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Systematic Evidence Mapping of Potential Exposure Pathways for Per- and Polyfluoroalkyl Substances Based on Measured Occurrence in Multiple Media

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Abstract

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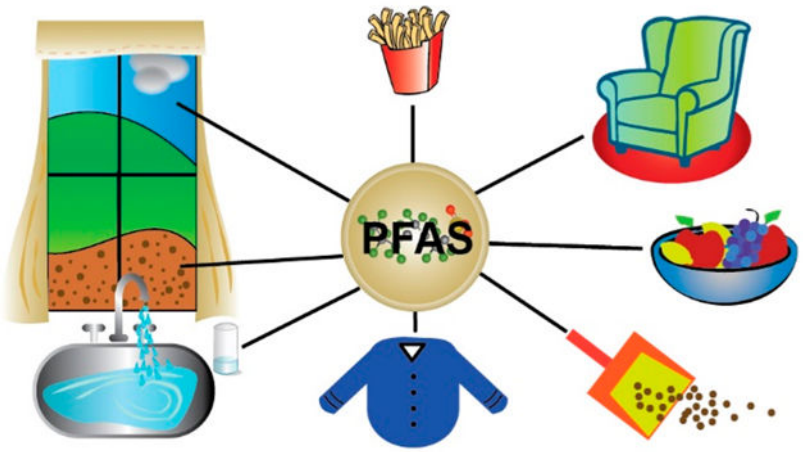
ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.2c07185.
Database file containing the data extractions for the first batch of eight PFAS (XLSX)
Database file containing the data extractions for the second batch of 12 PFAS (XLSX)
Literature search strategy, filters used in SWIFT-Review, specific information fields extracted from each study that underwent full-text screening and data extraction, information on incidental extractions, and descriptions on information extracted from biomonitoring/cohort papers (PDF)

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.est.2c07185

Given that human biomonitoring surveys show per- and polyfluoroalkyl substances (PFAS) to be ubiquitous, humans can be exposed to PFAS through various sources, including drinking water, food, and indoor environmental media. Data on the nature and level of PFAS in residential environments are required to identify important pathways for human exposure. This work investigated important pathways of exposure to PFAS by reviewing, curating, and mapping evidence for the measured occurrence of PFAS in exposure media. Real-world occurrence for 20 PFAS was targeted primarily in media commonly related to human exposure (outdoor and indoor air, indoor dust, drinking water, food, food packaging, articles, and products, and soil). A systematic-mapping process was implemented to conduct title-abstract and full-text screening and to extract PECO-relevant primary data into comprehensive evidence databases. Parameters of interest included the following: sampling dates and locations, numbers of collection sites and participants, detection frequencies, and occurrence statistics. Detailed data were extracted on PFAS occurrence in indoor and environmental media from 229 references and on PFAS occurrence in human matrices where available from those references. Studies of PFAS occurrence became numerous after 2005. Studies were most abundant for PFOA (80% of the references) and PFOS (77%). Many studies analyzed additional PFAS, particularly, PFNA and PFHxS (60% of references each). Food (38%) and drinking water (23%) were the commonly studied media. Most studies found detectable levels of PFAS, and detectable levels were reported in a majority of states in the United States. Half or more of the limited studies for indoor air and products detected PFAS in 50% or more of the collected samples. The resulting databases can inform problem formulation for systematic reviews to address specific PFAS exposure queries and questions, support prioritization of PFAS sampling, and inform PFAS exposure measurement studies. The search strategy should be extended and implemented to support living evidence review in this rapidly advancing area.

Graphical Abstract



Keywords

forever chemicals; measurement database; human exposure; residential environment; nondrinking water sources

INTRODUCTION

Addressing human exposure and health impacts of both legacy and emerging per- and polyfluoroalkyl substances (PFAS) poses a pressing environmental health challenge.[1,2] Humans can be directly exposed to PFAS through various exposure media, including drinking water, food, indoor dust, soil, indoor and outdoor air, and consumer and personal care products.

The most significant source of PFAS exposure to impacted communities is through contaminated drinking water. Drinking water supplies for over six million U.S. residents were estimated to exceed the former U.S. EPA lifetime health advisory levels of 70 ng/L for perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS), with military sites and civilian airports with fire training areas using aqueous film forming foams (AFFF), industries manufacturing or using PFAS, and wastewater treatment plants associated with increased drinking water levels of PFAS.[3] Hu et al. demonstrated that while tap water contributions in a general population cohort of U.S. women were substantially lower than those for impacted communities, water concentrations were still significant predictors of plasma PFOA and perfluorononanoic acid (PFNA).[4] In addition, the presence of PFAS in 98% of samples in the National Health and Nutrition Examination Survey (NHANES)[5] suggests that multiple exposure sources and pathways likely play roles in widespread human exposure to PFAS.

De Silva et al.[6] summarized the current knowledge and key gaps for understanding PFAS exposure pathways. Literature-based estimates for the general population showed diet to contribute most to exposures for many PFAS, with dust, drinking water, and consumer goods also contributing. Sunderland et al.[7] reviewed studies of exposure pathways for selected PFAS. In general, dietary sources contributed most to human exposures, followed by tap water, house dust, and other sources, but the contributions varied substantially across different populations and PFAS, and in some cases, they depended on which media were examined or considered in the reviewed studies. In another review, Jian et al. found important sources and pathways included diet (primarily through fish, shellfish, and meat consumption) and drinking water (well and tap), and neutral PFAS were dominant in indoor air and dust.[8] For young children, ingestion of breastmilk[9] as well as house dust[10] may be particularly important exposure pathways.

In the residential environment, PFAS may be present in and released from building materials, textiles, and consumer products, creating the potential for human exposure by multiple routes through contaminated dust, surfaces, indoor air, and soil. PFAS may also be present in some personal care products, with the potential for more direct dermal and inhalation exposures. House dust measurements suggest widespread presence of PFAS in U.S. residences[11,12] and dust measurements show the potential for exposures in other indoor environments including day care centers.[10] However, limited number of U.S. studies have characterized exposures to PFAS from these sources and pathways. For example, in a systematic review of studies with both residential indoor media and resident serum PFAS measurements, DeLuca et al. found only three U.S. and seven total studies.[13] Given the limited information available and the rapid increase in studies being published,

understanding important sources of exposure and maintaining current curated data remain challenges for decision makers.

Systematic mapping approaches can be applied to collate, describe, and catalogue available evidence relating to a topic of interest in a transparent manner to identify available evidence for policy-relevant questions, assess critical data gaps, and enable further investigation of the identified information. Evidence maps pull together and categorize primary research studies in a particular area, and visually distill the scope of the resulting information.[14] James et al. present a methodology for systematic mapping in environmental sciences where a sparsity of empirical data may limit application of systematic review methodologies to answer specific study questions.[15] In turn, results of systematic evidence mapping may facilitate identification of trends, which can be used to facilitate efficient systematic reviews or targeted studies.[16] The National Academies of Science notes that "systematic evidence maps also have considerable potential value in and of themselves as a public good by providing a publicly accessible database that could be queried and used by any research organization to identify knowledge gaps and clusters" to inform research and policy prioritization.[17] Recently, systematic−evidence−mapping (SEM) methods were used to summarize epidemiology and toxicology evidence for PFAS. Of over 150 PFAS reviewed, only 15 were measured in human studies.[18]

The objective of this work was to investigate evidence for important pathways of human exposure to PFAS by considering the measured occurrence of PFAS in exposure media. The focus of this investigation is to understand the potential for direct exposures in non-occupational settings. We applied a SEM approach to gather and collect quantitative information where available for the occurrence of PFAS in selected media including environmental samples collected in residential environments. The result is a catalogue of available evidence that can be leveraged to describe the state of knowledge and critical gaps as well as to identify subsets of evidence or topics suitable for further secondary synthesis.

METHODS FOR SYSTEMATIC MAPPING

We largely followed the methodological framework presented by DeLuca et al.[19] (adapted from the EPA ORD Staff Handbook for Developing IRIS Assessments[20]) from the problem formulation through data extraction steps (Figure 1). For this SEM, we visualized and explored the resulting evidence base[15] but did not evaluate quality of studies or fully synthesize the evidence.

