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The PFAS-Tox Database: A systematic evidence map of health studies on 29 per- and polyfluoroalkyl substances

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ABSTRACT

Background: PFAS (per-and polyfluoroalkyl substances) are a large class of synthetic chemicals widely used in consumer products and industrial processes. The scientific literature on PFAS has increased dramatically in the last decade. Many stakeholders, including regulators, scientists, non-governmental organizations, and concerned individuals could benefit from an efficient way to access the health and toxicological literature related to PFAS.
Objective: To create a systematic evidence map of the available peer-reviewed health or toxicological research for 29 PFAS.
Methods: A protocol for conducting this systematic evidence map was initially published on Zenodo (Pelch et al. 2019c), then peer reviewed and published in Environment International (Pelch et al. 2019d). PubMed database was searched through January 25, 2021. Studies were screened for inclusion and exclusion according to the Populations, Exposures, Comparators, and Outcomes (PECO) statement. Inclusion criteria were intentionally broad and included any human, animal, and/or *in vitro* study that investigated exposure to one of the 29 PFAS of interest and a human health or toxicological effect. Selected study details were extracted from included studies as described in the protocol. Study appraisal was not conducted. The included studies and extracted *meta*-data are freely available in the online, interactive systematic evidence map at https://pfastoxdatabase.org.
Results: Over 15,000 studies were retrieved from the PubMed literature searches. After manual screening, 1,067 studies were identified and included as investigating the health or toxicological effect of one or more PFAS of interest. There were 505 human, 385 animal, and 220 *in vitro* studies. Summary tables of the extracted data and overall observations are included in this report.
Conclusions: The PFAS-Tox Database is a useful tool for searching, filtering, and identifying peer reviewed research on the health and toxicological effects of the included PFAS. In this summary of the evidence map we provide examples of data gaps and clusters revealed by the database, with the goal of helping direct future

Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; CASRN, Chemical Abstract Service Numbers; BMI, body mass index; CalEPA, California Environmental Protection Agency; CDC, Centers for Disease Control and Prevention; COI, Conflict of interest; DMSO, dimethyl sulfoxide; EU, European Union; FTOHs, fluorotelomer alcohols; OSF, Open Science Framework; PECO, Populations, Exposures, Comparators, and Outcomes; PFAS, Per- and polyfluoroalkyl substances; PFHxDA, Perfluorohexadecanoic acid; PFOA, Perfluorooctanoic acid; PFOS, Perfluorooctane sulfonic acid; PFOSA, Perfluorooctanesulfonamide; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; US EPA, United States Environmental Protection Agency; 8:2 FTCA, 8:2 fluorotelomer acrylate; 8:2 FTUCA, 8:2 fluorotelomer unsaturated carboxylic acid.

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research efforts, facilitate systematic reviews (e.g. on immune effects, mixtures of PFAS, or effects of short chain PFAS), inform regulatory risk assessments, and improve opportunities for cross-disciplinary coordination. We also discuss how this tool supports scientists, regulatory agencies, and other individuals by increasing awareness and access to current evidence regarding the health effects associated with PFAS exposure.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large class of synthetic chemicals that do not naturally degrade, thus they are continuously accumulating in our environment (Ghisi et al. 2019; Giesy and Kannan 2001; Kwiatkowski et al. 2020; Pan et al. 2017; Yeung et al. 2017). Some PFAS travel long distances from their source, contributing to global contamination, and some have been found to bioaccumulate in humans and animals. Nearly all people living in the United States have multiple PFAS in their blood (CDC 2018).

PFAS are used in a wide variety of consumer and industrial products and processes (Gluge et al. 2020), for purposes such as grease or water proofing, friction reduction, and as surfactants, emulsifiers, and dispersants. Examples include food packaging and non-stick cookware, cosmetics, waterproof and stain-proof textiles and carpet, aqueous film forming foam to fight Class B fires, and in metal plating and plastic extrusion processes.

Some PFAS, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), have been thoroughly studied and found to be associated with harmful health effects, including cancer, immune system dysfunction, liver damage, developmental and reproductive harm, and hormone disruption (ATSDR 2021; Barry et al. 2013; C8 Science Panel 2011; 2012b; CalEPA 2021; OEHHA 2021). The body of evidence for health effects of PFAS is growing rapidly, particularly for PFAS that serve as replacements for PFOA and PFOS, which have been largely phased out in the United States and Europe due to health and environmental concerns. Access to the scientific literature is important for federal and state government agencies, as well as for scientists and impacted communities, to help make informed decisions about PFAS exposure.

This paper describes a systematic evidence map designed to improve scientific, regulatory, and individual access to current evidence regarding the health effects associated with exposure to PFAS beyond the well studied PFOA and PFOS. Using transparent and reproducible methods that are consistent with recent guidance adapted from best practices for systematic review methodology (Whaley et al. 2020; Wolffe et al. 2019), we created an interactive database of references and *meta*-data extracted from individual health and toxicology studies of PFAS. Our goal was to provide users with the means of exploring the evidence to easily identify studies relevant to their interests and work and trends which might form the basis of future research or further synthesis, such as systematic reviews. The result is a user-friendly, interactive, online resource called the PFAS-Tox Database that supports research and decision making by diverse stakeholders.

2. Methods

The goal of this work was to identify and organize the available peer-reviewed literature investigating health or toxicological effects of 29 PFAS (Table 1) in support of addressing the broader research question, "what health impacts are associated with PFAS?" A protocol for conducting this systematic evidence map was initially published on Zenodo (Pelch et al. 2019c), then peer reviewed and published in Environment International (Pelch et al. 2019d). An update to the protocol and a summary of the changes (see below) was made available on the project webpage on the Open Science Framework (OSF), available at https://osf.io/f9upx/, which is also where additional guidance and supplemental files are housed (Pelch et al. 2021). PFAS were prioritized

Table 1
List of PFAS included in the systematic evidence map.

Abbreviation	Chemical Name	CASRN	Molecular Formula
PFBA	Perfluorobutanoic acid	375–22-4	$C_4HF_7O_2$
PFPeA	Perfluoro-n-pentanoic acid	2706–90-3	$C_5HF_9O_2$
PFHxA	Perfluorohexanoic acid	307–24-4	$C_6HF_{11}O_2$
PFHpA	Perfluoroheptanoic acid	375–85-9	$C_7HF_{13}O_2$
PFNA	Perfluorononanoic acid	375–95-1	$C_9HF_{17}O_2$
PFDA	Perfluorodecanoic acid	335–76-2	$C_{10}HF_{19}O_2$
PFUnDA	Perfluoroundecanoic acid	2058–94-8	$C_{11}HF_{21}O_2$
PFDoDA	Perfluorododecanoic acid	307–55-1	$C_{12}HF_{23}O_2$
PFTrDA	Perfluorotridecanoic acid	72629–94-8	$C_{13}HF_{25}O_2$
PFTeDA	Perfluorotetradecanoic acid	376–06-7	$C_{14}HF_{27}O_2$
PFBS	Perfluorobutanesulfonic acid	375–73-5	$C_4HF_9O_3S$
PFPeS	Perfluoropentanesulfonic acid	2706–91-4	$C_5HF_{11}O_3S$
PFHxS	Perfluorohexanesulfonic acid	355–46-4	$C_6HF_{13}O_3S$
PFHpS	Perfluoroheptanesulfonic acid	375–92-8	$C_7HF_{15}O_3S$
PFNS	Perfluorononanesulfonic acid	68259–12-1	$C_9HF_{19}O_3S$
PFDS	Perfluorodecanesulfonic acid	335–77-3	$C_{10}HF_{21}O_3S$
EtFOSAA	2-(N-ethyl-perfluorooctane sulfanamido) acetic acid	2991–50-6	$C_{12}H_8F_{17}NO_4S$
MeFOSAA	2-(N-Methyl-perfluorooctane sulfanamido) acetic acid	2355–31-9	$C_{11}H_6F_{17}NO_4S$
GenX	Hexafluoropropylene Oxide (HFPO) Dimer Acid	13252–13-6	$C_6HF_{11}O_3$
HFPO-TA	Hexafluoropropylene Oxide (HFPO) Trimer Acid	13252–14-7	$C_9HF_{17}O_4$
ADONA	4,8-dioxa-3H-perfluorononanoic acid	919005–14-4	$C_7H_2F_{12}O_4$
6:2Cl-PFESA	6:2 chlorinated polyfluorinated ether sulfonic acid	73606–19-6	$C_8ClF_{16}KO_4S$
8:2Cl-PFESA	8:2 chlorinated polyfluorinated ether sulfonic acid	83329–89-9	$C_{10}ClF_{20}KO_4S$
Nafion BP2	Nafion Byproduct 2	749836–20-2	$C_7H_2F_{14}O_5S$
PFO4DA	Perfluoro-3,5,7,9-tetraoxadecanoic acid	39492–90-5	$C_6HF_{11}O_6$
PFO5DoDA	Perfluoro-3,5,7,9,11-pentaoxadodecanoic acid	39492–91-6	$C_7HF_{13}O_7$
Hydro-Eve	2,2,3,3-Tetrafluoro-3-((1,1,1,2,3,3-hexafluoro -3-(1,2,2,2-tetrafluoroethoxy)propan-2-yl)oxy)propanoic acid	773804–62-9	$C_8H_2F_{14}O_4$
6:2 FTSA	1 h,1h,2h,2h-Perfluorooctanesulfonic acid	27619–97-2	$C_8H_5F_{13}O_3S$
8:2 FTSA	2-(Perfluorooctyl)ethane-1-sulfonic acid	39108–34-4	$C_{10}H_5F_{17}O_3S$

for inclusion in this systematic evidence map based on their inclusion in the ATSDR Draft Toxicological Profile for Perfluoroalkyls (ATSDR 2018), the US Environmental Protection Agency's (US EPA's) Method 537.1 for determining PFAS in drinking water (Shoemaker and Tettenhorst 2018), NHANES biomonitoring efforts (CDC 2018), and the author's knowledge of PFAS that have been measured in humans or the environment. The two most well studied PFAS (PFOA and PFOS) were not included in this systematic evidence map because the purpose was to identify research on less well studied PFAS, and assessing the large number of studies on PFOA and PFOS would have required as much time and funding as assessing the other 29 chemicals combined.

