th percentiles (less protective) for all age groups are listed in Tables S11 (irrigation water) and S12 (lettuce). These estimates are useful for gaging exposure via vegetable consumption for farm families (or other growers and consumers of local crops) with identified PFAS contamination in their irrigation water or soils.

Figure 5 shows the range for estimated risk-based threshold concentrations for 15 individual PFASs; the median risk-based concentrations for irrigation water for these compounds are greater than 100 ng/L and can exceed 10 000 ng/L for some (PFBA, PFBS) based on the exposure of children 1−2 years old (values for the highest exposed population). Notably, the median estimates for PFOA and PFOS in irrigation water were 10−100-fold greater than the current EPA lifetime health advisory level of 70 ng/L without resulting in elevated risks. The longer-chain PFAAs generally had lower risk-based concentrations as compared to the short-chain compounds due to their higher toxicity and consequently lower RfDs (Figure 5); however, C3−C6 PFCAs did not follow this pattern, likely due to the balancing of higher RfDs with higher transfer factors. Table S13 summarizes the transfer factor sensitivity analysis for the risk-based concentrations; using conservative transfer factors (95th percentile) reduced the median concentrations by a factor between 0.1 and 0.4 (e.g., PFOA 180 ng/L reduced to 34 ng/L using the lowest RfD).

When calculated directly for lettuce (as opposed to irrigation water), the lowest median risk-based concentration was 220 ng/kg_{ww} for PFOA (Table S12; 1−2 years). Most predicted median risk-based concentrations for individual PFASs in lettuce were greater than 1000 ng/kg_{ww}—indicating individual PFASs in lettuce can be in the hundreds or thousands of ng/kg_{ww} without exceeding the risk-based threshold concentration when only that compound is considered and other sources of exposure to PFASs are negligible.

Boxplots showing the range of risk-based threshold concentrations for children 1−2 years old for 15 PFASs in irrigation water calculated from identified state and federal toxicity reference values (Figure S8) demonstrate the sensitivity of model predictions to the toxicity reference doses, with risk-based concentration estimates ranging over 1−3 orders of magnitude; results for when the vegetable consumption pathway is 20% of exposure are also shown. The choice of toxicity reference values—which vary between states, between states and the EPA, and between the EPA and EFSA—employed in human health risk assessment is a critical factor in risk analyses. Median risk-based concentrations are the lowest for PFOA, PFPeA, and PFNA for the youngest children (1-2 years, 180, 240, and 260 ng/L, respectively); differences between median concentrations across the five age groups are small, as shown in Figure S9 for PFNA.

Risk assessors may need to reduce the relative source contribution for vegetables to include other exposure sources of PFASs, such as drinking water, household dust, and other food groups. When the relative source contribution changed from 1 to 0.2, risk-based concentrations for vegetables were reduced by a factor of 5 (Figure S8), and the range of concentrations for PFOA approached or included concentrations at or below the EPA lifetime health advisory level, depending on the toxicity reference value (Figure S8d). The relative source contribution is influential and should be based on other known or likely exposures in an impacted community. Deriving a reliable relative source contribution requires additional evaluation of PFASs exposure pathways, which can vary between communities.

An important uncertainty in the risk-based calculation is that the predicted concentrations for individual compounds and for a single food type (e.g., vegetables) may not be representative of a complex diet of PFAS-impacted foods due to varying uptake from water to different food items and a lack of mixture toxicity considerations. Predicting risk-based threshold concentrations for multiple compounds is challenging as the ratios of individual compounds likely vary between sites; for simple additive compounds, a relative potency factor approach can be applied to calculate thresholds—this approach may be useful for some mixtures of PFAAs. The lack of established toxicity reference values for many PFASs is also a barrier to estimating risk-based concentrations.

■ IMPLICATIONS AND NEXT STEPS

The persistence of legacy PFASs in the environment indicates PFASs will remain a continuing challenge for impacted communities. In the United States, more than 2230 PFAS-contaminated sites have been identified, including public water systems, military bases, airports, industrial plants, disposal areas, and firefighter training areas found in 49 states.[69] Proximity of agricultural areas to fluorochemical production facilities or landfills are a potential source of novel and legacy PFASs to food crops.[70] Biosolids land application also has been identified as a potential source of PFAS contamination to food crops; however, limited data exist on specific locations where applications have occurred.[31,71,72] Though the biosolids-amended soil itself is a source of PFASs to crops grown in that soil, if contamination has reached groundwater in the vicinity of these sites, it may also result in impacted food crops if used for irrigation.

