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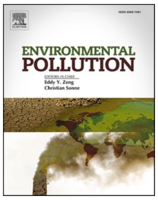

Comparison of four PFAS mixtures assessment approaches based on extensive tap water and groundwater data☆

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) are persistent and toxic contaminants widely detected in drinking water systems. Regulatory responses have varied globally, with a growing need for science-based approaches to assess the health risks posed by PFAS mixtures. However, existing studies have mainly relied on isolated theoretical examples or small datasets, leaving the real-world implications of these approaches poorly understood. This study addresses this gap by applying to two high-quality datasets from large-scale PFAS monitoring campaigns conducted by the USGS four leading PFAS mixtures assessment approaches: (i) the EU approach based on thresholds for total PFAS and the sum of 20 specific PFAS; (ii) Maximum Contaminant Levels established by the US EPA; (iii) the Relative Potency Factor method under evaluation in the EU; and (iv) the Risk Assessment (US EPA RAGS) approach. These datasets cover more than 1700 groundwater and tap water samples, providing a robust basis to investigate the practical differences and consequences of each method. Results reveal significant discrepancies across methods. The EU approach, although applicable to all samples, does not consider toxicological differences among individual compounds, often underestimating health impacts. The Maximum Contaminant Levels approach offers a more health-based evaluation, though it applies to only a subset of compounds. In contrast, the Relative Potency Factor and Risk Assessment (US EPA RAGS) methods provide toxicity-weighted evaluations, offering a more robust and consistent characterization of health risks. Notably, only the Risk Assessment (US EPA RAGS) evaluates carcinogenicity effects in the PFOA and PFOS assessment, though its estimates rely on evolving and debated toxicological assumptions, requiring cautious interpretation. These findings underscore how methodological choices influence PFAS risk evaluation, offering useful insights for future environmental policy and risk assessment practices.

1. Introduction

Among the most complex environmental challenges of recent and coming years is the widespread contamination caused by per- and polyfluoroalkyl substances (PFAS) (Evich et al., 2022; Monk et al., 2025). Available data on their high toxicity, bioaccumulation, and persistence in the environment are limited to legacy compounds, such as perfluoroalkyl carboxylic (PFCAs) and perfluoroalkyl sulfonic (PFSAs) acids, which have been detected as mixtures in water bodies and supply systems worldwide (Ackerman Grunfeld et al., 2024; Dvorakova et al., 2023; Evich et al., 2022; Guelfo and Adamson, 2018; Smalling et al., 2023; US EPA, 2025a; Zhao et al., 2025). For instance, an insightful study by Tokranov et al. (2024) estimated that up to 95 million of people in the United States potentially rely on tap water from groundwater with detectable concentrations of PFAS. As analytical methodologies improve, the number of distinct PFAS identified as co-occurring in water samples continues to increase (Jiménez-Skrzypek et al., 2023). Water intended for human consumption is thereby one of the primary and most concerning exposure pathways, and approaches for the PFAS mixtures assessment aimed to protect human health are highly needed (Ackerman Grunfeld et al., 2024; Alam et al., 2024; Du et al., 2025; Ojo et al., 2021; Romanok et al., 2023). Nevertheless, the environmental regulation of PFAS remains unresolved and subject to ongoing debate, because of their large number and related scientific uncertainties (Brennan et al., 2021; Schymanski et al., 2023). The dose-addition model, which assumes that the overall toxicological effect of a PFAS mixture corresponds to the combined effects of each individual compound based on their

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Glossary

ASTM	Advancing Standards Transforming Markets
DWD	Drinking Water Directive
EC	European Commission
EQS	environmental quality standard
EU	European Union
GW	groundwater
HI	hazard index
HI MCL	hazard index maximum contaminant level
MCL	maximum contaminant level
OECD	Organisation for Economic Co-operation and Development
PFAS	per- and polyfluoroalkyl substances
PFAAs	perfluoroalkyl acids
PFCAs	perfluoroalkyl carboxylic acids
PFECAs	perfluoroalkylether carboxylic acids
PFSAs	perfluoroalkyl sulfonic acids
PolyFACs	polyfluoroalkyl alcohols
PolyFECAs	polyfluoroalkylether carboxylic acids
PolyFESAs	polyfluoroalkylether sulfonic acids
PolyFSAs	polyfluoroalkyl sulfonic acids
RAGS	Risk Assessment Guidance for Superfund
RfD	reference dose
RBCA	Risk-Based Corrective Action
RMSE	root mean squared error
RPFs	relative potency factor
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SF	slope factor
TW	tap water
US EPA	United States Environmental Protection Agency
USGS	United States Geological Survey
WIR	water ingestion rate

respective doses or concentrations (US EPA, 2024a), is currently the most widely accepted approach for risk assessment, although some studies have indicated possible non-additive toxicological effects (Cousins et al., 2020a; Ojo et al., 2021). In this context, international legislations worldwide have typically established thresholds for the sum of various PFAS, whose grouping has been carried out on the basis of precautionary assumptions and the available technologies (CRC CARE, 2018; US EPA, 2024a). For instance, Sweden and Denmark were among the first countries to establish regulatory limits for the sum of 11 and 12 specific PFAS in drinking water, respectively, based on the assumption that the toxicological profiles of the selected compounds were comparable to that of PFOS (Danish Environmental Protection Agency, 2015; Swedish Food Agency, 2021). Besides, several authors propose regulating PFAS as a chemical class, since focusing on individual substances or small groups appears unfeasible (Brennan et al., 2021; Cousins et al., 2020b; Kwiatkowski et al., 2020; Wang et al., 2017). To date, only the European Union (EU) has established a threshold of 500 ng/L for the totality of PFAS, together with a limit of 100 ng/L for the sum of 20 specific PFAS (EU, 2020). However, concerns have been raised regarding both the lack of scientific evidence supporting the selected threshold values and the rationale for the grouping of PFAS to which these limits apply (Cousins et al., 2020a; Reinikainen et al., 2024). In 2024, the United States Environmental Protection Agency (US EPA) established Maximum Contaminant Levels (MCLs) for PFAS in drinking water, introducing a cumulative hazard index for certain PFAS mixtures, while also incorporating economic and technological feasibility considerations (US EPA, 2024b). Additionally, the US EPA published in the same year a noteworthy framework concerning existing data-driven approaches based on the dose-addition model for assessing the non-carcinogenic health risks posed by PFAS mixtures, which included: Hazard Index, Relative Potency Factor, and Mixture-Benchmark Dose (US EPA, 2024a). Among these, the Relative Potency Factor approach gained increasing consensus in recent years and is currently under evaluation by the European Union for regulating PFAS mixtures in both tap water and surface water (EU, 2022).

Overall, these developments suggest a progressive transition toward environmental regulations that are more aligned with scientific understanding of PFAS. Despite the growing scientific and regulatory focus on PFAS, a comprehensive understanding of how different assessment approaches for PFAS mixtures translate into practical outcomes in real environmental contexts is still lacking. In particular, the comparative implications of these methodologies, especially when applied to extensive field data, have not yet been systematically explored. Most existing studies remain theoretical or are limited to small-scale applications (Ao et al., 2019; Bil et al., 2023, 2020; Cara et al., 2022; Chang et al., 2025; Goodrum et al., 2021; Liu et al., 2024; Reinikainen et al., 2024), offering little insight into how the choice of one method over another might influence risk perception and regulatory decisions.

This study addresses this gap by providing a data-driven evaluation of the four most prominent approaches currently adopted or under discussion for the assessment of PFAS mixtures in water intended for human consumption. These include: (i) the EU approach based on thresholds for the totality of PFAS and the sum of 20 specific PFAS; (ii) the Maximum Contaminant Levels approach, currently adopted by the US EPA (EU, 2020; US EPA, 2024b); (iii) the Relative Potency Factor approach, investigated by the EU for the upcoming regulation of PFAS (EU, 2022); (iv) the Risk Assessment (US EPA RAGS) approach, which is one of the most widely utilized tools for the estimation of human health risk arising from the exposure to chemical mixtures (Pinedo et al., 2014).