Literature search strings were written for 29 individual PFAS (Table 1). The search strings included the full chemical name, common abbreviations, synonyms identified from PubChem, as well as Chemical Abstract Service Numbers (CASRN). An additional search string to capture the general term PFAS and per- and polyfluoralkyl substances was also constructed. No search terms were included that would restrict health outcomes in the systematic evidence map. All search strings and PubMed results are available at https://osf.io/f9upx/.

Searches were run in PubMed on May 17, 2019, with no restrictions on language or publication date, and results were uploaded to Endnote X9 where duplicates were removed. A literature search update was run on January 25, 2021 by amending the search logic to only return results that were added to the PubMed database on April 1, 2019 or later. Upon uploading the search results to EndNote X9, duplicates were removed, including those from the original PubMed search.

After duplicate removal, search results were exported from EndNote X9 and uploaded into DistillerSR (Evidence Partners, Ottawa, Canada), an online project management software for systematic review. In order to be eligible for inclusion, studies needed to comply with the criteria specified by the Populations, Exposures, Comparators, and Outcome (PECO) statement (Table 2). Studies that did not meet the criteria outlined in the PECO statement were excluded. In addition, studies that did not contain original data, such as reviews, editorials, or commentaries, or conference abstracts, were excluded.

After initial piloting of the process, members of the review team independently conducted title and abstract screening of the search results to determine whether a study met the inclusion criteria. Studies marked by a single reviewer as included or unclear during title and abstract screening were moved to full text review. Exclusion of studies at any level required agreement by two reviewers. All disagreements were resolved through discussion by two or more review team members.

Though this systematic evidence map is focused only on the health and toxociological studies of PFAS, we are aware that other individuals and agencies may be interested in additional information about PFAS. In an effort to serve the larger scientific community, reasons for exclusion were noted during title and abstract and full-text screening, which were then used to broadly categorize the non-health and non-toxicology studies that were excluded from our systematic evidence map. As these topics were not the focus of the systematic evidence map, disagreements in reasons for exclusion between reviewers were not resolved. Included studies that contained these categories of information were also noted during full text review. Categories included:

- biomonitoring (human);
- wildlife detection;
- environmental detection fate or transport;
- adsorption, distribution, metabolism, excretion / pharmacokinetics / toxicokinetics;
- ecotox/plants/bacteria;
- *in silico* or read across;
- exposure (human);
- risk assessment/hazard identification;
- remediation/treatment;
- pharmaceutical/medical use;
- commentary/editorial;
- review, systematic review/*meta*-analysis;
- contains info about a PFAS not in this database;
- chemical properties;
- other studies about PFAS;
- not PFAS relevant.

For studies included after title and abstract screening, the full text was obtained and reviewed. Reviewers were asked to confirm that each study contained health or toxicological information on one or more of the PFAS included in this systematic evidence map. For included studies, reviewers noted the types of studies that were present: human epidemiological (henceforth referred to as human), experimental or observational animal (henceforth referred to as animal), or *in vitro* or *ex vivo* (henceforth referred to as *in vitro*). Bibliographic citation information, funding statements, acknowledgments, and declarations of conflict of interest (COI) were extracted for each study.

Potential financial COI was determined by the reviewers, regardless of whether the authors reported a potential COI. Reviewers checked the following information within each study for potential financial COI: COI statements, funding statements, acknowledgements, author affiliations, disclaimers, and transparency documents provided in Supplemental Materials. A study was flagged for potential COI if funding came from, or authors were employed by, a company that makes PFAS such as 3 M, DuPont, Dow, Daiken, Solvay, or Arcadis. Government funded research (e.g. US Environmental Protection Agency (EPA) or Department of Defense) or research funded by private foundations with no control over results were not considered a potential financial COI. Additionally, potential financial COI was not flagged if authors had provided testimony as expert witnesses in toxic tort litigation.

Data coding and extraction of included studies was performed in DistillerSR using custom forms specific to each study type (i.e. evidence stream) as described in the study protocol and protocol update (https://osf.io/f9upx/). All full text review, data coding, and extraction was performed by one member of the review team and reviewed for accuracy and completeness by a senior member of the review team. Upon completion of full text data coding and extraction, an additional consistency check of how specific elements were categorized throughout the project was performed. Any necessary changes were discussed by the review team. Note that this evidence map represents the overall peer-reviewed body of literature for which health or toxicological endpoints were evaluated for these 29 PFAS; the direction of association or effect (positive, negative, or not associated) was not a requirement for inclusion, nor was it documented in the evidence map.

Data coding and extraction were similar across the three study types. Guidance documents for data coding and extraction were developed and maintained in order to provide consistency across reviewers and across

Table 2
Populations, Exposures, Comparators, and Outcomes (PECO) Statement.

PECO Element	Evidence
Populations	Any human, animal (whole organism including experimental and observational studies), or *ex vivo/in vitro* models utilizing organs, tissues, cell lines, or cellular components (e.g. cell-free receptor binding assays).
Exposures	Exposure to at least one of the PFAS or the associated salts listed in Table 1 (e.g. perfluorobutane sulfonic acid (PFBS; CASRN 375–73-5) and potassium perfluorobutane sulfonate (K + PFBS; CASRN 29420–49-3)). Exposures may include, for example: biomarkers of exposure, modeling of potential exposures, and/or administered exposures. Mixtures of PFAS including at least one PFAS in Table 1 were also included and listed as $PFAS_{mix}$. There were no limitations on the timing, route, level, or determination of estimated exposure.
Comparators	Humans, animals, organs, tissues, cell lines, or cellular components exposed to a lower level of a PFAS than the more highly exposed subjects or treatment groups, or vehicle-only treatment.
Outcomes	Any health outcome or type of biological response measured in the exposed population.

time and are available in the Supplemental Materials (https://osf.io/f9upx/). Reviewers coded and extracted the identity of the PFAS and information about the timing and magnitude of PFAS exposure. Because reporting of PFAS exposure units varies across study designs, reviewers were instructed to extract the smallest exposure value and the largest exposure value provided by the study authors. Health outcomes were categorized into one or more health outcome categories and information was coded and extracted about the age at outcome assessment. Study type specific data (e.g. species, cell type, study design) were also extracted. Data that were coded were supported by extracting the native text used by the study authors.

Reviewers were instructed to categorize studies in as many health outcome categories as warranted. For example, the specific health outcome "asthma" was categorized in both the Immune System and Respiratory System so that studies on asthma would be retrieved when either category was searched. Examples of specific endpoints within each health outcome category are listed in the glossary provided on the Health Outcomes tab of the PFAS-Tox Database.

In vitro studies posed a unique challenge as many aim to investigate mechanistic endpoints that are relevant for many different health outcomes. Reviewers were instructed to code health outcome categories for *in vitro* studies based on variables such as the bioactivity probed by the assay or the cell type. In some cases, the context of the paper helped determine the categorization. For example, estrogen receptor activity assays are often conducted in HepG2 human liver cells because the cellular components can be experimentally manipulated (e.g. hormone receptors and the corresponding DNA response elements can be transfected into the cells). These studies address questions about the endocrine activity of the PFAS and thus were categorized as Endocrine System rather than Digestive & Metabolic System. *In vitro* assays also may contain cellular components from one species inserted into cells of another species, for example when human and mouse peroxisome proliferator activated receptor (PPAR) are transfected into COS-1 monkey kidney cells to evaluate the species differences in receptor activity. In such cases, the species of the cell line and the cellular components were extracted. In an effort to provide more context for the *in vitro* studies, reviewers also coded broad endpoint categories to reflect the most frequently studied mechanisms (e.g. Estrogen related, Cytotoxicity, Protein binding). These are reported as 'Types of Endpoints' in the individual study details section of the PFAS-Tox Database.

Developing organisms are particularly susceptible to chemical exposures. To build a filter that allows users to search for health effects that may be relevant to development, the extracted health outcome categories were coded as having been evaluated during early life or not. To be most inclusive (e.g., of effects during puberty), we chose an early life cut-off of < 20 years for the human epidemiological studies. For animal studies, which included a variety of species, the early life cut-off was anything other than adulthood (e.g., embryonic, juvenile, larval). We identified *in vitro* studies as early life outcomes if cells or tissues of placental, embryonic, or fetal origin were used.

