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Review article

Estimation of per- and polyfluoroalkyl substances (PFAS) half-lives in human studies: a systematic review and meta-analysis

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ABSTRACT

Background: Per- and polyfluoroalkyl substances (PFAS) constitute a heterogeneous group of synthetic compounds widely used in industrial applications. The estimation of PFAS half-life ($t_{1/2}$) is essential to quantify their persistence, their toxicity and mechanism of action in humans.
Objectives: The purpose of this review is to summarize the evidence on PFAS half-lives in humans from the available literature, and to investigate the limitations and uncertainties characterizing half-life estimation.
Methods: The search was conducted on PubMed, Scopus, and Embase databases up to July 03, 2023 and was aimed at identifying all papers that estimated PFAS half-life in human populations. We excluded studies on temporal trends or providing estimates of half-life based solely on renal clearance. As persistent and ongoing exposures can influence half-life estimation, we decided to include only studies that were conducted after the main source of exposure to PFAS had ceased. A random-effects meta-analysis was conducted on studies that reported perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS) or perfluorohexanesulfonic acid (PFHxS) half-life estimation. Risk of bias was evaluated using the OHAT tool.
Results: A total of 13 articles were included in the review, with 5 studies conducted in exposed general populations and 8 studies conducted in exposed workers; the estimated mean half-life ranged from 1.48 to 5.1 years for PFOA, from 3.4 to 5.7 years for total PFOS, and from 2.84 to 8.5 years for PFHxS. High heterogeneity among studies was observed; potential reasons include the variability among the investigated populations, discrepancies in considering ongoing exposures, variability in PFAS isomeric compositions, accounting for background exposure, time since exposure stopped and methods used for half-life estimation.
Discussion: Despite the efforts made to better understand PFAS toxicokinetics, further studies are needed to identify important characteristics of these persistent chemicals. Biomonitoring studies should focus on persistent and unaccounted sources of exposure to PFAS and on individual characteristics potentially determining half-life, to ensure accurate estimates.

1. Introduction

Per- and Polyfluoroalkyl Substances (PFAS) constitute a heterogeneous group of synthetic compounds characterized by the presence of at least one perfluorinated methyl group or methylene group (Wang et al., 2021). Since the 1940s, PFAS have been widely used in industrial applications and to produce various consumer products (Glüge et al., 2020; Panieri et al., 2022). They were originally used for the manufacturing of Teflon® and Scotchgard™ and can be found in food packaging, cosmetics, waterproof textiles, and aqueous film forming foams (AFFF) used to suppress flammable liquid fires (Pelch et al., 2019). The most well-known and studied PFAS compounds are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), yet the PFAS class comprises more than 1000 chemicals (Kwiatkowski et al., 2020).

Common features of all PFAS are represented by their chemical stability and oil and water repellence, which cause environmental persistence, together with a tendency to bioaccumulate in biota through the contamination of food chains (Giesy and Kannan, 2001; Kwiatkowski et al., 2020; Su and Rajan, 2021). Human exposure to PFAS occurs primarily through food, drinking water, and occasionally through

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air and dust in heavily polluted surroundings (Domingo and Nadal, 2019). Exposure to PFAS is ubiquitous, and, as a result, many of these substances have been detected in the serum of human populations in the United States (Calafat et al., 2019; Rogers et al., 2021), China (Zhang et al., 2019), Australia (Toms et al., 2019) and Europe (Gebbink et al., 2015; Göckener et al., 2020; Pitter et al., 2020). Numerous recent epidemiological biomonitoring studies have associated PFAS exposure with various adverse health effects, as these compounds can dysregulate the functioning of the immune, endocrine, cardiometabolic and reproductive systems, and pose an increased risk of cancer and developmental effects (Sunderland et al., 2019; Fenton et al., 2021; US EPA, 2021; Schrenk et al., 2020).

Depending on their terminal functional group, PFAS can be distinguished as perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) (Buck et al., 2011). Commonly, PFAS subclasses are also distinguished based on their carbon-chain length. According to the Organization for Economic Co-operation and Development (OECD), the term "long-chain compound" refers to PFCAs with eight or more carbons and PFSAs with six or more carbons, while "short-chain" is used for PFCAs with seven or fewer carbons and PFSAs with five or fewer carbons (OECD, 2013).

PFAS are easily absorbed and slowly excreted from the human body, demonstrating a high affinity for transport proteins found in serum, nuclear receptors and cell membranes (Fan et al., 2020; Zhao et al., 2023). Due to the slower elimination of long-chain PFAS compared to short-chain PFAS, production of PFOA and PFOS in particular has been regulated and gradually phased out since the 2000s (Post, 2021; Rickard et al., 2022). However, various short-chain PFAS and PFAS mixtures are still produced today, together with emerging replacement PFAS, raising significant environmental and public health concerns (Brendel et al., 2018).

Estimation of PFAS half-life ($t_{1/2}$), defined as the time required for the PFAS concentrations in serum or plasma to fall by half from the starting concentration (Hallare and Gerriets, 2022), is fundamental to quantify PFAS persistence in people and to better investigate their toxicity and mechanism of action in humans (Fenton et al., 2021). The rate at which a chemical is eliminated from the human body is an important feature of its respective hazard profile. Toxicants with long half-lives generally show a greater bioaccumulative potential following repeated/continuous exposure (Tonnelier et al., 2012), exhibiting high absorption levels and low excretion rates (Pasecnaja et al., 2022). Therefore, data on elimination half-lives are important toxicokinetic parameters for risk assessment of many PFAS compounds that are still under regulatory scrutiny or are already regulated in some jurisdictions (Cousins et al., 2020; Langenbach and Wilson, 2021).