Our analyses confirm that the produce exposure pathway should be included in environmental assessment and management of sites at which food crops are irrigated with water-containing PFASs, even if the water is not directly used for drinking water. Numerous studies acknowledge dietary intake as a predominant source of exposure to PFASs after contaminated drinking water,[9,14,62,73] but there is a clear need for more data on the uptake of additional PFASs and including a wider variety of food crops. Indeed, researchers continue to identify and characterize novel and previously unmeasured PFASs, and very limited data exist on their uptake into food crops.[74−76] The model developed herein employed one of the larger transfer factor data sets available for a single crop (lettuce as a proxy for vegetables) that included as many as seven studies (for PFOS) but only one study for several compounds. Notably, the decision as to which uptake values to use can influence risk outcomes. Future work may include modeling additional food crops with uptake data with an expanded model to better characterize the extent of exposure and risk in impacted agricultural communities.

Our study finds exposures to individual PFASs from vegetable consumption vary for different age groups, with the youngest children and adults having the highest exposure. Updated region-specific ingestion rates for homegrown foods reflective of increased local food consumption would inform this application and other dietary uptake risk models. Additional model parameters that may be appropriate to re-evaluate for exposed communities include body weights and growing season. While not explicitly included in this model, a precipitation (i.e., dilution effect) component may be a logical addition for predicting uptake in areas where growers apply irrigation water sporadically. Characterization of source contributions to PFAS-impacted agricultural communities from household dust, indoor air, and animal-based food products is also necessary.

This study highlights the need to clarify toxicity reference doses and cumulative exposure approaches for assessing risk to consumers from PFASs in food. Modeling dietary uptake and assessing risk from exposure to PFASs from food consumption are complex with many uncertainties and highly variable input data. Despite this challenge, state and federal authorities, risk assessors, and consumers need to be able to answer the frequently asked question, "Is it safe for me to eat this locally grown food that was irrigated with PFAS-contaminated water?" The outcomes from this tiered stochastic modeling approach provide several useful tools for assessing risk in terms of exposure intake, hazard analysis, and risk-based concentrations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.0c03411.

> Additional details of methods, model parameters, and model results; tables and figures showing information on PFASs, hypothetical farm concentrations and human health toxicity reference values evaluated, transfer factor data and related sensitivity analyses, and daily dietary exposure intake estimates for individual PFASs (10th, 50th, and 90th percentiles), hazard analyses (5th, 50th, and 95th percentiles), and risk-based threshold concentrations (5th and 95th percentiles) (PDF)

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Notes

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REFERENCES

(1) OECD/UNEP Global PFC Group. *Synthesis Paper on Per- and Polyfluorinated Chemicals (PFCs)*; OECD Environment, Health and Safety Publications: UNEP, 2013; p 60, https://www.oecd.org/env/ehs/risk-management/PFC_FINAL-Web.pdf.

(2) Lindstrom, A. B.; Strynar, M. J.; Libelo, E. L. Polyfluorinated Compounds: Past, Present, and Future. *Environ. Sci. Technol.* **2011**, *45*, 7954−7961.

(3) *Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances*; DeWitt, J. C., Ed.; Springer International Publishing: Switzerland, 2015.

(4) Wang, Z.; DeWitt, J. C.; Higgins, C. P.; Cousins, I. T. A Never-Ending Story of Per- and Polyfluoroalkyl Substances (PFASs)? *Environ. Sci. Technol.* **2017**, *51*, 2508−2518.

(5) Conder, J. M.; Hoke, R. A.; De Wolf, W.; Russell, M. H.; Buck, R. C. Are PFCAs Bioaccumulative? A Critical Review and Comparison with Regulatory Criteria and Persistent Lipophilic Compounds. *Environ. Sci. Technol.* **2008**, *42*, 995−1003.