What distinguishes this work is the systematic and comparative application of all four methods to two extensive and high-quality datasets derived from large-scale environmental sampling campaigns conducted by the United States Geological Survey (USGS), covering more than 1700 groundwater and tap water samples. Specifically, for tap water, the dataset by Romanok et al. (2023), which includes samples collected from both private wells and public supply locations, was analyzed, whereas for groundwater, the dataset by Tokranov et al. (2024) was used. By applying these different assessment frameworks to the same robust empirical datasets, the study provides a concrete comparison of how methodological choices can influence the interpretation of PFAS contamination and related health risks. This analysis helps to clarify the practical implications of each approach when used on real-world data, offering useful insights for both scientific evaluations and regulatory applications. In this way, the study contributes to a better understanding of the strengths and limitations of current methods and may support more consistent and informed practices in PFAS risk assessment.

Table 1
Summary of the approaches included in this study to address PFAS mixtures in water intended for human consumption. The definition of the PFAS compounds listed in Table 1, along with their classification according to OECD (2021), are provided in Table S1 of the Supporting Information. Limits are expressed by showing the significant figures, in accordance with the original sources.

Approach	Parameter	Compounds	Limit	Method of analysis	Data requirements
EU approach (EU, 2020)	PFAS Total	The totality of PFAS	0.50 μg/L (500 ng/L)	TOP assay, EOF-CIC, and LC-HRMS suspect and non-target analysis	PFAS concentrations
	Sum of PFAS	PFBA, PFDA, PFDoA, PFHpA, PFHxA, PFNA, PFOA, PFPeA, PFTrDA, PFUnA, PFBS, PFDS, PFHpS, PFHxS, PFNS, PFOS, PFPeS, PFUnDS, PFDoS, PFTrDS	0.10 μg/L (100 ng/L)	LC-MS with DI or SPE (EN 17892:2024)	
Maximum Contaminant Levels (US EPA approach) US EPA (2024b)	HI MCL	Two or more of PFHxS, PFNA, HFPO-DA (GenX), and PFBS	1 (–)	SPE LC-MS/MS (EPA Method 533 or EPA Method 537.1, Version 2.0)	PFAS concentrations, HBWCs
	MCL	PFOA	4.0 ng/L		
		PFOS	4.0 ng/L		
		PFHxS	10 ng/L		
		PFNA	10 ng/L		
		HFPO-DA (GenX)	10 ng/L		
Relative Potency Factor (EU proposal) EU (2022)	Sum of 24 PFAS	6:2 FTOH, 8:2 FTOH, PFBA, PFDA, PFDoA, PFHpA, PFHxA, PFNA, PFOA, PFPeA, PFTeDA, PFTrDA, PFUnA, PFHxDA, PFODA, HFPO-DA (GenX), C6O4, PFBS, PFDS, PFHpS, PFHxS, PFOS, PFPeS, ADONA	0.0044 μg/L PFOA-equivalents (4.4 ng/L PFOA-equivalents)	To be defined	PFAS concentrations, RPFs
Risk Assessment (US EPA RAGS) (ASTM, 2022; US EPA, 1991; 1989)	HI	The totality of PFAS with RfD	1 (–)	Not specified	PFAS concentrations, RfDs, SFs, WIR
	R	The totality of PFAS with SF	$1\cdot10^{-6}$ (–)		

DI: direct injection; EOF-CIC: combustion ion chromatography after extraction of fluorine; MCL: Maximum Contaminant Level; HBWCs: health-based water concentrations; HI: cumulative hazard index; HI MCL: hazard index maximum contaminant level; LC-HRMS: liquid chromatography-high resolution mass spectrometry; LC-MS/MS: liquid chromatography–tandem mass spectrometry; R: cumulative risk; RfD: reference dose; RPFs: relative potency factors; SF: slope factors; SPE: solid phase extraction; TOP assay: total oxidizable precursor assay; WIR: water ingestion rate.

2. Overview of the approaches for the PFAS mixtures assessment

Table 1 summarizes, for the four approaches considered for assessing PFAS mixtures in tap water or groundwater, the parameters adopted, the compounds included, their respective thresholds, methods of analysis, and data requirements. The definition of the PFAS compounds listed in Table 1, along with their classification according to the Organisation for Economic Co-operation and Development (OECD) (OECD, 2021), are provided in Table S1 of the Supporting Information.

Among the four methods, the EU approach is characterized by its straightforward applicability, as it evaluates PFAS mixtures by applying two distinct thresholds to the cumulative concentrations of the totality of PFAS and to a specific subset of 20 PFAS, without requiring any additional data (EU, 2020). The Maximum Contaminant Levels approach of the US EPA, on the other hand, requires verifying compliance with a hazard index threshold for mixtures of two or more of PFHxS, PFNA, HFPO-DA (also known as GenX), and PFBS, by applying health-based water concentrations (HBWC). In addition, individual concentration thresholds are set for five individual PFAS (i.e., PFOA, PFOS, PFHxS, PFNA, HFPO-DA) (US EPA, 2024b). The Relative Potency Factor approach, as currently proposed by the EU, aims to evaluate the health risks posed by PFAS mixtures by converting the concentrations of individual PFAS into PFOA-equivalents using compound-specific factors (i.e., RPFs), and comparing the total to a single reference limit (EU, 2022). Finally, the Risk Assessment (US EPA RAGS) method can be used to estimate both toxic and carcinogenic risks from PFAS mixtures by calculating cumulative health effects based on the toxicological profiles of the compounds and the defined exposure scenario (i.e., water ingestion, in this study) (ASTM, 2022; US EPA, 1991; 1989). Therefore, both toxicological parameters (i.e., Reference Doses and Slope Factors) and exposure parameters (i.e., Water Ingestion Rate) are required. The resulting values of cumulative hazard index (HI) and cumulative risk (R) are compared to their respective acceptable thresholds for toxic and carcinogenic effects (i.e., 1 and 10^{-6}, respectively) (ASTM, 2022; US EPA, 1991; 1989). Further details regarding the four assessment approaches are provided in the following sections.

2.1. EU approach

The Drinking Water Directive recast (DWD, Directive, 2020/2184), adopted by the European Union in 2020, regulates PFAS mixtures through two chemical parameters: "PFAS Total", which refers to the sum of the concentrations of the totality of PFAS, and "Sum of PFAS", which refers to the sum of the concentration of 20 individual PFAS that are considered to be a concern. Namely, "PFAS Total" and "Sum of PFAS" in drinking water shall not exceed 500 ng/L and 100 ng/L, respectively. These parametric values shall be complied with by Member States by January 2026 (EU, 2020). The selection of these thresholds was driven by political agreements and is not based on a data-driven evaluation of the human health risks posed by PFAS (Cousins et al., 2020a; Reinikainen et al., 2024; SCHEER, 2025). Additionally, a technical guidance for monitoring these two parameters has been included in the Commission Notice C/2024/4910 established in 2024 (EU, 2024). Briefly, the accurate quantification of the "PFAS Total" parameter is considered currently not possible by the European Commission (EC), therefore three methods have been recommended as a proxy for measuring this parameter: (i) total oxidizable precursor (TOP) assay; (ii) combustion ion chromatography after extraction of fluorine (EOF-CIC); (iii) liquid chromatography-high resolution mass spectrometry (LC-HRMS) suspect and non-target analysis. Conversely, the recommended methods of analysis for the "Sum of PFAS" parameter are the liquid chromatography mass spectrometry (LC-MS) coupled with direct injection (DI) or solid phase extraction (SPE) methods, in accordance with the standards EN 17892:2024 (part A) and EN 17892:2024 (part B), respectively, or equivalent standard methods.