Problem Formulation.

This systematic mapping to identify evidence for potentially important exposure pathways aimed to answer the question, "For the studied communities, what media in their immediate environment are contaminated with measurable levels of PFAS?" To address this question, we conducted a systematic review of peer-reviewed literature from scientific journals to identify references with occurrence data in indoor or environmental media. The goal was to identify and extract available information to understand the contribution of exposure sources to levels measured in human biomonitoring studies. We targeted a subset of 16 perfluoroalkyl acids (PFAAs) that have been measured in NHANES and four fluorotelomer

alcohols (FTOH; PFAA precursors) that may be relevant precursors for understanding exposure pathways (Table 1). These substances were selected for this SEM because measurement methods were available, and as a result, these were the most well studied.

The population, exposure, comparator, and outcome (PECO) criteria were as follows:

- Population: Adults and children in communities in the US, Canada, and Europe.
- Exposure: Real-world occurrence of any of the target PFAS in the following environmental media: outdoor air, indoor air, (indoor) dust, drinking water, food (breast milk is included as a food), food packaging, products (articles and consumer products), and soil.
- Comparator: [not applicable].
- Outcomes: [not applicable].

Note that we required the occurrence data to be measurements (not modeled values) and obtained through primary data collection. The geographic scope was limited for this review to demonstrate the search strategy and SEM methodology for this research question. We considered data from narrative review articles and studies using data that were previously presented elsewhere to be secondary data.

Strategy for Literature Search.

We used the results from literature searches previously conducted by EPA to obtain the initial list of 8112 unique references. A separate search was not performed for this SEM. The search strategies and search dates are described in DeLuca et al.[19] and Carlson et al.,[18] and the search results are available in EPA's Health and Environmental Research Online (HERO) database.[21] We provide in Table S1 (in Supporting Information) the link to each relevant HERO web page, the date on which we accessed them, and the search strategies that EPA used for the Web of Science (Thomson Reuters), PubMed (National Library of Medicine), and ToxNet/ToxLine (National Library of Medicine) literature databases. (Note: ToxNet was retired in 2019. HERO used an offline version of the data set for their searches.)

We downloaded the search results directly from HERO and filtered the references to those published 2003−2020 (or 2021, depending on when the search was conducted). The resulting 7345 unique references were then imported into Sciome Workbench for Interactive computer-Facilitated Text-mining (SWIFT)-Review software (a product of Sciome[22]) to further filter the references for relevancy. In brief, the SWIFT-Review filters function like a search strategy where studies are tagged to a category if the search terms appear in the title or abstract. We used pathway-specific filters (e.g., environmental media, food packaging, etc.) previously developed by De Luca et al.[19] (see Table S2 in the Supporting Information) to further narrow down the list of studies for manual screening. This filtering process resulted in 3840 unique references that were exported as a RIS file for title-abstract screening for relevance (i.e., we excluded 3505 references) (see the top of Figure 2).

Evidence Screening.

We established a team of over 30 environmental and health scientists, including persons with subject-matter expertise and experience in screening and data extraction, to screen the references, extract the data from the references into a database, and conduct quality assurance and quality control (QA/QC). For all stages of the process, an experienced project manager led team trainings, provided verbal and written guidance, facilitated question-and-answer sessions, and provided real-time feedback as needed. Prior to title-abstract (TiAb) screening, all team members calibrated on a set of ten pilot articles, purposefully selected to represent a range of studies encountered. Similarly, team members were required to complete two full-text screenings and data extractions, which underwent full QC with feedback provided before participating in the project. In this section, we describe our relevancy screens for the literature—first with TiAb screens and then with full-text screens.

Title-Abstract Screens.—For the 3840 references entering TiAb screening, we followed the PECO criteria to screen their titles and abstracts for relevance, using *litstream*.[23] We set up *litstream* to indicate PECO relevancy (or not) and the media being sampled, and we provided an optional text field to enter the geographic regions where the PFAS measurements were made. While human biomonitoring data were not the focus of this SEM, we also asked reviewers to tag studies with biomonitoring data for potential future use. Each study was screened by two independent reviewers, with conflicts resolved by a third independent expert.

As shown in Figure 2, 305 studies moved to full-text screening for relevancy. Of the 3535 studies that we excluded from full-text screening, the vast majority (over 3000 references) were not PECO-relevant, while the remaining either did not have their full text available in HERO, their full text was not in English, and/or they were not peer-reviewed in a scientific journal. References which we tagged as having only human biomonitoring data were part of the studies excluded, and we do not discuss them here; however, in Supporting Information section C, we provide a brief description of how we screened a subset of these biomonitoring studies for potential future use.

Full-Text Screens.—For all 305 references tagged as PECO-relevant during TiAb screens, with full texts in English originating from a peer-reviewed scientific journal and available in HERO, we further screened their full text for PECO relevance. We utilized only the information presented in the main text of the reference, which may have included statements about the content of Supporting Information (SI), though we did not screen the SI itself. In addition to screening for PECO relevancy, we also asked screeners to answer basic questions about the presence of SI, markers for information on other PFAS, participant questionnaires, and secondary data (see Table S3 and Table S4 in the Supporting Information for the screening questions). Each reference was screened by a primary reviewer, and a second independent expert performed QA/QC. As shown in Figure 2, 250 references were identified as PECO-relevant during FT screens and proceeded to data extraction, while 55 were non-PECO relevant and did not proceed.

Data Extraction.

We used *litstream* to extract information from the 250 references that we determined were PECO-relevant during full-text screens. We extracted from each reference the information shown in Table S5 (in the Supporting Information), with one person conducting the extraction and a second person performing a QA/QC review. Specifically, we extracted a combination of summary information (e.g., study populations and geographies) and topic-specific information (e.g., occurrence medium and PFAS sampled, sampling and analytical details, etc.), with a comprehensive extraction protocol to capture quantitative information such as numeric values for limits of detection/quantification, detection frequencies, and occurrence statistics. While team members could make simple calculations of chemical detection frequency based on information provided in a study (e.g., if the study authors stated that a PFAS was detected in 5 out of 20 samples, we computed a detection frequency of 0.25), we did not make our own calculations of occurrence statistics (e.g., we did not compute means from available information). We encouraged team members to use several different text fields to provide additional helpful information such as names of nontarget PFAS, specific kinds of media (e.g., apples, if the selected medium was food:fruit), short descriptions of sampling and analytical methods, and where in the study paper certain information was presented. For references that contained data both from relevant exposure media and from human biomonitoring data, we also extracted the biomonitoring data, recognizing that these paired data may be of potential future interest.

The QA/QC review focused most especially on ensuring that the extraction accurately captured or recognized: the relevant populations, geographies, media, and stats; the numbers of participants and collection sites; impacted locations; the limits of detection or quantification; the types of occurrence statistics, numbers of samples, and occurrence values. All data fields were reviewed during QA/QC. Once we completed QA/QC on every extraction, we implemented a final QC step on the databases to improve the extraction accuracy and consistency where appropriate. This step included checks such as ensuring that the concentration units were consistent with expected units for a medium, that a specified submatrix correctly fell under the selected medium, and that detection frequencies were specified as fractions, among other checks. For items that were flagged during the database QC step, an expert reviewed the reference and resolved any issues. We identified that a relatively small number of references ($n = 21$) did not meet our PECO-inclusion criteria but whose data we unintentionally extracted (referred to as incidental extractions). For a small number of PECO-relevant references, we also unintentionally extracted non-PECO relevant media from them. We retained these incidental data, although we separated them from the main database.

The results of our work are available as Excel files (Supporting Information section B). From the 229 references which we confirmed sampled for at least one of the target PFAS from the target indoor or environmental media and were, upon final decision, PECO-relevant, there are 8389 data sets (defined by unique combinations of data fields of interest including population/geographic group, media, location type, data period, and sampled PFAS), and most of these ($n = 7724$) had quantitative information available on PFAS detection frequencies and/or occurrence.