(6) Wang, Z.; Cousins, I. T.; Scheringer, M.; Hungerbühler, K. Fluorinated Alternatives to Long-Chain Perfluoroalkyl Carboxylic Acids (PFCAs), Perfluoroalkane Sulfonic Acids (PFSAs) and Their Potential Precursors. *Environ. Int.* **2013**, *60*, 242−248.

(7) Ghisi, R.; Vamerali, T.; Manzetti, S. Accumulation of Perfluorinated Alkyl Substances (PFAS) in Agricultural Plants: A Review. *Environ. Res.* **2019**, *169*, 326−341.

(8) European Food Safety Authority. Perfluoroalkylated Substances in Food: Occurrence and Dietary Exposure. *EFSA J.* **2012**, *10*, No. 2743ff. https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2012.2743

(9) Domingo, J. L.; Nadal, M. Per-and Polyfluoroalkyl Substances (PFASs) in Food and Human Dietary Intake: A Review of the Recent Scientific Literature. *J. Agric. Food Chem.* **2017**, *65*, 533−543.

(10) Poothong, S.; Papadopoulou, E.; Padilla-Sánchez, J. A.; Thomsen, C.; Haug, L. S. Multiple Pathways of Human Exposure to Poly- and Perfluoroalkyl Substances (PFASs): From External Exposure to Human Blood. *Environ. Int.* **2020**, *134*, No. 105244.

(11) Sunderland, E. M.; Hu, X. C.; Dassuncao, C.; Tokranov, A. K.; Wagner, C. C.; Allen, J. G. A Review of the Pathways of Human Exposure to Poly- and Perfluoroalkyl Substances (PFASs) and Present Understanding of Health Effects. *J. Exposure Sci. Environ. Epidemiol.* **2019**, *29*, 131−147.