2.2. Maximum Contaminant Levels (US EPA approach)

The finalized National Primary Drinking Water Regulation (NPDWR), released by the US EPA in 2024, established standards to manage PFAS in drinking water (US EPA, 2024b). Specifically, an enforceable limit was introduced for PFAS mixtures containing at least two or more of PFHxS, PFNA, HFPO-DA, and PFBS, using the hazard index of 1 (unitless) as Maximum Contaminant Level (named as HI MCL in the regulation). Specifically, the HI MCL (–) for the PFAS mixture is calculated based on the assumption of dose-additivity as follows:

$$\text{HI MCL} = \sum \frac{C_i}{\text{HBWC}_i} = \frac{C_{\text{PFHxS}}}{10\ \text{ng/L}} + \frac{C_{\text{PFNA}}}{10\ \text{ng/L}} + \frac{C_{\text{HFPO-DA}}}{10\ \text{ng/L}} + \frac{C_{\text{PFBS}}}{2000\ \text{ng/L}} \tag{1}$$

where C_i (ng/L) and HBWC_i (ng/L) are the concentration at the point of exposure and the Health-Based Water Concentration of the individual PFAS, respectively. The HBWCs represent the levels below which no adverse health effects are known or expected from ingestion of drinking water contaminated by these PFAS (US EPA, 2024b). Additionally, MCLs (ng/L) listed in Table 1, for five individual PFAS (i.e., PFOA, PFOS, PFHxS, PFNA, and HFPO-DA) must be complied with. If multiple PFAS are present in the water sample, compliance with the MCL of individual PFAS does not imply compliance with the HI MCL, which was established to account for dose-additive health concerns related to their co-occurrence (US EPA, 2024b). Hence, both individual MCLs and HI MCL need to be verified. To quantitatively monitor these standards, the US EPA developed two analytical methods for targeted PFAS (i.e., EPA Method 533 and EPA Method 537.1, Version 2.0), which are based on the SPE liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Rosenblum and Wendelken, 2019; Shoemaker and Tettenhorst, 2018). In May 2025, the US EPA announced its intent to reconsider the regulatory determinations for PFHxS, PFNA, HFPO-DA (GenX), and the HI MCL for a mixture of these three compounds and PFBS (US EPA, 2025b). While this regulation may therefore be subject to changes in the future, we applied this method as currently in force.

2.3. *Relative Potency Factor (EU proposal)*

The Relative Potency Factor approach is a dose-addition method that is used to assess risks posed by a chemical mixture through the evaluation of the toxic potency of individual components relative to a specific index chemical compound (IC), whose selection is based on the quality of its toxicological data and occurrence (US EPA, 2000). Within this approach, a total mixture index chemical equivalent concentration (ICEC_{mix}) (ng/L IC-equivalents) is calculated as the sum of the concentrations of the individual compounds in the mixture (ICEC_i) (ng/L IC-equivalents) expressed in IC-equivalents as follows (EFSA, 2012; US EPA, 2000):

$$\text{ICEC}_{\text{mix}} = \sum \text{ICEC}_i = \sum C_i \cdot \text{RPF}_i \tag{2}$$

where C_i (ng/L) is the concentration at the point of exposure of the individual PFAS, RPF_i (–) is the Relative Potency Factor of the compound, which is a proportionality coefficient derived by evaluations regarding the toxicity of the mixture component, relative to the toxicity of the specific index chemical compound (EFSA, 2012; US EPA, 2000). The ICEC_{mix} has typically been used to evaluate health risks or compliance with maximum allowable levels for mixtures of contaminants, such as pesticides and dioxins (EFSA, 2012; EU, 2023; 2013; US EPA, 2003; 2000). More recently, the Relative Potency Factor approach has been adapted for PFAS mixtures by the Dutch National Institute for Public Health and the Environment, which selected PFOA as IC because of its well-known occurrence and toxicity (Bil et al., 2020; Zeilmaker et al., 2018). Furthermore, this approach has been included in the proposal by the European Commission (EC) to amend the Water Framework Directive and related legislation, and recommended by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) as a policy option for addressing PFAS in groundwater and surface water (EU, 2022; European Commission, 2022; SCHEER, 2023). In this context, the EU proposed an Environmental Quality Standard (EQS) of 4.4 ng/L PFOA-equivalents for the "Sum of 24 PFAS" parameter (ng/L PFOA-equivalents), which corresponds to the calculation of the ICEC_{mix} for 24 individual PFAS. The RPFs values proposed have been adapted from those provided by Bil et al. (2020), where the hepatic toxicity in male rats was selected as a common toxicological endpoint. On the other hand, the EQS has been derived from the Tolerable Weekly Intake (TWI) of 4.4 ng/kg_{bw} per week estimated by EFSA (2020) for the combined exposure to four PFAS (i.e., PFOA, PFOS, PFNA, and PFHxS), which is based on the decreased response of the immune system to vaccination (EU, 2022). Recently, the SCHEER has suggested to extend the Relative Potency Factor approach to all the PFAS that could be determined reliably (SCHEER, 2025). Therefore, additional RPFs should be estimated and, in the case of PFAS not covered by a RPF, it has been suggested to consider them as potent as PFOA, i.e., assuming an RPF of 1 (SCHEER, 2025; 2023).

2.4. *Risk Assessment (US EPA RAGS)*

The human health risk assessment approach of the US EPA, referred to in this study as Risk Assessment (US EPA RAGS), is derived from the "Risk Assessment Guidance for Superfund" (RAGS) and it is aimed to develop a Risk-Based Corrective Action (RBCA) program in the field of contaminated sites (ASTM, 2022; US EPA, 1991; 1989). The Risk Assessment (US EPA RAGS) approach represents one of the most consolidated methodologies for quantifying human health risks posed by pollutants in environmental media (Pinedo et al., 2014; Zhang et al., 2023). This approach allows to estimate the human health risks associated with chemical substances under various exposure scenarios, including the ingestion of water (US EPA, 1991). Specifically, this approach is based on the dose-additivity assumption, assessing non-carcinogenic and carcinogenic health effects, based on the cumulative hazard index, HI (–), and the cumulative risk, R (–) estimated as follows (US EPA, 1989):

$$\text{HI} = \sum \text{HI}_i = \sum \frac{E_{\text{nc,i}}}{\text{RfD}_i}\ (\text{non} - \text{carcinogenic}) \tag{3}$$

$$R = \sum R_i = \sum E_{\text{c,i}} \cdot \text{SF}_i\ (\text{carcinogenic}) \tag{4}$$

where HI_i (–) is the hazard index for non-carcinogenic toxic effects and R_i (–) is the carcinogenic risk related to the ith compound in the mixture. $E_{\text{nc,i}}$ (mg/kg_{bw}/d) and $Ec_{,i}$ (mg/kg_{bw}/d) indicate the oral chronic dose for non-carcinogenic and carcinogenic effects, while RfD_i (mg/kg_{bw}/d) and SF_i $(\text{mg/kg}_{\text{bw}}/\text{d})^{-1}$ refer to the reference dose and the slope factor, respectively, for the same compound. The Reference Dose (RfD_i) represents a conservative threshold below which chronic exposure to a chemical is considered unlikely to cause adverse effects. The Slope Factor (SF_i) is the quantitative toxicological parameter used in risk assessment to estimate the increase in cancer risk per unit of chemical intake. RfD_i and SF_i are parameters established by environmental authorities (e.g. US EPA) based on evaluations of the toxicological profile of the i^{th} compound. On the other hand, E_i depends on the assumed exposure pathway and the considered health effects, including both carcinogenic and non-carcinogenic toxic effects (ASTM, 2022).

For residential receptors where both adults and children are present, different exposure assumptions are applied depending on whether non-carcinogenic or carcinogenic effects are being assessed. For non-carcinogenic effects, a precautionary approach is typically adopted by calculating the oral chronic dose ($E_{\text{nc,i}}$) based on exposure parameters related to children, as they are generally considered the most sensitive population due to their higher intake rates relative to body weight (US EPA, 2020). In this context, the exposure is calculated using the expression (US EPA, 1991):

$$E_{\text{nc,i}} = C_i \cdot \text{WIR}_{\text{children,nc}} \tag{5}$$

with:

$$\text{WIR}_{\text{children,nc}} = \frac{\text{IR}_{\text{w,children}} \cdot \text{EF}_{\text{children}} \cdot \text{ED}_{\text{children}}}{\text{BW}_{\text{children}} \cdot \text{AT}_{\text{nc}} \cdot 365\,\frac{\text{day}}{\text{year}}} \tag{6}$$

where C_i (mg/L) is the concentration at the point of exposure of the individual PFAS, $WIR_{children,nc}$ (L/kg_{bw}/day) is the water ingestion rate for children for non-carcinogenic effects, $IR_{w,children}$ (L/day) is the daily water ingestion rate, $BW_{children}$ (kg_{bw}) is the body weight, $EF_{children}$ (day/year) is the exposure frequency, $ED_{children}$ (year) is the exposure duration, all of which refer to the child receptor. AT_{nc} (year) is the averaging time for non-carcinogenic effects that is typically assumed equal to the exposure duration (ASTM, 2022; US EPA, 2020).