Finalized data were downloaded from DistillerSR to Microsoft Excel where the information was collated and used for visualization in Tableau Desktop Professional Edition v 2020.4 (Tableau Software; Seattle, WA). An interactive display was created in Tableau Desktop that allows users to filter data based on study type, PFAS, health outcome category, potential financial COI, or the presence of assessment of early life health effects. Additional study type specific filters were also created for 1) human study design, exposure type, and study location; 2) animal study design, species evaluated, and route of exposure; and 3) *in vitro* cell or cellular component species. All additional study details that were coded and extracted are viewable within the interactive display. The interactive display and supporting contextual documentation was published to Tableau Public and PFASToxDatabase.org where it is freely and publicly available. The entire data set and all supplementary materials are also available at the project website on Open Science Framework (https://osf.io/f9upx/) as detailed in the Data Availability section (Pelch et al. 2021).

As noted previously, a protocol update was made available on the project website at https://osf.io/f9upx/. The protocol update included the following points:

- We decided to extract data for PFOA and PFOS when they were analyzed in included studies so that these two well-studied chemicals could be more easily added in the future.
- We reported that supplemental data, including the list of excluded studies, would be housed on the Open Science Framework (https://osf.io/f9upx/) rather than on https://www.TEDX.org.
- We added the binary question addressing potential financial COI so this information could be used to create a filter.
- We clarified that we used DistillerSR's AI feature to prioritize screening studies at Level 1 title and abstract screening.
- We reported a change to the health outcome categorization scheme to condense the number of health outcome categories.
- We reported that "chemicals studied" would be a separate question from "chemicals evaluated for an associated health effect" which allowed us to capture both types of information.
- We decided to include health-related variables that are often reported as covariates in epidemiological studies (primarily body weight, body mass index (BMI), breastfeeding, and glomerular filtration rate) as outcomes if a statistical analysis was conducted on the variable's relationship to PFAS. For example, studies that reported regression coefficients on BMI were included, even if BMI was only evaluated as a covariate rather than a primary health outcome.

3. Results and discussion

The PubMed searches on May 17, 2019 and January 25, 2021, returned 16,313 and 4,111 results, respectively (Fig. 1). After duplicate removal, 15,066 unique literature results were obtained and uploaded to DistillerSR for screening and data coding and extraction. After title and abstract screening 1,794 studies were considered relevant and moved forward for full-text review. The full text for three studies from foreign

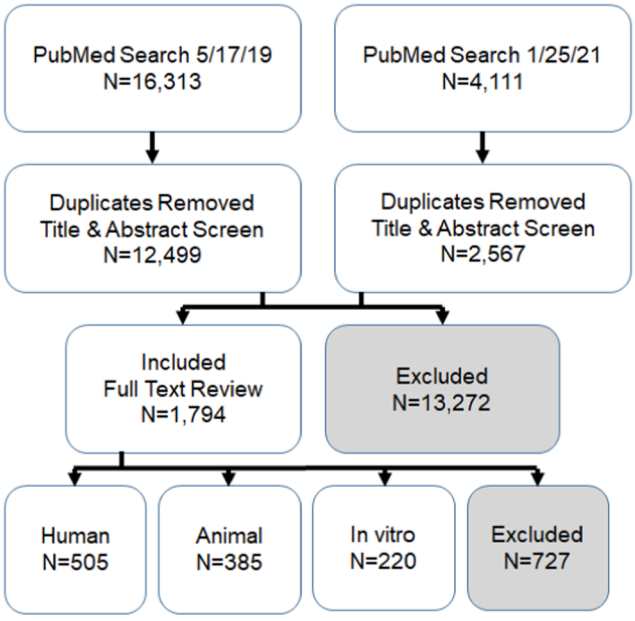

Fig. 1. Flowchart of studies through the review process. This describes the number of studies evaluated at each step of the review process. In total 1,067 studies are included, with some studies containing data for more than one study type. Reasons for exclusion after title and abstract screening and full text review are available in the supplemental materials .
available at https://osf.io/f9upx/

language journals and one study from an English language journal could not be obtained and these studies were excluded from further analysis. Reasons for exclusion at any level are available at https://osf.io/f9upx/. At the title and abstract level the majority of studies were excluded because they contained non-health or toxicological data for PFAS or they were not at all relevant to PFAS (for example, the search for PFDS brought in studies on personal flotation devices). At the full text level, nearly three quarters of the studies were excluded because they did not contain information about one of the PFAS included in this review. The remainder lacked a health or toxicological endpoint.

After full-text review, 1,067 studies remained for final inclusion in the evidence map: 505 human studies, 385 animal studies, and 220 *in vitro* studies. Most of the studies (96%; n = 1024) contained data from only one study type. A small proportion of the studies (4%; n = 43) contained data from two study types, for example, animal and *in vitro*. No studies contained data from all three study types.

Overall, the rate of publication of PFAS health and toxicology studies has been steadily increasing in the last 10 years, with a dramatic increase in human studies in recent years (Fig. 2). The first animal studies we captured for these PFAS were published in German language journals in 1969 and 1972 and investigated the impacts of PFBA or PFPeA on the mouse liver. Of note, the first peer reviewed toxicity reports for the well-studied PFOA were not published until 1980 (Griffith and Long 1980) though internal documents from the manufacturer of PFOA warn of toxicological effects as early as 1961 (EWG 2018). The rise in animal studies published in the early 1990′s largely reflects research on PFBA and PFDA. Animal research on the PFAS in this evidence map began its upward trend in 2007, similar to human studies, which began in 2006. The first *in vitro* study we identified was published in 1982. Charts showing time trends of publication of included studies for PFAS by year and health outcome by year can be found in the supplemental materials available at https://osf.io/f9upx/.

The coded and extracted data from all included studies is available in an interactive format at PFASToxDatabase.org (Fig. 3; also see Data Availability for information on accessing and using the database). In the PFAS-Tox Database, included studies can be filtered by study type (human, animal, *in vitro*), PFAS, and health outcome category. Studies can also be filtered based on whether or not they had a potential financial COI and whether they contained information on a health or toxicological effect observed during early life (prior to adulthood).

3.1. PFAS in the systematic evidence map

We identified one or more health or toxicological studies for 27 of the 29 included PFAS. There were no studies identified for 8:2 FTSA or Hydro-Eve. The number of studies for each PFAS ranges from 1 (PFNS) to 631 (PFNA) (Fig. 3). Based on our collective experience reading over a thousand studies, very few other PFAS have been evaluated in the types of studies included in this systematic evidence map. Besides PFOA and PFOS, a few that we noted were the fluorotelomer alcohols (FTOHs), perfluorooctanesulfonamide (PFOSA), and perfluorohexadecanoic acid (PFHxDA). In May 2022 US EPA released a systematic evidence map of 150 PFAS, the so-called PFAS-150 (described in more detail in the Conclusions section), which confirms these observations (Carlson et al. 2022). It may be worthwhile to explore these as possible additions to the systematic evidence map.

PFOA and PFOS were specifically excluded from the systematic evidence map due to the overwhelming amount of research already conducted on these two PFAS and their well documented health outcomes. Our intention was to determine how much research has been conducted on other known PFAS, such as GenX and PFBS, replacement chemicals (respectively) for the largely phased out PFOA and PFOS. These and other ‘short-chain’ PFAS have been previously touted to be safer based on having fewer carbons in their carbon–fluorine chains (indicated in the molecular formulas in Table 1). Recent research indicates that short chain PFAS may be just as harmful as long chain PFAS (Brendel et al. 2018; Conley et al. 2021; Gomis et al. 2018). This systematic evidence map contains the literature base to conduct systematic reviews to address these types of questions.

The human studies and over a fifth of the animal studies were observational in nature and may reflect exposure to mixtures of PFAS and other chemicals, as chemicals and dosages are not selected in observational studies the way they are in experimental studies. Studies investigating effects of mixtures are important, as this is the true nature of human exposure to environmental chemicals, and the interaction of exposures may have distinct effects that cannot be captured in single pollutant models. To identify such studies, we noted when study authors conducted analyses on mixtures of PFAS (noted as “PFAS mix”) or on mixtures of PFAS with other chemicals (noted as “PFAS + other”). Studies categorized as “PFAS mix” included any studies where distinct PFAS were analyzed together, usually as a summed concentration, but also included a small number of studies where environmental mixtures methods such as Bayesian Kernel Machine Regression (BKMR), Weighted Quantile Sum (WQS), Principal Component Analysis (PCA), etc. were employed. Mixtures of PFAS were investigated in 108 human studies, 70 animal studies, and 30 *in vitro* studies. In studies categorized as “PFAS + other”, PFAS were studied in combination with other environmental chemicals, with the most common being PCB’s, dioxins, and pesticides. PFAS were studied in combination with other environmental chemicals in 10 human studies, 37 animal studies, and 14 *in vitro* studies.