(12) Bao, J.; Yu, W.-J.; Liu, Y.; Wang, X.; Jin, Y.-H.; Dong, G.-H. Perfluoroalkyl Substances in Groundwater and Home-Produced Vegetables and Eggs around a Fluorochemical Industrial Park in China. *Ecotoxicol. Environ. Saf.* **2019**, *171*, 199−205.
(13) Su, H.; Shi, Y.; Lu, Y.; Wang, P.; Zhang, M.; Sweetman, A.; Jones, K.; Johnson, A. Home Produced Eggs: An Important Pathway of Human Exposure to Perfluorobutanoic Acid (PFBA) and Perfluorooctanoic Acid (PFOA) around a Fluorochemical Industrial Park in China. *Environ. Int.* **2017**, *101*, 1−6.
(14) Noorlander, C. W.; van Leeuwen, S. P. J.; te Biesebeek, J. D.; Mengelers, M. J. B.; Zeilmaker, M. J. Levels of Perfluorinated Compounds in Food and Dietary Intake of PFOS and PFOA in The Netherlands. *J. Agric. Food Chem.* **2011**, *59*, 7496−7505.
(15) Liu, Z.; Lu, Y.; Shi, Y.; Wang, P.; Jones, K.; Sweetman, A. J.; Johnson, A. C.; Zhang, M.; Zhou, Y.; Lu, X.; Su, C.; Sarvajayakesavaluc, S.; Khan, K. Crop Bioaccumulation and Human Exposure of Perfluoroalkyl Acids through Multi-Media Transport from a Mega Fluorochemical Industrial Park, China. *Environ. Int.* **2017**, *106*, 37−47.
(16) Herzke, D.; Huber, S.; Bervoets, L.; D'Hollander, W.; Hajslova, J.; Pulkrabova, J.; Brambilla, G.; De Filippis, S. P.; Klenow, S.; Heinemeyer, G.; De Voogt, P. Perfluorinated Alkylated Substances in Vegetables Collected in Four European Countries; Occurrence and Human Exposure Estimations. *Environ. Sci. Pollut. Res.* **2013**, *20*, 7930−7939.
(17) Li, P.; Oyang, X.; Zhao, Y.; Tu, T.; Tian, X.; Li, L.; Zhao, Y.; Li, J.; Xiao, Z. Occurrence of Perfluorinated Compounds in Agricultural Environment, Vegetables, and Fruits in Regions Influenced by a Fluorine-Chemical Industrial Park in China. *Chemosphere* **2019**, *225*, 659−667.
(18) Wang, J. M.; Shi, Y. L.; Pan, Y. Y.; Cai, Y. Q. Perfluorinated Compounds in Milk, Milk Powder and Yoghurt Purchased from Markets in China. *Chin. Sci. Bull.* **2010**, *55*, 1020−1025.
(19) Guruge, K. S.; Manage, P. M.; Yamanaka, N.; Miyazaki, S.; Taniyasu, S.; Yamashita, N. Species-Specific Concentrations of Perfluoroalkyl Contaminants in Farm and Pet Animals in Japan. *Chemosphere* **2008**, *73*, S210−S215.
(20) Emmett, E. A.; Shofer, F. S.; Zhang, H.; Freeman, D.; Desai, C.; Shaw, L. M. Community Exposure to Perfluorooctanoate: Relationships Between Serum Concentrations and Exposure Sources. *Int. J. Occup. Environ. Med.* **2006**, *48*, 759−770.
(21) FSANZ*Hazard Assessment Report − Perfluorooctane Sulfonate (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorohexane Sulfonate (PFHxS)*; Food Standards Australia New Zealand, 2016; p 164, https://www1.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas-hbgv.htm.
(22) EFSA Panel on Contaminants in the Food Chain (CONTAM); Knutsen, H. K.; Alexander, J.; Barregård, L.; Bignami, M.; Brüschweiler, B.; Ceccatelli, S.; Cottrill, B.; Dinovi, M.; Edler, L.; Grasl-Kraupp, B.; Hogstrand, C.; Hoogenboom, L. Ron.; Nebbia, C. S.; Oswald, I. P.; Petersen, A.; Rose, M.; Roudot, A.; Vleminckx, C.; Vollmer, G.; Wallace, H.; Bodin, L.; Cravedi, J.; Halldorsson, T. I.; Haug, L. S.; Johansson, N.; van Loveren, H.; Gergelova, P.; Mackay, K.; Levorato, S.; van Manen, M.; Schwerdtle, T. Scientific Opinion on the Risk to Human Health Related to the Presence of Perfluorooctane Sulfonic Acid and Perfluorooctanoic Acid in Food. *EFSA J.* **2018**, *16*, No. e05194. https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5194
(23) CONTAM Schrenk, D.; Bignami, M.; Bodin, L.; Chipman, J. K.; del Mazo, J.; Grasl-Kraupp, B.; Hogstrand, C.; Hoogenboom, L. Ron.; Leblanc, J.; Nebbia, C. S.; Nielsen, E.; Ntzani, E.; Petersen, A.; Sand, S.; Vleminckx, C.; Wallace, H.; Barregård, L.; Ceccatelli, S.; Cravedi, J.; Halldorsson, T. I.; Haug, L. S.; Johansson, N.; Knutsen, H. K.; Rose, M.; Roudot, A.; Van Loveren, H.; Vollmer, G.; Mackay, K.; Riolo, F.; Schwerdtle, T. Scientific Opinion on the Risk to Human Health Related to the Presence of Perfluoroalkyl Substances in Food. *EFSA J.* **2020**, *18*, No. 6223. https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2020.6223