When assessing carcinogenic effects, exposure is instead estimated by considering cumulative intake over a lifetime, which includes both children and adults. In this case, the oral chronic dose (E_{ci}) is calculated as follows (US EPA, 1991):

$$E_{c,i} = C_i \cdot \left(WIR_{children,c} + WIR_{adults,c}\right) \tag{7}$$

with:

$$WIR_{children,c} = \frac{IR_{w,children} \cdot EF_{children} \cdot ED_{children}}{BW_{children} \cdot AT_c \cdot 365 \frac{day}{year}} \tag{8}$$

$$WIR_{adults,c} = \frac{IR_{w,adults} \cdot EF_{adults} \cdot ED_{adults}}{BW_{adults} \cdot AT_c \cdot 365 \frac{day}{year}} \tag{9}$$

where WIR_c (L/kg_{bw}/day) is the water ingestion rate for children for carcinogenic effects, IR (L/day) is the daily water ingestion rate, BW (kg_{bw}) is the body weight, EF (day/year) is the exposure frequency, and ED (year) is the exposure duration. The subscripts of these parameters indicate whether the values refer to child or adult receptors. AT_c (year) is the averaging time for carcinogenic effects that is typically assumed equal to the average lifetime (e.g., 70 years) (ASTM, 2022; US EPA, 2020).

By substituting Eqs. (5)–(9) into Eqs. (3) and (4), it is possible to calculate the hazard indices and the cumulative risks associated with the PFAS mixture. The cumulative hazard index (HI) and the cumulative risks (R), can be compared to their respective thresholds of 1 and 10^{-6} to determine whether the estimated human health risks can be considered acceptable (ASTM, 2022; US EPA, 1991; 1989).

3. Methodology

3.1. Datasets used for tap water and groundwater

To access quality data on PFAS concentrations in mixtures, in this study, two datasets from the United States Geological Survey (USGS) were used, which were obtained adopting a reliable methodology for extensive sampling campaigns throughout United States on groundwater and tap water samples (Romanok et al., 2023; Tokranov et al., 2024). Specifically, for tap water (TW), the dataset provided by Romanok et al. (2023) was used, that contains the concentrations of 34 PFAS in 497 samples collected from private wells and public supply locations between 2021 and 2022. For groundwater (GW), the dataset provided by Tokranov et al. (2024) was used, which contains the concentrations of 28 PFAS in 1238 samples collected from different types of aquifers between 2019 and 2022. Note that, to ensure consistency with the

Table 2

Overview of the datasets used in this study. The definition of the PFAS compounds listed in the table, along with their classification according to OECD (OECD, 2021), are provided in Table S1 of the Supporting Information. Detection frequencies are reported relative to the total number of samplings ($n_{samplings}$).

Parameter	Tap water (TW)	Groundwater (GW)
Reference	Romanok et al. (2023)	Tokranov et al. (2024)
Time interval of sampling campaign (year)	2021–2022	2019–2022
Number of individual PFAS analyzed	32	28
Total number of samplings ($n_{samplings}$)	497	1238
Total number of samplings with detected PFAS ($n_{detected}$)	155 (31 %)	461 (37 %)

Primary class	Substance	Secondary class	Detections	Frequency	Detections	Frequency
PFAA precursors	EtFOSA	PASF-based substances	0	0.0 %	N.I.	N.I.
	FBSA	PASF-based substances	0	0.0 %	N.I.	N.I.
	FHxSA	PASF-based substances	0	0.0 %	N.I.	N.I.
	FOSA	PASF-based substances	0	0.0 %	9	0.7 %
	MeFOSA	PASF-based substances	0	0.0 %	N.I.	N.I.
	N-EtFOSAA	PASF-based substances	0	0.0 %	2	0.2 %
	N-MeFOSAA	PASF-based substances	0	0.0 %	0	0.0 %
PFAAs	PFBA	PFCAs	10	2.0 %	212	17.1 %
	PFDA	PFCAs	1	0.2 %	9	0.7 %
	PFDoA	PFCAs	0	0.0 %	0	0.0 %
	PFHpA	PFCAs	7	1.4 %	179	14.5 %
	PFHxA	PFCAs	13	2.6 %	243	19.6 %
	PFNA	PFCAs	31	6.2 %	48	3.9 %
	PFOA	PFCAs	107	21.5 %	299	24.2 %
	PFPeA	PFCAs	31	6.2 %	242	19.5 %
	PFTeDA	PFCAs	0	0.0 %	0	0.0 %
	PFTrDA	PFCAs	0	0.0 %	0	0.0 %
	PFUnA	PFCAs	0	0.0 %	5	0.4 %
	HFPO-DA (GenX)	PFECAs	2	0.4 %	1	0.1 %
	PFBS	PFSAs	64	12.9 %	305	24.6 %
	PFDS	PFSAs	1	0.2 %	0	0.0 %
	PFHpS	PFSAs	0	0.0 %	22	1.8 %
	PFHxS	PFSAs	24	4.8 %	293	23.7 %
	PFNS	PFSAs	0	0.0 %	0	0.0 %
	PFOS	PFSAs	7	1.4 %	301	24.3 %
	PFPeS	PFSAs	2	0.4 %	67	5.4 %
Polyfluoroalkyl acids	ADONA	PolyFECAs	0	0.0 %	0	0.0 %
	11Cl-PF3OUds	PolyFESAs	0	0.0 %	0	0.0 %
	9Cl-PF3ONS	PolyFESAs	0	0.0 %	0	0.0 %
	4:2 FTS	PolyFSAs	0	0.0 %	0	0.0 %
	6:2 FTS	PolyFSAs	0	0.0 %	26	2.1 %
	8:2 FTS	PolyFSAs	0	0.0 %	1	0.1 %

N.I. = not included in the sampling campaign.

original studies, the same terminology was adopted in this study to refer to the samples (i.e., tap water and groundwater). PFAS included in the sampling campaigns of TW and GW were the same, except for four compounds (i.e., EtFOSA, FBSA, FHxSA, and MeFOSA) which were not analyzed in the GW. An overview of the datasets used in the present work is reported in Table 2, while the methodology applied for the PFAS measurements in each campaign and more detailed information can be found in the original works. For TW and GW datasets, detection limits (DLs) typically ranged between 1.9 and 20 ng/L and 1.9–50 ng/L, respectively. For each dataset, the total number of samples ($n_{samplings}$) and the number of samples with detected PFAS ($n_{detected}$) were determined. Table 2 also reports, for both TW and GW, the number of detections of each PFAS and their detection frequency relative to $n_{samplings}$. In the TW dataset, concentrations of linear and branched isomers of the same compounds (i.e., PFOS and PFHxS) were aggregated, yielding a final set of 32 individual PFAS analyzed.

PFAS detected and their detection frequencies were similar in both the TW and GW datasets. PFAAs accounted for the majority of detections, with PFCAs and PFSAs together representing 97 % and 99 % of PFAS detections in TW and GW, respectively. At least one PFAS has been detected in 31 % and 37 % of the TW and GW samplings, respectively. Furthermore, samples in which PFAS were detected frequently contained mixtures, with two or more PFAS compounds identified in the same sample, as detailed in Table S2. Specifically, in the same sample, up to 9 and 14 individual PFAS were detected in TW and GW, respectively. Both TW and GW datasets were processed only for the purposes of this study, without any alteration of the data. Python 3.12 was used for data curation and analysis, while the main results were presented as datasheets in the Supporting Information.

3.2. *Assumptions and application of the different approaches*

The application of the four approaches described in Section 2 required selecting reasonable parameters and making assumptions in specific situations (e.g., detection of PFAS not included in the respective approach). For both TW and GW samplings, PFAS concentrations below the DL were assumed as not detected in accordance with US EPA (2024b). Among the 20 PFAS regulated by the "Sum of PFAS" parameter of the EU approach, PFUnDS, PFDoS, and PFTrDS were not present in both TW and GW datasets because they were not included in the monitoring campaigns. Therefore, the concentrations of these 3 substances were not considered in the calculations of this parameter. Within the Maximum Contaminant Levels approach, the health risks posed by potential cases of co-occurrences of PFAS different from those included in the legislation were not addressed (US EPA, 2024b). Hence, when other PFAS have been detected in the sampling, the MCL HI was calculated as indicated by the US EPA without accounting for these. Furthermore, the compliance of the MCL for the individual PFAS was verified, even if other PFAS not regulated by this approach were detected.