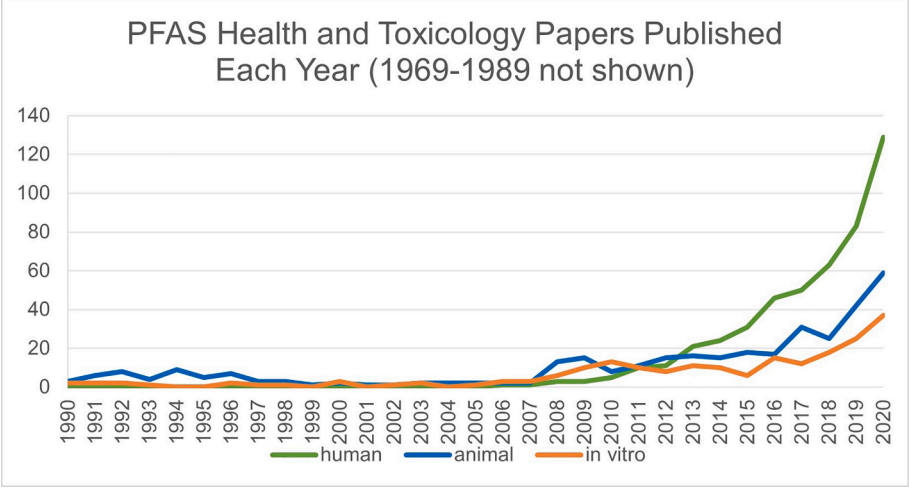

Fig. 2. Number of studies published by year and study type (1990–2020). Note: there were 28 animal studies and 9 *in vitro* studies published prior to 1990.

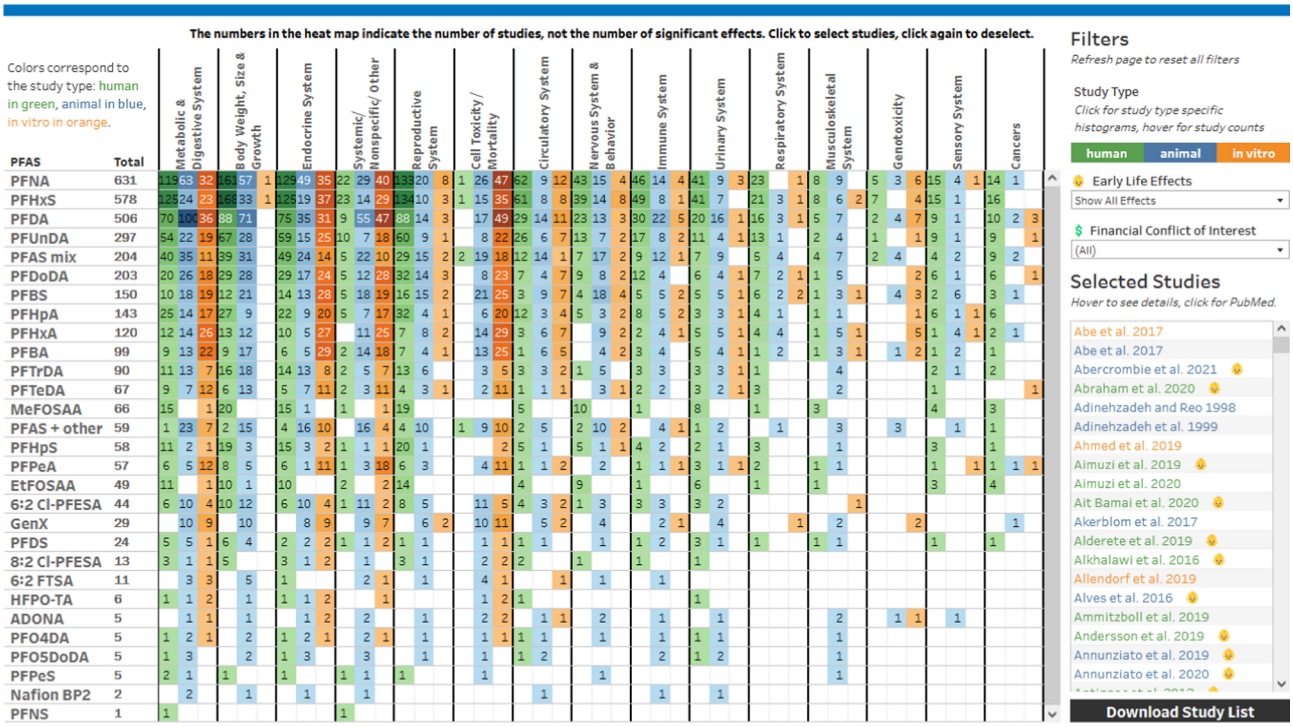

Fig. 3. The PFAS-Tox Database is an interactive systematic evidence map available at PFASToxDatabase.org. Users can search the included literature by PFAS, health outcome category, study type, early life effects, and potential financial conflict of interest. More guidance on how to access and use the PFAS-Tox Database is available in the supplemental materials available at https://osf.io/f9upx/ and in the onscreen "How To Use" feature. In the heatmap PFAS are listed in rows and health outcome categories are listed in columns. The total number of studies for each PFAS is shown next to the chemical name. The heatmap is color coded to match the three study types: human in green, animal in blue, and *in vitro* in orange. Darker colors indicate more studies. Each cell in the heatmap indicates the number of studies that were identified for that study type, PFAS, and health outcome category combination. These numbers represent a count of studies, not the number of significant findings.

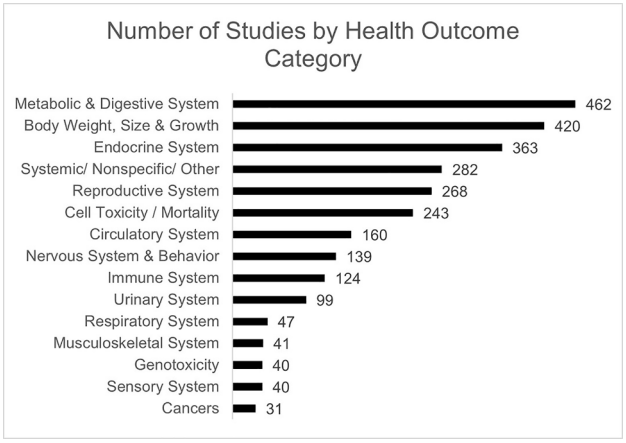

Fig. 4. Number of studies from all study types (human, animal or *in vitro*) by health outcome category.

Identifying mixture studies in the PFAS-Tox Database in this way may be useful for those trying to better understand the effect of mixture exposures on health, including through conducting systematic reviews.

3.2. Health outcome categories

The majority of studies evaluated several unique endpoints, which were often coded to two to three health outcome categories. The health outcome categories most commonly studied were: Metabolic & Digestive System (n = 462), Body Weight, Size & Growth (n = 420), Endocrine System (n = 363), Systemic/Nonspecific/Other (n = 282), and Cell Toxicity/Mortality (n = 268) (Fig. 4). Within these evidence clusters, each health outcome category encompasses several unique endpoints. For example, the health outcome category "Endocrine System" includes effects related to the testes, ovaries, thyroid and other endocrine organs, glands, and mechanisms. Systematic reviews, particularly *meta*-analyses, require several studies on identical or sufficiently similar endpoints in order to aggregate data across studies. This systematic evidence map makes the process of conducting a systematic review easier by identifying both the health outcome categories as well as the specific endpoints reported.

The five health outcome categories with the fewest studies were: Respiratory System (n = 47), Musculoskeletal System (n = 41), Genotoxicity (n = 40), Sensory System (n = 40), and Cancers (n = 31). In particular, we were surprised by the dearth of studies on cancer related outcomes, given that kidney and testicular cancer were identified a decade ago as adverse outcomes associated with exposure to PFOA (C8 Science Panel 2012a). This data gap is discussed more thoroughly in the Conclusions section.

Conflict of interest

In our evidence map, the scope of COI data extraction was restricted to financial COI, since this type of COI is both easier to identify and more likely to bias research than non-financial COI (Bero and Grundy 2016). Systematic bias resulting from financial conflicts of interest (COI) can appear in research by way of study design, implementation, analysis, and reporting of conclusions (Anglemyer et al. 2015; Bero et al. 2016; Lundh et al. 2017; Lundh et al. 2012; vom Saal and Hughes 2005). Research that could impact regulatory decisions is particularly susceptible to COI, as documented in the case of tobacco, among others (Michaels 2006; Soskolne et al. 2020). As PFAS regulation is currently being

debated on a national scale (Energy & Commerce Committee, 2021; Dingell 2021), data on COI was thus deemed important to extract from the included studies.

Out of the 1,067 studies, 51 (4.8%) were marked as having a potential COI. Within study types, potential COI was identified for four human studies (0.8%), 33 animal studies (8.6%), and 14 *in vitro* studies (6.4%). The higher proportion of animal and *in vitro* studies with potential COI is not surprising given that the chemical industry is more likely to conduct animal and *in vitro* studies, which are typically requested by regulatory programs and used in government risk assessments. Further analyses of the impact of COI in the reporting of health and toxicological impacts of PFAS could be worthwhile and would be facilitated by the use of this systematic evidence map.

3.4. Human studies

Human studies were identified for 24 PFAS as well as PFAS mix and PFAS + other (Fig. 5). The PFAS most commonly analyzed in relation to human health outcomes were: PFHxS (n = 449), PFNA (n = 443), PFDA (n = 277), PFUnDA (n = 199), and PFDoDA (n = 102). Note that often additional PFAS were measured, but were below detection frequency thresholds. If detection frequencies for individual PFAS were below a certain value (for example if 50% of samples were below the detection limit), study authors typically did not include those PFAS in further analysis. These additional PFAS that were measured but not evaluated for an association with a health outcome are listed in the PFAS-Tox Database in the specific details for each study, but are not included in the heatmap that pairs PFAS with health outcomes.