RESULTS AND DISCUSSION

For our exploration of the evidence of PFAS occurrence from the extracted data, we focused on the 229 unique references, which we confirmed were PECO-relevant and sampled for the target PFAS from the target indoor or environmental media.

In the databases, which are limited to references that sampled locations in the United States, Canada, and Europe, 198 references sampled locations in continental Europe including Scandinavian countries (particularly Italy, Norway, Spain, Germany, and Sweden), while 11 references sampled locations in the United Kingdom or Ireland (not shown). In Figure 3, we show the state and provincial locations that references sampled in the United States and Canada, where the counts refer to the number of references detecting PFAS relative to the number not detecting PFAS. References presented quantitative PFAS occurrence results for samples from 29 states and 4 provinces, and at least one reference reported PFAS occurrences above levels of detection in each of those states and provinces except for Colorado. Across all results from the United States, Canada, and Europe, it is important to note that 39 references obtained measurements from locations with known PFAS sources, most commonly from firefighting training facilities and manufacturing, production, or treatment facilities (together comprising over half of the studies of sites with known sources), but also including military airports, landfills and other waste flows, accident zones, and other types of industrially impacted areas (not shown). Given the limited scope of this review and mounting data indicating broad environmental PFAS contamination, we expect that the literature reporting measurements of occurrence for increasing numbers of PFAS in residential media across the globe will increase.

In Figure 4, we show the number of references sampling different combinations of media and PFAS. We count some references several times because they sampled multiple PFAS and media, though the “total counts” column and row indicate unique references separately by PFAS and medium. As expected, the PFAS we most frequently extracted (i.e., were most frequently studied in the references) were PFOA (80% of references) and PFOS (77%). Food (38%) and drinking water (23%) were the target indoor or environmental media most frequently studied. Among the references studying food, the most frequently studied foods were seafood (40 references) and “other” (28 references, the majority studying herbs and spices, diet composites, eggs, or soft drinks, pastries, or other sweets) (not shown). The least studied PFAS were PFNS and PFPeS (each <1% of references) and PFHpS (5%). The 6:2, 8:2, and 10:2 FTOHs were the most commonly studied PFAS in indoor and outdoor air. The least studied target indoor/environmental media were consumer products and articles (9%), indoor and outdoor air (8% each), and food packaging (5%). Consumer products and articles included clothing, bedding, and linens, as well as cookware, other household items, flooring, building materials, and aqueous film-forming foams. Food packaging included cooking foils and papers, food wrappers, popcorn bags and containers, and food and beverage containers. These sparse data provide evidence of important and understudied human exposure pathways. To this end, recent and current studies are actively advancing and deploying methods to measure a larger suite of PFAS in air[24] and articles.[25]

Users of these databases may wish to study the time trends in reported PFAS occurrence. In Figure 5, we indicate the number of references sampling each PFAS, organized by the years during which the sampling took place. For convenience, these are the years that the sampling ended, so for a reference with sampling that took place in 2009−2011, we count it only in the 2011−2015 period. If a reference had more than one sampling period, then we also included the different end years of sampling across each period, effectively counting the reference multiple times. Some references also are counted multiple times if they sampled multiple PFAS. We do not include in this figure the references where the sampling end dates were unclear. As shown in Figure 5, which comprises references published from 2003 through mid-2020 (or 2021, depending on when the search was conducted), most of the PFAS sampling concluded in the period of 2006−2015.

Of particular interest in examining pathways of PFAS exposure are references that make PFAS measurements both in target indoor or environmental media and in biomatrices. A small number ($n = 17$) of references meet this criterion,[26−42] and in Figure 6, we display the PFAS and media sampled in these references. Note that we do not determine here whether the people supplying biomatrix samples were in contact with the indoor or environmental media being sampled; we only which references sampled the same PFAS in these multiple media. Food (8 references) and drinking water (7 references) were the target media most commonly sampled concurrently with biomatrices, with smaller numbers of references examining dust (3 references), indoor air (2 references), and consumer products and articles (2 references) and no references concurrently examining biomatrices with food packaging, soil, or outdoor air. Fifteen references had concurrent measurements in biomatrices and target media for PFOA and PFOS, 14 references had concurrent measurements for PFHxS, 9 references had concurrent measurements for PFNA, and 10 other PFAS had 1−6 studies with concurrent measurements.

In Figure 7, we look more closely at the evidence for PFAS occurrence by considering the frequency of detection. For each combination of PFAS and medium, we identified the references quantifying chemical detection (including non-detects), and then we present the fractions of those references where the PFAS was detected in that medium in 50% or more of samples. PFOA and PFOS were the most frequently detected (particularly in human biomatrices, indoor dust, and soil), while PFBS, PFDA, and PFHxA were less frequently detected relative to the large number of studies which sampled for them. PFAS were more frequently detected in human biomatrices, indoor dust, soil, and consumer products and articles (though the numbers of references studying some PFAS and media combinations were quite small), and they were less frequently detected in food, food packaging, and outdoor air. Three of the perfluoroalkyl acid precursors, 6:2, 8:2, and 10:2 FTOH, were frequently detected in several media (indoor and outdoor air, indoor dust, food packaging, and consumer products and articles), but like most of the PFAS on the bottom half of the figure they were relatively less studied in the body of literature compared to the other PFAS.

CONCLUDING DISCUSSION

The results of our SEM are databases with, altogether, over 17000 rows of meta-data from peer-reviewed studies and, where available, quantitative information on the occurrence of

PFAS in scenarios potentially relevant to human exposure. These data should enable or improve interpretation of PFAS biomonitoring data and inform understanding and modeling of important sources and pathways related to personal exposure to PFAS. These data can be used as the starting point to (a) answer specific research questions through a focused systematic review of subsets of the data, (b) improve interpretations of PFAS biomonitoring, (c) increase the understanding of important PFAS sources, (d) understand pathways of personal exposure, and (e) prioritize future research efforts.

For example, these results indicate the potential for exposure to PFAS from multiple media. In addition to diet and drinking water, exposures from product use in the residential environment may be important and would benefit from further study. Generally, the scientific understanding of sources of PFAS intake and modeling of PFAS body burden related to exposure to PFAS-containing media would benefit from additional studies that make concurrent measurements in these media and human biomatrices, as our research identified only 17 such studies meeting our relevancy criteria. Absent concurrent measurements, our SEM indicated less research on occurrences of PFAS like PFPeA, PFDS, PFHpS, PFPeS, and the FTOHs (relative to the other PFAS studied here) and less research on PFAS occurrences in indoor and outdoor air, products, and food packaging (relative to the other media studied here). Additional sampling of these PFAS and media would help define their possible contributions to human exposure.

Of course, there has been a notable increase in the last 20 years in industrial/commercial, scientific, and public attention on the growing number of PFAS being manufactured and their potential uses as well as fate-and-transport characteristics and human and environmental health impacts. Despite these advances, there remain important questions related to sources and pathways of exposure for vulnerable groups, including children. Where untreated household water is used to shower and clean, PFAS and precursors may partition to indoor air and house dust, resulting in continued exposures for communities impacted by contaminated water supplies. More generally, emissions of PFAS from products and materials in the home will also be distributed throughout and may result in inhalation and dermal exposures.[43] In addition, as uses of PFOS and PFOA have been phased out and levels measured in biomonitoring have been declining, new shorter chain PFAS are being substituted, and these are levels are rising.[44] As analytical chemistry methods advance, increasing numbers of PFAS have been identified in environmental samples.[45] The sources, distribution, and exposure pathways for these newer PFAS may be different. The fast pace of this area of research means that there is a need for a “living evidence” approach to keeping this body of evidence compiled and current (e.g., Elliott et al.[46]). The strategy and approach described here can enable regular review to identify and curate new data about PFAS occurrence.

Users may find these databases useful in conducting a meta-analysis to synthesize results across multiple studies for the purposes of a more robust statistical analysis of environmental occurrences than may be possible with individual studies. Users are encouraged to conduct their own critical appraisal of the data that suits their specific research needs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

(1). U.S. EPA. PFAS Strategic Roadmap: EPA's Commitments to Action 2021−2024; EPA-100-K-21–002, October 2021; https://www.epa.gov/system/files/documents/2021-10/pfas-roadmap_final-508.pdf.