Despite its relatively simple visualization and mathematical derivation, the role of half-lives in PFAS toxicokinetics studies is surprisingly complex (Smith et al., 2018). Knowledge of the various mechanisms of PFAS toxicokinetics in humans, such as absorption, distribution, metabolism and excretion is still limited, as most available studies have been carried out in animals and have shown high interspecies differences in absorption and elimination pathways (Chou and Lin, 2019; Pizzurro et al., 2019; Drew et al., 2022). Most human studies on PFAS toxicokinetic processes focused on long chain PFAS, showing heterogeneous estimates among chemical compounds and investigated populations (Chiu et al., 2022), potentially due to the variability of exposure settings and concentration levels (Worley et al., 2017). Another significant source of uncertainty in half-life estimation could be due to the possible ongoing and/or unaccounted background exposures (Dourson and Gadagbui, 2021), and to the possible role of individual determinants (such as sex, age, genetics and general health), which may contribute to interindividual variation (Bois et al., 2010; Chiu et al., 2022). For example, it appears that PFAS half-lives strongly vary among sexes, with males generally showing longer half-lives compared to females (DeWitt, 2015).

The purpose of this systematic review and meta-analysis is to summarize the evidence on PFAS half-lives in humans from the available literature, and to investigate the limitations and uncertainties that characterize half-life estimation, while providing suggestions for future studies regarding this topic.

2. Materials and methods

A systematic review was conducted following the general methodology of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Page et al., 2021). The search was carried out in the PubMed, Scopus and Embase databases, using a string that included a broad range of words and synonyms related to "PFAS" and "half-life" and without limitations on publication date (Table S1). Following the PEO framework (Munn et al., 2018) we aimed at identifying original studies conducted on human populations (P) exposed to PFAS (E) in which estimates of PFAS half-lives were provided (O). The search was performed up to March 7th, 2023.

We decided to include only studies that were conducted after the cessation of the most substantial exposure to PFAS (i.e. principally contaminated drinking water or occupational exposure), as persistent and ongoing exposures can influence half-life estimation, leading to a potential overestimation of results (Russell et al., 2015; Chiu et al., 2022). Additionally, we excluded all studies that provided an estimate of half-life solely based on renal clearance, since PFAS are also excreted through blood loss, maternal transfer to the fetus, breastfeeding, menstruation (Rickard et al., 2022), as well as through bile and faeces (Roberts, 2013; Chambers et al., 2021; Fletcher et al., 2022). We included studies that calculated half-lives using repeated serum measurements (at least two samples per participant) obtained on the same population. Furthermore, we excluded studies on temporal trends, as these studies measure PFAS concentrations in different populations using different time points. All PFAS were considered for inclusion. Inclusion and exclusion criteria are fully specified in Table 1.

The selection process was performed by two independent reviewers (I.R. and T.B.), and conflicts were solved with the intervention of a third reviewer (E.B.). Both reviewers checked the reference list of included papers for potentially relevant additions. For each of the selected articles, each reviewer independently collected the following information: study characteristics (location, setting, years of sample collection, sampling intervals); population characteristics (sample size, sex, mean age), half-life estimation details (model used, adjustments, stratification

Table 1
General and specific inclusion and exclusion criteria for papers' selection.

Inclusion criteria
General criteria
• English language • Original articles • Human studies
Specific criteria
• Estimation of half-life with 2+ measurements performed on the same participants at different time points • Defined cessation of main exposure
Exclusion criteria
General criteria
• Languages different from English • Reviews, commentaries, conference abstracts, editorials, letters, responses to authors, protocols, pilot studies • Animal or environmental studies
Specific criteria
• Estimation of half-life with measurements performed on different populations in different time points (temporal trend studies) • Estimation of half-life through renal clearance

groups); exposure information (end of exposure, initial PFAS levels), along with the provided estimates for PFAS half-lives, including 95% confidence intervals (CI) when available. When relevant information was not directly available in the text, the reviewers contacted the corresponding authors to request additional data.

Risk of bias for included studies was independently evaluated by both reviewers (I.R. and T.B.), using the US National Toxicology Program's Office of Health Assessment and Translation (OHAT) risk of bias tool (OHAT, 2015), which comprises different domains investigating various possible sources of bias: confounding, attrition/exclusion, detection, selective reporting and others (Eick et al., 2020). Conflicts among the reviewers were solved with the intervention of a third reviewer (E.B.)

In the meta-analysis, we included only studies that provided estimates of the mean half-life and the respective standard error, as well as those from which standard errors could be computed using the published 95% CI; in each forest plot, we focused on a single PFAS substance, considering the studies providing the most comprehensive information on the substance of interest, for example reporting half-lives for different isomers of the investigated PFAS. We focused on PFAS compounds for which half-life estimates were available in at least three different studies, and when studies were conducted on the same populations, we included only the most recent publication. To account for the variability in the degrees of exposure, the covariates considered for the adjustment, and the statistical models used for half-life estimation, a random-effects model was chosen for the meta-analysis. The heterogeneity among the studies was investigated using the I^2 statistic. We defined heterogeneity as moderate or high using the I^2 cut-offs of 50% and 75%, respectively (Higgins et al., 2003). When possible, stratified meta-analyses were performed for studies on exposed workers or exposed general populations. In addition, as sensitivity analyses, we excluded studies in which half-life was estimated for a PFAS whose measured concentrations were not the highest among all the PFAS investigated, and therefore that substance could not be considered the principal exposure of interest and excluded studies that did not meet the criteria for very low/low risk of bias for the domains used in the OHAT risk of bias tool. We employed an informal narrative approach for certainty assessment. Statistical analyses were performed using the "meta" package in the statistical software R (R Core Team, 2022). The protocol for this systematic review was not registered.