(24) Blaine, A. C.; Rich, C. D.; Sedlacko, E. M.; Hyland, K. C.; Stushno, C.; Dickenson, E. R. V.; Higgins, C. P. Perfluoroalkyl Acid Uptake in Lettuce (*Lactuca sativa*) and Strawberry (*Fragaria ananassa*) Irrigated with Reclaimed Water. *Environ. Sci. Technol.* **2014**, *48*, 14361−14368.
(25) Lechner, M.; Knapp, H. Carryover of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) from Soil to Plant and Distribution to the Different Plant Compartments Studied in Cultures of Carrots (*Daucus carota* ssp. Sativus), Potatoes (*Solanum tuberosum*), and Cucumbers (*Cucumis Sativus*). *J. Agric. Food Chem.* **2011**, *59*, 11011−11018.
(26) Zhang, L.; Sun, H.; Wang, Q.; Chen, H.; Yao, Y.; Zhao, Z.; Alder, A. C. Uptake Mechanisms of Perfluoroalkyl Acids with Different Carbon Chain Lengths (C2-C8) by Wheat (*Triticum acstivnm* L.). *Sci. Total Environ.* **2019**, *654*, 19−27.
(27) Yoo, H.; Washington, J. W.; Jenkins, T. M.; Ellington, J. J. Quantitative Determination of Perfluorochemicals and Fluorotelomer Alcohols in Plants from Biosolid-Amended Fields Using LC/MS/MS and GC/MS. *Environ. Sci. Technol.* **2011**, *45*, 7985−7990.
(28) Tian, Y.; Yao, Y.; Chang, S.; Zhao, Z.; Zhao, Y.; Yuan, X.; Wu, F.; Sun, H. Occurrence and Phase Distribution of Neutral and Ionizable Per- and Polyfluoroalkyl Substances (PFASs) in the Atmosphere and Plant Leaves around Landfills: A Case Study in Tianjin, China. *Environ. Sci. Technol.* **2018**, *52*, 1301−1310.
(29) Rankin, K.; Mabury, S. A.; Jenkins, T. M.; Washington, J. W. A North American and Global Survey of Perfluoroalkyl Substances in Surface Soils: Distribution Patterns and Mode of Occurrence. *Chemosphere* **2016**, *161*, 333−341.
(30) Seo, S.-H.; Son, M.-H.; Shin, E.-S.; Choi, S.-D.; Chang, Y.-S. Matrix-Specific Distribution and Compositional Profiles of Perfluoroalkyl Substances (PFASs) in Multimedia Environments. *J. Hazard. Mater.* **2019**, *364*, 19−27.
(31) Blaine, A. C.; Rich, C. D.; Hundal, L. S.; Lau, C.; Mills, M. A.; Harris, K. M.; Higgins, C. P. Uptake of Perfluoroalkyl Acids into Edible Crops via Land Applied Biosolids: Field and Greenhouse Studies. *Environ. Sci. Technol.* **2013**, *47*, 14062−14069.
(32) Lau, C.; Thibodeaux, J. R.; Hanson, R. G.; Narotsky, M. G.; Rogers, J. M.; Lindstrom, A. B.; Strynar, M. J. Effects of Perfluorooctanoic Acid Exposure during Pregnancy in the Mouse. *Toxicol. Sci.* **2006**, *90*, 510−518.
(33) Luebker, D. J.; Case, M. T.; York, R. G.; Moore, J. A.; Hansen, K. J.; Butenhoff, J. L. Two-Generation Reproduction and Cross-Foster Studies of Perfluorooctanesulfonate (PFOS) in Rats. *Toxicology* **2005**, *215*, 126−148.
(34) USEPA. *Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA) EPA 822-R-16-005*; U.S. Environmental Protection Agency, Office of Water: Washington, DC, 2016; pp 1−103, https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final-plain.pdf.
(35) USEPA. *EPA Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS); EPA 822-R-16-004*; U.S. Environmental Protection Agency, Office of Water: Washington, DC, 2016; p. 1-88, https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final-plain.pdf.
(36) Zeilmaker, M. J.; Fragki, S.; Verbruggen, E. M. J.; Bokkers, B. G. H. *Mixture Exposure to PFAS: A Relative Potency Factor Approach; RIVM Report 2018-0070*; National Institute of Public Health and the Environment (RIVM): The Netherlands, 2018; p 76.
(37) Health Canada*Guidelines for Canadian Drinking Water Quality: Guideline Technical Document: Perfluorooctane Sulfonate (PFOS)*; Guideline Technical Documents; Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch, Health Canada: Ottawa, Ontario, 2018, http://publications.gc.ca/collections/collection_2018/sc-hc/H144-13-9-2018-eng.pdf.
(38) Health Canada*Guidelines for Canadian Drinking Water Quality: Guideline Technical Document: Perfluorooctanoic Acid (PFOA)*; Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch, Health Canada: Ottawa, Ontario, 2018, http://publications.gc.ca/collections/collection_2018/sc-hc/H144-13-8-2018-eng.pdf.