(2). Bulka CM; Avula V; Fry R. Associations of exposure to perfluoroalkyl substances individually and in mixtures with persistent infections: Recent findings from NHANES 1999−2016. Environ. Pollut 2021, 275, 116619.

(3). Hu XC; Andrews DQ; Lindstrom AB; Bruton TA; Schaider LA; Grandjean P; Lohmann R; Carignan CC; Blum A; Balan SA; Higgins CP; Sunderland EM Detection of polyand perfluoroalkyl substances (PFAS) in U.S. drinking water linked to industrial sites, military fire training areas, and wastewater treatment plants. Environ. Sci. Technol. Lett 2016, 3 (10), 344–350. [PubMed: 27752509]

(4). Hu XC; Tokranov AK; Liddie J; Zhang X; Grandjean P; Hart JE; Laden F; Sun Q; Yeung LWY; Sunderland EM Tap water contributions to plasma concentrations of poly- and perfluoroalkyl substances (PFAS) in a nationwide prospective cohort of U.S. women. Environ. Health Perspect 2019, 127 (6), 067006.

(5). Centers for Disease Control and Prevention, National Center for Health Statistics; National Health and Nutrition Examination Survey (NHANES), 2022; https://www.cdc.gov/nchs/nhanes/index.htm.

(6). De Silva AO; Armitage JM; Bruton TA; Dassuncao C; Heiger-Bernays W; Hu XC; Kärrman A; Kelly B; Ng C; Robuck A; Sun M; Webster TF; Sunderland EM PFAS exposure pathways for humans and wildlife: A synthesis of current knowledge and key gaps in understanding. Environ. Toxicol. Chem 2021, 40 (3), 631−657. [PubMed: 33201517]

(7). Sunderland EM; Hu X; Dassuncao C; Tokranov AK; Wagner CC; Allen JG A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. J. Expo Sci. Environ. Epidemiol 2019, 29, 131–147. [PubMed: 30470793]

(8). Jian J-M; Guo Y; Zeng L; Liang-Ying L; Lu X; Wang F; Zeng EY Global distribution of perfluorochemicals (PFCs) in potential human exposure source − A review. Environ. Int 2017, 108, 51–62. [PubMed: 28800414]

(9). VanNoy BN; Lam J; Zota AR Breastfeeding as a Predictor of Serum Concentrations of Per- and Polyfluorinated Alkyl Substances in Reproductive-Aged Women and Young Children: A Rapid Systematic Review. Curr. Environ. Health Rep 2018, 5 (2), 213–224. [PubMed: 29737463]

(10). Zheng G; Boor BE; Schreder E; Salamova A. Indoor exposure to per- and polyfluoroalkyl substances (PFAS) in the childcare environment. Environ. Pollut 2020, 258, 113714.

(11). Hall SM; Patton S; Petreas M; Zhang S; Phillips AL; Hoffman K; Stapleton HM Per- and polyfluoroalkyl substances in dust collected from residential homes and fire stations in North America. Environ. Sci. Technol 2020, 54, 14558−14567.

(12). Karásková P; Venier M; Melymuk L; Bečanová J; Vojta S; Prokeš R; Diamond ML; Klánová J. Perfluorinated alkyl substances (PFASs) in household dust in Central Europe and North America. Environ. Int 2016, 94, 315–324. [PubMed: 27295048]

(13). DeLuca NM; Minucci JM; Mullikin A; Slover R; Cohen Hubal EA Human exposure pathways to poly- and perfluoroalkyl substances (PFAS) from indoor media: A systematic review. Environ. Int 2022, 162, 107149.

(14). McKinnon MC; Cheng SH; Garside R; Masuda YJ; Miller DC Map the evidence. Nature. 2015, 528, 185–7. [PubMed: 26659166]

(15). James KL; Randall NP; Haddaway NR A methodology for systematic mapping in environmental sciences. Environ. Evid 2016, 5, 7.

(16). Wolffe TAM; Whaley P; Halsall C; Rooney AA; Walker VR ystematic evidence maps as a novel tool to support evidence-based decision-making in chemicals policy and risk management. Environ. Int 2019, 130, 104871.

(17). National Academies of Sciences, Engineering, and Medicine. Review of U.S. EPA's ORD Staff Handbook for Developing IRIS Assessments: 2020 Version; The National Academies Press: Washington, DC, 2022; DOI: 10.17226/26289.

(18). Carlson LM; Angrish M; Shirke AV; Radke EG; Schulz B; Kraft A; Judson R; Patlewicz G; Blain R; Lin C; Vetter N; Lemeris C; Hartman P; Hubbard H; Arzuaga X; Davis A; Dishaw LV; Druwe IL; Hollinger H; Jones R; Kaiser JP; Lizarraga L; Noyes PD; Taylor M; Shapiro AJ; Williams AJ; Thayer KA Systematic evidence map for over one hundred and fifty per- and polyfluoroalkyl substances (PFAS). Environ. Health Perspect 2022, 130 (5), 056001–1.

(19). DeLuca NM; Angrish M; Wilkins A; Thayer K; Cohen Hubal EA Human exposure pathways to poly-and perfluoroalkyl substances (PFAS) from indoor media: A systematic review protocol. Environ. Int 2021, 146, 106308.

(20). U.S. Environmental Protection Agency (EPA). ORD staff handbook for developing IRIS assessments (public comment draft, Nov. 2020), U.S. EPA Office of Research and Development: Washington, DC, 2020; EPA/600/R-20/137; https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=541571.

(21). U.S. EPA. EPA's Health and Environmental Research Online (HERO) database, 2021; https://hero.epa.gov/hero/.

(22). Howard BE; Phillips J; Miller K; Tandon A; Mav D; Shah MR; Holmgren S; Pelch KE; Walker V; Rooney AA; Macleod M; Shah RR; Thayer K. SWIFT-Review: A text-mining workbench for systematic review. Syst. Rev 2016, 5, 87. [PubMed: 27216467]

(23). ICF. Litstream, 2021; https://www.icf.com/technology/litstream.

(24). Morales-McDevitt ME; Becanova J; Blum A; Bruton TA; Vojta S; Woodward M; Lohmann R. The Air that we Breathe: Neutral and volatile PFAS in Indoor Air. Environ. Sci. Technol. Lett 2021, 8 (10), 897–902. [PubMed: 35359817]

(25). Xia C; Diamond ML; Peaslee GF; Peng H; Blum A; Wang Z; Shalin A; Whitehead HD; Green M; Schwartz-Narbonne H; Yang D; Venier M. Per- and Polyfluoroalkyl Substances in North American School Uniforms. Environ. Sci. Technol 2022, 56 (19), 13845−13857.

(26). Beesoon S; Genuis SJ; Benskin JP; Martin JW Exceptionally high serum concentrations of perfluorohexanesulfonate in a Canadian family are linked to home carpet treatment applications. Environ. Sci. Technol 2012, 46, 12960−12967.