Across the human studies the most commonly studied health outcome category was Body Weight, Size & Growth (n = 195), followed by Reproductive (n = 158), Endocrine (n = 149), and Metabolic & Digestive systems (n = 143) (Fig. 6). A partial reason for the large number of studies under the first two categories is due to our inclusion of studies evaluating body weight, BMI or breastfeeding duration as covariates, even if the study did not evaluate any other health outcomes. Health outcome categories with the fewest number of studies include Cell Toxicity/Mortality (n = 3), Genotoxicity (n = 7), Musculoskeletal System (n = 9), Sensory System (n = 15), and Cancer (n = 20).

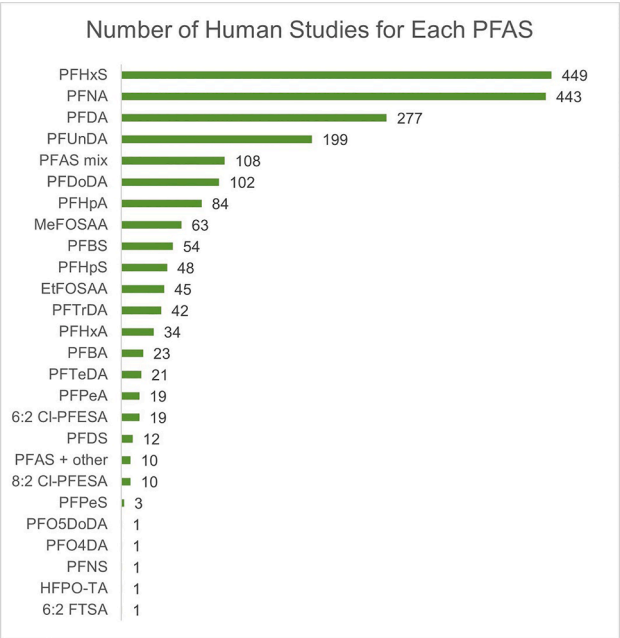

Fig. 5. Number of human studies identified for each PFAS. There were no human studies identified for GenX, Nafion BP-2, ADONA, 8:2 FTSA, or Hydro-Eve.

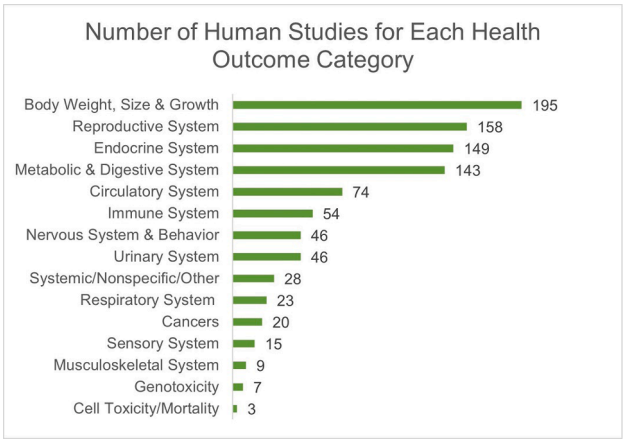

Fig. 6. Number of human studies by health outcome category.

Summary data on human studies is presented in Table 3. The large majority were either cross-sectional (48%) or cohort (39%) studies. However, categorization of study design was challenging and our rule was to default, where possible, to the study design reported by the authors. This may have led to miscategorizations, for example, when the authors identified the study as a cohort, but the data was only from baseline measures. In this case the data analyses were technically cross-sectional, but the overall study was reported as a cohort. We also did not label studies as prospective, retrospective, or nested designs, and only one study design was listed for each study.

Studies were primarily conducted in North America (45%), Europe (33%), and Asia (26%). See Table 3 for individual countries with the largest numbers of studies. Females and males were represented in 71% of the human studies, with most of the remainder (25%) conducted in females only. Among the studies conducted only in females, 65% were in pregnant women. There were also 7 pre-conception studies, 4 of which included men. The number of subjects in each study, categorized as shown in Table 3, was relatively normally distributed, with the majority (61%) falling between 100 and 1,000 subjects. Another 25% of the studies had up to 10,000 subjects.

Nearly all the studies (98%) were non-occupational, which typically suggests lower exposure concentrations than worker populations. However, some studies were conducted in highly exposed populations. Data on exposure concentrations are not summarized in this report due to the complexity of aggregating ranges across different units of measure and in different media (e.g. plasma, breast milk etc.). Exposure concentration values for each study can be found in the PFAS-Tox Database. Eighty-nine percent of studies evaluated PFAS in plasma or serum, while 12% studied PFAS in cord blood (some studies measured both). While only 1% of studies assessed PFAS in whole blood, it is important to note that some PFAS partition to the plasma and blood cell fractions differently, so comparisons between studies for a given PFAS should note which blood fraction is evaluated (Hanssen et al. 2013; Poothong et al. 2017).

A total of 40% of the human studies assessed exposures before birth, 38% assessed participants between birth and 20 years of age, and 42% assessed exposures in adults. With regard to age at outcome assessment, within the two largest categories, 44% of studies evaluated participants aged 0–12 years, and 49% evaluated adults older than 20 years. Another 15% studied outcomes during pregnancy and preconception.

3.5. Animal studies

There were animal studies available for 26 PFAS as well as PFAS mix and PFAS + other (Fig. 7). Overall, the PFAS most commonly analyzed in relation to animal health outcomes were: PFDA (n = 146), PFNA (n = 109) and PFAS mix (n = 70).

Table 3
Human Study Summary Data (N = 505 studies).

	Variable	N (%)
Study type		
	Cross sectional	240 (47.5%)
	Cohort	198 (39.2%)
	Case control	58 (11.5%)
	Randomized control	7 (1.4%)
	Ecological	2 (0.4%)
Continent (countries)*		
	North America (US, Canada, Greenland)	228 (45.1%)
	Europe (Denmark, Norway, Sweden and many others)	164 (32.5%)
	Asia (Taiwan, Korea, China, Japan, Vietnam, Malaysia, Saudi Arabia)	129 (25.5%)
	Oceania (Australia)	4 (<1%)
	Africa (Guinea Bissau, Africa)	2 (<1%)
Sex of subjects		
	Female and Male	357 (70.7%)
	Female only	124 (24.6%)
	Male only	24 (4.8%)
Number of subjects		
	10–100	53 (10.5%)
	101–500	209 (41.4%)
	501–1,000	98 (19.4%)
	1,001–10,000	124 (24.6)
	>10,001	20 (4.0%)
PFAS Exposure		
	Non-occupational exposure	497 (98.4%)
Age of subjects at exposure assessment*		
	Preconception + Pregnancy	201 (39.8%)
	Birth to 12	100 (19.8%)
	12 + to 20	90 (17.8%)
	20+	210 (41.6%)
Exposure media*		
	Serum	326 (64.6%)
	Plasma	122 (24.2%)
	Cord blood	56 (11.7%)
	Other (urine, breast milk, whole blood etc)	40 (7.9%)
Outcome data		
Age of subjects at outcome assessment*		
	Preconception + Pregnancy	77 (15.2%)
	Birth to 12	223 (44.2%)
	12 + to 20	99 (19.6%)
	20+	246 (48.7%)

* Numbers and percentages exceed the total number and percent of studies due to representation of some studies in multiple categories.

Across all animal studies, the most commonly studied health outcome category was Metabolic & Digestive System (n = 254) followed by Body weight, Size and Growth (n = 224), Systemic/Nonspecific/Other (n = 162), Endocrine System (n = 147), Cell Toxicity/Mortality (n = 126), and Reproductive System (n = 95) (Fig. 8). Categories with the fewest number of studies include Musculoskeletal System (n = 30), Sensory System (n = 24), Genotoxicity (n = 16), and Cancer (n = 8).

Summary data on animal studies is presented in Table 4. Most animal studies were experimental in design (79%) and conducted in rats (41%),

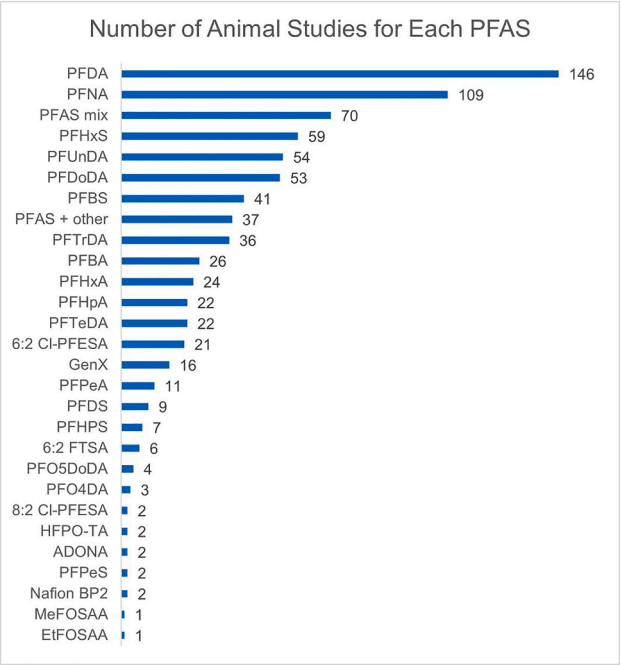

Fig. 7. Number of animal studies identified for each PFAS. There were no animal studies identified for PFNS, 8:2 FTSA, or Hydro-Eve.