3. Results

After the screening process, a total of 13 studies were included in the present review, with 5 studies conducted on exposed general populations and 8 studies conducted on exposed workers (Fig. 1).

A total of 10 studies reporting temporal trends of serum concentrations of PFAS were excluded (Olsen et al., 2008, 2012; Spliethoff et al., 2008; Glynn et al., 2012; Wong et al., 2014; Gebbink et al., 2015; Gomis et al., 2017; Nguyen et al., 2019; Kim et al., 2020; Norén et al., 2021), along with 7 studies in which the main exposure was still present at the time of blood sampling for half-life estimation, or cessation of exposure was not clearly defined or explicitly stated (Ding et al., 2020; Fu et al., 2016; Gribble et al., 2015; Harada et al., 2005, 2007; Worley et al., 2017; Zhang et al., 2013a, 2013b), and five studies that estimated PFAS half-life based only on renal clearance (Zhou et al., 2014; Zhang et al., 2015; Gao et al., 2015; Fujii et al., 2015; Shi et al., 2016). In addition, a total of 83 studies were excluded because they did not assess PFAS half-lives among the outcomes; 15 studies were excluded as they provided theoretical estimates for half-life and 21 were excluded because they were reviews or conference abstracts (Fig. 1). The characteristics of the included studies are presented in Table 2 and Table 3 (half-lives reported for PFAS other than PFOA, PFOS, and PFHxS are instead reported in Table S2 and Table S3). Most studies were conducted in Europe (53.8%) and the United States (30.8%), followed by Australia (15.4%). The sample sizes were relatively small, especially for the workers subgroup, ranging from 4 to 200 subjects (with an average number of subjects of 69).

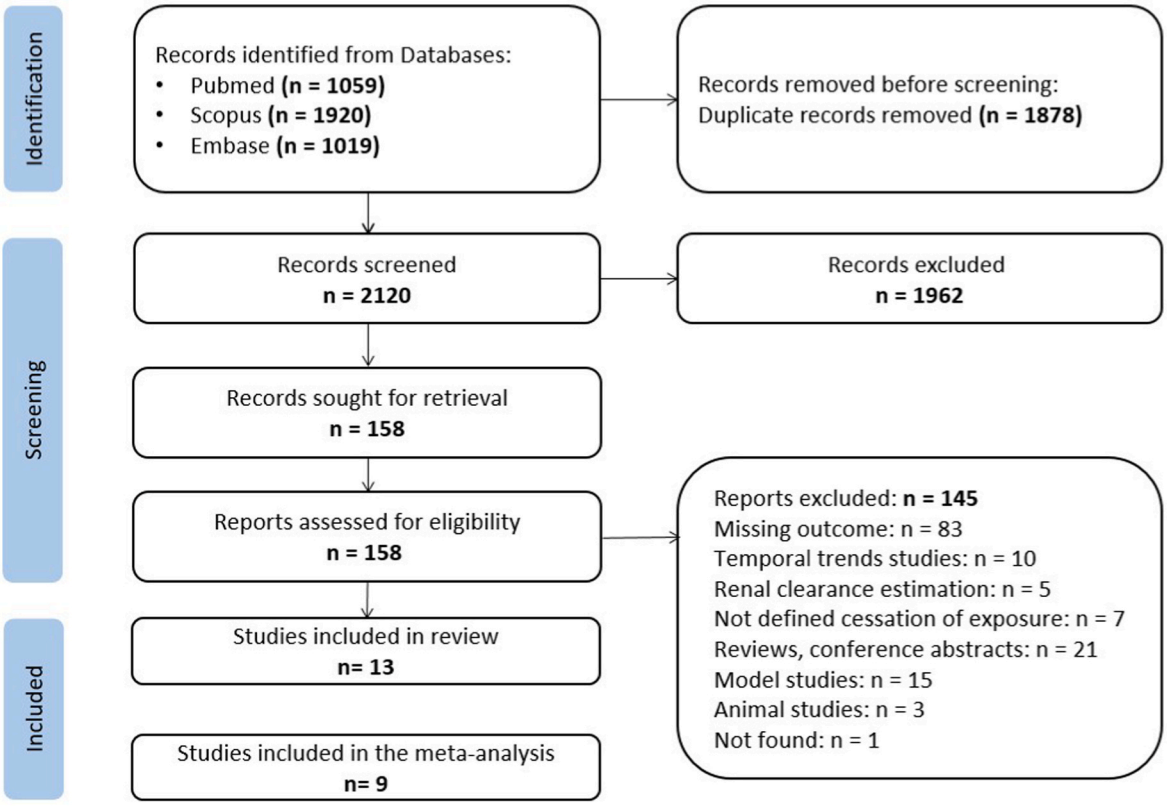

Fig. 1. Flowchart for studies' selection.

Table 2
Studies conducted on exposed general populations.