(27). Byrne S; Seguinot-Medina S; Miller P; Waghiyi V; von Hippel FA; Buck CL; Carpenter DO Exposure to polybrominated diphenyl ethers and perfluoroalkyl substances in a remote population of Alaska Natives. Environ. Pollut 2017, 231, 387–395. [PubMed: 28818814]

(28). Cariou R; Veyrand B; Yamada A; Berrebi A; Zalko D; Durand S; Pollono C; Marchand P; Leblanc J-C; Antignac J-P; Le Bizec B. Perfluoroalkyl acid (PFAA) levels and profiles in breast

milk, maternal and cord serum of French women and their newborns. Environ. Int 2015, 84, 71–81. [PubMed: 26232143]

(29). Falandysz J; Taniyasu S; Gulkowska A; Yamashita N; Schulte-Oehlmann U. Is fish a major source of fluorinated surfactants and repellents in humans living on the Baltic Coast? Environ. Sci. Technol 2006, 40, 748–751. [PubMed: 16509313]

(30). Fraser AJ; Webster TF; Watkins DJ; Nelson JW; Stapleton HM; Calafat AM; Kato K; Shoeib M; Vieira VM; Mcclean MD Polyfluorinated compounds in serum linked to indoor air in office environments. Environ. Sci. Technol 2012, 46, 1209–1215. [PubMed: 22148395]

(31). Hölzer J; Midasch O; Rauchfuss K; Kraft M; Reupert R; Angerer J; Kleeschulte P; Marschall N; Wilhelm M. Biomonitoring of perfluorinated compounds in children and adults exposed to perfluorooctanoate-contaminated drinking water. Environ. Health Perspect 2008, 116 (5), 651–7. [PubMed: 18470314]

(32). Hölzer J; Göen T; Just P; Reupert R; Rauchfuss K; Kraft M; Müller J; Wilhelm M. Perfluorinated compounds in fish and blood of anglers at Lake Möhne, Sauerland area, Germany. Environ. Sci. Technol 2011, 45, 8046–8052. [PubMed: 21534594]

(33). Kärrman A; Ericson I; van Bavel B; Darnerud PO; Aune M; Glynn A; Lignell S; Lindström G. Exposure of perfluorinated chemicals through lactation: Levels of matched human milk and serum and a temporal trend, 1996−2004, in Sweden. Environ. Health Perspect 2007, 115, 226–230. [PubMed: 17384769]

(34). Kuklenyik Z; Reich JA; Tully JS; Needham LL; Calafat AM Automated solid-phase extraction and measurement of perfluorinated organic acids and amides in human serum and milk. Environ. Sci. Technol 2004, 38, 3698–3704. [PubMed: 15296323]

(35). Laitinen JA; Koponen J; Koikkalainen J; Kiviranta H. Firefighters' exposure to perfluoroalkyl acids and 2-butoxyethanol present in firefighting foams. Toxicol. Lett 2014, 231, 227–232. [PubMed: 25447453]

(36). Li Y; Fletcher T; Mucs D; Scott K; Lindh CH; Tallving P; Jakobsson K. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ. Med 2018, 75, 46–51. [PubMed: 29133598]

(37). Li Y; Barregard L; Xu Y; Scott K; Pineda D; Lindh CH; Jakobsson K; Fletcher T. Associations between perfluoroalkyl substances and serum lipids in a Swedish adult population with contaminated drinking water. Environ. Health 2020, 19, 33. [PubMed: 32169067]

(38). Pitter G; Da Re F; Canova C; Barbieri G; Zare Jeddi M; Dapra F; Manea F; Zolin R; Bettega AM; Stopazzolo G; Vittorii S; Zambelli L; Martuzzi M; Mantoan D; Russo F. Serum levels of perfluoroalkyl substances (PFAS) in adolescents and young adults exposed to contaminated drinking water in the Veneto region, Italy: A cross-sectional study based on a health surveillance program. Environ. Health Perspect 2020, 128, 027007.

(39). Poothong S; Papadopoulou E; Padilla-Sánchez JA; Thomsen C; Haug LS Multiple pathways of human exposure to poly- and perfluoroalkyl substances (PFASs): From external exposure to human blood. Environ. Int 2020, 134, 105244.

(40). von Ehrenstein OS; Fenton SE; Kato K; Kuklenyik Z; Calafat AM; Hines EP Polyfluoroalkyl chemicals in the serum and milk of breastfeeding women. Reprod Toxicol. 2009, 27, 239–245. [PubMed: 19429402]

(41). Weiss O; Wiesmüller GA.; Bunte A; Göen T; Schmidt CK; Wilhelm M; Hölzer J. Perfluorinated compounds in the vicinity of a fire training area−human biomonitoring among 10 persons drinking water from contaminated private wells in Cologne, Germany. Int. J. Hyg Environ. Health 2012, 215, 212–215. [PubMed: 22001330]

(42). Xu Y; Fletcher T; Pineda D; Lindh CH; Nilsson C; Glynn A; Vogs C; Norström K; Lilja K; Jakobsson K; Li Y. Serum half-lives for short- and long-chain perfluoroalkyl acids after ceasing exposure from drinking water contaminated by firefighting foam. Environ. Health Perspect 2020, 128, 077004.

(43). Eichler CMA; Bi C; Wang C; Little JC A modular mechanistic framework for estimating exposure to SVOCs: Next steps for modeling emission and partitioning of plasticizers and PFAS. J. Expo Sci. Environ. Epidemiol 2022, 32 (3), 356–365. [PubMed: 35318457]

(44). Zheng G; Schreder E; Dempsey JC; Uding N; Chu V; Andres G; Sathyanarayana S; Salamova A. Per- and Polyfluoroalkyl Substances (PFAS) in Breast Milk: Concerning Trends for Current-Use PFAS. Environ. Sci. Technol 2021, 55 (11), 7510–7520. [PubMed: 33982557]

(45). Evich MG; Davis MJB; McCord JP; Acrey B; Awkerman JA; Knappe DRU; Lindstrom AB; Speth TF; Tebes-Stevens C; Strynar MJ; Wang Z; Weber EJ; Henderson WM; Washington JW Per- and polyfluoroalkyl substances in the environment. Science. 2022, 375 (6580), No. eabg9065.

(46). Elliott J; Lawrence R; Minx JC; Oladapo OT; Ravaud P; Tendal Jeppesen B; Thomas J; Turner T; Vandvik PO; Grimshaw JM Decision makers need constantly updated evidence synthesis. Nature. 2021, 600 (7889), 383–385. [PubMed: 34912079]

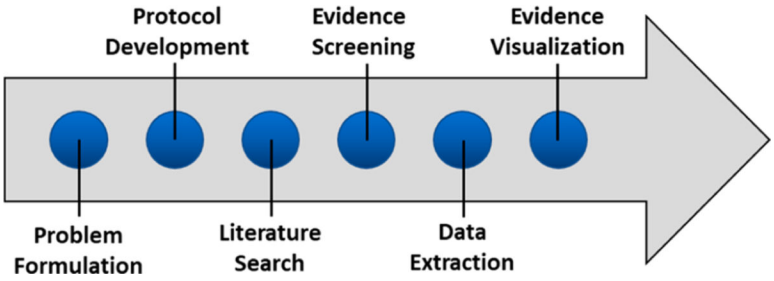


Figure 1.
Workflow of systematic evidence mapping.