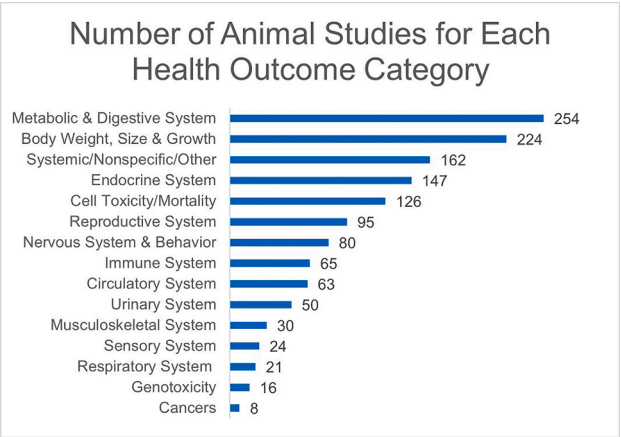

Fig. 8. Number of animal studies by health outcome category.

mice (22%), or fish (26%). Notably, for some health outcomes, rats are less sensitive to PFAS than mice (ATSDR 2021). The PFAS most commonly analyzed in experimental animal studies were: PFDA (n = 106), PFNA (n = 68), and PFBS (n = 36). Eighty-six studies (22%) were observational, most of which included studies of birds (37%), fish (21%), polar bears (9%) or other wildlife (36%). The PFAS most commonly analyzed in relation to health outcomes in observational animal studies were: PFNA (n = 41), PFUnDA (n = 41), and PFDA (n = 40).

With regard to age of exposure, most studies (75%) were of animals exposed to PFAS as adults. The remainder of studies explored the health impacts of animals exposed in various stages of development, depending on the species. As with human studies, dose and exposure data are not summarized due to the challenges of collapsing data across different units of measurement in different species using different routes of exposure. Dose and exposure values for individual studies are presented in the study details of the online database.

Routes of exposure depended on the study type and species, but most experimental rodent studies used oral exposures (mostly gavage) or

Table 4
Animal Study Summary Data (N = 385 studies).

	Variable	N (%)
Experiment type and species*		
Experimental		303 (78.7%)
	Rat	123 (40.6%)
	Mouse	67 (22.1%)
	Fish (mostly zebrafish)	79 (26.1%)
	Bird	9 (3.0%)
	Other (mussels, frog, daphnia +)	37 (12.2%)
Observational		86 (22.3%)
	Bird	32 (37.2%)
	Fish	18 (20.9%)
	Polar Bear	8 (9.3%)
	Other (alligator, pinnipeds, cat +)	31 (36.0%)
PFAS exposure		
Age at exposure*		
	Gestational	19 (4.9%)
	Postnatal	10 (2.6%)
	Developmental	6 (1.6%)
	Juvenile	66 (17.1%)
	Adult	289 (75.0%)
	Embryonic	75 (19.5%)
	Incubation	8 (2.1%)
	Larval	46 (11.9%)
	Hatchling	2 (0.3%)
Route of exposure*		
	Environmental	91 (23.6%)
	In treatment media	85 (22.1%)
	Intraperitoneal injection	85 (22.1%)
	Oral gavage	87 (22.6%)
	Oral feed/diet/water	29 (7.5)
	Other	17 (4.4%)
Number of subjects (using highest number in group range)		
	<10	161 (41.8%)
	10–100	206 (53.5%)
	>100	14 (3.6%)
Sex of subjects		
	Female and Male	227 (59.0%)
	Female	24 (6.2%)
	Male	134 (34.8%)
Outcome data		
Generations outcomes were measured in		
	F0 only	326 (84.7%)
	F1 only	4 (1.0%)
	F0 and F1	46 (11.9%)
	F0, F1, and F2+	9 (2.3%)
Age at outcome assessment*		
	Gestational	6 (1.6%)
	Postnatal	29 (7.5%)
	Juvenile	69 (17.9%)
	Adult	310 (80.5)
	Embryonic	43 (11.2%)
	Larval	63 (16.4%)
	Hatchling	5 (1.3%)

* Numbers and percentages exceed the total number and percent of studies due to representation of some studies in multiple categories.

intraperitoneal injection. The majority of intraperitoneal injection studies were conducted with PFDA. Only three animal studies examined dermal exposure and only one used inhalation exposure, routes of exposure that are potentially relevant for human exposure, even if understudied (De Silva et al. 2021; Poothong et al. 2020). Most experimental studies on non-rodent species occurred through treatment media (e.g. fish in water tanks). Of note, US EPA's Office of Research and Development Staff Handbook for Developing Integrated Risk Information System Assessments indicates that US EPA may prioritize routes of exposure based on relevancy for the specific chemical (US EPA 2020). As such, recently conducted US EPA health assessments of PFAS have prioritized oral or inhalation routes (US EPA 2021a; 2021b; 2021c; 2021e). Exposure in observational wildlife studies occurs throughout the lifecourse of the animals and can be determined by quantifying proximity to a specific pollution source, by measuring PFAS in environmental samples (e.g. water, sediment) or by measuring PFAS in tissues (e.g. blood plasma, liver, muscle).

External exposures to PFAS are not easily comparable across species due to variability in absorption, distribution, metabolism, and excretion of PFAS. Therefore risk assessment usually relies on measured or modeled internal concentrations of PFAS in rodent toxicological studies for determining the amount of PFAS associated with a health effect. Internal PFAS concentrations are difficult to estimate from externally administered doses, thus it is beneficial if the internal serum level of PFAS is concurrently measured in toxicological studies. However, only 16 of the 123 rat studies (13%) and 20 of the 67 mouse studies (30%) reported internal PFAS concentrations.

Most studies (53%) analyzed between 10 and 100 animals, and 42%

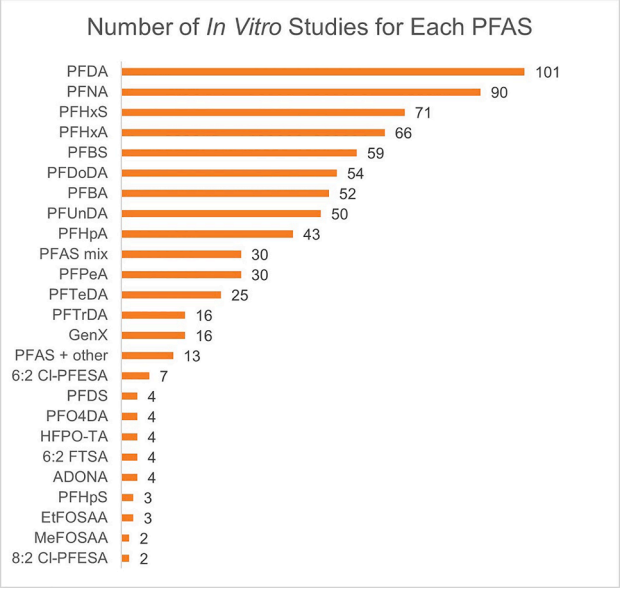

Fig. 9. Number of *in vitro* studies identified for each PFAS. There were no *in vitro* studies identified for PFPeS, PFNS, PFO5DoDA, Nafion BP2, 8:2 FTSA, or Hydro-Eve.

used fewer than ten animals in their largest group. Over half of the studies examined both males and females (59%) with 35% studying only males. Eighty five percent of the studies looked at one generation only (F0), while 12% looked at two generations (F0 and F1) and nine studies (2%) looked at three generations or more (F2 and beyond). Only one rodent study evaluated three or more generations. Two studies in insects measured up to 9 and 10 generations, and the remainder of studies evaluating three or more generations were in aquatic animals. Accordingly, outcomes were measured in adults in 81% of studies, with the remainder of studies measuring outcomes in various stages of development depending on the species (juvenile, embryonic, larval etc.).

3.6. *In vitro studies*

There were *in vitro* studies available for 23 PFAS as well as PFAS mix and PFAS + other (Fig. 9). The PFAS most commonly analyzed in relation to health outcomes in *in vitro* studies were: PFDA (n = 101), PFNA (n = 90), and PFHxS (n = 71). Across the *in vitro* studies, the most commonly studied health outcome category was Cell Toxicity/Mortality (n = 122), followed by Systemic/Nonspecific/Other (n = 100), Metabolic & Digestive System (n = 81), and Endocrine System (n = 81)

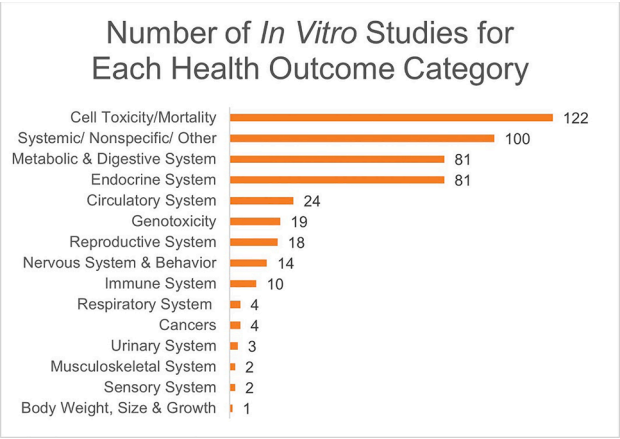

Fig. 10. Number of *in vitro* studies by health outcome category.