(39) Craig, E. A.; Zhao, Q. J. *EPA Provisional Peer-Reviewed Toxicity Values for Perfluorobutane Sulfonate and Related Compound Potassium Perfluorobutane Sulfonate; Final; National Center for Environmental Assessment*; U.S. Environmental Protection Agency, 2014; p 50, https://cfpub.epa.gov/ncea/pprtv/documents/PotassiumPerfluorobutaneSulfonate.pdf.
(40) Banks, C.; Flores-Avila, I.; Soshilov, A.; Steinmaus, C. *Notification Level Recommendations for Perfluorooctanoic Acid and Perfluorooctane Sulfonate in Drinking Water; Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment (OEHHA)*; California Environmental Protection Agency, 2019; p 70, https://oehha.ca.gov/media/downloads/water/chemicals/nl/final-pfoa-pfosnl082119.pdf.
(41) Office of Research and Standards, Massachusetts Dept of Environmental Protection. *Per- and Polyfluoroalkyl Substances (PFAS): An Updated Subgroup Approach to Groundwater and Drinking Water Values*; Technical Support Document; Bureau of Waste Site Cleanup and Bureau of Water ResourcesDrinking Water Program MassDEP: Boston, MA, 2019; p 295, https://www.mass.gov/doc/per-and-polyfluoroalkyl-substances-pfas-an-updated-subgroup-approach-to-groundwater-and/download.
(42) Michigan Dept of Health and Human Services, Division of Environmental Health. *Public Health Drinking Water Screening Levels for PFAS*; Michigan Department of Health and Human Services: 2019; p 158, https://www.michigan.gov/documents/pfasresponse/MDHHS_Public_Health_Drinking_Water_Screening_Levels_for_PFAS_651683_7.pdf.
(43) Minnesota Department of Health (MDH)*Health Based Guidance for Water - Toxicological Summary for: Perfluorobutanoate*; Minnesota Dept of Health, Health Risk Assessment Unit, Environmental Health Division August, 2018, https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfba2summ.pdf.
(44) Minnesota Department of Health (MDH)*Health Based Guidance for Water - Toxicological Summary for: Perfluorooctanoate*; Minnesota Dept of Health, Health Risk Assessment Unit, Environmental Health Division August, 2018, https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfoa.pdf.
(45) Minnesota Department of Health (MDH)*Health Based Guidance for Water - Toxicological Summary for: Perfluorobutane Sulfonate*; Minnesota Dept of Health, Health Risk Assessment Unit, Environmental Health Division August, 2020, https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbssummary.pdf.
(46) Minnesota Department of Health (MDH)*Health Based Guidance for Water - Toxicological Summary for: Perfluorohexane Sulfonate*; Minnesota Dept of Health, Health Risk Assessment Unit, Environmental Health Division August, 2020, https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf.
(47) Minnesota Department of Health (MDH)*Health Based Guidance Value for Water - Toxicological Summary for: Perfluorocta-neSulfonate*; Minnesota Dept of Health, Health Risk Assessment Unit, Environmental Health Division August, 2020, https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf.
(48) New Hampshire Department of Environmental Service-s*Technical Background Report for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane Sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane Sulfonic Acid (PFHxS); Technical Support Document.* New Hampshire Department of Environmental Services, 2019; p 60, https://www4.des.state.nh.us/nh-pfas-investigation/wp-content/uploads/June-PFAS-MCL-Technical-Support-Document-FINAL.pdf.
(49) New Jersey Department of Environmental Protection (NJDEP). NJ Ground Water Quality Standard for Perfluorononanoic Acid (CASRN #375-95-1). New Jersey Department of Environmental Protection (NJDEP), Water Monitoring and Standards, Bureau of Environmental Analysis, Restoration and Standards October, 2015, https://www.state.nj.us/dep/wms/bears/docs/pfna_fact_sheet.pdf.