The RPFs adopted by European Commission (2022) (listed in Table 3) have been used to evaluate the "Sum of 24 PFAS" parameter and verify the compliance with the proposed EQS of 4.4 ng/L PFOA-equivalents. PFAS with no RPFs were not included in the calculation, since the SCHEER assumption of adopting the RPF of PFOA (i.e., 1) for PFAS without a RPF is not currently implemented within the EU proposal. However, the impact of this assumption was subsequently evaluated.

To apply the Risk Assessment (US EPA RAGS) approach, the RfDs and SFs reported in final human health toxicity assessments and regional screening level tables of US EPA have been used for the detected PFAS (Table 4) (US EPA, 2025c; 2024c).

Additionally, to estimate the exposure from PFAS mixtures, adults (>6 years) and children (0–6 years) in a residential scenario were assumed as receptors. The exposure parameters considered within this study for the calculation of the WIR parameters (see Eqs.(8) and (9)) are reported in Table 5.

As a result, the estimated WIR parameters resulted $6.39 \cdot 10^{-2}$ L/kg_{bw}/day for non-carcinogenic toxic effects (i.e., $WIR_{children,nc}$) and $1.49 \cdot 10^{-2}$ L/kg_{bw}/day for carcinogenic ones (i.e., $WIR_{children,c} + WIR_{adults,c}$).

Table 3
Relative potency factors (RPFs) proposed by the European Union (EU, 2022). The definition of the PFAS compounds listed in the table is provided in Table S1 of the Supporting Information.

Primary class	Substance	Secondary class	RPF
PFAA precursors	6:2 FTOH	PolyFACs	0.02
	8:2 FTOH	PolyFACs	0.04
PFAAs	PFBA	PFCAs	0.05
	PFDA	PFCAs	7
	PFDoA	PFCAs	3
	PFHpA	PFCAs	0.505
	PFHxA	PFCAs	0.01
	PFNA	PFCAs	10
	PFOA	PFCAs	1
	PFPeA	PFCAs	0.03
	PFTeDA	PFCAs	0.3
	PFTrDA	PFCAs	1.65
	PFUnA	PFCAs	4
	PFHxDA	PFCAs	0.02
	PFODA	PFCAs	0.02
	HFPO-DA (GenX)	PFECAs	0.06
	C6O4	PFECAs	0.06
	PFBS	PFSAs	0.001
	PFDS	PFSAs	2
	PFHpS	PFSAs	1.3
	PFHxS	PFSAs	0.6
	PFOS	PFSAs	2
	PFPeS	PFSAs	0.3005
Polyfluoroalkyl acids	ADONA	PolyFECAs	0.03

4. Results and discussion

The detailed results of the application of the different assessment methods to the two datasets are provided in Supporting Information,

Table 4
Oral chronic reference doses (RfD) and oral slope factors (SF) for detected PFAS. The definition of the PFAS compounds listed in the table is provided in Table S1 of the Supporting Information.

Primary class	Substance	Secondary class	RfD (mg/kg_{bw}/d)	SF (mg/kg_{bw}/d)$^{-1}$	Reference
PFAAs	PFBA	PFCAs	$1 \cdot 10^{-3}$		US EPA (2025c)
	PFDA	PFCAs	$2 \cdot 10^{-9}$		US EPA (2025c)
	PFDoA	PFCAs	$5 \cdot 10^{-5}$		US EPA (2024c)
	PFHxA	PFCAs	$5 \cdot 10^{-4}$		US EPA (2025c)
	PFNA	PFCAs	$3 \cdot 10^{-6}$		US EPA (2025c)
	PFOA	PFCAs	$3 \cdot 10^{-8}$	$2.93 \cdot 10^{+4}$	US EPA (2025c)
	PFTeDA	PFCAs	$1 \cdot 10^{-3}$		US EPA (2024c)
	PFUnA	PFCAs	$3 \cdot 10^{-4}$		US EPA (2024c)
	HFPO-DA (GenX)	PFECAs	$3 \cdot 10^{-6}$		US EPA (2025c)
	PFBS	PFSAs	$3 \cdot 10^{-4}$		US EPA (2025c)
	PFHxS	PFSAs	$2 \cdot 10^{-5}$		US EPA (2024c)
	PFOS	PFSAs	$1 \cdot 10^{-7}$	$3.95 \cdot 10^{+1}$	US EPA (2025c)

Table 5
Exposure parameters assumed for the estimation of the water intake rate within the Risk Assessment (US EPA RAGS) approach.

Exposure parameter	Health effects	UM	Receptor		Reference
			Adults (>6 years)	Children (0–6 years)	
Daily water ingestion rate (IR_w)	NC C	L/day	2	1	(ASTM, 2022; US EPA, 2020)
Exposure frequency (EF)	NC C	day/year	350	350	(ASTM, 2022; US EPA, 2020)
Exposure duration (ED)	NC	year	–	6	(US EPA, 2020; 1991)
	C		24	6	
Body weight (BW)	NC C	kg_{bw}	70	15	(US EPA, 2020; 1991)
Averaging time (AT)	NC	year	–	6	(ASTM, 2022; US EPA, 2020)
	C		70	70	

NC = non-carcinogenic; C = carcinogenic.

where the outcomes of each method are reported for every individual sample analyzed. In the following sections, a summary of the results from the different assessment methods is presented.

4.1. Applicability of PFAS mixtures approaches to the selected datasets

Although with certain challenges, current analytical methodologies proved to be advanced enough to detect several PFAS in water samples (Jiménez-Skrzypek et al., 2023). For instance, the monitoring campaigns conducted by the USGS encompassed 28 PFAS in the TW dataset and 34 PFAS in the GW dataset, including isomers (Romanok et al., 2023; Tokranov et al., 2024). However, except for the EU approach, the PFAS mixtures assessment approaches applied in this study target a lower number of compounds. This is because these approaches are based on toxicological data, that are still limited for most of PFAS. Therefore, the applicability of these approaches was evaluated, in terms of their capacity to support meaningful comparisons with regulatory limit, including cases involving multiple PFAS or compounds other than the legacy group. Significant differences were observed in the number of TW and GW samplings that could be compared with the limits of the selected approaches. As shown in Table S3, only the EU approach allowed to assess all the samples in relation to the regulatory threshold, as it considers all detected PFAS under the "PFAS Total" parameter, including those not included in the "Sum of PFAS' parameter. The Maximum Contaminant Levels approach proved to be the most restrictive in terms of applicability, as 20 % and 12 % of TW and GW samples, respectively, could not be compared with any limit due to the absence of established MCLs for the detected PFAS. Indeed, these samples contained PFAS mixtures composed exclusively of compounds not included in the HI MCL calculation, or individual PFAS for which no MCL has been established. Furthermore, as this approach targets a small subset of compounds, most of the detected PFAS were excluded from the assessment. The application of the Relative Potency Factor approach showed that most of the samples could be expressed in terms of PFOA-equivalents and therefore compared with the proposed EQS of 4.4 ng/L. In the TW dataset, all detected PFAS had an established RPF, and could therefore be compared with the EQS. In contrast, the larger GW dataset included some frequently detected PFAS (e.g., 6:2 FTS and PFPeS) that could not be considered in the calculation, as no RPF has yet been established for them. Moreover, 3 % of GW samples contained exclusively PFAS without RPFs and were thus not comparable with the threshold. Finally, 9 % of TW samples and 4 % of GW samples could not be evaluated using the Risk Assessment (US EPA RAGS), as no RfDs or SFs were available for the detected PFAS. In summary, these results demonstrate that the adoption of approaches relying on toxicological data is very likely to leave certain samplings outside the scope of comparison with regulatory limits, and to result in mixtures being evaluated solely based on a small subset of the detected PFAS. Furthermore, since these approaches are computationally more intensive than the EU approach, their practical application can be limited by the lack of clear criteria for handling certain cases, which may affect the consistency of the assessment. In this context, precautionary assumptions, such as the SCHEER recommendation to treat PFAS without an assigned RPF as equally toxic as PFOA, can support the evaluation of water samples across a broader range of scenarios, while still allowing for a meaningful interpretation of potential health risks.