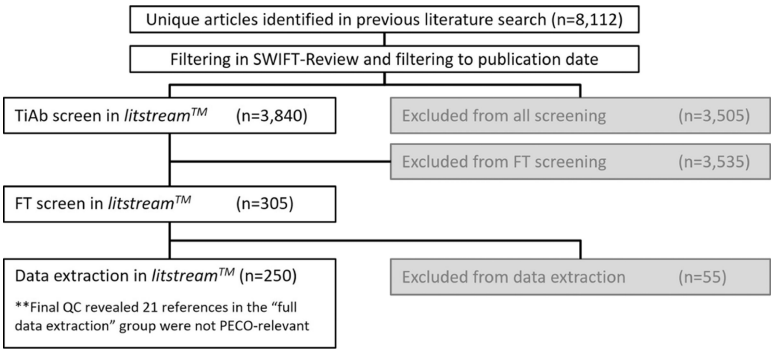
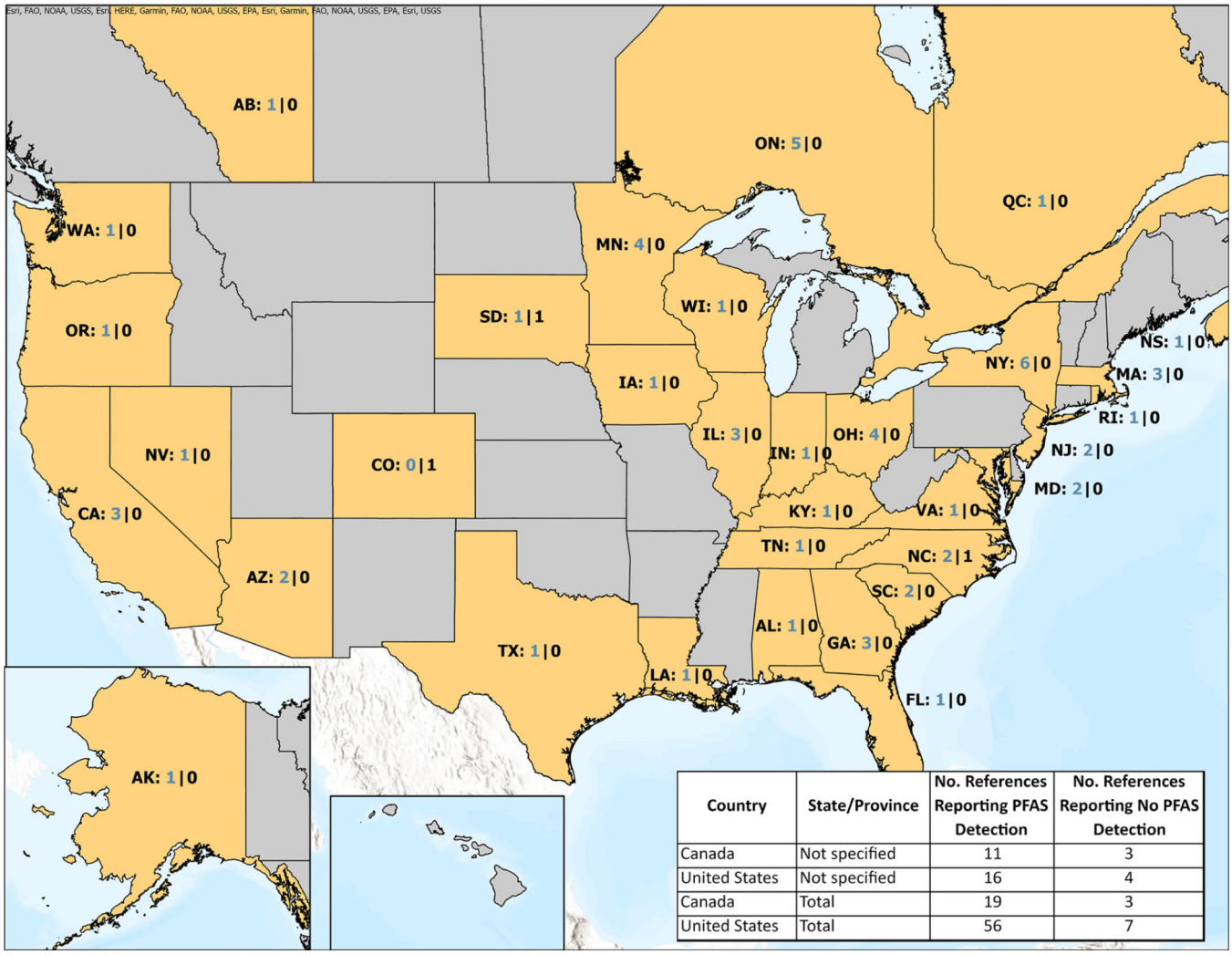


Figure 2.

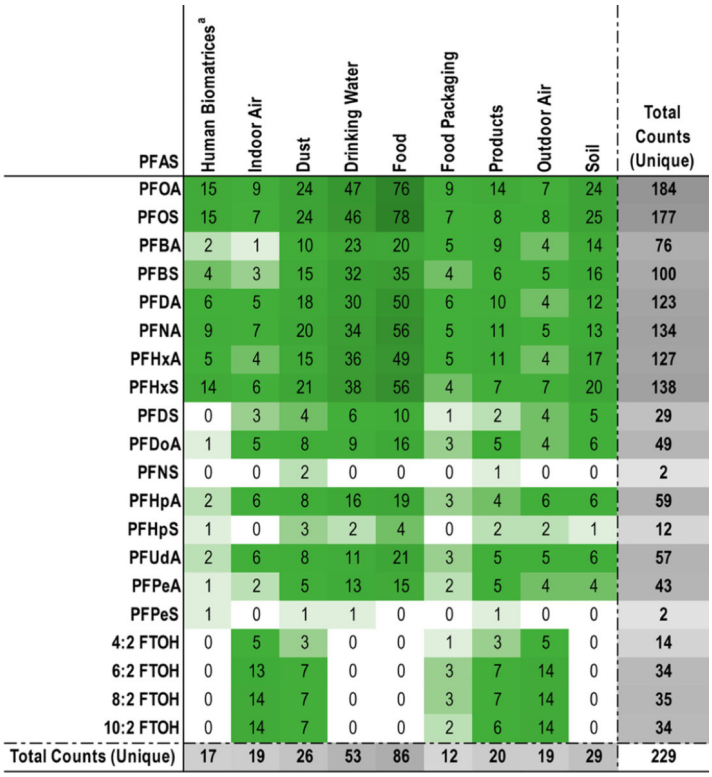
Diagram of the literature workflow, with counts of references. SWIFT-Review is a product of Sciome;[22] *litstream* is a product of ICF;[23] TiAb = title-abstract; FT = full-text; PECO = population, exposure, comparator, outcome.



Country	State/Province	No. References Reporting PFAS Detection	No. References Reporting No PFAS Detection
Canada	Not specified	11	3
United States	Not specified	16	4
Canada	Total	19	3
United States	Total	56	7

Figure 3.

United States and Canada locations of PFAS sampling from PECO-relevant references. Note: Shaded states and provinces are where the PECO-relevant references reported quantitative sampling results for at least one target PFAS in at least one target human, indoor, or environmental medium. The labels show state or province abbreviation, followed by the number of unique references reporting PFAS occurrences above levels of detection (in blue font) and then the number of unique references reporting no PFAS occurrences above levels of detection (in black font). The embedded table shows these counts for references that did not specify the state or province location as well as the total counts for the United States and Canada regardless of state or province.



PFAS	Human Biomatrices[a]	Indoor Air	Dust	Drinking Water	Food	Food Packaging	Products	Outdoor Air	Soil	Total Counts (Unique)
PFOA	15	9	24	47	76	9	14	7	24	184
PFOS	15	7	24	46	78	7	8	8	25	177
PFBA	2	1	10	23	20	5	9	4	14	76
PFBS	4	3	15	32	35	4	6	5	16	100
PFDA	6	5	18	30	50	6	10	4	12	123
PFNA	9	7	20	34	56	5	11	5	13	134
PFHxA	5	4	15	36	49	5	11	4	17	127
PFHxS	14	6	21	38	56	4	7	7	20	138
PFDS	0	3	4	6	10	1	2	4	5	29
PFDoA	1	5	8	9	16	3	5	4	6	49
PFNS	0	0	2	0	0	0	1	0	0	2
PFHpA	2	6	8	16	19	3	4	6	6	59
PFHpS	1	0	3	2	4	0	2	2	1	12
PFUdA	2	6	8	11	21	3	5	5	6	57
PFPeA	1	2	5	13	15	2	5	4	4	43
PFPeS	1	0	1	1	0	0	1	0	0	2
4:2 FTOH	0	5	3	0	0	1	3	5	0	14
6:2 FTOH	0	13	7	0	0	3	7	14	0	34
8:2 FTOH	0	14	7	0	0	3	7	14	0	35
10:2 FTOH	0	14	7	0	0	2	6	14	0	34
Total Counts (Unique)	17	19	26	53	86	12	20	19	29	229

Figure 4.

Counts of PECO-relevant references by PFAS and medium.

Notes: See Table 1 for full chemical names. The green shading corresponds to the magnitude of the reference count within each combination of medium and PFAS. We use gray shading for the total counts individually by PFAS and medium. Breast milk is included in the food category.

[a] The references counted under “Human Biomatrices” are those which sampled human biomatrices AND at least one of the target indoor or environmental media.