(50) New Jersey Drinking Water Quality Institute. *Maximum Contaminant Level Recommendation for Perfluorooctanoic Acid in Drinking Water: Basis and Background*; New Jersey Drinking Water Quality Institute: Trenton, NJ, 2017; p 10, https://www.nj.gov/dep/watersupply/pdf/pfoa-recommend.pdf.
(51) New Jersey Drinking Water Quality Institute. *Maximum Contaminant Level Recommendation for Perfluorooctane Sulfonate in Drinking Water: Basis and Background*; New Jersey Drinking Water Quality Institute: Trenton, NJ, 2018; p 10, https://www.state.nj.us/dep/watersupply/pdf/pfos-recommendation-summary.pdf.
(52) Texas Commission on Environmental Quality (TCEQ)*TCEQ Perfluoro Compounds (PFCs); Toxicity Evaluation Document. January 4*, 2016, https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf.
(53) Levine, M. A. *MD. MEMORANDUM: Drinking Water Health Advisory for Five PFAS (per- and Polyfluorinated Alkyl Substances)*. Vermont Department of Health: July 10, 2018, https://www.healthvermont.gov/sites/default/files/documents/pdf/ENV_DW_PFAS_HealthAdvisory.pdf.
(54) USEPA. *Exposure Factors Handbook*; 2011 ed.; U.S. Environmental Protection Agency, 2011; Vol. *EPA/600/R-090/052F*.
(55) Xiao, X.; Ulrich, B. A.; Chen, B.; Higgins, C. P. Sorption of Poly-and Perfluoroalkyl Substances (PFASs) Relevant to Aqueous Film-Forming Foam (AFFF)-Impacted Groundwater by Biochars and Activated Carbon. *Environ. Sci. Technol.* **2017**, *51*, 6342−6351.
(56) Brignole, A. J.; Porch, J. R.; Krueger, H. O.; Van Hoven, R. L. *PFOS: A Toxicity Test to Determine the Effects of the Test Substance on Seedling Emergence of Seven Species of Plants; Project No. 454-110*; Wildlife International, Ltd. (sponsored by 3M Company): St. Paul, MN, 2003; p 135.
(57) Bizkarguenaga, E.; Zabaleta, I.; Mijangos, L.; Iparraguirre, A.; Fernández, L. A.; Prieto, A.; Zuloaga, O. Uptake of Perfluorooctanoic Acid, Perfluorooctane Sulfonate and Perfluorooctane Sulfonamide by Carrot and Lettuce from Compost Amended Soil. *Sci. Total Environ.* **2016**, *571*, 444−451.
(58) Felizeter, S.; Mclachlan, M. S.; De Voogt, P. Uptake of Perfluorinated Alkyl Acids by Hydroponically Grown Lettuce (*Lactuca sativa*). *Environ. Sci. Technol.* **2012**, *46*, 11735−11743.
(59) AECOM. *Stage 2C Environmental Investigation - Human Health Risk Assessment - 2017: Army Aviation Centre Oakey (AACO), Oakey QLD; Stage 2C Environmental Investigation - HHRA 60533675; Department of Defence*; Army Aviation Center Oakey (AACO), Oakey QLD, 2017; p 214, https://www.healthvermont.gov/sites/default/files/documents/pdf/ENV_DW_PFAS_HealthAdvisory.pdf.
(60) Scher, D. P.; Kelly, J. E.; Huset, C. A.; Barry, K. M.; Hoffbeck, R. W.; Yingling, V. L.; Messing, R. B. Occurrence of Perfluoroalkyl Substances (PFAS) in Garden Produce at Homes with a History of PFAS-Contaminated Drinking Water. *Chemosphere* **2018**, *196*, 548−555.
(61) Fromme, H.; Tittlemier, S. A.; Völkel, W.; Wilhelm, M.; Twardella, D. Perfluorinated Compounds − Exposure Assessment for the General Population in Western Countries. *Int. J. Hyg. Environ. Health* **2009**, *212*, 239−270.
(62) Vestergren, R.; Cousins, I. T. Critical Review: Tracking the Pathways of Human Exposure to Perfluorocarboxylates. *Environ. Sci. Technol.* **2009**, *43*, 5565−5575.
(63) Vestergren, R.; Berger, U.; Glynn, A.; Cousins, I. T. Dietary Exposure to Perfluoroalkyl Acids for the Swedish Population in 1999, 2005 and 2010. *Environ. Int.* **2012**, *49*, 120−127.
(64) Gandhi, N.; Drouillard, K. G.; Arhonditsis, G. B.; Gewurtz, S. B.; Bhavsar, S. P. Are Fish Consumption Advisories for the Great Lakes Adequately Protective against Chemical Mixtures? *Environ. Health Perspect.* **2017**, *125*, 586−593.
(65) Reffstrup, T. K.; Larsen, J. C.; Meyer, O. Risk Assessment of Mixtures of Pesticides. Current Approaches and Future Strategies. *Regul. Toxicol. Pharmacol.* **2010**, *56*, 174−192.