Author, year	Setting	Follow-up duration	N (% female)	Mean age, years (SD)	Initial PFAS concentrations (ng/mL)	PFOS half-life (years)	PFOA half-life (years)	PFHxS half-life (years)	Adjustment
Bartell et al. (2010)	USA; drinking water exposure, installation of charcoal filters	1 year; 6 samples/ participant, collected at 1, 2, 3, 6, and 12 months	200 (50% female)	54.5 (15)	Mean PFOA: 180	–	mean 2.3 (95% CI 2.1–2.4)	–	Water district, public/ bottled water drinking, sex, age, local or homegrown produce consumer, public water service at work
Brede et al. (2010)	Germany; drinking water exposure, installation of charcoal filters	2 years; 2 samples/ participant, collected in 2006 and 2008	65 (50.8% female)	7.9 (0.3) in children, 38.1 (4.7) in women, 55.3 (13.1) in men	Median PFOS: 9 Median PFOA: 24 Median PFHxS: 2	22% relative reduction (women), 25% (men)	39% relative reduction (women), 25% (men); GM 3.26 (range 1.03–14.67)	30% relative reduction (women), 30% (men)	Age, gender, domicile, BMI, estimated daily exposure in the period between the samplings
Li et al. (2018)	Sweden; drinking water exposure	2 years; up to 7 samples per participant, collected between 2014 and 2016	106 (53% female)	Range: 4-84	Mean PFOS: 387 Mean PFOA: 21.2 Mean PFHxS: 353	Mean 3.4 (95%CI: 3.1–3.7)	Mean 2.7 (95%CI: 2.5–2.9)	Mean 5.3 (95%CI: 4.6–6.0)	Age, gender, BMI
Yu et al. (2021)	USA; drinking water exposure	3 years; 3 samples/ participant, collected between 2017 and 2020	91 (69.2% female)	47.9 (13.3)	Median PFNA: 2,882, GM PFNA 2979	–	–	–	Age, sex, BMI
Li et al. (2022)	Sweden; drinking water exposure	4.4 years; up to 10 samples/participant, collected between 2014 and 2018	114 (53% female)	Median 42, range: 4-84	GM PFOS: 150 GM PFOA: 16 GM PFHxS: 260	L-PFOS. Original: mean 2.87 (95%CI: 2.7, 3.06). After subtraction b.e.: mean 2.73 (95%CI: 2.55, 2.92); median 2.89 (95%CI: 1.62, 4.75)	Original: mean 2.99 (95% CI: 2.79, 3.21). After subtraction b.e.: mean 2.47 (95%CI: 2.27, 2.7); median 2.69 (95%CI: 1.37, 5.4)	Original: mean 4.55 (95% CI: 4.17, 5.01). After subtraction b.e.: mean 4.52 (95%CI: 4.14, 4.99); median 5.4 (95%CI: 2.34, 9.29)	Age, gender, BMI, time elapsed between the end of exposure and the blood sample collection

GM: geometric mean; b.e.: background exposure; L: linear.

Table 3
Studies conducted on overexposed workers.

Author, year	Setting	Follow-up duration	N (% female)	Mean age, years (SD)	Initial PFAS concentrations (ng/mL)	PFOS half-life (years)	PFOA half-life (years)	PFHxS half-life (years)	Adjustment
Olsen et al. (2007)	USA; retired fluorochemical workers	Up to 5.3 years; 4 to 7 samples/ participant collected	26 (7.7 % female)	61 range: 55–75	∑(L + B) mean PFOS: 799 ∑(L + B) mean PFOA: 691 ∑(L + B) PFHxS: 290	∑(L + B): mean 5.4 (95%CI 3.9–6.9) median 4.6, range 2.4–21.7 GM 4.8 (95%CI: 4.0–5.8)	∑(L + B): mean 3.8 (95% CI 3.1–4.4) median 3.4, range 1.5–9.1 GM 3.5 (95%CI: 3.0–4.1)	∑(L + B): mean 8.5 (95% CI 6.4–10.6) median 7.1, range 2.2–27.0 GM 7.3 (95% CI: 5.8–9.2)	Initial and end-of-study perfluoro-chemical concentration, age at study onset, years worked, years since retirement
Costa et al. (2009)	Italy; Formerly exposed workers	7 years; 7 samples/ participant collected from 2000 to 2007	16 (0% female)	52 (8.7)	Median PFOA: 11.92; mean PFOA: 18.8	–	mean 5.1 SD 1.7 range 2.6–9.7 GM 4.8	–	
Olsen et al. (2009)	USA; Workers exposed to PFBS	6 months; 10 samples/ participant	6 (16.7% female)	–	Mean PFBS: 397, median PFBS: 363	–	–	–	
Russell et al. (2013)	Sweden; Wax technicians	5 years; Samples collected during and after ski season between 2007 and 2011	7 (0% female)	–	Mean PFHxA: 1.9; median PFHxA: 0.68	–	–	–	
Gomis et al. (2016)	Sweden; Ski waxers	1 year; 10 samples/ participant collected from 2007 to 2008	4 (0% female)	–	PFOS range: 250-1050	–	mean 2.4, range 2.0–2.8	–	
Xu et al. (2020)	Sweden; airport employers provided with clean water	4 months; 5 samples/ participant collected in 2018	17 (35% female)	Median 50, range: 24-62	Median L PFOS: 11 Median T PFOA: 13 Median T PFHxS: 133	L-PFOS: original levels: mean 2.91 (95% CI 1.71 to 9.63); with subtraction of b.e.: 1.69 (95% CI 0.98 to 6.04)	Total. Original levels: mean 1.77 (95% CI 1.43 to 2.31); with subtraction of b.e.: 1.48 (95% CI 1.19 to 1.96)	Total. Original levels: mean 2.86 (95% CI 2.1 to 4.47); with subtraction of b.e.: 2.84 (95% CI 2.08 to 4.43)	Age, sex, background exposure
Nilsson et al. (2022b)	Australia; Firefighters exposed to aqueous-film forming foam	5 years; 2 samples/ participant collected in 2013–2014 and 2018–2019	120 (3.3% female)	Range: 33-72	Mean L PFOS: 26 Median L PFOS: 21 Mean T PFOS: 60	L: mean (SD) = 4.0 (1.4); median = 3.8 (95%CI: 2.5–6.8) range: 0.8–10 ∑B: mean (SD) = 5.5 (1.9); median = 5.4; 95%CI: 2.7–8.8	–	–	
Nilsson et al. (2022a)	Australia; Firefighters exposed to aqueous-film forming foam	5 years; 2 samples/ participant collected in 2013–2014 and 2018–2019	130 (3% female)	–	∑(L + B) PFOS: 27 Mean L PFOA: 1.7 Mean L PFHxS: 14	∑(L + B). Original levels: mean 6.5 (95% CI 6.1, 6.9); with subtraction of background exposure: mean 5.7 (95% CI 5.2, 6.2)	L. Original levels: mean 5.0 (95% CI 4.7, 5.4); with subtraction of background exposure: mean 2.0 (95% CI 1.7, 2.2)	L. Original levels: mean 7.8 (95% CI 7.3, 8.3); with subtraction of background exposure: mean 6.0 (95% CI 5.5, 6.5)	