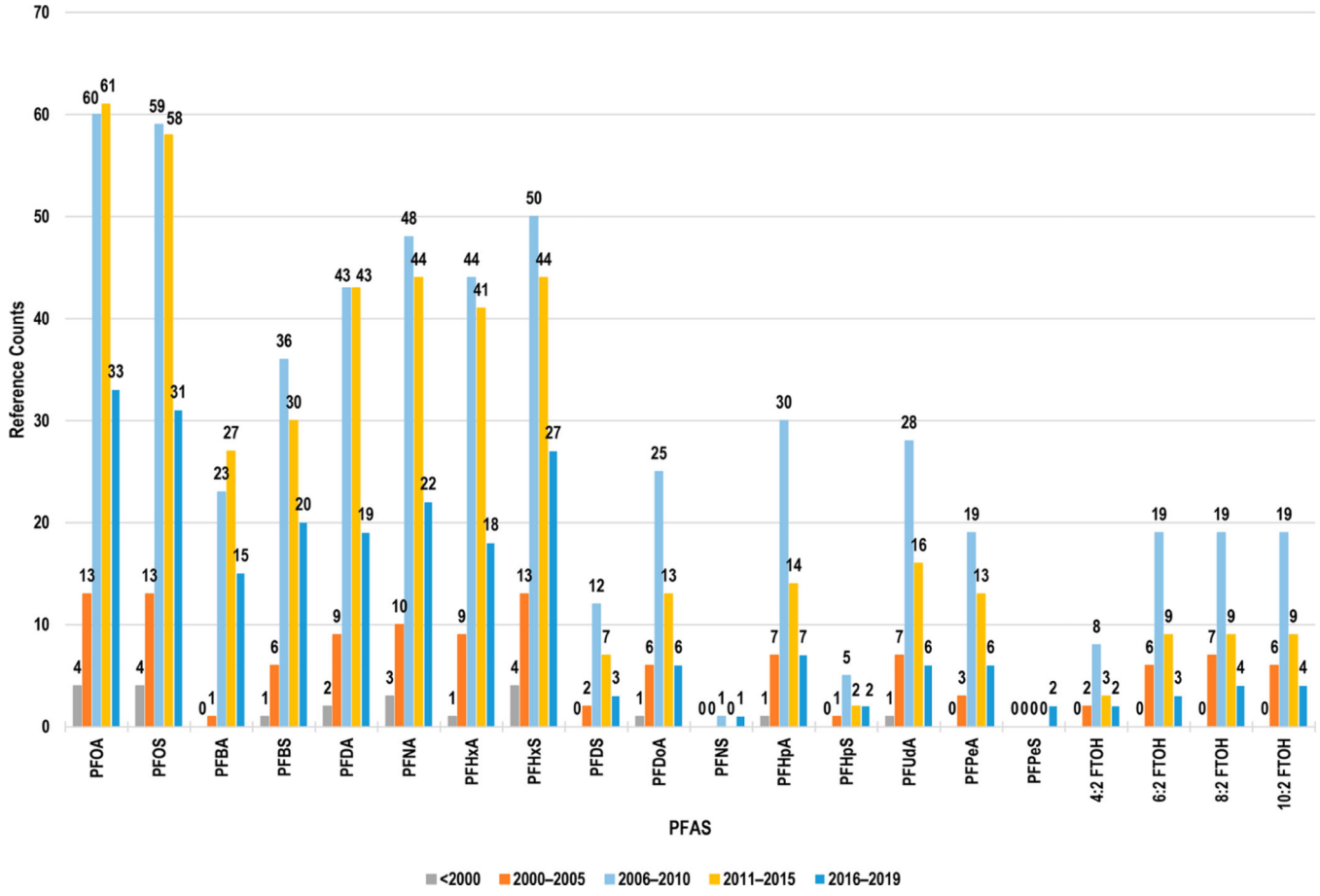
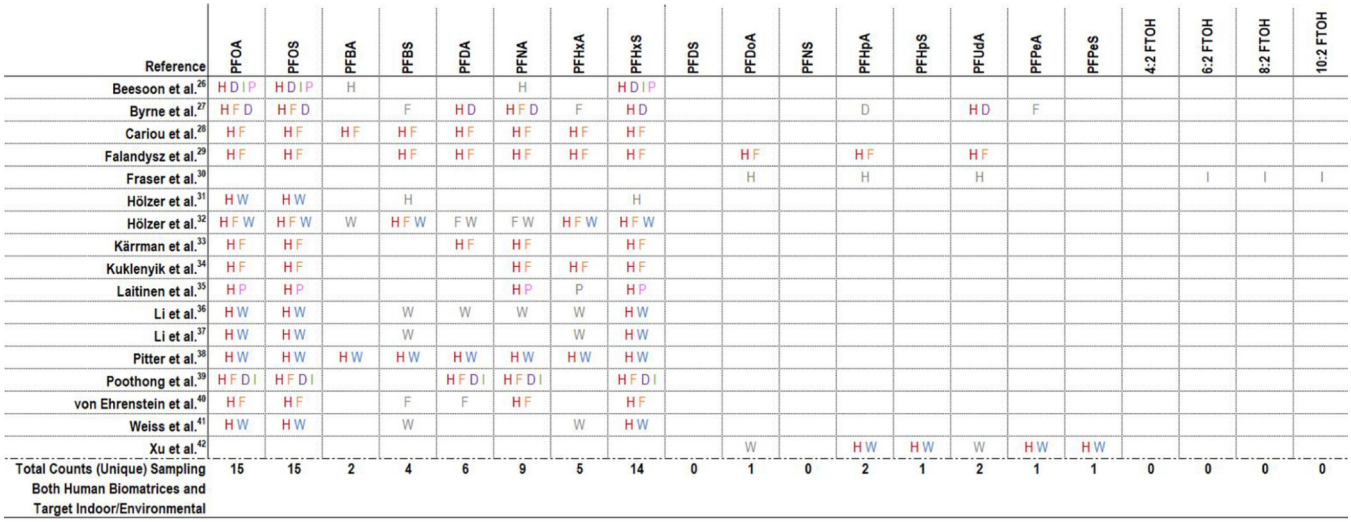


Figure 5.

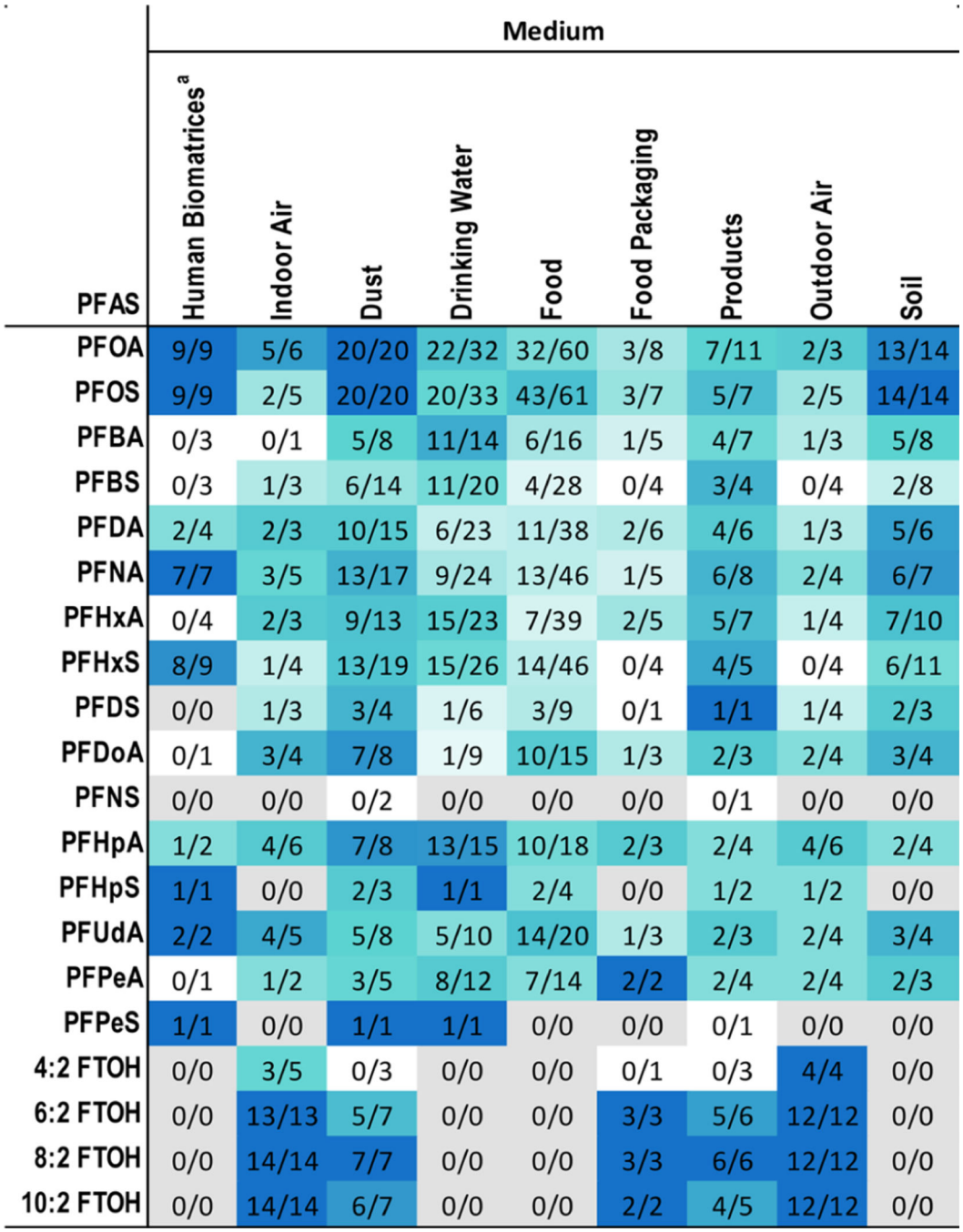
Counts of PECO-relevant references, by PFAS and the final year of sampling period(s). See Table 1 for full chemical names. If a reference had more than one sampling period, then we also included the different end years of sampling.