(66) van Duursen, M. B. M.; van Ede, K. I.; van den Berg, M. One TEF Concept Does Not Fit All: The Case for Human Risk Assessment of Polychlorinated Biphenyls. *Curr. Opin. Toxicol.* **2017**, *2*, 103−108.
(67) Gomis, M. I.; Vestergren, R.; Borg, D.; Cousins, I. T. Comparing the Toxic Potency in Vivo of Long-Chain Perfluoroalkyl Acids and Fluorinated Alternatives. *Environ. Int.* **2018**, *113*, 1−9.
(68) Reade, A.; Quinn, T.; Schreiber, J. S. *PFAS in Drinking Water 2019*; Natural Resources Defense Council, 2019; p 102, https://www.nrdc.org/sites/default/files/media-uploads/nrdc_pfas_report.pdf.
(69) EWG; SSEHRI. Interactive Map: Mapping Contamination in the U.S. (July 20, 2020). Mapping the PFAS Contamination Crisis: New Data Show 2,230 Sites in 49 States. https://www.ewg.org/interactive-maps/pfas_contamination/. (accessed Nov 2, 2020).
(70) Bao, J.; Li, C.-L.; Liu, Y.; Wang, X.; Yu, W.-J.; Liu, Z.-Q.; Shao, L.-X.; Jin, Y.-H. Bioaccumulation of Perfluoroalkyl Substances in Greenhouse Vegetables with Long-Term Groundwater Irrigation near Fluorochemical Plants in Fuxin, China. *Environ. Res.* **2020**, *188*, No. 109751.
(71) Lee, H.; Tevlin, A. G.; Mabury, S. A.; Mabury, S. A. Fate of Polyfluoroalkyl Phosphate Diesters and Their Metabolites in Biosolids-Applied Soil: Biodegradation and Plant Uptake in Greenhouse and Field Experiments. *Environ. Sci. Technol.* **2014**, *48*, 340−349.
(72) Washington, J. W.; Yoo, H.; Ellington, J. J.; Jenkins, T. M.; Libelo, E. L. Concentrations, Distribution, and Persistence of Perfluoroalkylates in Sludge-Applied Soils near Decatur, Alabama, USA. *Environ. Sci. Technol.* **2010**, *44*, 8390−8396.
(73) D'Hollander, W.; Herzke, D.; Huber, S.; Hajslova, J.; Pulkrabova, J.; Brambilla, G.; De Filippis, S. P.; Bervoets, L.; De Voogt, P. Occurrence of Perfluorinated Alkylated Substances in Cereals, Salt, Sweets and Fruit Items Collected in Four European Countries. *Chemosphere* **2015**, *129*, 179−185.
(74) D'agostino, L. A.; Mabury, S. A. Identification of Novel Fluorinated Surfactants in Aqueous Film Forming Foams and Commercial Surfactant Concentrates. *Environ. Sci. Technol.* **2013**, *48*, 121−129.
(75) Barzen-Hanson, K. A.; Roberts, S. C.; Choyke, S.; Oetjen, K.; McAlees, A.; Riddell, N.; McCrindle, R.; Lee Ferguson, P.; Higgins, C. P.; Field, J. A. Discovery of 40 Classes of Per-and Polyfluoroalkyl Substances in Historical Aqueous Film-Forming Foams (AFFFs) and AFFF-Impacted Groundwater. *Environ. Sci. Technol.* **2017**, *51*, 2047−2057.
(76) Pan, Y.; Zhang, H.; Cui, Q.; Sheng, N.; Yeung, L. W. Y.; Sun, Y.; Guo, Y.; Dai, J. Worldwide Distribution of Novel Perfluoroether Carboxylic and Sulfonic Acids in Surface Water. *Environ. Sci. Technol.* **2018**, *52*, 7621−7629.