T: total; L: linear; B: branched; b.e.: background exposure.

In all the studies involving exposed general populations, the contamination of PFAS compounds occurred through drinking water. In Sweden, the main source of contamination was the use of firefighting foam in a nearby airfield (Li et al., 2018, 2022), while in other countries it was attributed to local contamination generated by chemical plants (Bartell et al., 2010; Yu et al., 2021) or to soil improvers mixed with industrial waste applied in agricultural areas (Brede et al., 2010). In all these studies, the cessation of the primary exposure was achieved by implementing granulated activated carbon filters, which ensured the provision of clean water. In studies involving exposed workers, the participants included employees working in fluorochemical plants (Olsen et al., 2007, 2009; Costa et al., 2009), technicians working with fluorinated wax during the ski season (Russell et al., 2013; Gomis et al., 2016), employees at airports (Xu et al., 2020) and firefighters with historical exposure to aqueous film forming foams (Nilsson et al., 2022a, 2022b). In occupational settings, cessation of exposure occurred when workers retired or were transferred (Olsen et al., 2007, 2009; Costa et al., 2009), stopped working with ski wax (Russell et al., 2013; Gomis et al., 2016), or when carbon filters were installed in the airport facilities (Xu et al., 2020). For the studies conducted in Australia, the main exposure to PFAS ceased when fluorine-containing firefighting foams were replaced with alternative chemicals (Nilsson et al., 2022a, 2022b), although "apparent" half-lives were estimated, as firefighters continued to work in PFAS contaminated sites.

In general populations, the main exposure was to PFOA (Bartell et al., 2010; Brede et al., 2010), PFNA (Yu et al., 2021) or to PFOS and PFHxS (Li et al., 2018, 2022). In workers, the primary exposure was to PFOA (Costa et al., 2009; Gomis et al., 2016), PFOS (Nilsson et al., 2022a, 2022b), PFHxS (Xu et al., 2020) or to more than one of them (Olsen et al., 2007), and median measured concentrations were generally higher than those observed in general populations. In some studies, half-life was estimated only for a single compound measured in the participants' serum; it is the case of PFOA, with concentrations that ranged from 18.8 ng/mL in Italian workers (Costa et al., 2009), to 180 ng/mL in exposed populations of the Ohio Valley (Bartell et al., 2010) and 1050 ng/mL in occupationally exposed ski waxers (Gomis et al., 2016). In other studies, the authors estimated half-lives for perfluorononanoic acid (PFNA) (Yu et al., 2021), perfluorobutanesulfonic acid (PFBS) (Olsen et al., 2009) and perfluorohexanoic acid (PFHxA) (Russell et al., 2013) only. In all the remaining studies, concentrations of several PFAS were measured and half-life estimates were provided for more than one of them; in some cases, half-lives were estimated for substances that had relatively low initial concentrations, with mean PFOA levels of 1.7 ng/mL (Nilsson et al., 2022a), median PFOS levels of 11 ng/mL (Xu et al., 2020) and mean PFHxS levels 14 ng/mL (Nilsson et al., 2022a). In the remaining studies, measured concentrations were extremely high, with mean PFOA levels reaching up to 691 ng/mL (Olsen et al., 2007), mean PFOS levels up to 387 ng/mL and mean PFHxS levels up to 353 ng/mL (Li et al., 2018). In most of the included studies (76.9%), with few exceptions (Li et al., 2022; Nilsson et al., 2022a; Xu et al., 2020), information regarding background exposures was not provided, and the presence of ongoing exposures was not taken into account for half-life estimation.

In all the included studies, PFAS half-life was estimated using one-compartment models with first-order elimination. In this kinetic model, the body is considered as one homogeneous volume from which PFAS could be absorbed and eliminated according to a constant rate of elimination that is proportional to the concentration of PFAS in the body. Mathematically, the rate of elimination is described by an exponential decay equation, where the concentration of the substance decreases over time exponentially (Xu et al., 2020). Most of the included studies were evaluated as having "very low" or "low" risk of bias for most of the domains presented in the OHAT risk of bias tool; four studies (Costa et al., 2009; Olsen et al., 2009; Russell et al., 2013; Gomis et al., 2016) conducted on workers were evaluated as having "probably high" or "definitely high" risk of bias in 3 different domains: confounding, attrition and statistical methods applied (Table S4).