Reference	PFOA	PFOS	PFBA	PFBS	PFDA	PFNA	PFHxA	PFHxS	PFDS	PFDoA	PFNS	PFHpA	PFHpS	PFUdA	PFPeA	PFPeS	4:2 FTOH	6:2 FTOH	8:2 FTOH	10:2 FTOH
Beesoon et al.[26]	H D I P	H D I P	H			H		H D I P												
Byrne et al.[27]	H F D	H F D		F	H D	H F D	F	H D				D		H D	F					
Cariou et al.[28]	H F	H F	H F	H F	H F	H F	H F	H F												
Falandysz et al.[29]	H F	H F		H F	H F	H F	H F	H F		H F		H F		H F						
Fraser et al.[30]										H		H		H				I	I	I
Hölzer et al.[31]	H W	H W		H				H												
Hölzer et al.[32]	H F W	H F W	W	H F W	F W	F W	H F W	H F W												
Kärrman et al.[33]	H F	H F			H F	H F		H F												
Kuklenyik et al.[34]	H F	H F				H F	H F	H F												
Laitinen et al.[35]	H P	H P				H P	P	H P												
Li et al.[36]	H W	H W		W	W	W	W	H W												
Li et al.[37]	H W	H W		W			W	H W												
Pitter et al.[38]	H W	H W	H W	H W	H W	H W	H W	H W												
Poothong et al.[39]	H F D I	H F D I			H F D I	H F D I		H F D I												
von Ehrenstein et al.[40]	H F	H F		F	F	H F		H F												
Weiss et al.[41]	H W	H W		W			W	H W												
Xu et al.[42]										W		H W	H W	W	H W	H W				
Total Counts (Unique) Sampling Both Human Biomatrices and Target Indoor/Environmental	15	15	2	4	6	9	5	14	0	1	0	2	1	2	1	1	0	0	0	0

Figure 6.

Media sampled in 17 PECO-relevant references having concurrent PFAS Measurements in target indoor or environmental media and human biomatrices. See Table 1 for full chemical names. Sampled media: H = human biomatrices, W = drinking water, F = food, I = indoor air, P = products, D = indoor dust. We use gray font to indicate PFAS sampling that was not concurrent (i.e., where human biomatrices were sampled but not target indoor/environmental media or vice versa). For sampling that was concurrent, for ease of viewing, we use different font colors for different media.



PFAS	Medium: Human Biomatrices[a]	Indoor Air	Dust	Drinking Water	Food	Food Packaging	Products	Outdoor Air	Soil
PFOA	9/9	5/6	20/20	22/32	32/60	3/8	7/11	2/3	13/14
PFOS	9/9	2/5	20/20	20/33	43/61	3/7	5/7	2/5	14/14
PFBA	0/3	0/1	5/8	11/14	6/16	1/5	4/7	1/3	5/8
PFBS	0/3	1/3	6/14	11/20	4/28	0/4	3/4	0/4	2/8
PFDA	2/4	2/3	10/15	6/23	11/38	2/6	4/6	1/3	5/6
PFNA	7/7	3/5	13/17	9/24	13/46	1/5	6/8	2/4	6/7
PFHxA	0/4	2/3	9/13	15/23	7/39	2/5	5/7	1/4	7/10
PFHxS	8/9	1/4	13/19	15/26	14/46	0/4	4/5	0/4	6/11
PFDS	0/0	1/3	3/4	1/6	3/9	0/1	1/1	1/4	2/3
PFDoA	0/1	3/4	7/8	1/9	10/15	1/3	2/3	2/4	3/4
PFNS	0/0	0/0	0/2	0/0	0/0	0/0	0/1	0/0	0/0
PFHpA	1/2	4/6	7/8	13/15	10/18	2/3	2/4	4/6	2/4
PFHpS	1/1	0/0	2/3	1/1	2/4	0/0	1/2	1/2	0/0
PFUdA	2/2	4/5	5/8	5/10	14/20	1/3	2/3	2/4	3/4
PFPeA	0/1	1/2	3/5	8/12	7/14	2/2	2/4	2/4	2/3
PFPeS	1/1	0/0	1/1	1/1	0/0	0/0	0/1	0/0	0/0
4:2 FTOH	0/0	3/5	0/3	0/0	0/0	0/1	0/3	4/4	0/0
6:2 FTOH	0/0	13/13	5/7	0/0	0/0	3/3	5/6	12/12	0/0
8:2 FTOH	0/0	14/14	7/7	0/0	0/0	3/3	6/6	12/12	0/0
10:2 FTOH	0/0	14/14	6/7	0/0	0/0	2/2	4/5	12/12	0/0

Figure 7.

Counts of PECO-relevant references reporting chemical detection frequencies in 50% or more of samples, ratioed against counts of PECO-relevant references reporting any values of detection frequency, by PFAS and medium. [a]The references counted under “Human Biomatrices” are those which sampled human biomatrices AND at least one of the target indoor or environmental media, though not necessarily for the same PFAS. The counts in this column are specific to which PFAS was sampled in human biomatrices.

Notes: See Table 1 for full chemical names. The shading corresponds to the percentage implied by each fraction shown. Breast milk is included in the food category.

Table 1.

Target PFAS

name	abbreviation	Chemical Abstracts Service (CAS) registry number
perfluorooctanoic acid	PFOA	335-67-1
perfluorooctanesulfonate	PFOS	45298-90-6
perfluorobutanoic acid	PFBA	375-22-4
perfluorobutanesulfonate	PFBS	375-73-5
perfluorodecanoic acid	PFDA	335-76-2
perfluorononanoic acid	PFNA	375-95-1
perfluorohexanoic acid	PFHxA	307-24-4
perfluorohexanesulfonate	PFHxS	108427-53-8
perfluorodecanesulfonic acid	PFDS	335-77-3
perfluorododecanoic acid	PFDoA	307-55-1
perfluorononanesulfonic acid	PFNS	68259-12-1
perfluoroheptanoic acid	PFHpA	375-85-9
perfluoroheptanesulfonic acid	PFHpS	375-92-8
perfluoroundecanoic acid	PFUdA	2058-94-8
perfluoropentanoic acid	PFPeA	2706-90-3
perfluoropentanesulfonic acid	PFPeS	2706-91-4
4:2 fluorotelomer alcohol	4:2 FTOH	2043-47-2
6:2 fluorotelomer alcohol	6:2 FTOH	647-42-7
8:2 fluorotelomer alcohol	8:2 FTOH	678-39-7
10:2 fluorotelomer alcohol	10:2 FTOH	865-86-1