Table 5
In vitro Study Summary Data (N = 220 studies).

	Variable	N (%) or Mean (range)
Primary cells		54 (27.0%)
Cell or cell component species*		
	Cell-free system	51 (23.2%)
	Human	126 (57.3%)
	Rat	67 (30.5%)
	Mouse	29 (13.2%)
	Cow	12 (5.5%)
	Fish	11 (5.0%)
	Monkey	9 (4.1%)
	Hamster	8 (3.6%)
	Other	29 (13.2%)
Cell type*		
	Cell-free system	51 (23.2%)
	Liver	58 (26.4%)
	Kidney	27 (12.3%)
	Mammary	14 (6.4%)
	Adrenal	11 (5.0%)
	Ovary	10 (4.5%)
	Brain & Neuronal	10 (4.5%)
	Intestine & Colon	8 (3.6%)
	Bone	7 (3.2%)
	Blood	6 (2.7%)
	Colon	6 (2.7%)
	Lung	6 (2.7%)
	Leydig	5 (2.3%)
	Other	71 (32.3%)
Endpoints*		
	Cytotoxicity	119 (54%)
	Cell function/dysfunction	70 (32%)
	Gene Expression	42 (19%)
	Peroxisome proliferator activated receptor (PPAR) related	37 (17%)
	Protein binding	34 (15%)
	Metabolism	26 (12%)
	Adipocyte or lipid related	24 (11%)
	DNA damage	20 (9%)
	Estrogen related	19 (9%)
	Cell proliferation	19 (9%)
	Thyroid related	14 (6%)
	Androgen related	12 (5%)
	Steroidogenesis	12 (5%)
	Immune signaling	10 (5%)
	Cell differentiation	9 (4%)
	Nervous system signaling	9 (4%)
	Glucocorticoid related	8 (4%)
	Ah related (aryl hydrocarbon receptor)	5 (2%)
	Progesterone related	5 (2%)
	PXR (pregnane X receptor) related	4 (2%)
	Epigenetic changes	3 (1%)
	Aromatase	2 (1%)
	Constitutive androstane receptor related	2 (1%)
	Bone cell differentiation	2 (1%)
	Transporter activity	2 (1%)

* Numbers and percentages exceed the total number and percent of studies due to representation of some studies in multiple categories.

(Fig. 10). Categories with the fewest number of studies include Respiratory System (n = 4), Cancer (n = 4) Urinary System (n = 3), Musculoskeletal System (n = 2), Sensory System (n = 2), and Body Weight, Size and Growth (n = 1).

Summary data on *in vitro* studies is presented in Table 5. As with human and animal studies, dose and exposure data are not summarized due to the challenges of collapsing data across different units of measurement in different study designs. Dose and exposure values for individual studies are presented in the study details of the PFAS-Tox Database. Endpoint categories were created for *in vitro* studies to reflect the mechanisms most frequently studied. The most common categories were cytotoxicity and cell dysfunction, hormone related endpoints

(estrogen, androgen, thyroid, peroxisome proliferator-activated receptor (PPAR) etc.), DNA damage, nervous system signaling, metabolic processes, and protein binding. These are listed under study details in the PFAS-Tox Database for each study.

Cancer-related *in vitro* research may be underestimated in this evidence map because we did not include studies of bacteria in our PECO statement. However, we think the impact of this decision is minimal. *Salmonella* bacteria are often used to identify potentially carcinogenic chemicals (via the Ames Test). A keyword search for "Ames" or "mutagen" of the abstracts of excluded studies identifies only six potentially relevant studies, none of which contain data for the PFAS in the PFAS-Tox Database (see supplemental materials at https://osf.io/f9upx/). Cancer-related outcomes such as expression of specific cancer-related genes were captured in the Cancer Health Outcome category in the PFAS-Tox Database. Other endpoints evaluated in the *in vitro* literature may be relevant to cancer research but were not necessarily identified as such by the study authors and therefore were not categorized as cancer health outcomes. For example, cell functions like mitochondrial membrane potential, effects on cell cycle progression, or hormone receptor activity modulation, could be important mechanistic activities in carcinogenesis (Smith et al. 2016). These endpoints are included in the PFAS-Tox Database, but were not coded to the Cancer Health Outcome category if they were not evaluated in the context of carcinogenesis (Table 5). As such, the PFAS-Tox Database could serve as a starting point for a review evaluating the evidence that PFAS impact the key characteristics of carcinogenesis (Smith et al. 2016). The easiest way to identify relevant mechanistic endpoints is to search for them in the supplemental materials, available at https://osf.io/f9upx/.

Just over 20% of the *in vitro* studies included assays that were conducted in a cell-free system. These were primarily studies on albumin or other protein binding. About a quarter (27%) of the *in vitro* studies included assays conducted in primary cells. Primary cells are those harvested directly from human or animal subjects and are generally considered representative of the tissue from which they are derived. Primary cells were mostly hepatocytes, neurons, or Leydig cells. Over 80 immortalized cell lines were used in *in vitro* studies (see supplemental materials https://osf.io/f9upx/). These cell lines were derived from a variety of species and tissues and they vary in the degree to which they represent their tissues of origin. The most frequently used cell lines included HepG2 human liver cell line, Hek293 human embryonic kidney cell line, 3 T3-L1 mouse embryonic fibroblast cell line, CHO hamster ovarian epithelium, and MCF-7 human mammary gland adenocarcinoma cell line. The species of origin of cell lines or cellular components such as hormone receptors or ligand binding domains was extracted and can be searched for in the supplemental materials (https://osf.io/f9upx/). The majority of the studies (57%) used either a human cell line and/or human cellular components.

Health outcomes in *in vitro* studies were categorized as early life if cells, tissues or cellular components of placental, embryonic, or fetal origin were used. Some, but not all, of these studies assessed early life outcomes. For example, human placental JEG-3 cells were used to evaluate the impact of PFAS on placental lipidomics. On the other hand, some cell lines coded as "early life" were frequently used, not for their embryonic or fetal origins, but because they are useful and adaptable cellular models for studying other endpoints. For example, Hek293, human embryonic kidney cells, were often used in bioactivity assays in which reporter genes and nuclear hormone receptors, PPARs in particular, were transfected into the cell in order to determine the PFAS nuclear hormone activity.

4. General challenges and limitations

The PFAS-Tox Database is limited to studies indexed in PubMed, though there are other databases such as Web of Science that could have been interrogated. There are also non-peer reviewed research summaries available in US EPA's HERO database (US EPA, n.d.) and in data submitted to the European Chemicals Agency REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) program (ECHA n.d.). US EPA recently published a systematic evidence map that includes both peer reviewed and non-peer reviewed gray literature on 150 PFAS of interest to the agency (Carlson et al. 2022). Although we decided at this time to prioritize inclusion of the peer reviewed literature, the framework of the PFAS-Tox Database is flexible and can accommodate the addition of these types of studies in future updates.

Users of the PFAS-Tox Database may be surprised that PFOA and PFOS, two of the most well studied PFAS, are not included. We estimate that there are nearly as many health and toxicological studies for just PFOA and PFOS as there are in the entire PFAS-Tox Database of 29 other PFAS. Including these two chemicals would have required additional resources that we did not have. However, to facilitate future updates to the PFAS-Tox Database that would include the addition of PFOA and PFOS, data for these two chemicals were extracted from included studies that investigated PFOA and PFOS. Thus, the 790 studies in this systematic evidence map that also included PFOA and PFOS (which are available in supplemental data) would not have to be reviewed again.

Our goal in creating the PFAS-Tox Database was to make it as user-friendly as possible. Users will come to the database with different questions and the need for different types of information. Prior to initiating work on the systematic evidence map we queried community partners and colleagues in academia and government in order to better understand the types of study details most important for them. Several indicated that it would be useful to have a one sentence study summary indicating the direction or significance of effects. This was not feasible given the large number of chemicals and variety of study types included in this database, and that many studies report findings on multiple endpoints or multiple subgroups of participants. Conclusions about the association between exposure to a PFAS and a particular health outcome are best reached by conducting a systematic review which would include a quality (risk of bias) assessment of included studies. We do, however, make the abstracts easily available so that readers can relatively quickly identify each study's main conclusions as determined by the study authors.

Despite our outreach efforts and *a priori* publication of the protocol, there are a few data elements that we did not extract, but that we now realize would be helpful to users. We did not allow multiple study designs to be coded to human studies and we did not record which health outcomes were primarily included as covariates rather than as main outcomes. We did not extract or code the duration of exposure in the experimental animal studies. Though we categorized the age of the exposed animals, we did not note if the exposure was a single, repeat, or chronic exposure. Given that human exposure to PFAS is considered chronic, this information would be helpful for identifying the studies that are most relevant for human health hazard or risk assessment. We also did not record the solvent that was used in *in vitro* studies, a study design element that we now better appreciate as very important for *in vitro* studies of PFAS. US EPA has found that some PFAS are not soluble in the commonly used solvent dimethyl sulfoxide (DMSO) (US EPA 2021d).

To further support the varied needs of end users, all of the data that was extracted and coded for display are available as supplemental materials at https://osf.io/f9upx/. The supplemental materials are especially useful for end users who would like to search for specific outcomes, like IQ or vaccine response, which were extracted using the authors' language, not captured with a controlled vocabulary, nor searchable in the PFAS-Tox Database.