Forest plots were made only for the main studied PFAS, namely PFOA, PFOS, and PFHxS. Moreover, some studies were excluded from the meta-analysis due to their failure to provide all the essential information required for the estimation of half-life. For example, a study reported only relative reductions in PFAS concentrations and the geometric mean of PFOA half-life (Brede et al., 2010), providing only its corresponding range and therefore making it impossible to retrieve a confidence interval for their estimate. For PFOS, the information available in three studies (Olsen et al., 2007; Li et al., 2018; Nilsson et al., 2022a) regarded total PFOS, while other studies (Xu et al., 2020; Li et al., 2022; Nilsson et al., 2022b) provided information on half-life for linear PFOS (L-PFOS) and branched perfluorooctane sulfonates (1 m-PFOS, 3/4/5 m-PFOS, 2/6 m-PFOS). Total PFOS is calculated as the sum of both the branched and the linear isomers (Londhe et al., 2022), but half-life's estimates are not provided for the sum of different isomers in all cases (Xu et al., 2020). Therefore, for PFOS isomers, individual forest plots were created.

Fig. 2 shows PFOA half-life stratified according to the population category, with estimates of 2.35 years (95% CI: 2.20–2.51, $I^2 = 43\%$) in exposed general populations and 2.92 years (95% CI: 1.66–4.19, $I^2 = 93\%$) in exposed workers. Fig. 3 shows results for total PFOS and PFHxS half-life estimation, with half-life estimates of 4.77 years (95% CI: 3.26–6.29, $I^2 = 97\%$) and 5.35 years (95% CI: 3.16–7.55, $I^2 = 93\%$), respectively. Figure S1 shows the results for different PFOS isomers, with half-life estimates of 3.13 years (95% CI: 1.98–4.28) for L-PFOS, 3.94 years for 3,4,5 m PFOS, 2.55 years for 2,6 m PFOS and 5.86 years for 1 m-PFOS. In almost all cases, a significant amount of heterogeneity was observed, strongly limiting the interpretability and reliability of the results. For PFOA, a sensitivity analysis was conducted excluding the studies in which, according to serum measured PFAS concentrations, PFOA was not the PFAS present at highest concentrations (Figure S2, 1); we also excluded from the forest plot on PFOA half-life those studies that were evaluated as having high risk of bias in key domains of the OHAT tool (Figure S2, 2). However, heterogeneity remained high in both cases.

4. Discussion

This systematic review and meta-analysis included 13 studies with relatively small sample sizes, mainly conducted in Europe and USA and involving both general populations and workers exposed to PFAS. Half-life estimates were 2.73 years for PFOA (range: 1.48–5.1 years), 4.70 years for PFOS (range: 1.69–5.7 years), and 5.31 years for PFHxS (range: 2.84–8.5 years). The long half-lives observed for these compounds should be interpreted considering their chemical properties, which contribute to their resistance against metabolic degradation and varying solubility (East et al., 2023). The defining feature of PFAS lies in the C–F bond, recognized as the strongest covalent bond in organic chemistry, which confers thermal stability to these substances. Additionally, the hydrophobic and lipophobic nature of PFAS can be primarily attributed to the low polarizability of fluorine atoms, combined with the presence of a stable terminal functional group attached to the fluoroalkyl chain (Gagliano et al., 2020; Meegoda et al., 2020). As the number of hydrogen atoms is replaced with fluorine atoms and the carbon-chain length increases, PFAS progressively exhibit heightened chemical inertness. Conversely, a decrease in the carbon-chain length is associated with an increase in their water solubility (Kucharzyk et al., 2017).

Once PFAS enter into the human body, they do not undergo metabolization (Kemper and Nabb, 2005) and can be detected in various tissues (Pérez et al., 2013) and blood serum at concentrations typically measured in ng/mL. PFAS are predominantly distributed in the liver, lung, serum and kidney, but they can also be found in fat and brain tissues (Jian et al., 2018; Pizzurro et al., 2019). In blood, PFAS bind to serum albumin and liver fatty acid-binding protein (L-FABP) (L. Zhang et al., 2013a, 2013b). Elimination of PFAS from the body is limited, and they do not form conjugates or metabolites. Instead, they are excreted