4.2. Frequencies of threshold exceedances

Table 6 shows, for both TW and GW datasets, the individual and the total threshold exceedances, along with their frequencies relative to the total number of samplings (n_{sampings}). Individual exceedances refer to the number of samplings that exceed the threshold for a specific parameter considered by the approach. For example, in risk assessment, this may involve separate evaluations for non-carcinogenic and carcinogenic effects, each with its own reference threshold. The total exceedances, on the other hand, indicate the number of samplings that fail to comply with at least one of the required criteria within the selected assessment approach. Exceedances resulting from the EU approach accounted for 0.6 % and 2.0 % of total samplings in TW and GW, respectively. Although this was the only approach applicable to the entire datasets, as previously shown (Section 4.1), the percentage of total exceedances resulted in one order of magnitude lower than those obtained using the other approaches, suggesting an underestimation of the risks posed by PFAS mixtures. When the Maximum Contaminant Levels approach was applied, the 17.1 % and 16.7 % of TW and GW samples, respectively, were not compliant. Notably, there were no samplings in which the HI MCL was exceeded, while all individual MCLs were still met. Hence, all the total exceedances of samplings with detected PFAS, including those containing PFAS mixtures, were associated with concentrations above the MCLs for individual PFAS compounds. When the Relative Potency Factor approach was applied, total exceedances in TW and GW increased to 17.7 % and 24.2 %, respectively. In this case, 1 and 3 additional exceedances would have been recorded in TW and GW, respectively, if the SCHEER recommendation of assuming an RPF equal to 1 for these PFAS would have been adopted (EU, 2022; European Commission, 2022; SCHEER, 2023). Finally, the Risk Assessment (US EPA RAGS) resulted in the highest proportion of threshold exceedances, with 21.9 % in TW and 27.5 % in GW.

These results clearly show that the choice of assessment method can drastically influence the outcomes of the evaluation, leading to very different conclusions regarding compliance and potential risk. Consequently, the identification of threshold exceedances, and thus the definition of corrective or mitigation actions, can vary substantially depending on the selected approach.

4.3. Extent of threshold exceedances

In addition to the quantification of the number of samplings which met or exceeded the different thresholds, the extent of exceedance was evaluated. Fig. 1 presents the distribution of results from the four PFAS mixture assessment approaches applied to samples with detected PFAS. The figure displays box-and-whisker plots representing the 5th, 25th, 50th, 75th, and 95th percentiles of the evaluation results derived from the different methods for both TW and GW datasets. These distributions are compared to the respective threshold values defined by each approach, thereby highlighting the proportion and magnitude of threshold exceedances.

As shown in Fig. 1a, the distributions of the "PFAS Total" and "Sum of PFAS" parameters of the EU approach resulted almost identical, since the detected compounds were mostly the ones included in the list of 20 PFAS regulated by the "Sum of PFAS". Additionally, these parameters were frequently well below their respective thresholds, with

Table 6
Individual and total exceedances of the parameters adopted within the different approaches included in this study. Percentages of individual and total exceedances are reported relative to the total number of samplings ($n_{samplings}$). Results shown under the Relative Potency Factor approach are without applying the SCHEER suggestion. Note that, in order to estimate the number of exceedances, the measured concentration values and the corresponding indexes were rounded according to the significant figures specified by each approach (see Table 1).

Approach	Parameter	Tap water (TW) ($n_{samplings}$ = 497)		Groundwater (GW) ($n_{samplings}$ = 1238)	
		Individual exceedances	Total exceedances	Individual exceedances	Total exceedances
EU approach	PFAS Total	1 (0.2 %)	3 (0.6 %)	2 (0.2 %)	25 (2.0 %)
	Sum of PFAS	3 (0.6 %)		25 (2.0 %)	
Maximum Contaminant Level (US EPA approach)	HI MCL (PFHxS, PFNA, HFPO-DA (GenX), PFBS)	2 (0.4 %)	85 (17.1 %)	25 (2.0 %)	206 (16.7 %)
	MCL (PFOA, PFOS, PFHxS, PFNA, HFPO-DA (GenX))	85 (17.1 %)		206 (16.7 %)	
Relative Potency Factor (EU proposal)	Sum of 24 PFAS	88 (17.7 %)	88 (17.7 %)	300 (24.2 %)	300 (24.2 %)
Risk Assessment (US EPA RAGS)	HI	109 (21.9 %)	109 (21.9 %)	341 (27.5 %)	341 (27.5 %)
	R	108 (21.7 %)		335 (27.0 %)	

HI MCL: Hazard Index Maximum Contaminant Level; MCL: Maximum Contaminant Level; HI: cumulative Hazard Index; R: cumulative Risk.

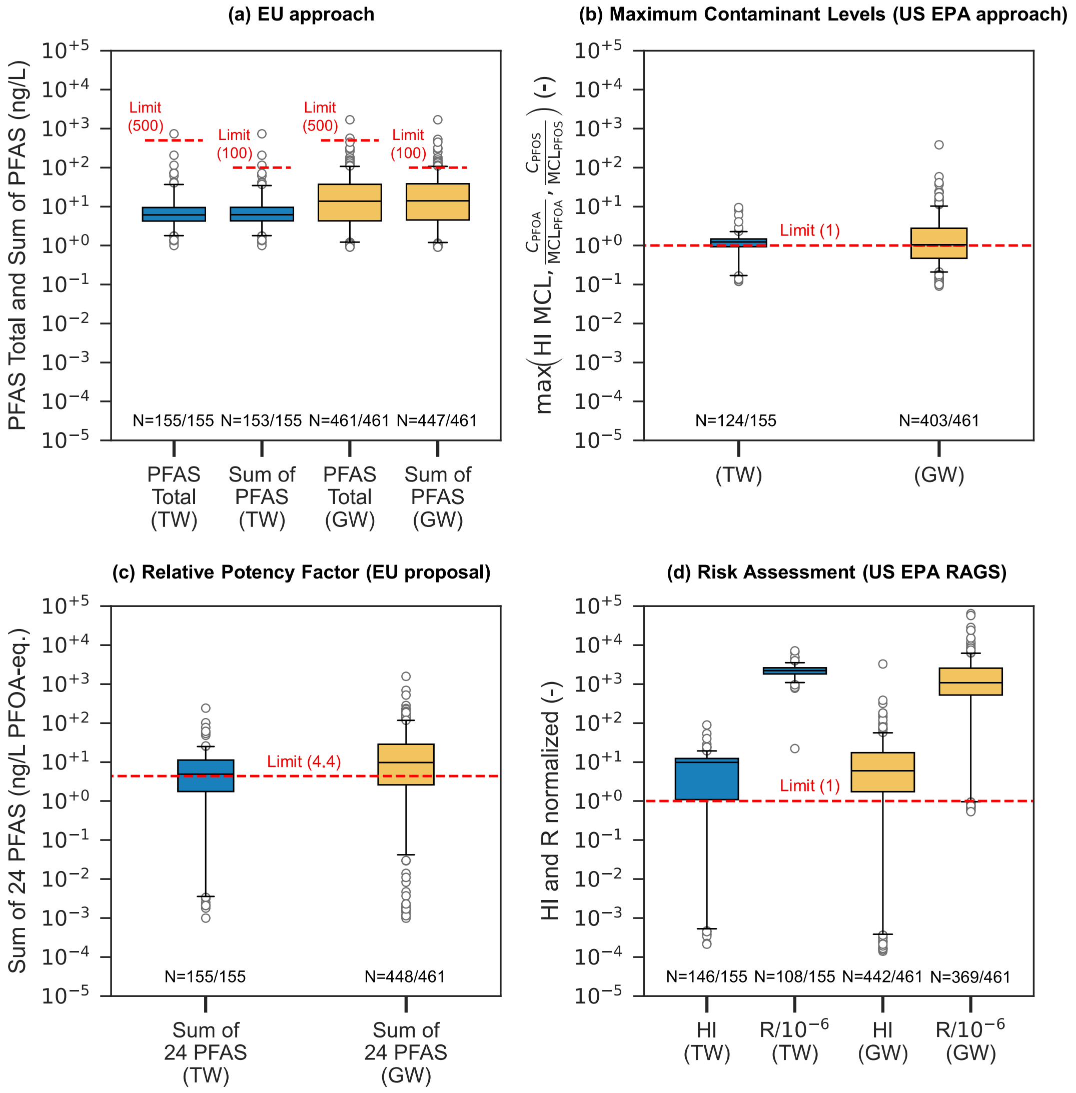

Fig. 1. Distribution of the parameters calculated for samplings with detected PFAS in TW (blue) and GW (yellow), and comparison with the threshold (red dotted line) adopted by the different approaches for PFAS mixtures considered in this study. Box: 25th-75th percentiles. Whiskers: 5th-95th percentiles. Horizontal black line: median (50th percentile). Circles: values outside the whiskers (potential outliers). N: number of PFAS samples with detected PFAS that can be included in the calculation of the respective parameter, over the total number of samplings with detected PFAS ($n_{detected}$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