The developing organism is particularly vulnerable and susceptible to PFAS exposure. Health effects observed in developing organisms have been used as the basis for risk assessment of several PFAS, most recently in EPA's draft approaches for the derivation of the maximum contaminant level goals for PFOA and PFOS (US EPA, 2021a; 2021b). There are at least two ways to approach categorizing developmental effects in a systematic evidence map. One option would be to create a health

outcome category labeled 'developmental' that combines effects across many different systems (e.g., endocrine, body weight). US EPA used this approach for it's PFAS systematic evidence map, PFAS-150 (Carlson et al. 2022). A second option, which we used in developing the PFAS-Tox Database, is to build an "early life" search filter that tags any health outcome that was assessed in developing organisms. With this filter, end-users can identify studies in any health outcome category that were assessed during "early life". This filter allows for all health outcomes from a category to be kept together regardless of the age in which the endpoint is evaluated (during development or in adulthood).

5. Conclusions

Our goal in producing this systematic evidence map was to facilitate scientific, regulatory and individual access to current evidence regarding the health effects associated with PFAS exposure. Here we provide examples of how the systematic evidence map and the PFAS-Tox Database online tool can support these audiences. One is to provide scientists, whether they work in academia, government, or the nonprofit sector, the foundation for conducting further evaluation of the PFAS and health outcomes assessed in the systematic evidence map. The PFAS-Tox Database allows easy identification of evidence clusters and the thorough documentation of our methods allows for the direct use of the studies without having to duplicate the search and screening steps for a systematic or narrative review. For example research questions could be designed to study effects of PFAS mixtures, or short chain PFAS (both discussed above), or immune system effects. Recent research has highlighted the relationship between PFAS and immune outcomes, which has raised considerable concern regarding the potential for reduced effectiveness of COVID and other vaccines among people with elevated exposure to certain PFAS (Grandjean et al. 2020; NTP 2016). We hope scientists can use this evidence map to more quickly and efficiently address pressing questions such as these.

The PFAS-Tox Database was also designed to facilitate application of research to clinical care. As more and more PFAS-contaminated sites and elevated drinking water levels are identified around the world, impacted residents and their doctors are looking for information on health impacts and body burdens. In this systematic evidence map we extracted data on specific clinical parameters, such as lipid biomarkers and thyroid hormone levels, that are easily measurable in a clinical setting. A systematic review of these outcomes would help determine if such parameters could provide valuable information to doctors and their patients. It also supports the recent call for research on clinical biomarkers and PFAS from the National Academies of Science (National Academies of Sciences 2021).

Another use of the systematic evidence map is to explore data gaps. For example, cancer was one of the least studied health outcomes, which was surprising given that kidney and testicular cancer were two out of the six health outcomes identified a decade ago for PFOA (C8 Science Panel 2012a). Cancer research is challenging to study in humans given the long delay between exposure and disease onset, and the difficulty in untangling exposure to complex mixtures of chemicals. However, even for animal and *in vitro* studies, which shorten the necessary duration of exposure and reduce confounders, there is a dearth of studies directly assessing cancer outcomes associated with PFAS exposure. However, there are animal toxicological and *in vitro* mechanistic endpoints included in the systematic evidence map that, although not in the "cancer" health outcome category, are among the ten key characteristics of cancer (for example epigenetic alterations and altered cell proliferation) (Smith et al. 2016). Using the PFAS-Tox Database to investigate the ten key characteristics of cancer could help fill this important data gap, and possibly reveal the extent to which more cancer studies of PFAS are warranted. The database, and the data gaps it reveals, are also a great resource for graduate students to develop research questions, conduct literature reviews, and design thesis experiments.

The systematic evidence map can facilitate communication and coordination between different scientific disciplines. For example, animal research is not always driven by comprehensive knowledge of human studies, and vice versa. Some PFAS, like Me-FOSSA and Et-FOSSA have mostly been studied in humans with very few animal or *in vitro* experiments. Nafion byproduct 2, which has been detected in drinking water and in humans near a Chemours facility in North Carolina, has only been studied in wildlife animals so far (Hopkins et al. 2018; Kotlarz et al. 2020). There are also a handful of epidemiological studies that report associations with PFAS exposure on bone health (e.g. bone mineral density, osteoporosis), but few animal toxicological studies have investigated this endpoint. The PFAS-Tox Database is a useful tool to identify areas such as these, where more cross-disciplinary communication and research would help move the field forward.

The PFAS-Tox Database can be useful to regulatory agencies for identifying data used in human health risk assessment. For example, filters allow selection of experimental studies conducted with certain species and routes of exposure. Mechanistic, observational animal and other types of data are typically considered only as supplemental information in risk assessments, and it is not always clear how or when these data are used to support decision making (US EPA, 2021a; 2021b; 2021e; 2021f). EPA's newly released (May 2022) PFAS-150 systematic evidence map is also limited to "studies that could inform human hazard identification," in other words, human epidemiological and mammalian animal bioassays with oral or inhalation routes of exposure (Carlson et al. 2022). In an accompanying invited perspective, we document the similarities and differences between the two tools, PFAS-Tox Database and PFAS-150 (Table 1 in (Pelch and Kwiatkowski 2022)). We note that the narrower PECO statement focused on human and experimental mammalian animal studies used by US EPA in developing PFAS-150 leads to the identification of far fewer studies.

With the PFAS-Tox Database, studies for a specific health outcome can be easily compared across human, animal and *in vitro* study types to investigate concordance across species and study designs. It is our hope that agencies engaged in human health risk assessment will make better use of the full suite of data that is available on the health and toxicological effects associated with PFAS. The PFAS-Tox Database is also useful for agencies interested in ecotoxicological risk assessment and management, as it contains studies that investigate the impact of PFAS exposures on birds, fish, arthropods, earthworms, and other wildlife species.

The PFAS health and toxicological literature is growing rapidly, as are the number of governments attempting to regulate PFAS. Keeping up with the literature is critical, but will be challenging. The PFAS-Tox Database was designed to be a "living" systematic evidence map that can be updated periodically. Ideas for updates to the PFAS-Tox Database include adding well-studied chemicals like PFOA and PFOS and additional PFAS that are detected in the environment or in humans; and adding results from NTP Toxicity Reports or non-peer reviewed research, such as summaries available in US EPA's HERO database and ECHA's REACH program. The framework is built to easily incorporate these additional types of evidence and to transparently document future additions and improvements.

The use of systematic evidence maps such as this one, that present a wealth of data in an easily accessible online public format, are invaluable to the field of environmental health. We (KEP) have already published a systematic evidence map and online database of the health and toxicological effects associated with exposure to bisphenol A analogues (Pelch et al. 2019b). Future efforts focusing on other classes of chemicals, such as phthalates or siloxanes, or larger questions, such as the health effects associated with climate change, would also be of great public health value. Systematic evidence maps that focus on the environmental contributors to one specific health outcome or disease, such as we (KEP and CFK) have published for autism, would also be helpful for research and public health (Pelch et al. 2019a). Using our model, the UCSF Program on Reproductive Health and the Environment recently published a systematic evidence map identifying environmental factors

that influence immune response to SARS-CoV-2, which includes an online database (UCSF Program on Reproductive Health and the Environment 2022) and a published protocol (Rayasam et al. 2022). We hope that our systematic evidence map continues to serve as a model for these and other urgent and complex research questions.

6. Data Availability

The extracted and coded data for this systematic evidence map are visualized in an online, interactive database at PFASToxDatabase.org. Selected data can be downloaded directly from PFASToxDatabase.org following the onscreen instructions or the additional instructions that are detailed in the "How To Use the PFAS-Tox Database" file. The entire data set and all supplementary data are also available at the project website on Open Science Framework at https://osf.io/f9upx/ (Pelch et al. 2021).

Available data files include:

- Protocol and conduct:
  - o L3_PRISMA Report.
  - o Published protocol.
  - o Protocol update.
  - o Instructions for reviewers on how to extract and code data.
  - o Look up tables that track specific decisions made for screening and extraction.
- Data outputs:
  - o Literature search strings.
  - o Results of PubMed searches.
  - o Reasons for exclusion at title and abstract or full text level.
  - o Lists of included or excluded studies grouped by other areas of interest to the scientific community.
  - o The collated data downloaded from DistillerSR used for visualization in Tableau Desktop.
  - o A code book to further describe the data structure of the collated data used for visualization in Tableau Desktop.
  - o Downloadable.ris files of all included studies for use in reference management software.
  - o Analyses of publication time trends.
  - o Image file of the study flow diagram.
- Reports:
  - o Instructions for how to use the PFAS-Tox Database (available at https://www.pfastoxdatabase.org).
  - o Screenshots of the PFAS-Tox Database.
  - o Announcements of the release and updates to the PFAS-Tox Database.

Author Contributions

All authors contributed to the screening and data extraction to develop the systematic evidence map. KEP and AR developed the online PFAS-Tox Database in Tableau desktop. KEP, AR, CFK, and JV contributed to the conceptualization, oversight, data aggregation and manuscript writing. All authors reviewed, edited, and approved the final submission.

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: [Katherine Pelch, Carol Kwiatkowski, Kim Schultz, Anna Reade reports financial support was provided by Natural Resources Defense Council.].

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Appendix A. Supplementary material

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