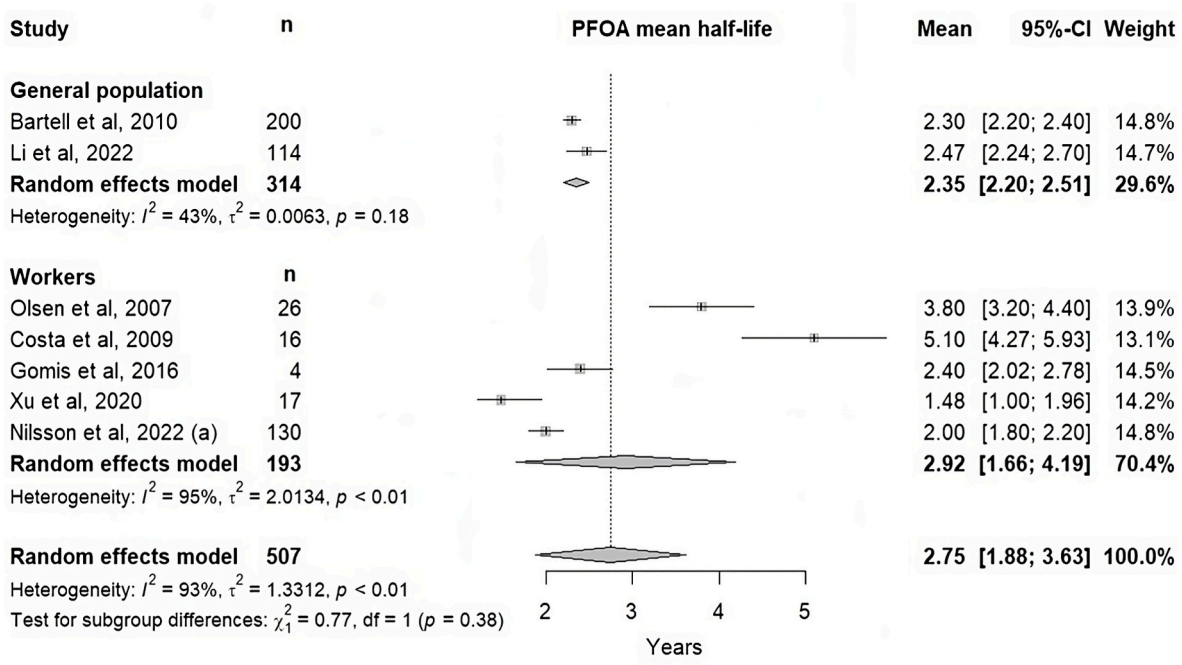

Fig. 2. PFOA mean half-life (years), stratified according to population type.

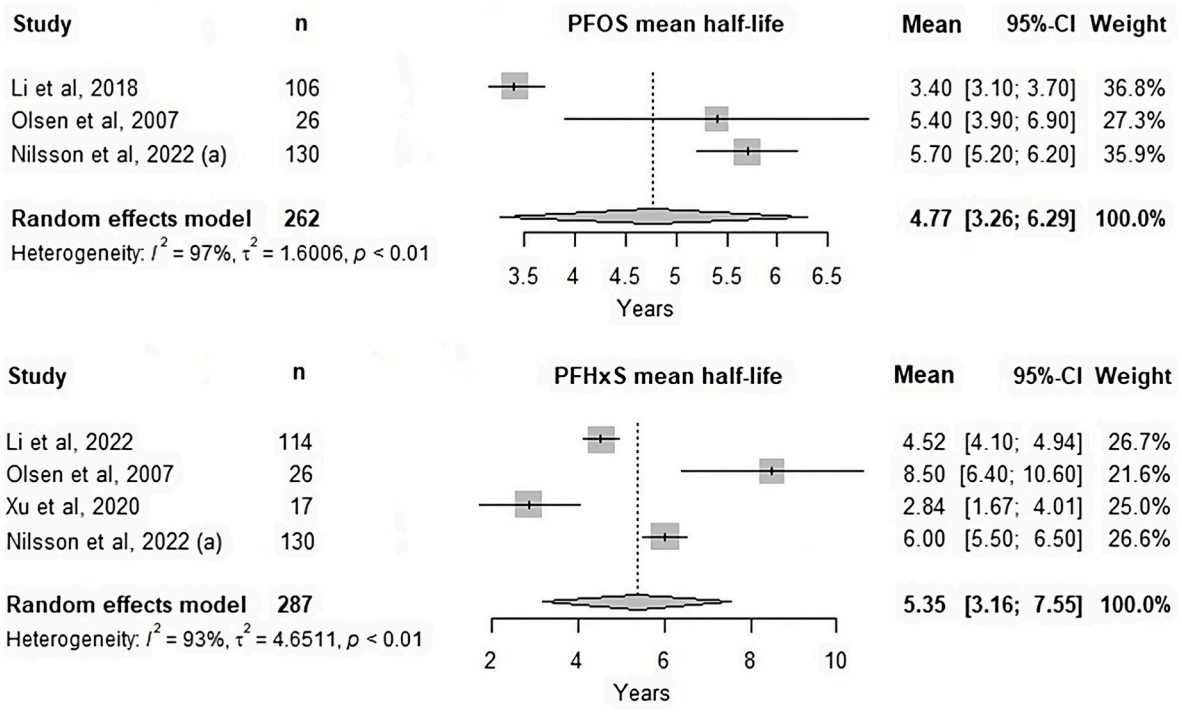

Fig. 3. Total PFOS and PFHxS mean half-life (years).

through urine, faeces, bile, lactation, transfer to the fetus and menstruation in women (De Silva et al., 2021). Urinary excretion, facilitated by renal tubular organic anion transporters (OATs), is considered the predominant elimination route for most PFAS in both animal models and human studies (Kudo and Kawashima, 2003). The extended half-lives of long-chain PFAS, such as PFOA and PFOS, are hypothesized to results from a saturable transport process in the proximal tubule of the kidney and to the presence of active renal reabsorption, mediated by OATs and organic anion-transporter polypeptides (Nakagawa et al., 2009; Yang et al., 2010; Ducatman et al., 2021). While renal elimination processes have been shown to depend on factors like sex, species and PFAS chain length, the relationship between renal secretion, reabsorption and excretion of these substances is complex and has not been thoroughly explored yet (Han et al., 2012; Ducatman et al., 2021).

All included papers employed a first-order elimination model and the interest was focused mostly around PFOA and PFOS, which is consistent with the findings of a recent scoping review of toxicokinetic models that have been put into practice (East et al., 2023). While a one-compartment model with first-order elimination may oversimplify the complex

processes occurring in real-world systems, it provides a useful approximation for understanding and predicting the behaviour of substances in terms of their change in concentrations over time. This model is often adopted in pharmacokinetics, toxicology, and environmental science to estimate parameters such as half-life, clearance, and steady-state concentration, aiding in the interpretation of experimental data and risk assessment (Dawson et al., 2023; East et al., 2023).