exceedances represented by values above the 95th percentile. Therefore, in addition to limited support from ecological and toxicological studies (Cousins et al., 2020a; Reinikainen et al., 2024; SCHEER, 2025), the application of these thresholds also appears to be misaligned with the PFAS concentrations observed in the selected datasets, meaning that most of the exceedances could be improperly interpreted as anomalies. When the other approaches have been applied, the parameters distributions resulted more comparable with their respective thresholds. The level of not compliance under the Maximum Contaminant Levels approach was assessed by analyzing the maximum between the HI MCL and the ratios of the individual PFAS concentrations over their respective MCL (i.e., C_i/MCL_i). Since the C_i/MCL_i ratios of PFAS different from PFOA and PFOS account for the calculation of the HI MCL, the distribution of the maximum values between the HI MCL, C_{PFOA}/MCL_{PFOA} and C_{PFOS}/MCL_{PFOS} parameters has been presented in Fig. 1b. Therefore, the compliance with the US EPA thresholds is met when the resulting value is lower than 1.

For both TW and GW datasets, distributions of the maximum values between the HI MCL, C_{PFOA}/MCL_{PFOA} and C_{PFOS}/MCL_{PFOS} are well centered around the respective threshold (i.e. ,1), with the resulting 95th percentiles reaching 2.3 and 11.1, respectively. Additionally, as shown in Table S4, more than one PFAS exceeded its MCL, particularly in GW. These results indicate that MCLs, being more closely aligned with PFAS concentrations, provide a more precautionary basis for determining compliance compared to the EU approach. Besides, threshold exceedances with this approach resulted one order of magnitude lower than those from the Relative Potency Factor and Risk Assessment (US EPA RAGS) approaches. For instance, in the case of Relative Potency Factor, the 95th percentile of the “Sum of 24 PFAS” parameter reached 25.2 and 117.7 ng/L PFOA-equivalents for TW and GW, respectively (Fig. 1c). Fig. 1d shows the distribution of HI and R parameters for the Risk Assessment (US EPA RAGS) approach, each normalized to its respective threshold (i.e., 1 and 10^{-6}, respectively). Similar to the Relative Potency Factor approach, HI resulted well above the threshold for both TW and GW, with 95th percentiles of 19.4 and 57.6, respectively.

The greater extent of exceedances observed with these two approaches can be attributed to the larger number of PFAS included in the calculation of the “Sum of 24 PFAS” and HI parameters, as well as to frequent detection of PFOA and PFOS, that are characterized by high RPFs and RfD (this aspect is further discussed in Section 4.4). Therefore, compared to the Maximum Contaminant Levels approach, both the Relative Potency Factor and Risk Assessment (US EPA RAGS) approaches not only result in a higher number of threshold exceedances, but also suggest the need for more stringent interventions. Overall, the distribution of the “Sum of 24 PFAS” and HI normalized parameters, as well as their proximity to the threshold, appear particularly aligned, indicating that these approaches yield a similar evaluation of the non-carcinogenic effects of the whole mixture. The most substantial differences are presumably related to the EQS of 4.4 ng/L, which is based on toxicological evaluation carried out by the EFSA (EFSA, 2020; SCHEER, 2025). For instance, if the EQS for the mixture would have been derived applying the ASTM E2081 standard, which is part of the Risk Assessment (US EAPA RAGS) methodology, and by adopting the toxicological parameters of PFOA (US EPA, 2025c), the resulting value would be $2.29 \cdot 10^{-3}$ ng/L. This value is significantly more conservative and closely aligned with the Risk Assessment (US EPA RAGS) outcomes. Nevertheless, when carcinogenic effects are taken into consideration under the Risk Assessment (US EPA RAGS) approach, significantly diverging results are obtained. As shown in Fig. 1d, the median values of R for both TW and GW were three orders of magnitude above the threshold, highlighting a risk profile that is far more concerning than that suggested by non-carcinogenic assessments alone.

In summary, this comparative analysis highlights that a simple summation of PFAS concentrations, as adopted in the EU approach, does not account for the actual toxicological profiles of the individual compounds within a mixture. As a result, this method may lead to an oversimplified evaluation of the health risks associated with PFAS exposure. It is evident that the misalignment of the EU approach compared to the others is largely due to the choice of current thresholds. Specifically, in addition to being applicable to multiple compounds, the “PFAS Total” and “Sum of PFAS” limits are between one and two orders of magnitude higher than those set by other approaches. While applying more stringent thresholds would increase the practical level of precaution, uncertainties would remain regarding their interpretability if they were not supported by toxicological evidence. Similarly, as “PFAS Total” and “Sum of PFAS” parameters represent a simple sum of different chemical compounds, the meaning of the values obtained appears more difficult to interpret compared to other approaches.

In contrast, both the Relative Potency Factor approach and the Risk Assessment (US EPA RAGS) approach incorporate information about the relative toxicity of each compound, allowing for a more accurate assessment that reflects the specific composition of the mixture.

Notably, the comparison also shows that these two approaches yield relatively consistent outcomes in terms of toxicological impact, reinforcing their reliability for mixture risk assessment. However, when considering carcinogenic effects, the Relative Potency Factor approach may not be sufficiently protective, particularly if an acceptable risk level is set at $R = 10^{-6}$, as exceedances under this threshold are more clearly identified through the Risk Assessment (US EPA RAGS) approach. Additionally, it should be noted that the cancer risks rely on slope factors based on toxicological knowledge that is still evolving (Boston et al., 2025; Zheng et al., 2024). Some of these values incorporate conservative assumptions or safety factors and may not yet reflect a fully consolidated scientific consensus (Boston et al., 2025; NHMRC, 2025; Zheng et al., 2024). For instance, the National Health and Medical Research Council (NHMRC) of Australia supported that current epidemiological studies concerning PFOA and PFOS carcinogenicity describe these compounds as carcinogens non-genotoxic, for which threshold-based guidance values are preferred over slope factor approaches (NHMRC, 2025). As a result, the outcomes of the Risk Assessment (US EPA RAGS) approach, though highly protective, should be interpreted considering these uncertainties.

4.4. *Role of PFOA and PFOS*

When PFAS mixtures assessments based on human health risks were applied, PFOA and PFOS detections played a predominant role in influencing the frequency and extent of exceedances in both TW and GW samplings. Table S5 shows that for the Maximum Contaminant Levels, Relative Potency Factor, and Risk Assessment (US EPA RAGS) approaches, most detections of PFOA and PFOS exceeded their respective thresholds. Notably, for the Risk Assessment (US EPA RAGS), all TW detections of these two PFAS were found to be non-compliant with HI or R, while in GW, threshold exceedances were observed in 100 % and 90 % of the PFOA and PFOS detections, respectively. In contrast, under the EU approach, the majority of PFOA and PFOS detections were found to be acceptable, highlighting a marked divergence in outcomes depending on the assessment applied. As shown in Table S6, under the MLCs approach, PFOA and PFOS were the compounds most frequently exceeding their respective MCL. However, the selection of the MCLs for both PFOA and PFOS has been driven by technical-economic feasibility considerations (US EPA, 2024b). This practically contributed to a lower frequency of non-compliant detections of PFOA and PFOS compared to the Relative Potency Factor and Risk Assessment (US EPA RAGS), where only toxicological evaluations are carried out.