4.1. Sources of heterogeneity

The results of the meta-analysis were half-lives of 2.73 (95% CI: 1.99–3.47) years for PFOA, 4.70 (95% CI: 3.27–6.13) years for PFOS and 5.31 (95% CI: 3.68–6.94) years for PFHxS; these estimates demonstrate limited interpretability and should be approached with caution, due to the substantial level of observed variability (Imrey, 2020). Potential sources of heterogeneity were hypothesized, including different initial serum PFAS levels, different elapsed periods of time between the cessation of exposure and the quantification of PFAS in serum samples, and variations in the characteristics of the studied populations. PFAS toxicokinetic has proven to be influenced by individual features (Li et al., 2022; Nilsson et al., 2022a), and the variability in the specific set of covariates examined across the included studies could contribute to the observed differences in half-life estimates. Some of the most recent studies evaluated the differences in half-life considering sex, kidney function and markers of gut inflammation (Li et al., 2022; Nilsson et al., 2022a), but information regarding the role of these determinants is limited and needs further evaluation. The longer PFOA half-life that was observed among workers in our meta-analysis could potentially be attributed, for instance, to the predominance of males among the worker participants; as previously discussed, males typically exhibit longer half-lives compared to females (DeWitt, 2015). However, even when conducting stratified analyses for PFOA, differentiating between exposed workers and exposed general population, there was no substantial reduction in heterogeneity. Due to the limited pool of available studies, unfortunately it was not possible to consider other potentially relevant variables for stratified analyses. Additional sensitivity analyses conducted on PFOA half-life with the aim of excluding studies where PFOA was not the primary exposure, failed to reduce the observed variability.

In addition, while we deliberately selected observational studies that assessed the cessation of the main exposure source to PFAS, not all studies provided information on other sources of exposure (background exposures). The presence of unaccounted sources of exposure makes it challenging to determine the intrinsic half-life because PFAS are nearly ubiquitous, and some degree of ongoing background exposures are expected. Studies that did not factor in background exposure by subtracting background levels before estimating half-lives (Xu et al., 2020; Li et al., 2022; Nilsson et al., 2022a) are considered to provide an overestimated result (Dourson and Gadagbui, 2021; Li et al., 2022). Therefore, we considered estimates that incorporated background exposure subtraction in forest plots whenever feasible.

Moreover, although all studies adhered to a shared toxicokinetic framework (the first-order elimination model), it's important to acknowledge the possible differences in the statistical approaches employed to estimate the quantities of interest, whether they had different assumptions or utilized a different mathematical framework. Furthermore, PFAS exist in various specific forms, including linear and branched configurations, but information regarding the forms considered for half-life estimation is not always available in the included papers, with some exceptions (Nilsson et al., 2022b). Recent studies included in the review have highlighted marked differences in the half-lives of different PFOS isomers (Li et al., 2022; Nilsson et al., 2022b), emphasizing the importance of epidemiological studies that specifically delve into PFAS isomeric configurations. The prevalence of linear isomers over branched isomers might contribute to longer estimated half-lives (Zhang et al., 2013a, 2013b), potentially offering an additional explanation for the variations in PFOA half-life estimates among the studies included. Despite these aspects, the results of the meta-analysis can serve as a starting point to discuss the current understanding of PFAS elimination and the methods used to estimate PFAS half-lives.

4.2. Studies' limitations and future objectives

The review identified a limited number of studies regarding PFAS half-life, and some studies were excluded due to the lack of pertinent information regarding the cessation of the main exposure, further restricting the already scarce number of papers on this topic. Some of the studies conducted on workers were characterized by the presence of high or extremely high risk when considering confounding bias. Additionally, the number of subjects investigated is relatively modest. When conducting studies to estimate PFAS half-lives, it is of utmost importance to incorporate larger sample sizes, that are adequate to assess variations in the elimination of these substances and the factors influencing their excretion. Also, very limited information is available regarding PFAS half-lives in specific subgroups, such as children and adolescents; subjects under 18 years of age were considered in a limited number of studies, and none of the studies performed a separate analysis on this specific group. Children and adolescents should be considered separately when estimating PFAS half-lives, as they likely have higher PFAS body burdens (Lee et al., 2021) and it is unknown if their excretion patterns are directly comparable with adults (Winkens et al., 2017).

The task of estimating half-lives of short-chain PFAS and other less-represented compounds within observational studies poses even greater challenges. Currently, very little information is available for these compounds, and as a result, no meta-analysis could be performed. It is important to note that PFAS toxicokinetics could also be shaped by the combined effect of joint exposures. Humans are exposed to complex mixtures of these substances, with their combined effects potentially being additive, synergistic or antagonistic (Glüge et al., 2020; Panieri et al., 2022). Nonetheless, there is a lack of thorough investigation regarding the interactions between PFAS compounds, as well as between PFAS and other substances, which could potentially influence the half-lives of PFAS within the human body (Ojo et al., 2020; Goodrum et al., 2021).

5. Conclusion

Despite the ongoing efforts made to enhance our understanding of PFAS toxicokinetics, further studies with larger sample sizes and consistent methodology are still needed to identify important characteristics of these persistent chemicals. The inaccurate reporting of half-lives can carry significant implications, leading to imprecise regulatory decisions and ineffective methodological strategies in future epidemiological studies (Langenbach and Wilson, 2021).

When reporting estimates for PFAS half-lives, studies should consistently consider the presence of background and ongoing sources of exposure, while also providing insights into the individual factors that may influence PFAS half-life. We strongly recommend taking into consideration all the aspects presented in this review to ensure the achievement of more accurate estimations of PFAS half-lives.

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Authors contributions

Isabella Rosato: Conceptualization, Data curation, Formal Analysis, Methodology, Writing - original draft; Tiziano Bonato: Data curation, Methodology, Writing - original draft; Tony Fletcher: Methodology,

Writing - review & editing; Erich Batzella: Conceptualization, Formal Analysis, Methodology, Writing - review & editing; Canova Cristina: Conceptualization, Methodology, Project administration, Writing - review & editing.

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.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117743.

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