In the case of the Relative Potency Factor approach, the concentrations of PFOA and PFOS account for the same threshold, with PFOS contributing twice as much as PFOA. Conversely, in the Maximum Contaminant Levels approach the precautionary level applied to PFOA and PFOS is equal, and their respective concentrations are evaluated independently, resulting in a lower number of exceedances compared to

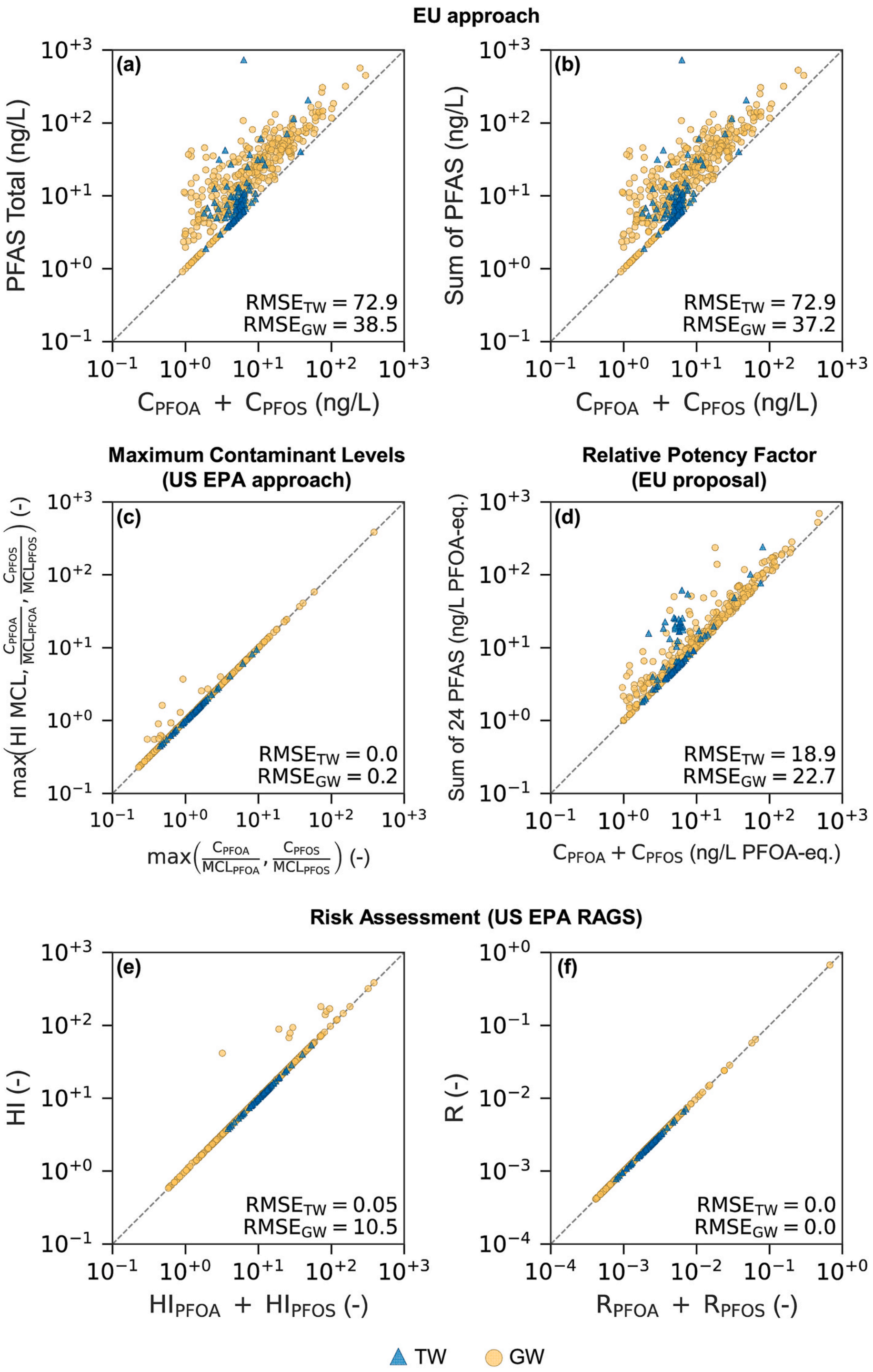

Fig. 2. Contribution of PFOA and PFOS on the calculation of the parameters covered by the different PFAS mixtures assessment approaches. The dashed grey line indicates the line of equality (1:1 relationship) between the horizontal and vertical axes. RMSE = Root Mean Squared Error. RMSE = 0 in (f) as only PFOA and PFOS contributed to the calculation of R.

the Relative Potency Factor approach. Given the significant impact of PFOA and PFOS, their effective contribution in the calculation of the different parameters has been addressed. Fig. 2 illustrates the linear correlation between parameter values derived from the entire PFAS mixture and those based only on PFOA and PFOS. The Root Mean Squared Error (RMSE) values have also been represented to describe the average discrepancies and assess how well estimates based only on PFOA and PFOS reflect full mixture values. Overall, the parameters of the EU approach are less determined by the concentrations of PFOA and PFOS (Fig. 2a and b), as concentrations of different PFAS contribute equally toward the same thresholds. Therefore, while PFOA and PFOS are among the most frequently detected, the detection of other PFAS also becomes relevant. Under the Relative Potency Factor approach, most PFAS show RPFs lower than those of PFOA and PFOS, including compounds commonly detected in water samples (e.g., PFHpA, PFNA, PFHxA, PFBS, and PFHxS). Consequently, their contribution is less relevant compared to that of PFOA and PFOS. Nevertheless, the relatively high RMSE values indicate that PFOA and PFOS detections are not entirely determinative. In the case of the Maximum Contaminant Levels and Risk Assessment (US EPA RAGS) approaches, on the other hand, the parameter values applied to PFOA and PFOS alone are more representative for the entire mixture, as highlighted by the RMSE values close to 0 (Fig. 2c-e, and f). To avoid ambiguity, the RMSE for carcinogenic effects was zero in both TW and GW samplings, as SFs have only been defined for PFOA and PFOS. While under the US EPA approach this can be clearly ascribed to the small number of PFAS with established MCLs, in the Risk Assessment (US EPA RAGS) approach this is also attributable to the lower toxicological values of commonly occurring PFAS different from PFOA and PFOS. Overall, these results suggest that in PFAS mixture assessment approaches based on toxicological evidence, the detection of PFOA and PFOS plays a key role in determining compliance. However, the lower correlation observed under the Relative Potency Factor approach suggests that this may be due to the inclusion of only a limited number of compounds at this stage.

5. Conclusions

This study presents a comprehensive and data-driven comparison of four major approaches for assessing PFAS mixtures in drinking water, applied to two extensive field datasets from the USGS, including 497 tap water samples and 1238 groundwater samples. The results clearly demonstrate how the choice of assessment method can lead to very different outcomes in terms of risk characterization, threshold exceedances and regulatory implications.

The EU approach was applicable to all samples due to its simplicity and reliance on total concentrations. However, this method does not account for the toxicological differences among individual PFAS compounds, limiting its ability to accurately reflect the potential health risks posed by complex mixtures.

The Maximum Contaminant Levels approach introduced by the US EPA in 2024 offers a more health-based evaluation but remains restricted to a limited number of PFAS. Although this method is more protective than the EU approach, many PFAS mixtures found in the environment are still not fully addressed.

More data-intensive approaches, such as the Relative Potency Factor approach and the Risk Assessment (US EPA RAGS), provide a toxicity-weighted evaluation of PFAS mixtures and offer a more robust representation of the associated health risks. These methods yielded more consistent outcomes and better alignment with the expected toxicological impact of PFAS mixtures.

Notably, significant differences emerged when carcinogenic risks were considered. The Relative Potency Factor approach does not currently address cancer endpoints and may not be sufficiently protective in these scenarios. Conversely, the Risk Assessment (US EPA RAGS) highlighted a more critical situation, with cumulative cancer risks substantially exceeding generally accepted risk thresholds across the datasets. However, it is important to note that the cancer risk estimates produced by the risk assessment approach are based on slope factors that, while grounded in current toxicological knowledge, are still evolving. Some of these values rely on conservative assumptions and safety factors. Therefore, although the outcomes of this approach are highly protective, they should be interpreted with caution, considering the underlying uncertainties.

Overall, this study clearly demonstrates that the choice of assessment method can substantially influence the interpretation of PFAS contamination and the associated human health risks. The same dataset may lead to significantly different conclusions depending on the evaluation approach applied. These findings emphasize the urgent need for regulatory harmonization and the adoption of scientifically sound toxicity-weighted methodologies for PFAS mixtures assessment.

CRediT authorship contribution statement

Giovanni Scaggiante: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Daniela Zingaretti:** Writing – review & editing, Supervision, Methodology. **Iason Verginelli:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2025.127177.

Data availability

Data will be made available on request.

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